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CADTH COMMON DRUG REVIEW

Clinical Review Report

SIPONIMOD (MAYZENT)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Secondary-progressive multiple sclerosis

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Abbreviations

9-HPT	9-hole peg test
AE	adverse event
ARR	annualized relapse rate
BVMT-R	Brief Visuospatial Memory Test-Revised
CDP	confirmed disability progression
CI	confidence interval
CIS	clinically isolated syndrome
CNS	central nervous system
CYP2C9	cytochrome P450 family 2 subfamily C member 9
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels
EQ VAS	EuroQol Visual Analogue Scale
FAMS	Functional Assessment of Multiple Sclerosis
FAS	full analysis set
HR	hazard ratio
HRQoL	health-related quality of life
Gd	gadolinium
ICC	intra-class correlation
ITC	indirect treatment comparison
MAIC	matching-adjusted indirect comparison
mFAS	modified full analysis set
MID	minimal important difference
MMRM	mixed-effects model for repeated measures
MOA	mechanism of action
MRI	magnetic resonance imaging
MS	multiple sclerosis

MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale
MSWS-12	Multiple Sclerosis Walking Scale
NMA	network meta-analysis
NOC	Notice of Compliance
PASAT	Paced Auditory Serial Addition Test
PPMS	primary-progressive multiple sclerosis
PPS	per-protocol set
RCT	randomized controlled trial
RRMS	relapsing-remitting multiple sclerosis
S1P	sphingosine 1-phosphate
SC	subcutaneous
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SF-36	Short Form (36) Health Survey
SPMS	secondary-progressive multiple sclerosis
T25-FW	Timed 25-Foot Walk Test

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Drug	Siponimod (Mayzent)
Indication	For the treatment of patients with secondary-progressive multiple sclerosis with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability
Reimbursement request	As per indication
Dosage form(s) and route of administration/strengths	0.25 mg and 2 mg oral tablets
NOC date	February 20, 2020
Sponsor	Novartis Pharmaceuticals Canada Inc.

Introduction

Multiple sclerosis (MS) is an immune-mediated, inflammatory, demyelinating disease of the central nervous system (CNS).[1] Clinical symptoms may include painful monocular vision loss, double vision, motor weakness, gait disturbance and balance problems, pain, spasticity, sensory symptoms in the limbs or face, and bladder and bowel symptoms.[1,2] It is more prevalent in females than in males and has a mean age of onset from 28 years to 31 years.[3] In Canada, estimates in 2015 for age-standardized prevalence and incidence of MS were 270 in 100,000 persons and 15 in 100,000 persons, respectively.[4]

Secondary-progressive MS (SPMS) is one of four main subtypes of MS. Most patients who initially present with relapsing-remitting MS (RRMS), representing approximately 85% of total MS, go on to develop SPMS, which is a progressive phase of the disease.[1,2] RRMS is characterized by episodes of symptom exacerbation, or relapses, that are followed by partial or complete remission. In contrast, progressive phenotypes are characterized by steadily increasing neurologic dysfunction and/or disability without recovery.[5] The onset of SPMS is typically identified in retrospect as there are no clear clinical, imaging, immunologic, or pathologic criteria for determining the point of transition between RRMS and SPMS.[5] Four phenotypes associated with SPMS were introduced in 2013: active with progression, active without progression, not active with progression, and not active without progression.[5] "Active" disease is defined by clinical relapses and/or magnetic resonance imaging (MRI) activity (contrast-enhancing lesions, and new and unequivocally enlarging T2 lesions). "Progression" refers to disease worsening, and is defined by clinical evaluation, which may use clinical history or a measure of change such as, but not limited to, the Kurtzke Expanded Disability Status Scale (EDSS).[5,6] The EDSS is an ordinal scale used to measure disability in MS, ranging from 0 (normal) to 10 (death). It addresses disability in eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation.[7]

Interferon beta-1a and interferon beta-1b are currently the only drugs approved by Health Canada that are indicated for patients with SPMS and are primarily used to treat relapses. According to the clinical experts consulted for this review, the use of interferons for treating patients with SPMS is rare as there are other disease-modifying therapies (DMTs) available for RRMS that also target relapses.[8-10] The currently approved DMTs for RRMS are

targeted toward patients with active MS (with clinical relapses and/or MRI activity) and there is no evidence to support that these DMTs reduce progression in patients with SPMS.[11,12] According to the clinical experts consulted for this review, due to the lack of treatments indicated specifically for SPMS, patients who have transitioned to SPMS may continue to receive a DMT that had been initiated during RRMS if they continue to have relapses. Treatment discontinuation may be considered in patients who have not experienced a recent relapse. Aside from DMTs, patients with MS may receive medications or non-pharmacological interventions for management of MS-related complications and symptoms.

Siponimod is a sphingosine 1-phosphate (S1P) receptor modulator available as oral film-coated tablets containing 0.25 mg or 2 mg siponimod.[13] The Health Canada indication is for the treatment of patients with SPMS with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability. The titration regimen includes a six-day titration period to reach the 2 mg maintenance dose on day 6.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of siponimod for the treatment of adult patients with SPMS with active disease, as per the Health Canada indication.

Stakeholder Engagement

Patient Input

At the time CADTH had requested patient input, siponimod was awaiting Health Canada approval. Therefore, the following summary of patient input received for this review is based on the proposed indication, which was for adult patients with SPMS. As previously noted, the final approved Health Canada indication is for adult patients with SPMS with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability. Of note, the number of patients with active SPMS versus non-active SPMS who contributed to the information used to inform the patient input submission is unknown.

One patient group, the Multiple Sclerosis Society of Canada (MS Society of Canada), submitted patient input for the review of siponimod for SPMS. An online survey in both English and French was used for data collection from September 9 to 23, 2019. A total of 408 responses were received for the survey, and the vast majority of respondents were patients with MS (SPMS = 60%, RRMS = 25%, and primary-progressive multiple sclerosis [PPMS] = 6%). The remainder of respondents were family members, caregivers, or colleagues. Based on the patient input, time since diagnosis with SPMS is as follows: 28% for more than 15 years, 17% for 10 years to 14 years, 18% for five years to 10 years, and 25% for less than five years. Among those with SPMS, the time to transition was also reported: 25% for 15 years or more, 23% for 10 years to 14 years, 23% for five years to 10 years, and 20% for less than five years.

The respondents described how a diagnosis of SPMS influenced their lives: loss of independence (81%), inability to participate in physical activity (76%), changes with the roles and responsibilities within their family (68%), and inability to maintain employment (56%). They expressed fear of the unknown impact that SPMS could bring to their lives and for the limited therapies available.

At the time of the survey, more than 80% of the respondents living with SPMS were not taking a DMT, while about 30% were taking some form of therapy. When asked about their perception of the drug after being provided a list of known common adverse events (AEs) associated with siponimod, 36% of the respondents said they would take siponimod, 35% said they would not take siponimod because of the lack of post-market long-term data, and 28% said they did not know.

Previously, when patients transitioned to SPMS, their DMT had little to no therapeutic benefit, or they were required to stop taking their DMT because they no longer met the reimbursement criteria for relapsing MS. Without an effective treatment after transitioning to SPMS, the disease progression worsens steadily. Despite this, the patient group states that as the first DMT targeted to SPMS in more than 20 years, siponimod fills a significant unmet need in the treatment of SPMS. Some respondents emphasized that "to ward off further disability would have a significant impact on the mental, physical, and emotional wellness of my entire family," and "improved, independent function is an economic benefit to our country."

The MS Society of Canada expects that treatment with siponimod may have the potential to allow people living with SPMS to remain in the workforce, sustain family and social roles and responsibilities longer, improve their quality of life, decrease the need for caregiving, and reduce the financial burden to health and social systems.

Clinician Input[1]

The clinical experts participating in this review stated that there are currently no treatments that slow or stop disease progression in patients with SPMS. Siponimod would be the first agent available that appears to address the underlying disease process in SPMS and would likely represent a paradigm shift. Consequently, siponimod would be a first-line treatment for SPMS and used as monotherapy. Prior to the availability of siponimod, patients with SPMS who have concurrent relapses are likely to continue on their current DMTs, with the rationale that reducing relapse activity may be beneficial, even if these treatments have no impact on the degenerative process thought to underlie the progressive disability in SPMS. Moreover, many patients would likely continue DMTs that they had already been taking for the relapsing-remitting phase of their MS up until they switch to a treatment like siponimod, as the distinction between the relapsing-remitting and secondary-progressive phases of MS is often not clear.

One of the clinical experts consulted for this review stated that patients who would be best suited for treatment with siponimod are those with SPMS who are demonstrating progression with or without relapse that can be objectively measured, and yet still have function to maintain. In the opinion of the other clinical expert consulted for this review, it would be difficult to define patients best suited for treatment with siponimod. Both agreed that patients with MS who are fully dependent (with an EDSS score of 8.0 or higher) would likely not benefit from treatment with siponimod.

To assess response to treatment, outcomes that evaluate functional ability and findings on neurological examinations would be used. One of the clinical experts noted that the measures used in clinical trials are broadly aligned with such clinical criteria. Halting or slowing the progressive disability over time and the ability to maintain mobility, upper limb function, and activities of daily living would be a clinically meaningful response. Stabilization

[1] This information is based on information provided in draft form by two clinical experts consulted by CADTH for the purpose of this review.

of function would be considered response to treatment, in contrast with the expected inexorable decline predicted by the natural history of SPMS. Factors that should be considered when deciding to discontinue treatment include expectations of continued benefit, whether there are any further impacts on quality of life by slowing progression, and safety. Disease progression while on treatment would likely lead to treatment discontinuation. The EDSS as well as the Timed 25-Foot Walk Test (T25-FW), the 9-hole peg test (9-HPT), and the Symbol Digit Modalities Test (SDMT) could be used to assess disease progression (in MS clinics), according to the clinical experts. Overall, there is currently no clear definition of disease progression; therefore, assessment of progression is ultimately made using the judgment of a clinician with expertise in MS.

Lastly, a neurologist with experience managing patients with MS or an MS clinic was recommended for the diagnosis, treatment, and monitoring of patients who may be treated with siponimod for SPMS.

Clinical Evidence

It should be noted that the CADTH submission for siponimod was filed on a pre-Notice of Compliance (NOC) basis. As per the CADTH procedure for pre-NOC reviews, siponimod was evaluated based on the indication proposed by the sponsor, which was for adults with SPMS. In order to conduct a comprehensive review of the evidence for the approved Health Canada indication, CADTH updated the systematic review protocol and conducted an updated literature search as appropriate. The original protocol has been made available in Appendix 5 of this report.

Pivotal Studies and Protocol Selected Studies

Description of Studies

The pivotal trial submitted by the sponsor was the only study that met the inclusion criteria for the systematic review. The EXPAND study was a double-blind, parallel-group, multi-centre, placebo-controlled, event-driven, exposure-driven, phase III randomized controlled trial (RCT) conducted between 2012 and 2016. A total of 1,651 patients with active SPMS (n = 779) and non-active SPMS (n = 872) were enrolled, including patients from sites in Canada. To be eligible for inclusion, patients needed to have a history of RRMS and a current diagnosis of SPMS, defined by a progressive increase in disability for at least six months, in the absence of relapses or independent of relapses. Patients also had to have an EDSS score of between 3.0 and 6.5 (inclusive) at screening, and documented progression in the two years prior to enrolment. Patients with various comorbidities and patients with homozygosity for the CYP2CP*3 haplotype were ineligible for this study. (CYP2C9 is cytochrome P450 family 2 subfamily C member 9.) Patients were randomized in a 2:1 ratio to either siponimod 2 mg or placebo. Randomization was stratified by region. The primary end point was the time to three-month confirmed disability progression (CDP). The definition of CDP was based on an established minimum important difference (MID), depending on the patient's baseline EDSS: a 1.0-point increase when the baseline EDSS score is 5.5 or less and a 0.5-point increase when the baseline EDSS score is greater than 5.5. Key secondary end points were the time to three-month confirmed worsening of at least 20% in the T25-FW and change from baseline in T2 lesion volume.

Of note, evidence that supports the indication under review was obtained from a subgroup analysis of the EXPAND study in patients with active SPMS. Planned subgroup analyses defined by disease activity (e.g., by patients with or without relapses in the two years prior

to screening visit, and by patients with or without T1 gadolinium-(Gd) enhancing lesions at baseline) were performed for the primary end points and secondary end points, and are of interest to this review. Other subgroup analyses of interest to this review included patients with rapidly evolving disease (change ≥ 1.5 in two years prior to study), and EDSS score at baseline.

The post-hoc active SPMS subgroup defined patients with active SPMS by the presence of superimposed relapses in the two years prior to screening and/or the presence of at least one T1 Gd-enhancing lesion at baseline. This is a combination of the two subgroups in the initial subgroup analyses. Of note, "superimposed relapses" refers to evidence of relapse in addition to progression and is referred to simply as "relapses" throughout the rest of the report. A total of 779 patients were included in the active SPMS subgroup; 516 and 263 patients were originally randomized to siponimod and placebo, respectively.

The baseline characteristics of patients included in the active SPMS subgroup analysis were similar between treatment groups and to the overall population. The active SPMS subgroup had a mean age of 46.3 years and the majority was female (63.8%). On average, patients were diagnosed with MS approximately [redacted] ago and had converted to SPMS 3.2 years ago. More than half of patients (55.6%) were severely disabled based on an EDSS score at baseline of 6.0 to 6.5; the remainder were moderately to severely disabled (26% and 17% had an EDSS score of 3.0 to 4.5 and 5.0 to 5.5, respectively). Overall, the characteristics of disease were consistent with a population that has moderate-to-severe disability and SPMS.

Efficacy Results

The results of the post-hoc active SPMS subgroup analyses are presented first, followed by the results of the full study population that has been included for reference. Where available, the preplanned subgroup analyses of relevance to this review have been summarized following the results of the full analysis set (FAS). A summary of the key efficacy results from the EXPAND study and sponsor-submitted post-hoc analysis of patients with active SPMS are available in Table 2. Key subgroup analyses of the primary end points and secondary end points of the EXPAND study are available in Table 3.

Based on a hazard ratio (HR) of 0.69 (95% confidence interval [CI], 0.53 to 0.91; P = 0.0094) in the active SPMS subgroup, treatment with siponimod at a maintenance dose of 2 mg once daily corresponded to a 30.7% risk reduction in the time to three-month CDP compared to placebo. In the overall population, an HR of 0.79 (95% CI, 0.65 to 0.95; P = 0.0134) was reported, corresponding to a 21.2% risk reduction for the time to three-month CDP with siponimod compared with placebo. [redacted] Further, in patients with more than one T1 Gd-enhancing lesion at baseline, the HR was 0.64 (95% CI, 0.42 to 0.95) and 0.82 (95% CI, 0.66 to 1.02) in patients without T1 Gd-enhancing lesions at baseline.

The results for the time to six-month CDP were also in favour of siponimod based on an HR of 0.63 (95% CI, 0.47 to 0.86) in the active SPMS subgroup. In the overall population, an HR of 0.74 (95% CI, 0.60 to 0.92) was reported; however, this analysis was not included in the statistical testing hierarchy. The established MID for the EDSS was used to inform the

definition of disease progression used for the primary end point. That is, a 1.0-point change when the baseline EDSS score was less than 5.5 and a 0.5-point change when the baseline EDSS score was 5.5 or greater.

The EXPAND study assessed health-related quality of life (HRQoL) at month 12 using the Multiple Sclerosis Walking Scale version 2 (MSWS-12), Multiple Sclerosis Impact Scale version 2 (MSIS-29), and EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) in the FAS, but none of the HRQoL outcomes were included in the statistical hierarchy. Only the MSWS-12 at month 12 was analyzed in a subgroup of patients with active SPMS. [redacted] Results of this subgroup analysis were consistent with the results in the FAS, which showed that at month 12, the between-groups difference for the MSWS-12 converted score was –1.83 (95% CI, –3.85 to 0.19; P = 0.0764). In summary, no conclusions regarding the potential benefit of siponimod on HRQoL can be made.

A patient's mobility was assessed using the time to three-month confirmed worsening of at least 20% from baseline based on the T25-FW. This was a key secondary outcome in the EXPAND study and the second outcome in the statistical hierarchy. In the post-hoc subgroup analysis of patients with active SPMS, an HR of 0.85 (95% CI, 0.68 to 1.07) for siponimod compared to placebo was reported for the time to three-month confirmed worsening in the T25-FW. In the overall population, this outcome did not demonstrate superiority of siponimod over placebo (HR = 0.94; 95% CI, 0.80 to 1.10; P = 0.4398). [redacted] The absolute risk difference between siponimod and placebo was 3.9% in the active SPMS subgroup and 1.7% in the overall population.

Cognitive function was assessed in the EXPAND study via the SDMT, Paced Auditory Serial Addition Test (PASAT), and Brief Visuospatial Memory Test-Revised (BVMT-R) (total recall and delayed recall). The outcomes related to cognitive function were not included in the statistical hierarchy and were not analyzed in any of the subgroup analyses of patients with active SPMS.

Specific MS-related symptoms, such as fatigue, were not reported as an efficacy outcome in the EXPAND study.

Relapse-related outcomes, including the annualized relapse rate (ARR) and percentage of relapse-free patients, were also assessed in the EXPAND study, but were not included in the statistical testing hierarchy. The sponsor-submitted post-hoc active SPMS subgroup analysis reported an ARR ratio of 0.544 (95% CI, 0.387 to 0.766; P = 0.0005) for confirmed relapses, which corresponds to a rate reduction of 45.6%. The sample size and adjusted ARR for each treatment group was not provided. This result was of a smaller magnitude than in the FAS, in which treatment with siponimod was associated with a 55.5% rate reduction in ARR (between-groups ARR ratio of 0.445; 95% CI, 0.337 to 0.587; P < 0.0001). This outcome was not controlled for multiplicity and therefore subject to risk of type I error.

The other key secondary outcome and third-ranked outcome in the statistical testing hierarchy was the change from baseline in T2 lesion volume at month 12. [redacted]

[redacted]The analysis of the overall population showed a treatment difference of –613.1 mm^3 (95% CI, –800.2 to –426.0; P < 0.0001) in favour of siponimod. However, this result violated the statistical testing hierarchy due to the failure of the second ranked outcome (confirmed worsening of ≥ 20% from baseline on the T25-FW, which was not statistically significant). Treatment group differences between siponimod and placebo were reported in [redacted] the overall population [redacted] for the additional imaging outcomes related to new or enlarging T2 lesions, but they were not controlled for multiplicity.

Harms Results

Safety was not assessed in any of the subgroup analyses pertaining to patients with active SPMS. The majority of patients in the full EXPAND study population reported at least one treatment-emergent AE while receiving the double-blind study drug and up to 30 days following discontinuation, with a slightly higher incidence of AEs among patients in the siponimod treatment group (88.7%) than in the placebo group (81.5%). The incidence of specific AEs was similar between the two treatment groups, although hypertension was slightly more common for patients treated with siponimod (10.5% versus 7.5%), as was nausea (6.7% versus 3.5%), alanine aminotransferase increase (5.9% versus 1.5%), and peripheral edema (4.5% versus 2.4%). Serious AEs were reported by 17.9% of patients treated with siponimod and 15.2% of patients treated with placebo; the number of specific events reported was low and similar between treatment arms. Proportions of withdrawal due to AEs were low (7.6% for siponimod and 5.1% for placebo). [redacted] As for the notable harms, bradycardia and macular edema were also more common in the siponimod group compared to the placebo group (4.5% versus 2.6% and 1.6% versus 0.2%, respectively). Four deaths from each treatment group were reported during the EXPAND study.

Table 2: Summary of Key Efficacy Results from Pivotal and Protocol Selected Studies

	EXPAND (FAS)		EXPAND (active SPMS subgroup)	
	Siponimod (N = 1,099)	Placebo (N = 546)	Siponimod (N = 516)	Placebo (N = 263)
Primary outcome: Time to 3-month CDP by EDSS[a]				
n/N (%)	288/1,096 (26.3)	173/545 (31.7)	[redacted]	[redacted]
Risk reduction (%)	21.2		30.7	
Hazard ratio[a] (95% CI)	0.79 (0.65 to 0.95)		0.69 (0.53 to 0.91)	
P value	0.0134		0.0094[b]	
MSWS-12 converted score, MMRM				
Number of patients contributing to the analysis	1,022	516	[redacted]	[redacted]
Baseline, mean (SD)	68.29 (23.37)	66.64 (22.25)	[redacted]	
Adjusted change from baseline, mean (SE)	1.53 (0.68)	3.36 (0.91)	[redacted]	[redacted]
Treatment group difference vs. control (95% CI)	–1.83 (–3.85 to 0.19)		[redacted]	
P value	0.0764[b]		[redacted]	
Key secondary outcome: Time to 3-month confirmed worsening of ≥ 20% from baseline in the T25-FW[c]				
n/N (%)	432/1,087 (39.7)	225/543 (41.4)	[redacted](41.7)	120/263 (45.6)
Risk reduction (%)	6.2		14.7	
Hazard ratio (95% CI)	0.94 (0.80 to 1.10)		0.85 (0.68 to 1.07)	
P value	0.4398		0.1747[b]	
ARR, confirmed relapses				
n/time (days)	134/691,980	143/343,285	NR	
Adjusted[b] ARR (95% CI)	0.071 (0.055 to 0.092)	0.160 (0.123 to 0.207)		
Rate reduction (%)	55.5		45.6	
Between-groups ARR ratio (95% CI)	0.445 (0.337 to 0.587)		0.544 (0.387 to 0.766)	
P value	< 0.0001[b]		0.0005[b]	
Key secondary outcome: Change from baseline in T2 lesion volume (mm^3),[d] MMRM				
Number of patients contributing to the analysis	995	495	473	244
Baseline, mean (SD)	[redacted]	[redacted]	NR	NR
Change from baseline, mean (SD)	[redacted]	[redacted]	NR	NR
Adjusted change from baseline, mean (SE)	204.9 (67.47)	818.0 (87.29)	93.5[redacted]	1,117.2[redacted]
Treatment group difference vs. control (95% CI)	–613.1 (–800.2 to –426.0)		[redacted]	
P value	< 0.0001[e]		< 0.001[b]	
Number of new or enlarging T2 lesions (relative to baseline)[f]				
N' (in analysis)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Rate reduction (%)	[redacted]		[redacted]	
Rate ratio (95% CI), P value	[redacted]		[redacted]	

	EXPAND (FAS)		EXPAND (active SPMS subgroup)	
	Siponimod (N = 1,099)	Placebo (N = 546)	Siponimod (N = 516)	Placebo (N = 263)
Number of T1 Gd-enhancing lesions per patient per scan[g]				
N' (in analysis)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Rate reduction (%)	[redacted]		[redacted]	
Rate ratio (95% CI), P value	[redacted]		[redacted]	
Percentage brain volume change (relative to baseline),[h] MMRM				
N' (in analysis)	894	436	431	222
Adjusted mean (SE)	–0.283 (0.0264)	–0.458 (0.0341)	–0.4 [redacted]	–0.6 [redacted]
Difference (95% CI), P value	0.175 (0.103 to 0.247); P < 0.0001		0.173 (0.064 to 0.283); P = 0.0020	

ARR = annualized relapse rate; CDP = confirmed disability progression; CI = confidence interval; EDSS = Expanded Disability Status Scale; FAS = full analysis set; Gd = gadolinium; MMRM = mixed-effects model for repeated measures; MRI = magnetic resonance imaging; MSWS-12 = Multiple Sclerosis Walking Scale; NR = not reported; SD = standard deviation; SE = standard error; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test; vs. = versus.

Note: The active SPMS subgroup defined patients with active disease as having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline.

[a] Used a Cox proportional hazards model with treatment, country and/or region, baseline EDSS, and SPMS group (with or without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1-hazard ratio) × 100.

[b] Outcome was not adjusted for multiplicity.

[c] The comparison used a Cox proportional hazards model with treatment, country and/or region, baseline EDSS, baseline T25-FW, and SPMS group (with or without superimposed relapses, baseline definition) as covariates.

[d] Model was adjusted for treatment, country and/or region, baseline T2 lesion volume, number of T1 Gd-enhancing lesions at baseline, SPMS group (with or without superimposed relapses, baseline definition).

[e] Included in the statistical hierarchy, but analyzed following a prior failure; therefore, violating the pre-specified statistical strategy.

[f] Model was adjusted for treatment, region and/or country, age, and baseline number of T1 Gd-enhancing weighted lesions (offset = time between visits).

[g] Obtained from fitting negative binomial regression model adjusted for treatment, age, and baseline number of T1 Gd-enhancing lesions (offset = number of scheduled MRI scans).

[h] Model was adjusted for treatment, country and/or region, age, normalized brain volume at baseline, number of T1 Gd-enhancing lesions at baseline, T2 volume at baseline, and SPMS group (with or without superimposed relapses, baseline definition).

Source: EXPAND Clinical Study Report[14] and CADTH submission for siponimod.[15]

Table 3: Summary of Key Subgroup Analyses of Efficacy from Pivotal and Protocol Selected Studies

	Siponimod	Placebo	
	n/N (%)	n/N (%)	HR (95% CI)
Time to 3-month CDP by EDSS (FAS)			
Relapses in the 2 years prior to study start[a]			
Without superimposed relapses	190/708 (26.8)	101/343 (29.4)	0.87 (0.68 to 1.11)
With superimposed relapses	98/388 (25.3)	72/202 (35.6)	0.67 (0.49 to 0.91)
Number of T1 Gd-enhancing lesions at baseline[a]			
0	219/828 (26.4)	128/415 (30.8)	0.82 (0.66 to 1.02)
≥ 1	61/236 (25.8)	40/114 (35.1)	0.64 (0.42 to 0.95)
Time to 3-month confirmed worsening of ≥ 20% from baseline in T25-FW[a] (FAS)			
Relapses in the 2 years prior to study start			
Without superimposed relapses	[redacted]	[redacted]	[redacted]
With superimposed relapses	[redacted]	[redacted]	[redacted]
	Estimate	**Estimate**	**Difference (95% CI)**
Change from baseline in T2 volume (mm^3)[a] (FAS)			
Relapses in the 2 years prior to study start			
Without superimposed relapses	[redacted]	[redacted]	[redacted]
With superimposed relapses	[redacted]	[redacted]	[redacted]

CDP = confirmed disability progression; CI = confidence interval; EDSS = Expanded Disability Status Scale; FAS = full analysis set; Gd = gadolinium; HR = hazard ratio; NR = not reported; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test.

Note: It is unclear whether the subgroup analyses were preplanned, but patients were not stratified by the subgroups in this table at randomization. All analyses were conducted using the FAS.

[a] Outcome was outside the statistical testing hierarchy.

Source: EXPAND Clinical Study Report.[14]

Table 4: Summary of Key Safety Results from Pivotal and Protocol Selected Studies

	EXPAND	
	Siponimod (N = 1,099)	Placebo (N = 546)
Harms, n (%) (SAF)		
AEs	975 (88.7)	445 (81.5)
SAEs	197 (17.9)	83 (15.2)
WDAEs (from study treatment)	84 (7.6)	28 (5.1)
Deaths	4 (0.4)	4 (0.7)
Notable harms, n (%) (SAF)		
Bradycardia	50 (4.5)	14 (2.6)
Neoplasia (neoplasms: benign, malignant, and unspecified)	[redacted]	[redacted]
Lymphocytopenia (lymphocyte counts)	9 (0.8)	0
Macular edema	18 (1.6)	1 (0.2)
Serious infections (progressive multifocal leukoencephalopathy)	[redacted]	[redacted]
Opportunistic infections (cryptococcal meningitis)	[redacted]	[redacted]

AE = adverse event; EDSS = Expanded Disability Status Scale; Gd = gadolinium; SAE = serious adverse event; SAF = safety set; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test; WDAE = withdrawal due to adverse event.

[a] Used a Cox proportional hazards model with treatment, country and/or region, baseline EDSS, and SPMS group (with or without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1-hazard ratio) × 100.

[b] The comparison used a Cox proportional hazards model with treatment, country and/or region, baseline EDSS, baseline T25-FW, and SPMS group (with or without superimposed relapses, baseline definition) as covariates.

[c] Model was adjusted for treatment, country and/or region, baseline T2 lesion volume, number of T1 Gd-enhancing lesions at baseline, and SPMS group (with or without superimposed relapses, baseline definition).

[d] Included in the statistical hierarchy, but analyzed following a prior failure; therefore, violating the pre-specified statistical strategy.

Source: EXPAND Clinical Study Report.[14]

Critical Appraisal

The internal validity of the EXPAND study, particularly on the active SPMS subgroup, was likely subject to several major limitations. The overall study discontinuation rate was relatively high in both the overall population and active SPMS subgroup (19.6% and 20.6%, respectively), which may have compromised randomization and rendered the study results to potential bias. Further, discontinuations were disproportionate between treatment groups in the active SPMS subgroup (18% in the siponimod group and 27% in the placebo group). Interpretation of statistical significance of the differences of outcomes, such as the ARR and imaging outcomes, is limited due to a lack of control of multiplicity. The subgroup analyses of patients with active SPMS were not pre-specified, but post-hoc analyses, which were based on a smaller sample size that included 47% of the overall population, and maintenance of randomization between treatment groups were probably compromised due to lack of randomization stratification at baseline. Statistical testing, where conducted, was not controlled for multiplicity and therefore was subject to potential inflated risk of type I error. Nevertheless, the findings from the active SPMS subgroup were generally consistent with that of the overall study population and the planned subgroup analyses, which may help enhance CADTH's confidence in the subgroup results; however, the limitations associated with the active SPMS subgroup data restrict the conclusions that can be drawn on the beneficial effect of siponimod on patients with active SPMS.

In terms of external validity, the patients enrolled in the study, particularly the active SPMS subgroup, were younger and healthier (in terms of comorbidities) than typical Canadian patients living with SPMS, according to the clinical experts consulted by CADTH, as patients with a variety of comorbidities were excluded. Moreover, the study only included patients with a baseline EDSS score of between 3 to 6.5 (inclusive), which would have limited the generalizability of the findings to patients with an EDSS score of 6.5 or greater who may also receive the treatment in clinical practice. The durability of long-term treatment effect and safety is unknown and therefore the results as observed by month 12 may be limited in their applicability to chronic use of siponimod in clinical practice. The titration regimen and dosage used in EXPAND appears to be representative of what will be used in Canadian clinical practice.

The choice of placebo as the sole comparator used in the pivotal trial for siponimod is a limitation of the evaluation of siponimod in the context of Canadian clinical practice. In the absence of treatment for SPMS, patients might be continued on treatment for RRMS when they progress to SPMS even if this only treats symptoms rather than the disease. This is particularly relevant since siponimod is indicated for patients with active SPMS evidenced by relapses or imaging, who are likely to be treated with any DMT for RRMS as indicated by the clinical experts consulted for this review.

Indirect Comparisons

Description of Studies

One sponsor-submitted indirect treatment comparison (ITC) was included that used matching-adjusted indirect comparison (MAIC) methods to conduct pairwise comparisons between siponimod to interferon beta-1a and interferon beta-1b, and natalizumab, in patients with SPMS. Individual patient data from the EXPAND trial was used to match and adjust patients to those included in the comparator interferon trials. MAIC was deemed necessary due to differences across trials in the patient populations enrolled and changes in the treatment paradigm.

Efficacy Results

The results of some pairwise comparisons suggest that disability progression may be delayed for siponimod versus interferon beta, while others found no differences. No differences were found between siponimod and natalizumab in terms of disability progression. In addition, no differences between treatments were found for the analyses of relapse rates, which showed wide CIs suggesting there was considerable uncertainty in the results.

Harms Results

There was no assessment of harms in the sponsor-submitted ITC.

Critical Appraisal

Although the methods used to conduct the MAIC follow technical guidance,[16] the analyses have a number of limitations that impact the internal and external validity. There are concerns regarding the overlap between the comparator and siponimod trial populations, and the availability of data to allow for matching and adjustment. Matching was not possible for all criteria, and for some analyses no, or limited, adjustment to balance potential effect modifiers was feasible. The small effective sample size of many analyses confirms that substantial differences exist between the patient populations in the siponimod and

comparator trials. Given these issues, there is substantial uncertainty in the results. Moreover, most patients included in the analyses did not have active SPMS, and the treatment effects reported for siponimod versus interferon apply to an interferon-naive patient population, which may have little relevance to the population of interest to Canadian decision-makers, as most patients who have developed SPMS would have previously received a DMT. The relevance of interferon and natalizumab as a comparator is also limited; thus, the utility of these data is poor.

Other Relevant Evidence

The long-term open-label extension phase (the extension part) of the EXPAND study is ongoing. No results from the extension part of the study were available at the time of this review.

Conclusions

One double-blind, parallel-group, multi-centre, placebo-controlled, event-driven, phase III RCT met the inclusion criteria for this review: the pivotal EXPAND study. The trial was conducted in patients with a broad range of SPMS phenotypes, but the indication approved by Health Canada is limited to patients with SPMS, defined as patients with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability. Data that were available to support efficacy of siponimod for this indication were limited to planned subgroup analyses based on disease activity and a post-hoc subgroup of patients with active SPMS, which was defined by the presence of relapses in the two years prior to screening and/or the presence of at least one T1 Gd-enhancing lesion at baseline. These post-hoc subgroup analysis results of patients with active SPMS, representing 47% of the overall study population, constituted the main body of evidence in support of this review.

Patients treated with siponimod 2 mg daily demonstrated a clinical benefit compared to placebo in reducing the time to three-month CDP at month 12 based on a minimal clinically important change of EDSS score. Further, results of the study suggest that siponimod may provide benefit in preventing relapses and in improving imaging outcomes. However, no impact on patient mobility was observed, and there is uncertainty regarding the improvement of disease-related symptoms and HRQoL. The observed benefits were generally consistent between the subgroup of active SPMS and the overall study population; however, the magnitude of the treatment effect of siponimod was more evident in the active SPMS subgroups. There were no major safety signals for siponimod based on the overall patient population, but this was limited by the lack of long-term data available at the time of this report. Results of the study are limited by issues with partial unblinding and high disproportional discontinuation. The subgroup analyses are subject to the same limitations, in addition to small sample size, potential for randomization that was not maintained, and results that may only be considered exploratory.

No direct evidence comparing siponimod to other DMTs for SPMS were identified in this review. No conclusions can be drawn from the sponsor-submitted ITC due to limitations that impact the internal and external validity of the findings. Key limitations included heterogeneity in the populations enrolled and the availability of data to allow for matching and adjustment of siponimod and comparator study populations. Moreover, the analyses were not specific to patients with active SPMS; thus, the utility of the results is limited.

Introduction

Disease Background

MS is an immune-mediated, inflammatory, demyelinating disease of the CNS.[1] It is more prevalent in females than in males and has a mean age of onset from 28 years to 31 years.[3] In Canada, estimates in 2015 for age-standardized prevalence and incidence of MS were 270 in 100,000 persons and 15 in 100,000 persons, respectively.[4] While the etiology of MS remains unknown, it is commonly accepted that autoreactive lymphocytes are implicated.[3] MS is characterized by focal demyelinated plaques in the CNS, which can be accompanied by inflammation and gliosis.[3] Symptoms of MS are varied and include painful monocular vision loss, double vision, motor weakness, gait disturbance and balance problems, pain, spasticity, sensory symptoms in the limbs or face, and bladder and bowel symptoms.[1,2]

The McDonald Criteria, most recently updated in 2017, are used in diagnosing MS.[17] Clinical evidence can be sufficient to meet the diagnostic criteria, though MRI evidence can be used in conjunction with clinical evidence to make a diagnosis.[17,18] More specifically, the criteria for diagnosis are based on the occurrence of one or more attacks (relapse, exacerbation, and/or clinically isolated syndrome [CIS]) and objective clinical evidence of one or more lesions.[17,18] Depending on the number of attacks or lesions present, additional data may be required to make the diagnosis. This may include the dissemination in time, demonstrated by evidence of an additional lesion, and/or dissemination in space, demonstrated by evidence of lesions in at least two CNS regions.[17]

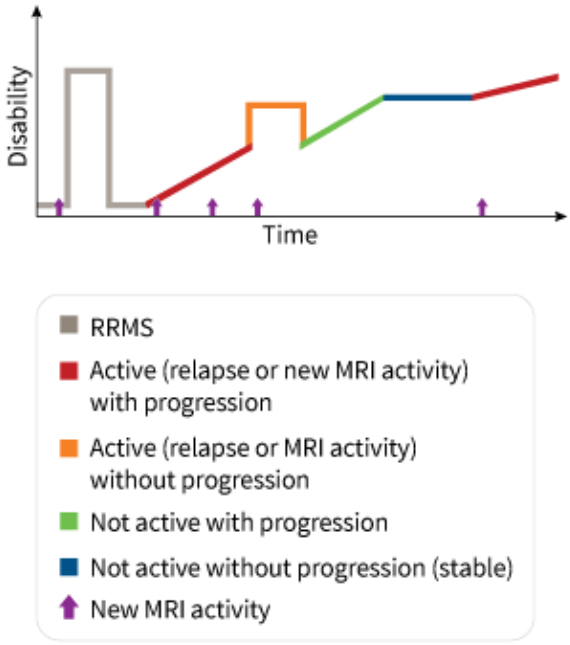
There are four main disease courses or subtypes of MS that should be specified at the time of diagnosis. They include CIS, RRMS, PPMS, and SPMS.[17] Approximately 85% of patients with MS experience the RRMS phenotype at disease onset.[1,2] RRMS is characterized by episodes of symptom exacerbation, or relapses, that are followed by partial or complete remission. During these episodes, symptoms generally develop over hours or days and then go into remission over weeks or months.[19] Most patients who initially present with RRMS go on to develop SPMS, which is a progressive phase of the disease.[1,2] According to the MS Society of Canada, about 50% of patients with RRMS develop SPMS within 10 years of their diagnosis of RRMS.[20]

Progressive phenotypes of MS, such as SPMS, are characterized by steadily increasing neurologic dysfunction and/or disability without unequivocal recovery.[5] Relapses, minor remissions, and plateaus can still occur during the progressive phase, though active CNS lesions (as identified using MRI) become less frequent during the SPMS phase.[21] Figure 1 provides a graphical depiction of the four phenotypes associated with SPMS introduced in 2013: active with progression, active without progression, not active with progression, and not active without progression.[5] "Active" disease is defined by clinical relapses and/or MRI activity (contrast-enhancing lesions, and new and unequivocally enlarging T2 lesions). "Progression" refers to disease worsening and is defined by clinical evaluation.

The delineation between RRMS and SPMS is unclear and the onset of SPMS is typically identified in retrospect as there are no clear clinical, imaging, immunologic, or pathologic criteria for determining the point of transition between RRMS and SPMS.[5] Progression can be determined retrospectively using a patient's clinical history or by a measure of change such as the EDSS.[5,6] The time from onset of MS and the onset of the SPMS phase is

19 years on average, but it varies widely.[21] It is possible that there is no distinct boundary between the phases and that the transition is a gradual one.[21,22]

Figure 1: SPMS Phenotypes



MRI = magnetic resonance imaging; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
Source: Lublin et al. (2014)[5] and National Multiple Sclerosis Society.[23]

Standards of Therapy

Before siponimod, interferon beta-1a and interferon beta-1b were the only drugs approved by Health Canada with an indication for SPMS (specifically in those who experience relapses in the case of interferon beta-1a).[8-10] However, their use in treating SPMS is limited as they only treat the occurrence of relapses. As per the opinions of the clinical experts consulted for this review, the use of interferons for the treatment of patients with SPMS is no longer clinically relevant as there are other DMTs available for other forms of MS that also target relapses. The currently approved DMTs for RRMS (aside from ocrelizumab for PPMS) are targeted toward patients with active MS as there is no evidence of reduced disease progression in patients with SPMS.[11,12] For example, the European Academy of Neurology and European Committee for Treatment and Research in Multiple Sclerosis guideline contains a weak recommendation to consider treatment with interferon beta-1a or interferon beta-1b for patients with active SPMS, noting its "dubious efficacy."[24] Due to the lack of treatments indicated specifically for SPMS, patients who have transitioned to SPMS may continue to receive a DMT that had been initiated during RRMS. Treatment discontinuation of a DMT used during the RRMS phase of the disease may be considered in patients who have not experienced a recent relapse. This is recommended in the guidelines published by the American Academy of Neurology, which states, "Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses

(or gadolinium-enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 of greater) for at least 2 years."[25]

Aside from DMTs, patients with MS may receive medications or non-pharmacological interventions for management of MS-related complications and symptoms. These include medications for bladder dysfunction, bowel dysfunction, depression, fatigue, pain, paroxysmal attacks, seizures, and spasticity.[26] However, some MS symptoms and treatments can exacerbate other symptoms and potential underlying causes should also be addressed. There are several non-pharmacological approaches to managing complications and symptoms, such as behavioural modification techniques, physical therapy, mobility aids, feeding tubes, and non-invasive ventilation.[26] For patients with MS and mild to moderate disability, the Canadian Physical Activity Guidelines recommend at least 30 minutes of moderate-intensity aerobic activity and strength training exercises for major muscle groups, both twice a week.[27]

Drug

Siponimod is a S1P receptor modulator available as film-coated tablets containing 0.25 mg or 2 mg siponimod (as siponimod fumaric acid) for oral administration.[13] Siponimod acts as a functional antagonist of S1P receptors on lymphocytes, preventing egress from lymph nodes and reducing recirculation of T cells into the CNS to limit central inflammation. The Health Canada indication is for the treatment of patients with SPMS with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability. The dosing regimen includes a six-day titration period starting with 0.25 mg and progressing up to 1.25 mg on day 5, followed by a 2 mg maintenance dose starting on day 6. If a titration dose is missed on one of the first six days of treatment, the patient must re-initiate the titration period beginning at day 1 (0.25 mg) of the titration regimen using a new starter pack.[13] The recommended maintenance dose of siponimod is 2 mg beginning on day 6, taken once daily, at about the same time each day, with or without food. If maintenance treatment is interrupted for four or more consecutive daily doses, treatment must be re-initiated with day 1 of the titration regimen, using a new starter pack.

As per the product monograph, patients should be genotyped for CYP2C9 to determine the CYP2C9 metabolizer status prior to initiating treatment with siponimod. Siponimod should not be used in patients homozygous for the CYP2C9*3 haplotype. A reduced maintenance dose of 1 mg of siponimod daily is recommended in patients with the CYP2C9*2*3 or CYP2C9*1*3 genotype.

The sponsor's reimbursement request is the same as the Health Canada indication. Of note, the FDA has approved siponimod for the treatment of relapsing forms of MS to include CIS, relapsing-remitting disease, and active secondary-progressive disease, in adults.[28] The European Medicines Agency (EMA) approved siponimod for treatment of adults with advanced forms of MS, to be used in patients with active disease, noting this means "patients still have relapses or signs of inflammation that can be seen in scans."[29]

Table 5: Key Characteristics of DMTs Approved for MS

	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious side effects or safety issues
Siponimod (Mayzent)	A S1P receptor modulator that binds selectively to 2 out of 5 GPCRs for S1P (S1P1 and S1P5). Acts as a functional antagonist on S1P1 receptors on lymphocytes, preventing egress from lymph nodes and consequently reducing recirculation of T cells into the CNS to limit central inflammation	For the treatment of patients with SPMS with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability	Oral tablet	2 mg daily with 5-day titration period Note: A 1 mg daily maintenance dose is recommended for patients with the CYP2C9*2*3 or CYP2C9*1*3 genotype	Bradyarrhythmia, atrioventricular conduction, liver function, infections (cryptococcal meningitis and herpes), macular edema, fetal harm Contraindicated in patients with known hypersensitivity, homozygous for CYP2C9*3*3 genotype
Cladribine (Mavenclad)[30]	Inhibits lymphocyte proliferation	Monotherapy for the treatment of adult patients with RRMS	Oral	3.5 mg/kg over 2 years	Lymphocytopenia, infections (herpes zoster, TB/latent TB reactivation, PML), malignancies, teratogenic
Ocrelizumab (Ocrevus)[31]	Reduction in CD20	RRMS	IV infusion	600 mg every 6 months	Infusion reactions, infections (herpes, respiratory tract) Contraindicated in patients with active/severe infection or with PML
Pegylated IFN beta-1a (Plegridy)[32]	Its effects in MS are not completely understood. It exerts its biological effects by binding to type I IFN receptors on the surface of human cells	RRMS	SC injection	125 mcg every 2 weeks	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection site reactions, depression/suicide Patients with a history of hypersensitivity to natural or recombinant IFN beta or peginterferon or any other component of the formulation or the container
Alemtuzumab (Lemtrada)[33]	Binds to CD52	• RRMS • Patients who have had an inadequate response to IFN beta or other DMTs	IV infusion	Initial treatment cycle: 12 mg/day for 5 consecutive days Second treatment cycle: 12 mg/day for 3	Autoimmune disorders, infections, infusion reactions Contraindicated in patients who:

	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious side effects or safety issues
				consecutive days administered 12 months after the initial treatment course	• are hypersensitive to alemtuzumab or to any ingredient in the formulation or component of the container • are infected with HIV • have active or latent TB, active severe infections, or active malignancies • are on antineoplastic or immunosuppressive therapies • have a history of PML
Dimethyl fumarate (Tecfidera)[34]	Not completely understood; activates the Nrf2 pathway	RRMS	Oral capsule	240 mg twice daily	PML, reduced lymphocyte counts Contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container
Fingolimod (Gilenya)[35]	Its effects in MS are not fully known; its active metabolite binds to receptors on lymphocytes, blocks lymphocytes from leaving lymph nodes, reduces the number of lymphocytes in peripheral blood, and reduces lymphocyte migration into CNS	• RRMS • Generally recommended in patients with MS who have had inadequate response to, or are unable to tolerate, 1 or more therapies for MS	Oral capsule	0.5 mg/day	PML, skin cancer, infections (varicella), heart block Contraindicated in patients who: • are hypersensitive to fingolimod • are at risk for an opportunistic infection • are immunocompromised due to treatment or to disease • have hepatic insufficiency, active severe infections, or known active malignancies Varicella zoster vaccination recommended
Glatiramer acetate (Copaxone)[36]	Likely modifies the immune processes responsible for pathogenesis of MS	• RRMS • Single demyelinating event, accompanied by abnormal MRI scans and considered to be at risk of developing CDMS	SC injection	20 mg/day	Contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol

	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious side effects or safety issues
IFN beta-1a (Avonex, Rebif)[9,10]	Its effects in MS are not completely understood. It exerts its biological effects by binding to specific receptors on the surface of human cells, and inducing the expression of numerous IFN-induced gene products	• RRMS • SPMS with relapses • Single demyelinating event, accompanied by abnormal MRI scans, with lesions typical of MS	IM injection (Avonex) SC injection (Rebif)	IM: 30 mcg/week (increase up to 60 mcg/week if needed) SC: 22 mcg or 44 mcg 3 times/week	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection site reactions, depression/suicide Contraindicated in patients with known hypersensitivity to natural or recombinant IFN, patients with liver disease, and pregnant women
IFN beta-1b (Betaseron, Extavia)[8,37]	Its effects in MS are not completely understood. It exerts its biological effects by binding to specific receptors on the surface of human cells, and inducing the expression of numerous IFN-induced gene products	• RRMS • SPMS • Single demyelinating event accompanied by at least 2 clinically silent lesions typical of MS	SC injection (Betaseron, Extavia)	0.25 mg every other day	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection site reactions, depression/suicide Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, and pregnant women
Natalizumab (Tysabri)[38]	Binds to the α4-subunit of human integrin: blocks interaction of alpha 4 beta 1 integrin with VCAM-1 and blocks the interaction of alpha 4 beta 7 integrin with MadCAM-1	• RRMS • Generally recommended in patients with MS who have had an inadequate response to, or are unable to tolerate, other therapies for MS	IV infusion	300 mg every 4 weeks	PML, herpes Contraindicated in patients who: • have had PML or are at risk for PML • are hypersensitive to this drug or to any ingredient in the formulation or any component of the drug • are immunocompromised, including those immunocompromised due to immunosuppressant or antineoplastic therapies, or immunodeficiencies
Teriflunomide (Aubagio)[39]	Not completely understood; may reduce numbers of activated lymphocytes available for migration into the CNS	RRMS	Oral tablet	14 mg once daily	Hepatotoxicity Contraindicated in patients who: • are hypersensitive to this drug or to leflunomide • patients currently treated with leflunomide

	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious side effects or safety issues
					• have severe hepatic impairment • are pregnant women or women of child-bearing age who are not using contraception • have immunodeficiency states such as AIDS • have serious active infection • have impaired bone marrow function or are patients with significant anemia, leukopenia, neutropenia, or thrombocytopenia

CD20 = cluster of differentiation 20; CD52 = cluster of differentiation 52; CDMS = Clinically Definite Multiple Sclerosis; CNS = central nervous system; CYP2C9 = cytochrome P450 family 2 subfamily C member 9; DMT = disease-modifying therapy; GPCR = G-protein-coupled receptor; IFN = interferon; IM = intramuscular; MAdCAM-1 = mucosal addressin cell adhesion molecule 1; MRI = magnetic resonance imaging; MS = multiple sclerosis; Nrf2 = nuclear factor-erythroid-2–related factor 2; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting multiple sclerosis; S1P = sphingosine 1-phosphate; S1P1 = sphingosine 1-phosphate receptor 1; S1P5 = sphingosine 1-phosphate receptor 5; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; TB = tuberculosis; VCAM-1 = vascular cell adhesion molecule-1.

[a] Health Canada–approved indication.

Source: Product monographs for siponimod,[13] cladribine,[30] ocrelizumab,[31] Plegridy,[32] alemtuzumab,[33] dimethyl fumarate,[34] fingolimod,[35] glatiramer acetate,[36] Avonex,[10] Rebif,[9] Betaseron,[8] Extavia,[37] natalizumab,[38] and teriflunomide.[39]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

At the time CADTH had requested patient input, siponimod was awaiting Health Canada approval. Therefore, the following summary of patient input received for this review is based on the proposed indication, which was for adult patients with SPMS. As previously noted, the final approved Health Canada indication is for adult patients with SPMS with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability. Of note, the number of patients with active SPMS versus non-active SPMS that contributed to the information used to inform the patient input submission is unknown.

About the Patient Groups and Information Gathered

One patient group, the MS Society of Canada, submitted patient input for the review of siponimod for SPMS. Founded in 1948, the MS Society of Canada is a national voluntary organization that provides programs and services for people with MS and their families, and advocates for those living with MS, and funds research to help improve the quality of life for people living with MS to ultimately find a cure for this disease. Approximately 1,500 volunteers serve on the national and regional boards and committees of the MS Society of Canada, and 13,500 volunteers are involved in service programs, fundraising events, public awareness campaigns, and social action activities.

The MS Society of Canada used an online survey in both English and French for data collection from September 9 to 23, 2019. This survey mainly targeted people diagnosed with SPMS and those affected by SPMS. In addition, people currently diagnosed with RRMS and those affected by RRMS were also surveyed to obtain data on the perceived experience of transitioning from RRMS to SPMS. Patients with CIS, PPMS, and other subtypes of MS and their loved ones were also provided an opportunity to provide feedback related to the Canadian drug reimbursement approval process specific to MS therapies. A total of 408 responses were received for the survey. Although country of origin was not included in the survey, the MS Society of Canada reports that the respondents appeared to be Canadians based on the survey comments. The vast majority of the respondents were patients with MS (SPMS = 60%, RRMS = 25%, and PPMS = 6%) and the remainder were family members, caregivers, or colleagues. Approximately 95% of the respondents were 35 years of age or older, while 6% were aged between 18 and 34 years old.

Disease Experience

MS is an unpredictable, often disabling disease of the CNS. Patients with MS may experience a wide variety of symptoms. The respondents described how a diagnosis of SPMS influenced their lives: loss of independence (81%), inability to participate in physical activity (76%), changes with the roles and responsibilities within their family (68%), and inability to maintain employment (56%). The MS Society of Canada indicated that approximately 85% of all patients diagnosed with MS have RRMS, which is characterized by unpredictable but clearly defined relapses during which new symptoms appear or existing ones worsen. Eventually most patients with RRMS will transition to SPMS, a phase of the disease with irreversible disability progression. Therefore, SPMS has an enormous

impact on every aspect of daily life, including a negative impact on family, community, and society.

Only half of the respondents (53%) said that their prescribing clinician had discussed the possible transition to SPMS with them. The respondents expressed their fear of the unknown impact that SPMS could bring to their life, including the changes to family, employment, and health status. The respondents also feared for the limited therapies available for active SPMS (secondary progressive with relapses) and their suboptimal therapeutic effects on slowing disability progression. Based on the patient input, time since diagnosis of SPMS is as follows: 28% for more than 15 years, 17% for 10 years to 14 years, 18% for five years to 10 years, and 25% for less than five years. Among those with SPMS, the time to transition was also reported: 25% for 15 years or more, 23% for 10 years to 14 years, 23% for five years to 10 years, and 20% for less than five years.

Some examples of quotes from respondents are provided as follows:

- "I am afraid of this transition. I am worried about the fact that there are no treatments for SPMS."
- "It would greatly impact my career in the health field. I would no longer be able to follow the career path I want. I could teach as a backup plan, but the possibility of my MS changing is uncomfortable to think about."

Experience with Treatment

The patient group submission indicates that current DMTs for RRMS and SPMS generally work by targeting the inflammatory process to reduce relapses and slow disease progression. However, only interferon beta-1a and interferon beta-1b have been approved by Health Canada for the treatment of active SPMS, and there is a lack of evidence to demonstrate the effect of interferon in preventing the development of permanent physical disability.

At the time of the survey, more than 80% of the respondents living with SPMS were not taking a DMT, while about 30% were taking some forms of therapy. Not all respondents were able to provide the name of the treatment. The treatment effect and AEs related to DMT were not reported by the respondents in the submission.

The patient group input states that at present, siponimod is the only DMT specifically indicated for SPMS, and mentioned that evidence suggested that it is able to delay disability progression and slow cognitive function decline, and may preserve mobility and brain volume. Most of the survey respondents (80%) had not heard of siponimod through their prescribing neurologist, nor had experience with this treatment (98%). Patients were asked their perception of the drug after being provided a list of known common AEs associated with siponimod. Of the respondents, 36% said they would take siponimod, 35% said they would not take siponimod because of the lack of post-market long-term data, and 28% said they did not know. Two respondents had been treated with siponimod through clinical trials and reported different experiences. One respondent felt siponimod was effective (fewer relapses, improvement in symptoms, fewer lesions seen on MRI, no disability progression, and more energy overall), and did not report any side effects during siponimod therapy. Another respondent felt it was not effective (no details provided) and reported headache and nausea during the treatment with siponimod.

The following patient quotes provide insight into the challenges associated with treatment of SPMS:

- "Haven't been able to work for 30 years, no extended health coverage, no family support, no money for treatment."
- "To be able to choose from as many therapies as available is very important."

Improved Outcomes

Previously, when patients transitioned to SPMS, their DMT had little to no therapeutic benefit, or they were required to stop taking DMT because they no longer met the reimbursement criteria for relapsing MS. Without an effective treatment after transitioning to SPMS, the disease progression worsens steadily. All areas of a patient's life, such as employment stability, family income, increased need for assistance or caregiving, loss of independence, isolation, cognitive decline, and increased mobility challenges, are affected due to the burden of disease and increasing disability. The patient group states that as the first DMT targeting SPMS in over 20 years, siponimod fills a significant unmet need in the treatment of SPMS.

Some respondents emphasized that "to ward off further disability would have a significant impact on the mental, physical, and emotional wellness of my entire family," and "improved, independent function is an economic benefit to our country."

The MS Society of Canada expects that treatment with siponimod may have the potential to allow people living with SPMS to remain in the workforce, sustain family and social roles and responsibilities longer, improve their quality of life, decrease the need for caregiving, and reduce the financial burden to health and social systems.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by two clinical specialists with expertise in the diagnosis and management of SPMS.

Description of the Current Treatment Paradigm for the Disease

There are currently no therapies that specifically target the progressive aspect or stage of MS that initially presents as a relapsing form of the disease, referred to as SPMS. Although there are now a number of disease-modifying treatments for MS, these target the immune-mediated, inflammatory aspects of MS, and have only been shown to be effective in RRMS. However, patients with SPMS who have concurrent relapses may be maintained on DMTs, with the rationale that reducing relapse activity may be beneficial, even if these treatments have no impact on the degenerative process thought to underlie the progressive disability in SPMS. Loss of neurological function in SPMS is thought not to be related to inflammatory lesions in the brain and spinal cord, but to be rather a consequence of an incompletely defined degenerative process. At present there are no SPMS treatments that modify this underlying disease mechanism.

The existing therapies and current approach to treating SPMS are symptomatic therapies, and what could be considered supportive care. This includes strategies such as treatment with drugs for spasticity (e.g., baclofen) or physiotherapy. These treatments aim to help specific residual symptoms from previous relapses or ongoing progression and do help overall function and HRQoL, but do not address the underlying cause of the symptoms.

Treatment Goals

Ideally, treatment for SPMS would restore neurological function to normal, without adverse effects. More realistically, the most important goal for any treatment for SPMS would be to halt the underlying neurodegeneration that leads to progressive disease, thus preventing progression over time. This would lead to improved HRQoL. However, not all patients with SPMS demonstrate disease activity or active progression. Thus, treatment risk would need to be balanced with potential benefit.

Unmet Needs

While interferons are approved for SPMS, they do not stop or slow the progression of the disease. Therefore, there are currently no treatments that slow or stop the clinical progression of symptoms in patients with SPMS.

Place in Therapy

The drug under review (siponimod) would be the first agent available that would appear to address the underlying disease process in SPMS, and in this sense would represent a paradigm shift. Siponimod would be a first-line treatment for SPMS and used as monotherapy. Many patients would likely continue DMTs that they had already been taking for the relapsing-remitting phase of their MS up until they switch to a treatment like siponimod, as the distinction between the relapsing-remitting and secondary-progressive phases of MS is often not clear. Although approved DMTs for MS to date have a known mechanism of action (MOA), for almost all DMTs available, how that MOA translates into a benefit in this population is not well known. As there is currently no approved treatment for SPMS, any MOA would be acceptable if there is evidence that there is a clinical benefit.

The clinical experts felt that if SPMS was a definite diagnosis, it would not be appropriate to recommend patients try other treatments before initiating treatment with siponimod. If it is not clear if patients have not transitioned to a SPMS diagnosis (no evidence of progression independent of relapses), consideration of one of the currently available DMTs that are used to treat the relapsing phase of the disease could be appropriate. However, if a patient is in a SPMS phase but has not used a DMT in the past for their MS, this should not preclude the use of siponimod.

Patient Population

One of the clinical experts consulted for this review stated that patients who would be best suited for treatment with siponimod are patients with MS who are demonstrating progression with or without relapse activity that can be objectively measured, and yet still have function to maintain. In the opinion of the other clinical expert consulted for this review, it would be difficult to define patients best suited for treatment with siponimod. Both agreed that patients with MS who are fully dependent (with an EDSS score of 8.0 or higher) would likely not benefit from treatment with siponimod, and that it seems likely that patients who are treated at a stage when disability is relatively limited are likely to have a better long-term outcome than those who might begin treatment when they are already severely disabled. The clinicians did not identify any other disease characteristics that might make patients more or less well suited for treatment.

Patients best suited for treatment with siponimod should be identified by a neurologist with expertise in MS. There is no one perfect tool to determine if there is progression in a patient with MS; this is a challenge in clinical practice. Using tools such as the T25-FW, 6-minute walk test, 9-HPT, and possibly cognitive testing would be useful.

The judgment that a patient with MS has evolved from the relapsing-remitting phase to SPMS is essentially purely clinical. Imaging may contribute by failing to show inflammatory lesions that might otherwise account for a functional decline. The distinction between relapsing-remitting and secondary-progressive phases of MS is often not simple or straightforward, as is reflected by the use of the term "SPMS with active relapses." It is likely that the diagnosis of SPMS is frequently delayed, particularly as this is currently seen as a phase of the disease for which there is no treatment. The advent of a drug that appears to modify the underlying disease mechanism(s) will probably push clinicians to discuss the transition to SPMS with their patients earlier.

Patients who are fully dependent (e.g., bed-bound) and patients with MS who do not demonstrate progression independent of relapses were judged as being least suitable for treatment with siponimod.

Assessing Response to Treatment

Outcomes used to determine whether a patient is responding to treatment in clinical practice may include functional ability and findings on the neurological examination. It was noted that the measures used in clinical trials are broadly aligned with such clinical criteria; however, it was also acknowledged that since a treatment to slow or stop progression in MS has not been available in the past, the current tools typically used in clinical trials, such as the EDSS, are not sensitive enough to detect change over time.

A clinically meaningful response would be halting or slowing the progressive disability over time, and the providing the ability to maintain mobility (e.g., speed and distance walking), upper limb function, and activities of daily living (e.g., self-care). It is likely that stabilization of function would be considered a good outcome, contrasting with the expected inexorable decline predicted by the natural history of SPMS.

The experts reported different intervals for how often treatment response should be assessed. One expert suggested patients should be assessed at three-month to six-month intervals; the other suggested at least yearly.

Discontinuing Treatment

Factors that should be considered when deciding to discontinue treatment include expectations of continued benefit, if there are any further impacts on quality of life by slowing progression, and safety. Disease progression despite treatment would likely lead to treatment discontinuation. The EDSS as well as the T25-FW and 9-HPT were recommended for assessing disease progression, according to the clinical experts.

Prescribing Conditions

According to the clinical experts consulted by CADTH for this review, a specialist, such as a neurologist with experience managing patients with MS or a neurologist based at an MS clinic, should be required to diagnose, treat, and monitor patients who might receive siponimod (patients with SPMS). The clinical experts also felt that the most appropriate setting for a patient receiving treatment with siponimod would be within a specialty MS clinic.

Clinical Evidence

The clinical evidence included in the review of siponimod is presented in three sections. The first section, the Systematic Review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section is intended to include long-term extension studies submitted by the sponsor and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review; however, no such evidence was submitted or identified.

It should be noted that the CADTH submission for siponimod was filed on a pre-NOC basis. As per CADTH procedure for pre-NOC reviews, siponimod was evaluated based on the indication proposed by the sponsor, which was for adults with SPMS. Siponimod subsequently received NOC by Health Canada in February 2020 for the treatment of SPMS with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability, in adults. In order to conduct a comprehensive review of the evidence for the approved Health Canada indication, CADTH updated the systematic review protocol (see Table 6) and conducted an updated literature search as appropriate, described as follows. For transparency, the original protocol has been made available in Appendix 5 of this report.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of oral siponimod for the treatment of SPMS with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability, in adults.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 6.

Table 6: Inclusion Criteria for the Systematic Review

Patient population	Adults with secondary-progressive multiple sclerosis with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity **Subgroups** • EDSS at baseline • Patients with relapses vs. without relapses
Intervention	Siponimod administered orally once daily **Siponimod administration** • Treatment initiation period: Dosing is titrated from 0.25 mg to 1.25 mg over a 5-day period followed by a 2 mg maintenance dose beginning on day 6 • Maintenance period: 2 mg daily ○ 1 mg daily is recommended for the maintenance dose in patients with the CYP2C9*2*3 or CYP2C9*1*3 genotype
Comparators	• Interferon beta-1a • Interferon beta-1b • Glatiramer acetate • Natalizumab • Fingolimod • Dimethyl fumarate • Alemtuzumab • Teriflunomide • Ocrelizumab • Cladribine • Placebo/best supportive care
Outcomes	**Efficacy outcomes** • Disability progression or improvement[a] • Health-related quality of life[a] • Mobility[a] • Cognitive function[a] • Symptoms (e.g., fatigue)[a] • Relapse • Imaging outcomes (e.g., MRI brain lesions, MRI brain volume) **Harms outcomes** • AEs • SAEs • WDAEs • Mortality • Notable harms: Cardiac effects (e.g., bradycardia), neoplasia, serious infections (e.g., progressive multifocal leukoencephalopathy), opportunistic infections (e.g., cryptococcal meningitis), lymphocytopenia, macular edema
Study design	Published and unpublished Phase III and IV RCTs

AE = adverse event; CYP2C9 = cytochrome P450 family 2 subfamily C member 9; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[40]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search

strategy comprised both controlled vocabulary, such as the U.S. National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Mayzent (siponimod). Clinical trial registries were searched: the U.S. National Library of Medicine's ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on October 24, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on June 17, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist:[41] Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings from the Literature

One study was identified from the literature for inclusion in the systematic review (see Figure 2). The included study is summarized in Table 7. A list of excluded studies is presented in Appendix 2.

Figure 2: Flow Diagram for Inclusion and Exclusion of Studies

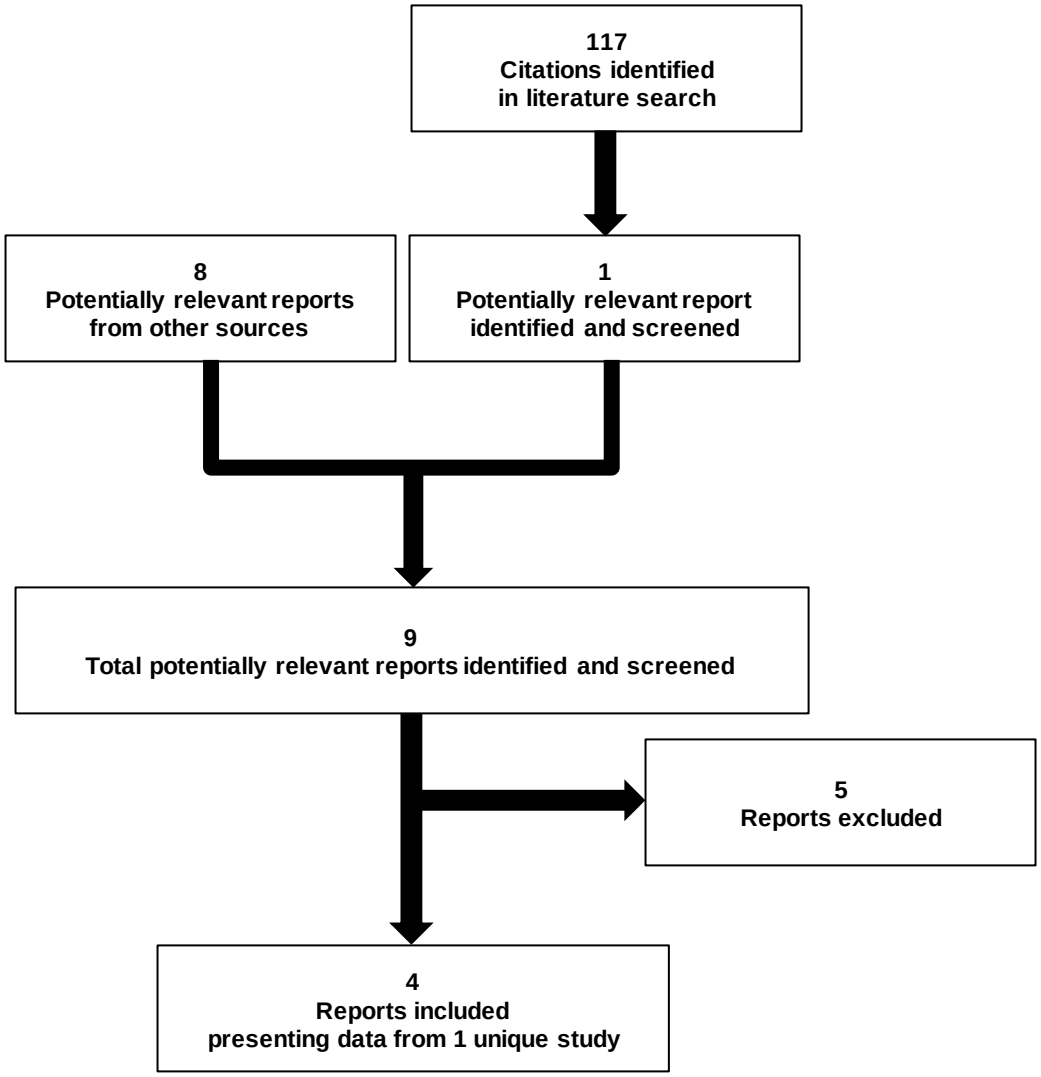


Table 7: Details of Included Study

		EXPAND
DESIGNS AND POPULATIONS	**Study design**	Double-blind, parallel-group, event-driven, exposure-driven, placebo-controlled phase III RCT
	Locations	294 centres in 31 countries (Canada, US, UK, Argentina, Australia, China, Japan, Europe)
	Randomized (N)	1,651
	Inclusion criteria	• 18 to 60 years of age at screening • History of RRMS according to 2010 revised McDonald Criteria • SPMS progressive increase in disability (≥ 6-month duration) without relapses or independent of relapses • Disability status: EDSS score of 3.0 to 6.5 (inclusive) • Documented EDSS progression during the previous 2 years (≥ 1 point if EDSS < 6.0; ≥ 0.5 point if EDSS ≥ 6.0 at screening); alternatively, a written summary of clinical evidence for review was considered • No evidence of relapse or corticosteroid treatment within 3 months prior to randomization
	Exclusion criteria	• Active chronic disease (or stable with immune therapy) of the immune system other than MS, or with a known immunodeficiency syndrome • Women of child-bearing potential, unless using a highly effective method of contraception during dosing and 30 days after the last dose of siponimod • History of malignancy within the past 5 years • Diabetes mellitus, unless well-controlled and without known organ complications • Diagnosis of macular edema during pre-randomization phase • Chronic or relevant acute infections (e.g., AIDS, HIV, hepatitis) • Conditions/treatments that may affect cardiovascular function, pulmonary conditions, hepatic conditions, or immune function • Neurologic/psychiatric disorders • Homozygosity for CYP2C9*3 or refusal to test for the haplotype • Treatment with certain medications: ○ siponimod, alemtuzumab ○ ≤ 2 weeks prior to randomization — teriflunomide ○ ≤ 2 months prior to randomization — IVIG, dimethyl fumarate, fingolimod ○ ≤ 6 months prior to randomization — natalizumab, immunosuppressive/ chemotherapeutic medications (e.g., azathioprine, methotrexate) ○ ≤ 1 year prior to randomization — cyclophosphamide ○ ≤ 2 years prior to randomization — rituximab, ofatumumab, ocrelizumab or cladribine, mitoxantrone (or evidence of cardiotoxicity following mitoxantrone or a cumulative life-time dose of more than 60 mg/m^2) ○ lymphoid irradiation, bone marrow transplantation, or other immunosuppressive treatments with effects potentially lasting more than 6 months • Unable to undergo MRI scans
DRUGS	**Intervention**	**Siponimod** • 6-day titration period, daily oral dose from 0.25 mg to 2 mg • Maintenance period, 2 mg daily, oral
	Comparator(s)	Placebo
DURATION	**Phase**	
	Run-in	"Screening epoch" (screening phase and baseline phase), 45 days
	Double-blind	"Treatment epoch," variable (event-driven)
	Follow-up	"Post-treatment follow-up epoch," 1 month

		EXPAND
Outcomes	**Primary end point**	Time to 3-month CDP based on EDSS score

	Secondary and exploratory end points	**Key secondary**
		• Time to 3-month confirmed worsening from baseline in T25-FW by ≥ 20%
		• T2 lesion volume, change from baseline
		
		Other secondary
		• Time to 6-month CDP based on EDSS score
		• Time to 6-month CDP based on EDSS score sustained until end of the core part of the EXPAND study
		• EDSS scores and change from baseline
		• MRI variables:
		  ○ number of new/enlarging T2 lesions
		  ○ number of T1 Gd-enhancing lesions
		  ○ proportion free of new/enlarging T2 lesions
		  ○ proportion free of T1 Gd-enhancing lesions
		  ○ T1 hypointense lesion volume, change from baseline
		  ○ number of new T1 hypointense lesions
		  ○ percentage brain volume change from baseline
		• All relapses and confirmed relapses
		• Time to first relapse and proportion of patients free of relapses
		• HRQoL (MSWS-12, MSIS-29, and EQ-5D-3L): Score and change from baseline
		
		Exploratory
		• Cognitive function tests (PASAT, SDMT, BVMT-R): Score and change from baseline
		• MSFC scores (z score and 3 subscale scores): Average and change from baseline
		• Evolution of acute lesions into chronic black holes
		• Time to 3-month CDP based on a composite end point of EDSS total score, T25-FW score, and 9-HPT score
		• Low-contrast visual acuity score and change from baseline

Notes	**Publications**	Kappos, L. et al. (2018)[42]

9-HPT = 9-hole peg test; BVMT-R = Brief Visuospatial Memory Test-Revised; CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; Gd = gadolinium; HRQoL = health-related quality of life; IVIG = intravenous immunoglobulin; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSIS-29 = Multiple Sclerosis Impact Scale; MSWS-12 = Multiple Sclerosis Walking Scale; PASAT = Paced Auditory Serial Addition Test; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SDMT = Symbol Digit Modalities Test; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test.

Note: Two additional reports were included: CADTH Common Drug Review submission[15] and Health Canada Reviewers Report.[43]

Source: Kappos, L. et al. (2018)[42] and EXPAND Clinical Study Report.[14]

Description of Studies

The pivotal trial submitted by the sponsor, the EXPAND study, was the only study that met the inclusion criteria for the systematic review. Details of the included study and the study design are provided in Table 7 and Figure 3. Of note, evidence that supports the indication under review is obtained from a subgroup analysis of the EXPAND study in patients with active SPMS.

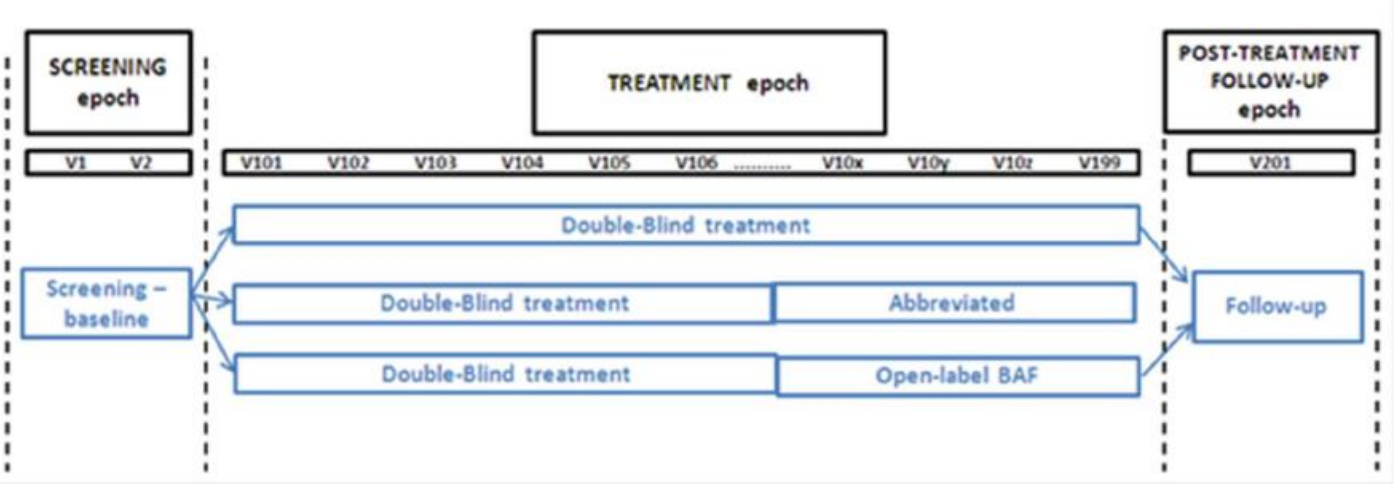
The primary objective of the EXPAND study was to demonstrate the superiority of siponimod relative to placebo in terms of its ability to delay the time to three-month CDP in patients with SPMS, as measured by the EDSS. The study also had two key secondary objectives, which were to demonstrate efficacy by delaying the time to three-month confirmed worsening of at least 20% in the T25-FW and reducing the increase in T2 lesion volume, both from baseline. A total of 1,651 patients with SPMS were included in the EXPAND study (December 20, 2012, to December 29, 2016), which was carried out across 31 countries and 294 centres, including 10 in Canada.

The EXPAND study was separated into a core part and extension part. The core part was a double-blind, parallel-group, multi-centre, placebo-controlled, event-driven, exposure-driven, phase III RCT conducted between 2012 and 2016 and is the focus of this review. Patients with a confirmed diagnosis of SPMS based on a prior history of RRMS and evidence of progression independent of relapses were included. The core part is composed of three phases or "epochs": namely, the screening epoch, treatment epoch, and post-treatment follow-up epoch (see Figure 3). The extension part is a single-arm open-label extension that enrolled 1,220 patients and is currently ongoing.[15] Results of the extension part were not available at the time of this report.

In the core part of the EXPAND study, the screening epoch included a screening phase and baseline phase that were implemented to determine and confirm eligibility and collect baseline assessments during the 45 days prior to randomization. Patients who were eligible continued to the treatment epoch where they were randomized (2:1) to receive siponimod or placebo using an interactive response technology. The interactive response technology procedure was designed to conceal treatment allocation from patients and investigator staff. In addition, randomization was stratified by region.

The treatment epoch followed an event-driven design that continued until 374 patients experienced three-month CDP and 95% of patients had been treated for at least one year; therefore, the length of time spent in the double-blind phase of the study varied between patients. Patients continued double-blind treatment for the duration of the trial unless they experienced six-month CDP, at which time they were counselled and offered one of three options: continue with no change in treatment, discontinue blinded study treatment and switch to open-label siponimod, or discontinue blinded study treatment and start any other MS treatment available to them (abbreviated schedule). At the end of the double-blind treatment phase, patients who did not continue to the open-label extension (or were not continuing within one month) entered the post-treatment follow-up epoch, with the exception of those who followed the abbreviated schedule. The follow-up epoch consisted of a follow-up visit one month after the end of study visit.

Figure 3: EXPAND Study Design



Screening Epoch=Screening Phase + Baseline Phase
Screening Phase=Day -45 to Day -8
Baseline Phase=Day -7 to Day 1 (before the first study drug administration)
The Treatment Epoch had a variable treatment duration

BAF = siponimod; V = visit.

Source: EXPAND Clinical Study Report.[14]

Populations

In the post-hoc active SPMS subgroup, patients with active disease were defined by the presence of superimposed relapses in the two years prior to screening and/or the presence of at least one T1 Gd-enhancing lesion at baseline. Of note, "superimposed relapses" refers to evidence of relapse in addition to progression and is referred to simply as "relapses" throughout the rest of the report. A total of 779 patients were included in the active SPMS subgroup; 516 and 263 were originally randomized to siponimod and placebo, respectively. The preplanned subgroup analyses of the overall population defined patients with active disease in two ways: by report of relapses in the two years prior to study start and by the presence of T1 Gd-enhancing lesions at baseline.

Inclusion and Exclusion Criteria

A list of key inclusion and exclusion criteria is available in Table 7.

In addition to having a prior history of RRMS, to be eligible for inclusion, patients were required to have a diagnosis of SPMS, which was defined in the EXPAND study as exhibiting a progressive increase in disability for at least six months in the absence of relapses or independent of relapses. A written statement from the investigator attesting to the patient meeting this definition was required. Patients also had to have an EDSS score of between 3.0 and 6.5 (inclusive) at screening, documented disability progression based on EDSS scores in the two years prior to enrolment, and no evidence of relapse in the three months prior to study enrolment. If this information was not available for patients, a written summary of clinical evidence of disability progression and a retrospective assessment of EDSS scores could be submitted for review by the adjudication committee. Patients with various comorbidities and patients with homozygosity for the CYP2CP*3 haplotype were

ineligible for this study. Of note, the genotype for CYP2C9 was determined for all patients included in the EXPAND study at screening, and patients who refused to test for the CYP2C9*3 haplotype were also excluded.

Baseline Characteristics

The baseline demographics and disease characteristics of all randomized patients (RAN) and patients in the post-hoc active SPMS subgroup are summarized in Table 8. The baseline characteristics of patients included in active SPMS subgroup analysis were similar between treatment groups. They were a mean (standard deviation [SD]) age of 46.6 (8.3) years and the majority were female (63.8%). Overall, 75.8% of the active SPMS subgroup had relapses in the two years prior to the start of the study and just over half (55.6%) of patients had an EDSS score of 6.0 to 6.5 at baseline, indicating severe disability. They were diagnosed with MS with a mean (SD) of [redacted], and it had been a mean (SD) of 3.2 (3.3) years since they converted to SPMS. The proportion of patients in the active SPMS subgroup with at least one T1 Gd-enhancing lesion was 44.9% [redacted]

Patients included in the FAS were a mean (SD) age of 48.0 (7.87) years, the majority were white (94.7%), and more than half were female (60.1%). They were diagnosed with MS a mean (SD) of 12.63 (7.78) years ago, with a mean (SD) of 3.76 (3.51) years since they converted to SPMS. The majority of patients (63.9%) reported zero relapses in the two years prior to screening and the time since onset of the most recent relapse was a mean (SD) of 59.26 (59.63) months. The EDSS score, T25-FW, 9-HPT, and SDMT as well as MRI-related outcomes were also reported for all patients at baseline (see Table 7). Just over half (55.4%) of patients had an EDSS score of 6.0 to 6.5 at baseline, indicating severe disability. Overall, the characteristics of disease were consistent with a population that has moderate-to-severe disability and SPMS, according to the clinical experts consulted for this review. In addition, the two treatment arms were well balanced by baseline characteristics.

The mean (SD) duration of MS since diagnosis, since first symptoms, and time since conversion to SPMS of the active SPMS subgroup were similar to the overall population. The mean (SD) number of relapses in the last year prior to screening was greater in the active SPMS subgroup than in the overall population (0.5 [0.7] versus 0.3 [0.6], respectively) and the proportion of patients with at least one T1 Gd-enhancing lesion was about double the proportion of patients in the overall population (44.9% versus 21.3%, respectively). The mean (SD) volume (mm^3) of T2 lesions was greater in the active SPMS subgroup than in the overall population as well ([redacted] versus 15,321.5 [16,057.6]), respectively.

Previous use of MS DMTs in the randomized analysis set are summarized in Table 8. This information was not available for the active SPMS subgroup. The majority of patients in the randomized analysis set had experience with a DMT (78.3% of patients overall for any DMT). The most commonly reported approved MS DMTs used by patients [redacted] It should be noted that a washout period was not required for patients who had prior treatment with interferon beta or glatiramer acetate. Patients also had experience with [redacted] The two treatment arms were similar in terms of prior use of MS-related

medications, with a slight difference in the proportion of patients by use of interferon beta-1a, interferon beta-1b, and glatiramer acetate; however, these were not clinically significant according to the clinical experts consulted by CADTH. The use of immunosuppressants was also reported, with the most common being [redacted]

Table 8: Summary of Baseline Characteristics

	EXPAND (RAN)		EXPAND (active SPMS subgroup)	
	Siponimod (N = 1,105)	Placebo (N = 546)	Siponimod (N = 516)	Placebo (N = 263)
Demographics and baseline characteristics				
Age (years), mean (SD)	48.0 (7.84)	48.1 (7.94)	46.2 (8.1)	47.2 (8.5)
Sex, n (%)				
Female	669 (60.5)	323 (59.2)	331 (64.1)	166 (63.1)
Male	436 (39.5)	223 (40.8)	185 (35.9)	97 (36.9)
Race, n (%)				
Asian	31 (2.8)	18 (3.3)	NR	
Black or African-American	7 (0.6)	3 (0.5)		
White	1,050 (95.0)	513 (94.0)		
Other	12 (1.1)	7 (1.3)		
Unknown	5 (0.5)	5 (0.9)		
Duration of MS since diagnosis (years), mean (SD)	12.88 (7.91)	12.11 (7.48)	[redacted]	[redacted]
Duration of MS since first symptom (years), mean (SD)	17.12 (8.39)	16.23 (8.23)	15.6 (7.9)	15.5 (8.2)
Time since conversion to SPMS (years), mean (SD)	3.85 (3.61)	3.56 (3.28)	3.2 (3.3)	3.1 (3.2)
SPMS group (baseline definition), n (%)				
With relapses in the 2 years prior to study start	NR		388 (75.2)	202 (76.8)
Without relapses in the 2 years prior to study start			127 (24.6)	61 (23.2)
Number of relapses in the last 2 years prior to screening (years), mean (SD)	0.7 (1.20)	0.7 (1.16)	NR	
Number of relapses in the last year prior to screening (years), mean (SD)	0.2 (0.54)	0.3 (0.57)	0.5 (0.7)	0.6 (0.7)
Number of relapses in the last 2 years prior to screening, n (%)				
0	712 (64.4)	343 (62.8)	NR	
1	199 (18.0)	104 (19.0)		
2 to 3	158 (14.3)	81 (14.8)		
4 to 5	26 (2.4)	13 (2.4)		
> 5	7 (0.6)	4 (0.7)		
Missing	3 (0.3)	1 (0.2)		

	EXPAND (RAN)		EXPAND (active SPMS subgroup)	
	Siponimod (N = 1,105)	Placebo (N = 546)	Siponimod (N = 516)	Placebo (N = 263)
Time since onset of most recent relapse (months)				
Mean (SD)	61.75 (61.53)	54.25 (55.33)	NR	
Median (range)	39.97 (3.1 to 430.8)	36.93 (2.7 to 315.9)		
EDSS (categories)				
< 3.0	6 (0.5)	2 (0.4)	3 (0.6)	2 (0.8)
3.0 to 4.5	312 (28.2)	148 (27.1)	138 (26.7)	68 (25.9)
5.0 to 5.5	165 (14.9)	100 (18.3)	84 (16.3)	50 (19.0)
6.0 to 6.5	620 (56.1)	295 (54.0)	290 (56.2)	143 (54.4)
> 6.5	2 (0.2)	1 (0.2)	1 (0.2)	0
T25-FW (seconds)				
Mean (SD)	17.08 (20.83)	16.00 (22.10)	NR	
Median (range)	10.30 (2.9 to 228.0)	9.55 (3.3 to 290.9)		
9-HPT (seconds)				
Mean (SD)	34.05 (18.26)	34.52 (19.87)	NR	
Median (range)	28.65 (12.5 to 192.3)	28.45 (14.7 to 174.3)		
SDMT oral score				
Mean (SD)	38.9 (13.99)	39.6 (13.34)	NR	
Median (range)	40.0 (0 to 83)	42.0 (0 to 81)		
Number of T1 Gd-enhancing lesions, n (%)				
0	833 (75.4)	415 (76.0)	236 (52.1)	144 (54.8)
≥ 1	237 (21.4)	114 (20.9)	236 (45.7)	114 (43.3)
Missing	35 (3.2)	17 (3.1)	11 (2.1)	5 (1.9)
Volume of T2 lesions (mm^3)				
Mean (SD)	15,631.8 (16,267.91)	14,694.0 (15,619.84)	[redacted]	[redacted]
Median (range)	10,286.0 (23 to 116,664)	9,994.0 (0 to 103,560)	[redacted]	[redacted]
Volume of unenhanced T1 lesions (mm^3)				
Mean (SD)	6,757.3 (8,682.22)	5,994.1 (7,959.58)	NR	
Median (range)	3,533.5 (0 to 61,537)	3,288.0 (0 to 62,149)		
Normalized brain volume (cc)				
Mean (SD)	1,422.0 (86.23)	1,424.5 (87.59)	NR	
Median (range)	1,420.5 (1,136 to 1,723)	1,425.2 (1,199 to 1,691)		
Prior medications				
Any MS DMT, n (%)	860 (77.8)	432 (79.1)	NR	

	EXPAND (RAN)		EXPAND (active SPMS subgroup)	
	Siponimod (N = 1,105)	Placebo (N = 546)	Siponimod (N = 516)	Placebo (N = 263)
Most commonly[a] used and approved MS DMTs				
Interferon beta-1a	[redacted]	[redacted]		
Interferon beta-1b	[redacted]	[redacted]		
Glatiramer acetate	[redacted]	[redacted]		
Natalizumab	[redacted]	[redacted]		

9-HPT = 9-hole peg test; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis; NR = not reported; RAN = randomized analysis set; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test.

Note: The active SPMS subgroup defined patients with active disease as those having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline.

[a] These DMTs were used by 5% or more of patients in either treatment group.

Source: EXPAND Clinical Study Report.[14]

Interventions

Patients were randomized 2:1 to either receive siponimod (2 mg) or matched placebo once daily. Treatment with siponimod or matched placebo began with a six-day titration period starting with 0.25 mg and progressing up to 1.25 mg on day 5 followed by a 2 mg maintenance dose starting on day 6. A dose reduction from 2 mg to 1 mg daily was implemented for patients with confirmed lymphocyte counts of less than $0.2 \times 10.^9$ An outline of the titration and re-titration schedules are provided in Table 9.

Table 9: Titration and Re-Titration Regimens

Target dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
2 mg	0.25 mg	0.25 mg	0.5 mg	0.75 mg	1.25 mg	2 mg
1 mg	0.25 mg	0.25 mg	0.5 mg	0.75 mg	1 mg	1 mg

Source: EXPAND Clinical Study Report.[14]

Siponimod (0.25 mg, 0.5 mg, 1 mg, and 2 mg) and the dose-matched placebo were taken orally and were provided as film-coated tablets, identical in appearance. If a patient missed four or more consecutive doses of the maintenance dose, or if they missed at least one dose during the titration period, they needed to restart the titration regimen.

If a patient met the criteria for six-month CDP, they were counselled and presented with one of three options: continue with the blinded study treatment, discontinue and switch to open-label siponimod, or discontinue and start any other MS treatment available to that patient. For those who opted to switch to open-label siponimod, a re-titration regimen was followed, regardless of the patient's previous treatment assignment. In addition, intravenous corticosteroids were used as a rescue medication for the treatment of MS relapses during the study. A standard course of methylprednisolone, defined as up to 1,000 mg/day for three to five days, was permitted, following standard of care procedures. Tapering with oral corticosteroids was not allowed.

Concomitant medications and significant non-drug therapies such as physical therapy and blood transfusions were permitted during the study. The use of dalfampridine was permitted for patients who were treated with a stable dose prior to enrolment. The dose could not be

changed or started during the double-blind treatment period, except for discontinuation due to AEs. Certain classes of medications were prohibited, including immunosuppressive and/or chemotherapeutic medications or procedures, monoclonal antibodies targeting the immune system, other immunomodulatory treatment or DMT for MS, medications that inhibit cardiac conduction, and potent inducers of CYP2C9.

Information regarding concomitant medication use was not available for the active SPMS subgroup. In the overall population, concomitant medication use was similar between the two treatment arms [redacted] A summary of commonly used concomitant medications is available in Appendix 3 (Table 40). [redacted]

Outcomes

A list of primary, secondary, and exploratory efficacy end points that were evaluated in the EXPAND trial are provided in Table 10. The end points of interest for this review are summarized as follows. Outcomes that were evaluated in the subgroup analyses are noted throughout this section of the report. A detailed discussion and critical appraisal of the outcome measures used in the EXPAND study are provided in Appendix 4.

Table 10: Outcome Measures Included in EXPAND

Outcome	Outcome measure
Primary[a]	• Disease progression: Time to 3-month CDP based on EDSS
Key secondary[a]	• Mobility: Time to 3-month confirmed worsening of ≥ 20% from baseline in T25-FW • Imaging outcome: Change from baseline in T2 lesion volume
Additional secondary	• Disease progression: Time to 6-month CDP based on EDSS • Relapse-related outcomes: ARR, time to first relapse, proportion of patients with relapse • HRQoL: MSWS-12 • Imaging outcomes for inflammatory disease activity and brain volume (number of new or enlarging T2 lesions, proportion of patients free of new or enlarging T2 lesions, number of T1 Gd-enhancing lesions, proportion of patients free of T1 Gd-enhancing lesions), and percentage brain volume change
Exploratory	• Mobility: MSFC (z score) and associated subscale scores (T25-FW, 9-HPT) • Cognitive function: SDMT, PASAT (subscale of MSFC), and BVMT-R • HRQoL: MSIS-29 and EQ-5D-3L

9-HPT = 9-hole peg test; ARR = annualized relapse rate; BVMT-R = Brief Visuospatial Memory Test-Revised; CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; Gd = gadolinium; HRQoL = health-related quality of life; MSFC = Multiple Sclerosis Functional Composite; MSIS-29 = Multiple Sclerosis Impact Scale; MSWS-12 = Multiple Sclerosis Walking Scale; PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modalities Test; T25-FW = Timed 25-Foot Walk Test.

[a] Included in the statistical hierarchy.

Source: EXPAND Clinical Study Report.[14]

Confirmed Disability Progression (EDSS)

The primary efficacy outcome in the EXPAND study was the time to three-month CDP based on the EDSS score. This outcome was included in the preplanned subgroup

analyses and post-hoc active SPMS subgroup analysis. Time to six-month CDP by EDSS was also reported as an additional secondary efficacy outcome for the FAS and was included in the post-hoc active SPMS subgroup analysis. Of note, every EDSS score between onset and confirmation needed to meet the criteria for disease progression, and time to this event was calculated from day 1 (last assessment before the start of study treatment) to CDP onset.

The EDSS is used to assess neurologic impairment in MS based on a neurological examination, which is performed by an independent EDSS rater. It is scored using an ordinal scale from 0 to 10, where 0 corresponds to no disability and 10 indicates death due to MS. An assessment of the EDSS score over time was used to define disability progression or CDP in the EXPAND study, with different definitions used depending on the baseline EDSS score. Disability progression was defined using the MID for the EDSS (see Appendix 4), i.e., as a 1.0-point increase from baseline for patients who had a baseline score of 3.0 to 5.0, or a 0.5-point increase for patients who had a baseline EDSS score of 5.5 to 6.5. Sustained disability progression over a period of time was determined by a sustained EDSS score over time, outside of an ongoing relapse. The maximum duration of a relapse was defined as 90 days in the context of the EXPAND study. Limitations of the EDSS include moderate intra-rater reliability,[44] poor assessment of upper limb and cognitive function, and lack of linearity between score difference and the clinical severity.[45-47]

Health-Related Quality of Life (MSWS-12, MSIS-29, and EQ-5D-3L)

HRQoL was evaluated using three measures: the MSWS-12, MSIS-29, and EQ-5D-3L. The MSWS-12 was a secondary outcome and the MSIS-29 and EQ-5D-3L were exploratory outcomes in the EXPAND trial. The MSWS-12 was included in the post-hoc active SPMS subgroup analysis.

The MSWS-12 is a patient-reported outcome that is used to evaluate the limitations of walking due to MS via 12 items. Three items include three response categories and nine items include five response categories, which together formulate a total score that ranges from 0 to 100 where a higher score indicates greater impairment. A range from 10.4 points to 22 points was identified as the MID for the MSWS-12. Also, high test-retest reliability as well as convergent and discriminant validity have been demonstrated in patients with MS.

The MSIS-29 is also a patient-reported outcome that uses a self-administered questionnaire to assess HRQoL in terms of the patient's views about the impact of MS on day-to-day life. The questionnaire is composed of 29 items and two domains, physical and psychological. Further, the responses are based on a two-week recall period and answered using a four-point ordinal scale from 1 (not at all) to 4 (extremely). Higher scores indicate a greater impact on day-to-day life. The physical subscale is associated with an MID of 8, and the MID for the psychological subscale is 6.25. The MSIS-29 has also demonstrated excellent reliability, and convergent and discriminant validity.

The EuroQol 5-Dimensions (EQ-5D) is a commonly used generic assessment of health status that includes five dimensions — namely, mobility, self-care, usual activity, pain and/or discomfort, and anxiety and/or depression. The three-level version of the EQ-5D (EQ-5D-3L) was used in the EXPAND study, meaning patients respond to each of the five dimensions according to one of three statements increasing in level of severity: no problem (1), some or moderate problem (2), and unstable, or extreme problem (3). Adequate test-retest reliability and validity of the EQ-5D-3L has been established in patients with MS and the MID for the EQ-5D-3L index score ranges from 0.050 and 0.084.

Mobility (MSFC: MSFC z Score, T25-FW, 9-HPT, and PASAT)

The Multiple Sclerosis Functional Composite (MSFC) is a composite outcome that incorporates measures of ambulation, upper extremity function, and cognitive function using the T25-FW, 9-HPT, and PASAT, respectively. The MSFC and corresponding subscales, except for the T25-FW, were included as exploratory outcomes in the EXPAND trial. Overall, the MSFC has demonstrated excellent test-retest reliability, and construct and convergent validity. An MID for the MSFC was not identified.

The T25-FW measures the time taken (in seconds) by a patient to walk 25 feet. The patient is directed to one end of a clearly marked course and instructed to walk as quickly and safely as possible. The test is then re-administered immediately by having the patient walk the same distance back to the start. Assistive devices may be used and there is a time limit of three minutes (180 seconds) per trial. The T25-FW was used to inform one of the key secondary outcomes in the EXPAND trial: time to three-month confirmed worsening of at least 20% from baseline in the T25-FW. A change of 20% in the T25-FW represents the MID for this outcome. This was defined as a decrease from baseline that was sustained for at least three months. This outcome was included in the preplanned subgroup analyses and post-hoc active SPMS subgroup analysis.

The 9-HPT is a functional outcome related to upper body mobility, which measures the time taken (in seconds) to insert and remove nine pegs. A score is provided for both the right and left arm, and both sides are measured twice. The time limit per trial is restricted to five minutes (300 seconds). A 20% change is considered the MID for the 9-HPT.

Lastly, the PASAT is a measure of cognitive function through an assessment of auditory information processing, speed, flexibility, and calculation ability. It is administered via an audio recording as a three-minute test with new digits presented every three seconds. Patients must add each new digit to the one before it. The number of correct answers is recorded and can range from zero to 60. Two different versions of the PASAT test (Form A and Form B) were used at alternating visits. Patients also completed the PASAT test during the screening phase because of a learning effect. An MID for the PASAT was not identified in the literature for patients with MS.

Cognitive Function-Related Outcomes (PASAT, SDMT, and BVMT-R)

In addition to the PASAT (previously described), two outcomes used to evaluate cognitive function were used in the EXPAND study; the SDMT and BVMT-R. All of the cognitive function tests were exploratory outcomes in the EXPAND study.

The SDMT is used to assess attention, concentration, and processing speed. The instrument used to administer the test includes a row of nine numbers paired with unique symbols, and an array of symbols paired with blank spaces. Patient must verbally match each symbol to its corresponding number as fast as possible. The test takes about five minutes to administer and is scored based on the number of correct answers in 90 seconds. The EXPAND study used three versions of this test — the Smith, Benedict 1, and Benedict 2 versions — to overcome learning effects. A raw score change of 4 points or a 10% change represents the MID for the SDMT. It has also demonstrated excellent test-retest reliability and validity has been demonstrated in patients with MS.

The BVMT-R provides a measure of visuospatial memory used to detect changes over time. Patients are shown a sheet of geometric designs for 10 seconds, then are asked to draw the designs and where they were seen, as accurately as possible. This is repeated

twice more for three consecutive tests. In addition, a delayed recall trial was administered after a 25-minute delay. Six versions of the BVMT-R were used at alternative visits. Scoring of the tests are based on the accuracy of the drawings and the location of the figures. For each figure, 1 point is awarded to each satisfactory domain resulting in a maximum of 12 points per test.[14,48] An MID of BVMT-R for patients with MS was not identified in the literature.

Relapse (ARR and Proportion of Relapse-Free Patients)

An MS relapse was defined according to the 2001 McDonald Criteria as the "appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event." The abnormality also must be present for at least 24 hours and absent of fever or known infection. A confirmed MS relapse was distinguished by an accompanying clinically relevant change in the EDSS score; however, the clinical experts on this review did not think that confirmation via EDSS score was necessary. The EXPAND study included two relapse-related variables as secondary outcomes — namely, ARR (number of relapses per year), and time to first relapse and proportion of patients free of relapses. The ARR based on confirmed relapses was included in the post-hoc active SPMS subgroup analysis.

Imaging Outcomes

A series of MRI outcomes was included in the EXPAND study. The change from baseline in T2 lesion volume was a key secondary outcome used as a proxy for severity of disease, and measured at month 12 and month 24. This outcome was included in the preplanned subgroup analyses and post-hoc active SPMS subgroup analysis. Inflammatory disease activity was measured by the number of new or enlarging T2 lesions, proportion of patients free of new or enlarging T2 lesions, number of T1 Gd-enhancing lesions, and proportion of patients free of T1 Gd-enhancing lesions. Percentage brain volume change from baseline was also reported. Gd-enhanced lesions are useful for identifying active inflammation, whereas the occurrence of T2 lesions requires interpretation based on a comparison with the number of T2 lesions observed in previous scans.[6] All of these outcomes were reported as secondary outcomes in the EXPAND trial. Outcomes regarding the number of lesions and the percentage brain volume change were included in the post-hoc active SPMS subgroup analysis.

Statistical Analysis

As the active SPMS subgroup analyses were conducted post hoc in response to questions from regulatory authorities, no specific statistical analysis plan was available. However, the sponsor noted that statistical analyses for the active SPMS population followed the same analysis methods used for the overall population, described as follows.

Power Calculation

The EXPAND study was designed to have 90% power to detect a 30% risk reduction (HR = 0.70) for three-month CDP using a log-rank test with a two-sided alpha level of 0.05. To observe at least 374 patients with disability progression, 1,530 patients and an overall study duration of 42 months were required, with the assumption that at two years, 30% of the placebo group would have disability progression — a dropout rate of 20%. The key secondary outcomes were powered at 90% for the three-month confirmed worsening in T25-FW of 20% or more from baseline and 87% for the change in T2 lesion volume from

baseline to month 24. The latter was estimated to have 900 patients (600 siponimod, 300 placebo) available for analysis and a mean change from baseline of 600 mm^3 (SD = 2.7). It was predicted that when the estimated number of 374 or more events of three-month CDP has been observed, 95% of patients would have been randomized for at least one year before the core part of the study was stopped. Further, a normally distributed change from baseline was assumed and other assumptions were made based on data available from two-year studies of patients with RRMS (see Freedman [2011][49]).

A hierarchical testing procedure was performed for the primary and key secondary end points in the following order:

1. time to three-month CDP based on EDSS score
2. time to three-month confirmed worsening of at least 20% from baseline in T25-FW
3. change from baseline in T2 lesion volume.

The first hypothesis relating to the primary end point was performed at a two-sided significance level adjusted according to O'Brien-Fleming, and calculated to be 0.0434. The second and third hypothesis tests were performed at a two-sided significance level of 0.05.

All other secondary and exploratory outcomes (as listed in Table 10) were analyzed at a significance level of 0.05 without control for multiplicity. Further, no test for statistical significance in the subgroups or test for consistency of treatment effect was performed across subgroups.

Statistical Test or Model

The primary outcome (time to three-month CDP) and time to six-month CDP were tested using a Cox proportional hazards model. Treatment, country, baseline EDSS (continuous scale), and SPMS group (with or without relapses in the two years prior to screening) were included as covariates. Estimated HRs (siponimod and placebo hazard rates) were obtained with 95% Wald CIs. The corresponding risk reduction was also calculated as (1-hazard ratio) × 100. Additionally, Kaplan–Meier estimates with 95% CI were summarized at month 12, month 24, and month 36, and a Kaplan–Meier curve was presented.

Analysis of the key secondary outcome of time to three-month confirmed worsening of at least 20% on the T25-FW was similar to the primary outcome analysis, but included baseline T25-FW (continuous scale) as a covariate.

A Cox proportional hazards model was also used for the other time-to-event variables, including time to first confirmed relapse and the composite time-to-event end point.

The change from baseline in T2 lesion volume used a mixed-effects model for repeated measures (MMRM) with visit as a categorical factor. The following were included as covariates: country, age, SPMS group (with or without relapses, and baseline definition), T2 volume at baseline (continuous scale), and number of T1 Gd-enhancing lesions at baseline (continuous scale). The model assumed that visits were equally spaced and the change from baseline followed a normal distribution. The change from baseline at month 12, month 24, and month 36 were also calculated.

The percentage brain volume change relative to baseline was analyzed using MMRM with visit as a categorical factor, and with baseline normalized brain volume as a covariate. The percentage brain volume change relative to baseline at month 12, month 24, and month 36 were also calculated.

The number of T1 Gd-enhancing lesions and number of new or enlarging T2 lesions were also analyzed using a MMRM. A negative binomial distribution for the counts was assumed, and age, country, and number of T1 Gd-enhanced lesions at baseline were included as covariates. ARR was analyzed with a negative binomial regression model with a log-link function and included the following covariates: country, continuous baseline EDSS, baseline number of T1 Gd-enhancing lesion categories, and SPMS group (with or without relapses, and baseline definition).

Data Imputation Methods

The primary and key secondary efficacy analyses used all available data from the core part of the study for all patients included in the FAS, irrespective of premature discontinuation of study medication. Patients who do not reach disability progression based on EDSS score by the end of the core part were censored at the latest date known to be at risk during the core part. Supportive sensitivity analyses were performed. A likelihood-based statistical modelling approach (e.g., MMRM) was used to account for missing data in the overall population (FAS) of the EXPAND study, as described in the previous section. Missing data were not accounted for in the active SPMS subgroup.

Subgroup Analyses

Subgroup analyses on the primary outcome were performed for the following: gender, previous interferon beta-1b treatment, previous MS DMT treatment, relapsing versus non-relapsing SPMS (with or without relapses in the two years prior to screening visit), rapidly evolving patients based on historical EDSS scores (change ≥ 1.5 in two years prior to study), disease course (Global Multiple Sclerosis Severity Score ≥ 4), and number of T1 Gd-enhancing lesions at baseline. Previous treatment with interferon beta was added as a post-hoc subgroup analysis.

Patients with or without at least one confirmed relapse at any time after day 1 were noted as the "post-treatment definition" of relapsing or non-relapsing SPMS.

The following subgroup analyses were performed for the key secondary outcomes: patients with SPMS with or without relapses (baseline definition); rapidly and not rapidly evolving patients; and patients with and without moderate or severe disease course (as defined by the Global Multiple Sclerosis Severity Score).

Sensitivity Analyses

A preplanned sensitivity analysis was performed for the primary outcome that excluded patients who were assessed by an EDSS rater that had access to potentially unblinding information. An analysis employing the per-protocol set (PPS) was used to supplement the FAS analysis by providing an analysis of on-treatment data for patients who had no major protocol violations. A modified FAS (mFAS) was also used.

Sensitivity analyses were also performed using the FAS and three predefined assumptions:

1. All patients with a start of a tentative disability progression based on EDSS score, who discontinued the core part prematurely within the three-month confirmation interval, had confirmed progression based on EDSS score.
2. All patients who discontinued the core part prematurely without reaching the end point had confirmed progression based on EDSS score at the time they stopped study participation.

3. All patients who discontinued the core part prematurely for reasons related to lack of efficacy without reaching the end point had confirmed progression based on EDSS score at the time they stopped study participation.

Analysis Populations

The randomized analysis set included all patients who were randomized.

The FAS included all randomized patients who received at least one dose of study medication. It was used for all efficacy analyses and followed an intention-to-treat principle. Patients receiving open-label therapy were included based on the original treatment group assignment. In addition, the post-hoc active SPMS subgroup analysis was based on the FAS.

The mFAS was the same as the FAS, except efficacy assessments for patients who prematurely discontinued study treatment and switched therapies (either started a new MS DMT or open-label siponimod) were only included up until the time of the switch. The mFAS was used for sensitivity analyses of the primary and key secondary efficacy outcomes.

The PPS comprised all patients included in the FAS who also did not have any major protocol deviations that may cause confounding. Depending on the protocol deviation, data for a patient may have only been excluded after the time at which the protocol deviation occurred. The PPS was primarily used for supportive analyses for the primary and key secondary efficacy outcomes.

The safety set included all patients who received at least one dose of study medication and was used for all safety analyses. Patients were analyzed based on the actual treatment received, including all available data up to and including 30 days following the last dose of the study drug or the day before the start of open-label siponimod in the extension study.

Results

Patient Disposition

A summary of patient study disposition at the end of the treatment epoch is presented in Table 11.

Patient disposition for the post-hoc active SPMS subgroup was provided in a poster presentation.[50] Of note, the poster included 519 patients in the siponimod group while the post-hoc analysis submitted by the sponsor reported 516.[50] The reason for the discrepancy between the patient population reported in the poster and the sponsor-submitted active SPMS data is unclear. A total of 782 of the 2,092 patients who were screened for the EXPAND study was included in the active SPMS subgroup. Data regarding screening failures were not available for the active SPMS subgroup, but for the overall population, 441 (21.1%) failed, primarily (80.0%) due to ineligibility based on the inclusion and exclusion criteria. The proportion of patients in the active SPMS subgroup that completed the study was 79.4% and similar to the overall population (80.4%).

In the active SPMS subgroup, the percentage of discontinuations in the placebo group was greater than in the siponimod group (27% and 18%, respectively). [redacted] Overall, discontinuation due to [redacted]

[redacted] were also common reasons for discontinuation, with similar proportions between the treatment groups.

In the overall population, the percentage of discontinuations in the placebo group was greater than in the siponimod group (22.3% and 18.3%, respectively). The most common reason for discontinuation from study in both treatment groups was patient or guardian decision (10.5% overall); however, this was more common in the placebo group (8.7% in the siponimod group versus 14.1% in the placebo group). Other reasons for discontinuation were reported for a similar proportion of patients in the siponimod and placebo treatment groups.

Additional information regarding patient disposition after discontinuation of the study drug in the overall population is available in Appendix 3 (Table 41).

Table 11: Patient Disposition

	EXPAND (RAN)		EXPAND (active SPMS subgroup)	
	Siponimod	Placebo	Siponimod	Placebo
Screened, N	2,092		782	
Randomized, N (%)	1,105 (66.9)	546 (33.1)	519 (66.4)	263 (33.6)
Completed study, N (%)	903 (81.7)	424 (77.7)	428 (83)	193 (73)
Discontinued study, N (%)	202 (18.3)	122 (22.3)	91 (18)	70 (27)
Reason for discontinuation, N (%)				
Adverse events	45 (4.1)	18 (3.3)	15 (2.9)	9 (3.4)
Lack of efficacy	[redacted]	[redacted]	9 (1.7)	7 (2.7)
Lost to follow-up	[redacted]	[redacted]	3 (0.6)	3 (1.1)
Non-compliance with study treatment	[redacted]	[redacted]	2 (0.4)	0
Physician decision	[redacted]	[redacted]	9 (1.7)	1 (0.4)
Progressive disease	[redacted]	[redacted]	1 (0.2)	3 (1.1)
Protocol deviation	[redacted]	[redacted]	1 (0.2)	1 (0.4)
Technical problems	[redacted]	[redacted]	1 (0.2)	0
Patient/guardian decision	[redacted]	[redacted]	47 (9.1)	45 (17.1)
Death	[redacted]	[redacted]	2 (0.4)	1 (0.4)
New therapy for indication	[redacted]	[redacted]	1 (0.2)	0
RAN, N	[redacted]	[redacted]	NR	NR
FAS, N	[redacted]	[redacted]	516[b]	263[b]
PPS, N	[redacted]	[redacted]	NR	NR
Safety set, N	[redacted]	[redacted]	NR	NR

FAS = full analysis set; NR = not reported; PPS = per-protocol set; SPMS = secondary-progressive multiple sclerosis; RAN = randomized analysis set.

[a] Patient disposition data were derived from the poster by Gold et al. (2019)[50] and include an N = 782 rather than N = 779, which was used for all other analyses for this patient population in this CADTH report.

[b] The N for the FAS is based on the subgroup analyses and not the poster by Gold et al. (2019).[50]

Source: EXPAND Clinical Study Report[14] and Gold et al. (2019).[50]

Exposure to Study Treatments

A summary of exposure to the study drug during the double-blind treatment period is provided in Table 12.

[redacted]The cumulative exposure to the double-blind study drug was similar between the two groups. [redacted]

Data regarding exposure to study treatments was not provided for any of the subgroup analysis sets.

Table 12: Exposure to Double-Blind Study Drug in the Overall Population — Safety Set

	Siponimod (N = 1,099)	Placebo (N = 546)
Cumulative exposure, n (%)		
≥ 1 day	[redacted]	[redacted]
≥ 7 days	[redacted]	[redacted]
≥ 1 month	[redacted]	[redacted]
≥ 3 months	[redacted]	[redacted]
≥ 6 months	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]
≥ 24 months	[redacted]	[redacted]
≥ 36 months	[redacted]	[redacted]
Exposure (months)		
Mean (SD)	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]

SD = standard deviation.

Source: EXPAND Clinical Study Report.[14]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported as follows. See Appendix 3 for detailed efficacy data. The results of the post-hoc active SPMS subgroup analyses are presented first, followed by the results of the full study population that has been included for reference. Where available, the preplanned subgroup analyses of relevance to this review have been summarized following the results of the FAS.

Disability Progression or Improvement

The results for primary efficacy outcome, time to three-month CDP, and time to six-month CDP for both the post-hoc active SPMS subgroup and the overall EXPAND population are provided in Table 13.

Based on an HR of 0.69 (95% CI, 0.53 to 0.91; P = 0.0094) in the active SPMS subgroup, treatment with siponimod corresponded to a 30.7% risk reduction in the time to three-month CDP compared to placebo. In the overall population, an HR of 0.79 (95% CI, 0.65 to 0.95; P = 0.0134) for treatment with siponimod compared to placebo, or a 21.2% risk reduction in the time to three-month CDP with siponimod, was reported. In the active SPMS subgroup, the absolute risk difference was [redacted] which was greater than the absolute risk difference of 5.4% in the overall patient population (26.3% in the siponimod group versus 31.7% in the placebo group).

The results for time to six-month CDP were also in favour of siponimod compared to placebo in the active SPMS subgroup based on an HR of 0.63 (95% CI, 0.47 to 0.86; P = 0.0040), which corresponded to a 36.5% risk reduction. In the overall population, based on an HR of 0.74 (95% CI, 0.60 to 0.92; P = 0.0058), treatment with siponimod corresponded to a 25.9% risk reduction. The six-month CDP outcome and active SPMS subgroup analyses were not included in the statistical testing hierarchy. The absolute risk difference in the active SPMS subgroup was 9.1% (19.0% in the siponimod group versus 28.1% in the placebo group), which was greater than the absolute risk difference of 5.6% in the overall population (19.9% in the siponimod group versus 25.5% in the placebo group).

Planned sensitivity analyses were performed for the primary efficacy outcome of the overall population using the PPS and mFAS as well as four scenarios previously described. The results of the sensitivity analyses were consistent with the primary analysis.

Table 13: Confirmed Disability Progression by EDSS

	EXPAND (FAS)		EXPAND (active SPMS subgroup)	
	Siponimod (N = 1,099)	Placebo (N = 546)	Siponimod (N = 516)	Placebo (N = 263)
Time to 3-month CDP by EDSS				
n/N (%)	288/1,096 (26.3)	173/545 (31.7)	128/515 (24.9)	91/263 (34.6)
Risk reduction (%)	21.2		30.7	
Hazard ratio[a] (95% CI)	0.79 (0.65 to 0.95)		0.69 (0.53 to 0.91)	
P value	0.0134		0.0094[b]	
Time to 6-month CDP by EDSS[b]				
n/N (%)	218/1,096 (19.9)	139/545 (25.5)	98/515 (19.0)	74/263 (28.1)
Risk reduction (%)	25.9		36.5	
Hazard ratio[a] (95% CI)	0.74 (0.60 to 0.92)		0.63 (0.47 to 0.86)	
P value	0.0058		0.0040	

CDP = confirmed disability progression; CI = confidence interval; EDSS = Expanded Disability Status Scale; FAS = full analysis set; SPMS = secondary-progressive multiple sclerosis.

[a] Used a Cox proportional hazards model with treatment, country and/or region, baseline EDSS, and SPMS group (with or without relapses, baseline definition) as covariates. Risk reduction is derived as (1-hazard ratio) × 100.

[b] Outcome was outside the statistical testing hierarchy.

Note: For time to three-month CDP, the null hypothesis was tested at a two-sided significance level of 0.0434, adjusted according to the O'Brien-Fleming alpha level correction. The active SPMS subgroup defined patients with active disease as having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline.

Source: EXPAND Clinical Study Report.[14]

A summary of the planned subgroup analyses of the primary outcome is presented in Table 14. In the planned subgroup analysis, the HR for patients with relapses in the two years prior to study start was 0.67 (95% CI, 0.49 to 0.91) and 0.87 (95% CI, 0.68 to 1.11) in

patients without relapses. Further, in patients with more than one T1 Gd-enhancing lesion at baseline, the HR was 0.64 (95% CI, 0.42 to 0.95) and 0.82 (95% CI, 0.66 to 1.02) in patients without T1 Gd-enhancing lesions at baseline. Therefore, in general, the risk reduction for time to three-month CDP tended to be more evident in subgroups of patients than in the overall population. More specifically, the HR (95% CI) for those with relapses in the two years prior to study start was 0.67 (0.49 to 0.91) and 0.64 (0.42 to 0.95) in patients with more than one T1 Gd-enhancing lesion at baseline, compared to an HR of 0.79 (0.65 to 0.95) in the overall population. The results did not suggest a difference in treatment effect by EDSS score at baseline; therefore, it is unknown whether the subgroup of patients with active SPMS would have similar patterns in risk reduction by disease status at baseline.

Table 14: Planned Subgroup Analyses of Time to Three-Month CDP — FAS

	EXPAND			
	Siponimod n/N (%)	Placebo n/N (%)	HR (95% CI)	P value
Relapses in the 2 years prior to study start[a]				
With relapses	98/388 (25.3)	72/202 (35.6)	0.67 (0.49 to 0.91)	NR
Without relapses	190/708 (26.8)	101/343 (29.4)	0.87 (0.68 to 1.11)	NR
Number of T1 Gd-enhancing lesions at baseline[a]				
≥ 1	61/236 (25.8)	40/114 (35.1)	0.64 (0.42 to 0.95)	NR
0	219/828 (26.4)	128/415 (30.8)	0.82 (0.66 to 1.02)	NR
Patients with rapidly evolving disease[a, b]				
Yes	82/264 (31.1)	60/145 (41.4)	0.65 (0.46 to 0.91)	NR
No	206/835 (24.7)	113/401 (28.2)	0.86 (0.69 to 1.09)	NR
EDSS at baseline[a]				
3.0	NR	NR	0.64 (0.41 to 1.01)	NR
4.0	NR	NR	0.70 (0.52 to 0.95)	NR
5.0	NR	NR	0.76 (0.63 to 0.93)	NR
6.0	NR	NR	0.83 (0.67 to 1.04)	NR

CDP = confirmed disability progression; CI = confidence interval; EDSS = Expanded Disability Status Scale; FAS = full analysis set; Gd = gadolinium; HR = hazard ratio; NR = not reported.

[a] Outcome was outside the statistical testing hierarchy.

[b] Patients with rapidly evolving disease are defined as patients with 1.5 or greater EDSS change in the two years prior to or at study start and disability progression in the two years prior to study start was not adjudicated.

Note: It is unclear whether the subgroup analyses were preplanned, but patients were not stratified by the subgroups in this table at randomization.

Source: EXPAND Clinical Study Report.[14]

As shown in Figure 4, the Kaplan–Meier curve for the subgroup of patients with active SPMS demonstrated a statistically significant difference in three-month CDP between siponimod and placebo. The difference was sustained over the entire course of the study (from about six months until approximately 30 months to 36 months). A log-rank test was performed for the survival curve, resulting in a P value of [redacted]. A similar pattern of difference on this primary outcome of three-month CDP was observed in the overall patient population (Appendix 3, Figure 5).

Figure 4: Patients With Active SPMS, Free of Three-Month CDP Based on EDSS, Kaplan–Meier Curve — Post-Hoc Active SPMS Subgroup

Figure 4 contained confidential information and was removed at the request of the sponsor.

CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; SPMS = secondary-progressive multiple sclerosis.

Note: Patients who did not have a baseline EDSS assessment were excluded from the analysis. The active SPMS subgroup defined patients with active disease as having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline.

Source: CADTH submission for siponimod.[15]

Health-Related Quality of Life

The only measure of HRQoL assessed in the active SPMS subgroup was the MSWS-12. Other measures of HRQoL were assessed in the overall population (FAS) of the EXPAND study, including the MSWS-12, MSIS-29, and EQ-5D-3L. The results of the MSWS-12 data at month 12 have been summarized in Table 15. The results related to the MSIS-29 and EQ-5D-3L are provided in Appendix 3 (Table 42).

None of the HRQoL outcomes were included in the statistical hierarchy. The adjusted mean change from baseline at month 12 is presented in Table 15. For the post-hoc active SPMS subgroup analysis, the between-groups difference for the MSWS-12 converted score was [redacted]. For the overall population, the between-groups difference for the MSWS-12 converted score was –1.83 (95% CI, –3.85 to 0.19; P = 0.0764). Further, the reported results for the HRQoL outcomes corresponding to the overall population [redacted] did not meet the MID described in Appendix 4, which ranged from 10.4 to 22.

Similarly at month 24, there was no difference between groups for the MSWS-12 in the total EXPAND population (–1.23; 95% CI, –3.89 to 1.44; P = 0.3671) or in the active SPMS subgroup [redacted].

Table 15: HRQoL — MSWS-12, Change from Baseline

	Total N	n	Baseline	At month 12		Treatment group difference vs. control		
			Mean (SD)	Mean (SD)	Adjusted mean change from baseline (SE)	N	Mean difference (95% CI)	P value
FAS: MSWS-12 converted score,[a] MMRM[b]								
Siponimod	1,099	917	68.29 (23.376)	69.57 (24.95)	1.53 (0.68)	1,022	–1.83 (–3.85 to 0.19)	0.0764
Placebo	546	448	66.64 (22.25)	70.08 (23.92)	3.36 (0.91)	516		
Active SPMS subgroup: MSWS-12 converted score,[a] MMRM[b]								
Siponimod	516	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	263	NR	NR	NR	[redacted]	[redacted]		

CI = confidence interval; FAS = full analysis set; Gd = gadolinium; HRQoL = health-related quality of life; MMRM = mixed-effects model for repeated measures; MSWS-12 = Multiple Sclerosis Walking Scale; NR = not reported; SD = standard deviation; SE = standard error; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

Note: The active SPMS subgroup defined patients with active disease as having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline.

[a] Outcome was not included in the statistical testing hierarchy.

[b] Model was adjusted for treatment, region and/or country, and corresponding baseline score.

Source: EXPAND Clinical Study Report[14] and CADTH submission for siponimod.[15]

Mobility

The time to three-month confirmed worsening of at least 20% from baseline in the T25-FW was a key secondary outcome in the EXPAND study and the second outcome in the statistical testing hierarchy. This outcome was also included in the post-hoc active SPMS subgroup analyses (see Table 16). For patients with active SPMS, an HR of 0.85 (95% CI, 0.68 to 1.07) for siponimod compared to placebo was reported for time to three-month confirmed worsening in the T25-FW. In the overall population, as presented in Table 16, treatment with siponimod compared to placebo resulted in an HR of 0.94 (95% CI, 0.80 to 1.10;
P = 0.4398) for time to three-month confirmed worsening in the T25-FW; however, this was not statistically significant. The absolute risk difference between siponimod and placebo was [redacted]1.7% in the overall population.

Sensitivity analyses were performed using the mFAS and PPS, and were consistent with the primary analysis.

The planned subgroup analyses by relapses in the two years prior to study start and in patients with rapidly evolving disease are shown in Table 17. The planned subgroup analysis by disease activity status at baseline showed no difference between treatment groups in time to three-month confirmed worsening of at least 20% from baseline in T25-FW; nor was there a pattern of differential treatment effect by relapsing compared to non-relapsing or rapid evolving disease.

Table 16: Time to Three-Month Confirmed Worsening of 20% or More From Baseline in the T25-FW

	EXPAND (FAS)		EXPAND (active SPMS subgroup)	
	Siponimod (N = 1,099)	Placebo (N = 546)	Siponimod (N = 516)	Placebo (N = 263)
Time to 3-month confirmed worsening of ≥ 20% from baseline in the T25-FW				
n/N' (%)	432/1,087 (39.7)	225/543 (41.4)	[redacted](41.7)	120/263 (45.6)
Risk reduction (%)	6.2		14.7	
Hazard ratio[a] (95% CI)	0.94 (0.80 to 1.10)		0.85 (0.68 to 1.07)	
P value	0.4398		0.1747	

CI = confidence interval; EDSS = Expanded Disability Status Scale; FAS = full analysis set; Gd = gadolinium; n= number of patients with events; N' = number of patients included in the analysis (i.e., with non-missing covariates); SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test.

Note: The active SPMS subgroup defined patients with active disease as having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline.

[a] The comparison used a Cox proportional hazards model with treatment, country and/or region, baseline EDSS, baseline T25-FW, and SPMS group (with or without relapses, baseline definition) as covariates.

Source: EXPAND Clinical Study Report.[14]

Table 17: Planned Subgroup Analyses of Time to Three-Month Confirmed Worsening of 20% or More From Baseline in the T25-FW — FAS

	EXPAND			
	Siponimod n/N (%)	Placebo n/N (%)	HR (95% CI)	P value
Time to 3-month confirmed worsening of ≥ 20% from baseline in T25-FW[a]				
Relapses in the 2 years prior to study start				
With relapses	[redacted]	[redacted]	[redacted]	NR
Without relapses	[redacted]	[redacted]	[redacted]	NR
Patients with rapidly evolving disease[b]				
Yes	[redacted]	[redacted]	[redacted]	NR
No	[redacted]	[redacted]	[redacted]	NR

CI = confidence interval; EDSS = Expanded Disability Status Scale; FAS = full analysis set; Gd = gadolinium; HR = hazard ratio; NR = not reported; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test.

Note: All analyses were conducted using the FAS. This outcome was not assessed by the number of T1 Gd-enhancing lesions at baseline.

[a] Outcome was outside the statistical testing hierarchy.

[b] Rapidly evolving patients are defined as patients with 1.5 or greater EDSS change in the two years prior to or at study start and disability progression in the two years prior to study start was not adjudicated.

Source: EXPAND Clinical Study Report.[14]

Multiple Sclerosis Functional Composite: T25-FW and 9-HPT

The MSFC is a composite outcome derived from a combination of the 9-HPT, T25-FW, and the PASAT. The results of the MSFC z score and mobility-related components (T25-FW and 9-HPT) at month 12 were assessed in the overall population and are provided in Appendix 3 (Table 43). None of these outcomes were included in the statistical hierarchy for the overall population and none of these outcomes were analyzed in an active SPMS patient subgroup.

Cognitive Function

Cognitive function was assessed in the EXPAND study via the SDMT, PASAT, and BVMT-R (total recall and delayed recall). The outcomes related to cognitive function were not included in the statistical hierarchy and were not analyzed in an active SPMS patient subgroup. The outcomes at month 12 for the FAS are provided in Appendix 3 (Table 44).

Symptoms

Specific MS-related symptoms, such as fatigue, were not reported as an efficacy outcome in the EXPAND study.

Relapse-Related Outcomes

The ARR was reported based on the number of confirmed relapses, and for all relapses (Table 18). The sponsor-submitted post-hoc active SPMS subgroup data reported a between-groups ARR ratio of 0.544 (95% CI, 0.387 to 0.766; P = 0.0005) for confirmed relapses, which corresponds to a rate reduction of 45.6%. The sample size and adjusted ARR for each treatment group was not provided. This outcome was also not controlled for multiplicity and therefore subject to the risk of type I error. In the FAS, the adjusted ARR for

confirmed relapses was associated with a rate reduction was 55.5% (between-groups ARR ratio of 0.445; 95% CI, 0.337 to 0.587; P < 0.0001).

The ARR including all relapses (confirmed and unconfirmed) was not reported for the active SPMS subgroup. [redacted]

A Kaplan–Meier curve for the percentage of relapse-free patients in the FAS is shown in Appendix 3 (Figure 6).

Table 18: Annualized Relapse Rate

	EXPAND (FAS)		EXPAND (active SPMS subgroup)
	Siponimod (N = 1,099)	Placebo (N = 546)	Patients with active SPMS (N = 779)
ARR: Confirmed relapses[a]			
n/time (days)	134/691,980	143/343,285	NR
Adjusted[b] ARR (95% CI)	0.071 (0.055 to 0.092)	0.160 (0.123 to 0.207)	
Rate reduction (%)	55.5		45.6
Between-groups ARR ratio (95% CI)	0.445 (0.337 to 0.587)		0.544 (0.387 to 0.766)
P value	< 0.0001		0.0005
ARR: All relapses (confirmed and unconfirmed)[a]			
n/time (days)	[redacted]	[redacted]	NR
Adjusted[b] ARR (95% CI)	[redacted]	[redacted]	
Rate reduction (%)	[redacted]		
Between-groups ARR ratio (95% CI)	[redacted]		
P value	[redacted]		

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; FAS = full analysis set; NR = not reported; SPMS = secondary-progressive multiple sclerosis.

Note: The analysis period extended from the first day of the study drug up to end of the core part of the study.

[a] Outcome was outside the statistical testing hierarchy.

[b] Negative binomial regression model adjusted for treatment, country and/or region, baseline EDSS, SPMS group (with or without relapses, baseline definition), and baseline number of T1 Gd-enhancing lesions (offset = time in analysis period in years).

Source: EXPAND Clinical Study Report.[14]

Imaging Outcomes

The change from baseline in T2 lesion volume was a key secondary outcome and the third outcome in the statistical testing hierarchy of the EXPAND study. This outcome was also assessed in the post-hoc active SPMS analysis. The results are presented in Table 19. [redacted] The subgroup analysis was not controlled for multiplicity and should be considered exploratory. In the FAS, the treatment group difference in T2 lesion volume (mm^3) at month 12 was –613.1 mm^3 (95% CI, –800.2 to –426.0; P < 0.0001), i.e., there was a smaller change in T2 lesion volume (from baseline) among patients treated with siponimod in comparison with those treated with placebo. Due to prior failure in the statistical testing hierarchy, this analysis in

the overall population can only be considered exploratory. [redacted] Sensitivity analyses using the PPS and mFAS were also performed and were consistent with the primary analysis.

Table 19: Change From Baseline in T2 Lesion Volume

	Total N	n	Baseline	Change from baseline		Treatment group difference vs. control		
			Mean (SD)	Mean (SD)	Adjusted mean (SE)	N	Mean difference (95% CI)	P value
FAS: Change from baseline in T2 lesion volume (mm^3)[a] at month 12, MMRM[b]								
Siponimod	1,099	997	[redacted]	[redacted]	204.9 (67.47)	995	–613.1 (–800.2 to –426.0)	< 0.0001
Placebo	546	497	[redacted]	[redacted]	818.0 (87.29)	495		
Active SPMS subgroup: Change from baseline in T2 lesion volume (mm^3)[a] at month 12, MMRM[b]								
Siponimod	516	NR	NR	NR	93.5 [redacted]	473	[redacted]	< 0.001
Placebo	263	NR	NR	NR	1,117.2 [redacted]	244		

CI = confidence interval; FAS = full analysis set; Gd = gadolinium; MMRM = mixed-effects model for repeated measures; NR = not reported; SD = standard deviation; SE = standard error; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

Note: The active SPMS subgroup defined patients with active disease as having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline.

[a] Included in the statistical hierarchy, but analyzed following a prior failure; therefore, violating the pre-specified statistical strategy.

[b] Model was adjusted for treatment, country and/or region, baseline T2 lesion volume, number of T1 Gd-enhancing lesions at baseline, and SPMS group (with or without relapses, baseline definition).

Source: EXPAND Clinical Study Report.[14]

Planned subgroup analyses by disease activity status at baseline of the change from baseline in T2 volume (mm^3) were also conducted as part of the original EXPAND study protocol (see Table 20). [redacted] Statistical testing was not conducted for this analysis.

A subgroup analysis of the change in T2 volume outcome was also conducted for patients with or without rapidly evolving disease, defined by the magnitude of the change in EDSS score in the two years prior to study start (see Table 20). [redacted] Statistical testing was not conducted for either of these subgroup analyses and an MID was not identified for this outcome; therefore, the conclusions that can be drawn from these results are limited.

Table 20: Planned Subgroup Analyses of Change From Baseline in T2 Volume (mm^3) — FAS

	EXPAND	
	Siponimod (N = 1,099)	Placebo (N = 546)
Change from baseline in T2 volume (mm^3)[a]		
Relapses in the 2 years prior to study start		
With relapses, n	[redacted]	[redacted]
Estimate	[redacted]	[redacted]
Difference (95% CI), P value	[redacted]	
Without relapses, n	[redacted]	[redacted]
Estimate	[redacted]	[redacted]
Difference (95% CI), P value	[redacted]	
Patients with rapidly evolving disease[b]		
Yes, n	[redacted]	[redacted]
Estimate	[redacted]	[redacted]
Difference (95% CI), P value	[redacted]	
No, n	[redacted]	[redacted]
Estimate	[redacted]	[redacted]
Difference (95% CI), P value	[redacted]	

CI = confidence interval; EDSS = Expanded Disability Status Scale; FAS = full analysis set; Gd = gadolinium; NR = not reported.

Note: All analyses were conducted using FAS. This outcome was not assessed by the number of T1 Gd-enhancing lesions at baseline.

[a] Outcome was outside the statistical testing hierarchy.

[b] Rapidly evolving patients are defined as patients with 1.5 or greater EDSS change in the two years prior to or at study start and disability progression in the two years prior to study start was not adjudicated.

Source: EXPAND Clinical Study Report.[14]

Additional imaging items related to T2 lesions, T1 Gd-enhancing lesions, and brain volume for both the FAS population and post-hoc active SPMS subgroup analysis are summarized in Table 21. For the active SPMS subgroup analysis at month 12, the rate ratio (siponimod to placebo) for the number of new or enlarging T2 lesions relative to baseline was 0.259 (95% CI, 0.202 to 0.332; P < 0.0001) and the rate ratio for the number of T1 Gd-enhancing lesions per patient per scan was 0.137 (95% CI, 0.083 to 0.226; P < 0.0001). These results were consistent with corresponding results in the overall population (T2 lesions: 0.266 [0.215 to 0.328]; P < 0.0001; and T1 lesions: 0.126 [0.083 to 0.191]; P < 0.0001). The proportion of patients free of T2 or T1 Gd-enhancing lesions in the overall population is available in Appendix 3 (Table 45). It was not reported in the active SPMS subgroup analyses.

As previously mentioned, percentage brain volume was also reported (see Table 21). In the active SPMS subgroup analysis, the treatment group difference (siponimod compared to placebo) based on the adjusted mean change from baseline at month 12 in percentage brain volume was 0.173 (95% CI, 0.064 to 0.283; P = 0.0020). The treatment group difference reported in the overall population was similar (0.175 [95% CI, 0.103 to 0.247; P < 0.0001]), but the adjusted mean (standard error) percentage brain volume change at month 12 was greater for both treatment groups in the subgroup analysis compared to the overall population.

Table 21: Additional Imaging Outcomes at Month 12

	EXPAND (FAS)		EXPAND (active SPMS subgroup)	
	Siponimod (N = 1,099)	Placebo (N = 546)	Siponimod (N = 516)	Placebo (N = 263)
T2 lesions				
Number of new or enlarging T2 lesions (relative to baseline)[a, b]				
N' (in analysis)	997	496	474	244
Adjusted mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Rate reduction (%)	[redacted]		[redacted]	
Rate ratio (95% CI), P value	[redacted]		[redacted]	
T1 Gd-enhancing lesions				
Number of T1 Gd-enhancing lesions per patient per scan[a, c]				
N' (in analysis)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Rate reduction (%)	[redacted]		[redacted]	
Rate ratio (95% CI), P value	[redacted]		[redacted]	
Brain volume				
Percentage brain volume change (relative to baseline)[a, d] MMRM				
N' (in analysis)	894	436	431	222
Adjusted mean (SE)	–0.283 (0.0264)	–0.458 (0.0341)	–0.4[redacted]	–0.6 [redacted]
Difference (95% CI), P value	0.175 (0.103 to 0.247; P < 0.0001)		[redacted]P = 0.0020	

CI = confidence interval; FAS = full analysis set; Gd = gadolinium; N' = number of patients included in analysis; NR = not reported; SE = standard error; SPMS = secondary-progressive multiple sclerosis.

[a] Outcome was outside the statistical testing hierarchy.

[b] Model was adjusted for treatment, region and/or country, age, baseline number of T1 Gd-enhancing weighted lesions (offset = time between visits).

[c] Obtained from fitting negative binomial regression model adjusted for treatment, age, and baseline number of T1 Gd-enhancing lesions (offset = number of scheduled MRI scans).

[d] Model was adjusted for treatment, country and/or region, age, normalized brain volume at baseline, number of T1 Gd-enhancing lesions at baseline, T2 volume at baseline, and SPMS group (with or without relapses, baseline definition).

Source: EXPAND Clinical Study Report.[14]

Harms

Only those harms identified in the review protocol are reported as follows. See Table 22 for detailed harms data corresponding to the overall EXPAND study population. Safety was not assessed in any of the subgroup analyses pertaining to patients with active SPMS.

Adverse Events

The majority of patients reported at least one treatment-emergent AE while receiving double-blind study drug and up to 30 days following discontinuation. A greater proportion of patients treated with siponimod (88.7%) reported at least one AE compared to placebo (81.5%). Rates of specific AEs were similar between the two treatment arms, although hypertension was slightly more common for patients treated with siponimod (10.5% versus 7.5%), as was nausea (6.7% versus 3.5%), alanine aminotransferase increase (5.9% versus 1.5%), and peripheral edema (4.5% versus 2.4%). Overall, the most common AEs

reported were headaches, urinary tract infection, falls, hypertension, and fatigue, but the frequency was similar between treatment groups.

Serious Adverse Events

Serious AEs were reported by 17.9% of patients treated with siponimod and 15.2% of patients treated with placebo. Specific events rates were low and similar between treatment groups.

Withdrawals due to Adverse Events

Rates of withdrawal due to AEs were low and similar between groups (7.6% in the siponimod group versus 5.1% in the placebo group). [redacted].

Mortality

Eight patients died during the EXPAND study (excluding one patient who died during screening, prior to treatment exposure): four from each treatment arm. Cause of death for patients treated with siponimod includes completed suicide, urosepsis, septic shock (stage IV colon cancer), and malignant melanoma (multiple organ dysfunction syndrome). Cause of death for patients receiving placebo includes hemorrhagic stroke, lung adenocarcinoma, gastric cancer, and an unknown cause.

Notable Harms

Cardiac effects, neoplasia, serious infections, opportunistic infections, lymphocytopenia, and macular edema were included as notable harms for this review (see Table 6). [redacted] Bradycardia was reported by 4.5% and 2.6% of patients, respectively, and macular edema was reported by [redacted] Lymphocytopenia was reported in less than 1% of patients in the siponimod group and no patients in the placebo group. The serious infection of interest was progressive multifocal leukoencephalopathy and the opportunistic infection of interest was cryptococcal meningitis; no events were reported for either notable harm in the EXPAND study.

Table 22: Summary of Harms — Safety Set

	EXPAND	
	Siponimod N = 1,099	Placebo N = 546
Patients with ≥ 1 adverse event		
n (%)	975 (88.7)	445 (81.5)
Most common events,[a] n (%)		
Headache	159 (14.5)	71 (13.0)
Nasopharyngitis	149 (13.6)	79 (14.5)
Urinary tract infection	133 (12.1)	80 (14.7)
Fall	128 (11.6)	59 (10.8)
Hypertension	115 (10.5)	41 (7.5)
Fatigue	100 (9.1)	51 (9.3)

	EXPAND	
	Siponimod N = 1,099	Placebo N = 546
Upper respiratory tract infection	91 (8.3)	41 (7.5)
Dizziness	75 (6.8)	26 (4.8)
Nausea	74 (6.7)	19 (3.5)
Influenza	73 (6.6)	40 (7.3)
Diarrhea	70 (6.4)	23 (4.2)
Back pain	67 (6.1)	43 (7.9)
Alanine aminotransferase, increased	65 (5.9)	8 (1.5)
Pain in extremity	60 (5.5)	21 (3.8)
Bradycardia	50 (4.5)	14 (2.6)
Peripheral edema	50 (4.5)	13 (2.4)
Arthralgia	49 (4.5)	35 (6.4)
Depression	49 (4.5)	30 (5.5)
Patients with ≥ 1 SAE		
n (%)	197 (17.9)	83 (15.2)
Most common events,[b] n (%)		
Nervous system disorders	40 (3.6)	17 (3.1)
MS relapse	2 (0.2)	7 (1.3)
Infections and infestations	33 (3.0)	15 (2.7)
Urinary tract infection	13 (1.2)	6 (1.1)
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	23 (2.1)	15 (2.7)
Basal cell carcinoma	11 (1.0)	6 (1.1)
Psychiatric disorders	22 (2.0)	7 (1.3)
Investigations	21 (1.9)	3 (0.5)
Injury, poisoning, and procedural complications	20 (1.8)	5 (0.9)
Renal and urinary disorders	14 (1.3)	3 (0.5)
Musculoskeletal and connective tissue disorders	12 (1.1)	3 (0.5)
Gastrointestinal disorders	9 (0.8)	9 (1.6)
Patients who stopped treatment due to adverse events		
n (%)	84 (7.6)	28 (5.1)
Most common events,[b] n (%)		
Macular edema	11 (1.0)	1 (0.2)
Deaths		
n (%)	4 (0.4)	4 (0.7)
Completed suicide	1 (0.1)	0
Urosepsis	1 (0.1)	0
Septic shock (colon cancer stage IV)	1 (0.1)	0
Malignant melanoma (multiple organ dysfunction syndrome)	1 (0.1)	0
Hemorrhagic stroke	0	1 (0.2)
Lung adenocarcinoma	0	1 (0.2)

	EXPAND	
	Siponimod N = 1,099	Placebo N = 546
Gastric cancer	0	1 (0.2)
Unknown reason	0	1 (0.2)
Notable harms, n (%)		
Bradycardia	50 (4.5)	14 (2.6)
Neoplasia (neoplasms: benign, malignant, and unspecified)	113 (10.3)	45 (8.2)
Serious infections		
Progressive multifocal leukoencephalopathy	0	0
Opportunistic infections		
Cryptococcal meningitis	0	0
Lymphocytopenia (lymphocyte counts)	9 (0.8)	0
Macular edema	18 (1.6)	1 (0.2)

DMT = disease-modifying therapy; MS = multiple sclerosis; SAE = serious adverse event.

Note: Deaths due to completed suicide, hemorrhagic stroke, lung adenocarcinoma, and gastric cancer occurred during the double-blind study treatment up until the safety cut-off. The death due to urosepsis occurred after the start of alternative MS DMT. The death due to septic shock occurred five days after discontinuation of open-label siponimod.

[a] Frequency of 5% or more in either treatment group.

[b] Frequency of 1% or more patients in either treatment group.

Source: EXPAND Clinical Study Report.[14]

Critical Appraisal

Internal Validity

Due to the progressive nature of SPMS, the event-driven study design was appropriate. An adequate method of randomization and allocation concealment was implemented during the double-blind study. Sample size calculations were performed for the overall population, and the study was adequately powered for the primary and key secondary end points. All of the subgroup analyses were based on a smaller sample size, which included 47% of the overall population at best (for the post-hoc active SPMS subgroup analyses).

In the FAS, treatment groups were balanced based on baseline and disease characteristics, except that the proportion of patients with an EDSS score of 5.0 to 5.5 at baseline was slightly higher for the placebo group (18.3% versus 14.9%). The baseline characteristics of patients included in active SPMS subgroup analysis were similar between treatment groups, but also had a slightly higher percentage of patients with an EDSS score of 5.0 to 5.5 in the placebo group (19.0% versus 16.3%). Compared to the overall population, the baseline characteristics of patients included in the post-hoc active SPMS subgroup that were available were similar, except that they reported having more relapses in the last year prior to screening and a greater proportion of patients had at least one T1 Gd-enhancing lesion at baseline. This is aligned with the criteria used to define the active SPMS subgroup, which was having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline. Of note, this is a combination of the two identifiers used to define patients with active disease in the initial subgroup analyses.

The study followed a double-blind design with matching placebo, although blinding was compromised during the double-blind period. Most notably, some of the site staff were

incorrectly given access to certain databases, which led to potential unblinding of an estimated 15.7% of the siponimod group and 15.8% of the placebo group as reported by the sponsor. The sponsor also reported that "there was no evidence of site staff accessing/modifying the incorrect database" in the electronic audit trial maintained for these systems; however, the FDA noted this issue was very concerning and raised questions regarding the integrity of treatment blinding.[28] According to an unadjusted analysis of the primary end point conducted by the FDA, which excluded 101 patients who were potentially unblinded as a result of the dual database access issue, the primary end point did not meet statistical significance.[28] Investigators were also unblinded at two sites as a result of suspected unexpected serious adverse reactions that were disclosed with information about treatment for three patients; however, all three patients had completed the double-blind treatment at this point. Blinding may have also been compromised for the independent EDSS rater who had access to the cardiac monitoring database. A sensitivity analysis was conducted that excluded 19 patients (12 from siponimod, seven from placebo) who may have been impacted. This analysis was consistent with the primary analysis.[14] The issues related to blinding represent a significant limitation of the EXPAND study. The Health Canada Reviewers Report also noted that the blinding/database issue raised concern about the robustness of the primary outcome.[43]

The primary objective of the EXPAND study was to demonstrate efficacy of siponimod in delaying the time to three-month CDP using the EDSS. While the EDSS is a widely used and accepted outcome measure for MS trials, it is not without limitations. As identified by the clinical experts consulted by CADTH for this review, one issue is the mobility-driven nature of the EDSS, which may not provide an accurate assessment of patients with MS due to the heterogeneous presentation of disease. According to the EMA guidance document, the EDSS is also subject to poor inter-rater and intra-rater reliability, and advises that steps, such as training the observers, are taken to limit this issue.[51]

In the overall patient population, the percentage of discontinuation from the study was around 20% overall and slightly higher among patients treated with placebo (22.3%) compared to patients treated with siponimod (18.3%). In the active SPMS subgroup, the percent of discontinuations in the siponimod treatment group was similar to the overall population (18% in the overall and subgroup populations), but was greater in the placebo arm (27% in the active SPMS subgroup versus 22.3% in the overall population). In the active SPMS subgroup, the most common reason for discontinuation from study in both treatment groups was patient or guardian decision (17.1 % versus 9.1%, placebo versus siponimod, respectively). The extent to which the greater proportion of discontinuations in the placebo arm of the active SPMS subgroup would have impacted the outcome assessments throughout the study, and highly disproportionate early withdrawal due to voluntary decisions in particular, is unknown. The early discontinuation from study due to lack of efficacy, loss to follow-up, or AEs was relatively small in percentage, but consistently higher in the placebo group than in patients on siponimod [redacted]. Moreover, [redacted] of patients assigned to placebo and siponimod, respectively, prematurely discontinued the study drug in the overall study population. Unfortunately, the percentages of early treatment discontinuation in the active SPMS subgroup is unknown.

Rescue medication was available for patients who met the criteria for six-month CDP. These patients were counselled and offered three options, which were to continue study drug treatment, switch to open-label siponimod, or start another MS treatment available to them. Patients who switched to open-label therapy were included in the FAS used for all efficacy analyses, and [redacted] of patients randomized to placebo switched to open-label

siponimod. It is unclear when the switch occurred, but this may have introduced bias against siponimod in terms of efficacy. In addition, the high proportion of patients who discontinued from the study introduces potential bias to the results reported at month 24. For example, data regarding the change from baseline in EDSS was only available for [redacted] of randomized patients at month 24. Therefore, the results presented in the CADTH review of efficacy focus on the outcome measures that occurred during the double-blind treatment period up to month 12.

The use of certain concomitant medications was permitted and used by almost all patients in the overall population (92.9% overall). Use of concomitant medications was similar between the two treatment arms and therefore an unlikely concern to the internal validity of the study. This is unknown for the active SPMS subgroup as concomitant medication use was not available.

Missing data were not accounted for in the active SPMS subgroup analyses. Data were missing for [redacted] at most in patients in the active SPMS subgroup and therefore was unlikely an issue. A likelihood-based statistical modelling approach was used to account for missing data in the overall population of the EXPAND study; however, it is uncertain whether the missing data are truly random as it appears to be the result of patient or guardian decision, disease progression, and AEs. Therefore, it is possible that this approach may not have been able to provide an unbiased estimate of treatment effect. Despite this, sensitivity analyses were performed and were consistent with the primary analysis in terms of statistical significance.

Statistical testing for the active SPMS subgroup analyses, where conducted, was not controlled for multiplicity and therefore subject to potential for increased risk of type I error where differences that were statistically significant were observed (time to three-month CDP, time to six-month CDP, ARR [confirmed relapses], and imaging outcomes). This may have compromised the statistical inference of the effect in the active SPMS subgroup, even though the treatment effect as observed on the primary outcomes and key secondary outcomes were generally consistent with the findings from the overall study populations. In the overall population, multiplicity was controlled for the primary and key secondary efficacy outcomes using a statistical testing hierarchy, where statistical significance could only be claimed if all higher-ranking tests claimed superiority in favour of siponimod. The second ranked efficacy outcome, disability progression by T25-FW, was not statistically significant, yet statistical testing was performed for the third-ranked outcome, i.e., change from baseline in T2 lesion volume. This violated the statistical testing procedure and the outcome may have suffered potential for increased risk of type I error. Further, several outcomes of interest were reported that fell outside the statistical testing hierarchy and were not controlled for multiplicity, limiting the interpretation of the findings. This includes the HRQoL outcomes that were noted as important to patients, as well as cognitive function and mobility-related outcomes.

The post-hoc analyses of patients with SPMS were defined by having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline. This is a combination of the two identifiers used to defined patients with active disease in the initial subgroup analyses. These post-hoc analyses of the active SPMS subgroup were also subject to limitations. Baseline information about scores on the T25-FW, 9-HPT, and SDMT, the number of relapses in the last two years, time since the onset of the most recent relapse, volume of T1 lesions, and normalized brain volume were not available for the active SPMS subgroup and could not be compared to the overall population.

Randomization was not performed within stratification by active versus non-active SPMS, which may lead to concerns of incomparability between treatment arms regarding unknown confounders.

Lastly, approximately 78% of patients in the overall population had prior experience with a DMT; [redacted] A washout period was not required for these therapies prior to the first dose of the study drug. The impact of prior medication use on efficacy of siponimod in the active SPMS subgroup is unknown as these data were not reported.

External Validity

Generalizability of the Study Population

The patients enrolled in the EXPAND study had a diagnosis of SPMS. The trial used a combination of history of RRMS based on the 2010 revised McDonald Criteria, a progressive increase in disability without relapses or independent of relapses, and EDSS score at baseline and to assess progression, as inclusion criteria. Following screening, 21% of patients were excluded at randomization, which may suggest a slightly selective population of patients with SPMS. While there is a lack of well-defined criteria for diagnosing SPMS, the clinical experts on this review indicated that the baseline characteristics described patients with SPMS; however, this includes both patients with active and non-active SPMS. The approved Health Canada indication for siponimod is specific to patients with SPMS with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, which only applies to 47% of the patients enrolled in the EXPAND study. Of note, the patients included in the post-hoc active SPMS analyses were younger, on average, than the overall EXPAND population. Baseline characteristics were not available for the subgroup analyses of patients with active SPMS defined by having had relapses in the prior two years to study start, thus limiting the ability to assess the generalizability of the results.

A variety of comorbidities excluded patients from the EXPAND study, including active chronic disease (other than MS), diabetes mellitus unless well-controlled and without organ complications, chronic or relevant acute infections, and conditions and/or treatments that may affect cardiovascular function, pulmonary conditions, hepatic conditions, and immune function. Patients also needed to be between the age of 18 and 60 years at screening and have an EDSS score of between 3.0 and 6.5 (inclusive). Overall, these criteria may have resulted in an overall younger and healthier population of patients with SPMS compared to what may be seen in clinical practice, based on input from the clinical experts on this review. Nonetheless, this could limit the generalizability of the treatment effect observed in the trial to real world clinical practice.

The study did include 31 (of 294) centres in Canada, and therefore included Canadian patients with SPMS. The majority of patients (78% overall) included in the study had experience with a DMT for MS. [redacted] In the context of Canadian clinical practice, most (approximately 80%) patients with SPMS in Canada will likely have tried IFNs or other DMTs at some point during their disease course, according to the clinical experts consulted for this review. There was a high proportion of patients who used concomitant medication in the study, [redacted] This was determined to be typical of patients with SPMS according to the clinical experts consulted by CADTH for this review. As previously

mentioned, the specific data regarding prior and concomitant medication use was not reported for the subgroup of patients with active SPMS, which rendered it uncertain if a similar pattern exists as observed in the overall study population.

Intervention and Comparators

The dosing regimen used in the EXPAND trial followed the general dosing recommendation included in the draft product monograph for siponimod. The treatment regimen is based on a phase II trial in patients with RRMS. The draft product monograph also includes a recommendation for a dosing adjustment to 1 mg siponimod once daily for patients with a CYP2C9*2*3 or CYP2C9*1*3 genotype. These patients were not excluded in the EXPAND trial, but the genotype did not affect the dose of siponimod received in the study. Based on the data that were available for the EXPAND trial, the treatment effect and harms associated with siponimod by genotype is unclear.

The choice of placebo as the sole comparator used in the pivotal trial for siponimod is a limitation of the evaluation of siponimod in the context of Canadian clinical practice. Interferon beta-1a and interferon beta-1b are indicated for patients with SPMS, but according to the clinical experts consulted by CADTH, are rarely used in this patient population. In the absence of treatment for SPMS, patients might be continued on treatment for RRMS when they progress to SPMS even if this only treats symptoms rather than the disease. This is particularly relevant since siponimod is indicated for patients with active SPMS evidenced by relapses or imaging who are likely to be treated with any DMT for RRMS. This was indicated by the clinical experts consulted for this review.

Outcomes

The primary efficacy outcome was based on the MID for the EDSS, which is a well-accepted measure of disability for patients with MS and is useful for facilitating comparisons with other studies. However, the applicability of the MID to patients with SPMS, specifically, is uncertain. One limitation associated with the EDSS is that it is a measure largely driven by mobility, particularly regarding the lower body, which may not be reflective of the true disability of patients with SPMS and, therefore, may not represent the actual benefit of the treatment in the target population (i.e., it may be overestimated or underestimated). According to the clinical experts consulted by CADTH for this review, the need for an alternative, validated, and sensitive scale is recognized but does not yet exist; therefore, use of the EDSS for MS trials is still recommended. Further, it is still used to assess patients with SPMS in clinical practice, although it is often supplemented by other measures such as the T25-FW as well, as noted by the clinical experts consulted for this review.

Patients were assessed every three months after the first month of treatment for up to 36 months. This assessment schedule was appropriate for assessing the efficacy of the study drug, but may have been more frequent than what is typical of clinical practice in Canada. [redacted] The clinical experts on this review indicated that the duration of exposure was sufficient to observe whether the treatment had an effect; however, it is likely that patients would be taking this treatment long term and therefore the results as observed at month 12 may be limited in their applicability to chronic use of siponimod in clinical practice. An open-label extension is currently ongoing, which will provide evidence of long-term efficacy and safety of siponimod; however, results of this study were not available at the time of this review. Moreover, it is an open-label extension of the overall population and is not limited to patients with active SPMS.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

As there was no direct evidence comparing siponimod to other therapies for SPMS, a review of indirect evidence was undertaken. CADTH conducted a literature search to identify potentially relevant ITCs in patients with SPMS, in addition to reviewing the sponsor's CADTH Common Drug Review submission. The Ovid MEDLINE database was searched using a combination of MeSH (Medical Subject Headings) and keywords. The main search concept was SPMS. A network meta-analysis (NMA) filter was applied to limit study type to NMAs. Retrieval was not limited by publication date or by language. Titles, abstracts, and full-text articles were screened for inclusion by one reviewer based on the population, intervention, comparator and outcome criteria outlined in Table 6.

No potentially relevant ITCs were identified in the literature search. One sponsor-submitted ITC was included in this review.[15] This ITC was used to inform the pharmacoeconomic model.

Description of Indirect Comparison(s)

The sponsor-submitted ITC included a review of the literature and an MAIC that compared siponimod to interferon beta-1a and interferon beta-1b, and natalizumab, in patients with SPMS.

This MAIC was accepted for publication in 2020.[52]

Methods of Sponsor-Submitted Indirect Treatment Comparison

Objectives

The objective of the sponsor-submitted report was to conduct a feasibility assessment and, if possible, an ITC, to evaluate the relative efficacy, safety, and tolerability of siponimod versus other DMTs for the treatment of adults with SPMS.[15]

Study Selection Methods

The RCTs that were used to inform the ITC were identified through a systematic literature search conducted by the sponsor, as well as through a supplemental grey literature search conducted by the ITC authors. The systematic literature search used broad population inclusion criteria and searched multiple databases to identify RCTs that evaluated the safety and efficacy of DMTs for MS (Table 23). The supplemental literature search was limited to trials in patients with SPMS and included additional interventions that were not part of the primary literature search. The supplemental search was limited to a search of ClinicalTrials.gov and a review of the bibliography of a recent Cochrane review in patients with SPMS. One researcher screened and extracted studies identified in the supplemental search, with extraction verified by a second reviewer. The methods for screening and data extraction used in the literature search conducted by the sponsor were not reported. The report did not state if the trials were evaluated for study quality.

Table 23: Study Selection Criteria and Methods for Literature Review

	Sponsor-conducted search	SPMS supplemental search
Population	Adults ≥ 18 years who were treated with disease-modifying therapies for relapsing MS, relapsing-remitting MS, PPMS, and SPMS	Patients with SPMS
Intervention	• Dimethyl fumarate • Fingolimod • Teriflunomide • Natalizumab • Ocrelizumab • Interferon beta-1a • Interferon beta-1b • Peginterferon beta-1a	All drugs in sponsor-conducted search plus: • Alemtuzumab • Glatiramer acetate • Cladribine • Rituximab • Mitoxantrone • Stem cell transplant
Comparator	Any disease-modifying therapy or placebo	Any disease-modifying therapy or placebo
Outcome	EDSS, time to 3-month or 6-month CDP, ARR, MRI outcomes (T2 lesion number, volume) Infections, bradyarrhythmia, vascular events, new onset ALT elevation, convulsion, malignancies, macular edema	EDSS, time to 3-month or 6-month CDP, ARR, MRI outcomes (T2 lesion number, volume) Infections, bradyarrhythmia, vascular events, new onset ALT elevation, convulsion, malignancies, macular edema
Study design	RCTs (parallel or crossover groups, active- or placebo-controlled)	RCTs (parallel or crossover groups, active- or placebo-controlled)
Exclusion criteria	Abstracts	Abstracts
Databases searched	PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched from 1995 to August 31, 2017	Targeted grey literature search of ClinicalTrials.gov up to August 13, 2018 Reference list of Cochrane review in SPMS reviewed
Selection process	Not reported	Screened by 1 reviewer
Data extraction process	Not reported	Data extracted by 1 reviewer and validated by a second reviewer. A third reviewer was consulted to resolve any discrepancies
Quality assessment	Not reported	Not reported

ALT = alanine aminotransferase; ARR = annualized relapse rate; CDP = confirmed disability progression; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; PPMS = primary-progressive multiple sclerosis; RCT = randomized controlled trial; SPMS = secondary-progressive multiple sclerosis.

Source: CADTH Common Drug Review submission for Mayzent.[15]

Feasibility Assessment Methods

The ITC authors carried out a feasibility assessment to determine if it was possible to conduct an ITC using summary level data or an MAIC. Studies that enrolled patients with SPMS or a mixed population that included patients with SPMS were identified from the literature search. For trials that did not specifically enroll patients with SPMS (e.g., those that enrolled populations described as relapsing MS or progressive MS), medical experts were consulted to determine if the patients enrolled could be defined as having SPMS and were appropriate for inclusion in the ITC. Studies were eligible for inclusion if published

data were available for baseline characteristics and outcome data for the SPMS population or subpopulation.

Based on a recent Institute for Clinical and Economic Review report[53] of siponimod in patients with SPMS, four treatments were considered relevant by the authors of the ITC for comparison with siponimod: interferon beta-1a (Rebif and Avonex), interferon beta-1b (Betaseron), ocrelizumab (Ocrevus), and natalizumab (Tysabri). Outcomes of interest were based on the primary and secondary outcomes from the EXPAND study: time to CDP of three months (CDP-3), time to CDP of six months (CDP-6), and ARR. All-cause discontinuation was explored as an outcome for the Bucher method ITC. The authors stated that safety outcomes were not considered for MAIC analyses because treatment effect modifiers related to AEs or discontinuation are not well reported and thus could not be matched or adjusted for.

A qualitative assessment of study heterogeneity was conducted based on the study design, inclusion and exclusion criteria, patient characteristics, and outcomes, comparing the EXPAND trial to those of other drugs. All characteristics were assessed to determine if they could be matched or adjusted for using individual patient data from EXPAND. The ARR and discontinuation rate in the placebo group of each trial was also compared.

Based on the feasibility assessment, the authors concluded that ITCs based on summary level data were likely to provide misleading results due to the presence of substantial clinical heterogeneity between trials. The interferon trials, which were published between 1998 and 2004, included patients who were interferon-naive whereas in the EXPAND study, most of the included patients had received DMTs including interferon. There were also differences between trials in the age of patients enrolled, disease duration, EDSS score, and relapse frequency. The authors of the ITC concluded it was possible to conduct an MAIC for siponimod versus interferon beta-1a and interferon beta-1b, and natalizumab, with the aggregate data available from the comparator trials and individual patient data for the EXPAND study. The sources of heterogeneity will be discussed further in the following sections.

ITC Analysis Methods

Pairwise, MAIC was conducted comparing siponimod to interferon beta-1a (Rebif, Avonex), interferon beta-1b (Betaseron), and natalizumab to siponimod. In the first step, individual patient data from EXPAND was used to exclude patients who would not have met the inclusion criteria for each comparator trial. Factors used for matching are listed in Table 24. Matching was not possible for all factors as, in some cases, individual patient data for a factor were not available, or the comparator trial enrolled a broader population than EXPAND. In the second step, patients from the matched EXPAND population were adjusted by a number of factors to balance the baseline characteristics of the EXPAND and comparator study population. EXPAND patient data were weighted by the inverse odds of being in the EXPAND trial compared to the comparator trial. A propensity score model using the generalized method of moments based on the aggregate data and the individual patient data were used. The adjustment factors were identified by European and Canadian neurologists. These factors were considered important treatment effect modifiers and were different for CDP and ARR outcomes (Table 24). Ranked lists of potential effect modifiers were generated separately by each physician and then compared for consistency. Discrepancies were discussed until consensus was reached. In the primary analysis (scenario A), all variables were adjusted for and given equal weight. In subsequent scenarios, the variable of lowest importance was dropped one by one from each analysis.

The effective sample size was calculated for each scenario. It was not possible to adjust for all factors due to data availability issues from the trials. This will be discussed in the following sections.

The effective sample size was calculated as the square of the summed weights divided by the sum of the squared weights. The mean baseline characteristics were presented for the matched and adjusted populations. A Bucher pairwise ITC and an NMA were also conducted for comparison.

Table 24: Matching and Ranked Adjustment Factors

Matching factors (all outcomes)	Ranked adjustment factors for CDP	Ranked adjustment factors for ARR
• Baseline EDSS range • Age range • Prior therapy (e.g., IFN) • No recent relapses • Recently documented progression • Duration of MS • Duration of SPMS • MS severity score • T25-FW test score	1. Age 2. EDSS score at screening 3. Duration of MS 4. Treatment experience (IFN- or DMT-experienced) 5. Normalized brain volume 6. Gadolinium-enhancing lesions on T1-weighted images 7. Duration of SPMS 8. Total volume of T2 lesions on T2-weighted images 9. Number of relapses per patient in 2 years prior to study (or if not reported, another relapse history variable) 10. Sex	1. Years since most recent relapse 2. Number of relapses per patient in year prior to study 3. Number of relapses per patient in 2 years prior to study 4. Gadolinium-enhancing lesions on T1-weighted images 5. Total volume of lesions on T2-weighted images

ARR = annualized relapse rate; CDP = confirmed disability progression; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IFN = interferon; MS = multiple sclerosis; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test.

Source: CADTH Common Drug Review submission for Mayzent.[15]

Results of Sponsor-Submitted ITC

Summary of Included Studies

A total of [redacted] RCTs were identified from the literature review and these studies included patients with any form of MS. All trials, plus the EXPAND trial for siponimod, were evaluated in the feasibility assessment to determine if it was possible to conduct an ITC in patients with SPMS. Of these trials, seven RCTs comparing siponimod, interferon beta-1a or interferon beta-1b, and natalizumab to placebo met the inclusion criteria for the ITC (see Table 25). No studies for ocrelizumab in patients with SPMS were identified in the literature search.

Table 25: Summary of Trials Included in the MAIC

Study	Study design	N	Population	Interventions	Control
EXPAND[42]	DB RCT	1,651	SPMS	Siponimod 2 mg daily orally	Placebo oral
Nordic SPMS study[54]	DB RCT	371	SPMS	Interferon beta-1a 22 mcg SC weekly	Placebo SC
SPECTRIMS[55,56]	DB RCT	618	SPMS	Interferon beta-1a 22 mcg SC 3 times weekly	Placebo SC

Study	Study design	N	Population	Interventions	Control
				Interferon beta-1a 44 mcg SC 3 times weekly	
IMPACT[57]	DB RCT	436	SPMS	Interferon beta-1a 60 mcg IM weekly	Placebo IM
North American study[58]	DB RCT	939	SPMS	Interferon beta-1b 160 mcg/m^2 SC every 2 days Interferon beta-1b 250 mcg SC every 2 days	Placebo SC
European study[59,60]	DB RCT	718	SPMS	Interferon beta-1b 8 MIU (250 mcg) SC every 2 days	Placebo SC
ASCEND[61]	DB RCT	889	SPMS	Natalizumab 300 mg IV every 4 weeks	Placebo IV

DB = double-blind; IM = intramuscular; MAIC = matching-adjusted indirect comparison; MIU = million International Units; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; RCT = randomized controlled trial.

Source: CADTH Common Drug Review submission for Mayzent.[15]

All trials used similar study designs and were randomized, parallel-group, double-blind, placebo-controlled RCTs. The patients enrolled had SPMS with a maximum EDSS score of 6.5 points at baseline (Table 26). All the interferon trials restricted enrolment to patients with no prior treatment with interferon, whereas in the EXPAND trial, only 22% had received no prior DMTs. The ASCEND trial (natalizumab) enrolled patients who had received interferon therapy as long as therapy had been stopped at least four weeks prior. Other differences included the age range of patients enrolled, the time prior to enrolment with no relapses, and documentation of disease progression. Two comparator trials were two years in duration and all others were three years; however, three interferon trials were terminated early (mean duration of follow-up ranged from 31.1 months to 35.1 months). All trials used the same definition for ARR and discontinuation (defined as the proportion of randomized patients who discontinued treatment for any reason). The criteria for CDP was the same for the EXPAND trial compared with the SPECTRIMS and Nordic studies, but varied compared with the North American, European, IMPACT, and ASCEND studies. In these studies, patients with a baseline EDSS score of 5.5 required a 1.0-point increase to be categorized as having progressed; however, in the EXPAND study, these patients only required a 0.5-point increase. Based on input from experts, the ITC authors considered the CDP outcome definitions for change in EDSS score sufficiently similar to conduct the MAIC. In the ASCEND trial, disability progression was a composite based on change in EDSS score, T25-FW test, or the 9-HPT. Using the individual patient data from EXPAND, it was not possible to generate comparable outcome data for the T25-FW test or the 9-HPT; however, the proportion of patients with CDP-6 by week 96 as defined by EDSS score could be calculated for the EXPAND study and compared to the EDSS component of CDP-6 outcome data that were reported in the ASCEND study.

The North American study evaluated two doses of interferon beta-1b; however, only the 250 mcg dose was analyzed in the MAIC as the authors state this was the only clinically relevant dosage regimen. The clinical experts consulted by CADTH confirmed that the doses of interferon and natalizumab were consistent with approved dosage regimens in Canada.

Table 26: Comparison of Study Characteristics Between MAIC Trials

	EXPAND	Nordic study	SPECTRIMS	IMPACT	North American study	European study	ASCEND
	Siponimod	IFN beta-1a	IFN beta-1a	IFN beta-1a	IFN beta-1b	IFN beta-1b	Natalizumab
Intervention dosage	2 mg daily	22 mcg SC weekly	22 mcg and 44 mcg SC 3 times weekly	60 mcg IM once weekly	250 mcg SC every 2 days	250 mcg SC every 2 days	300 mg IV every 4 weeks
Inclusion criteria							
MS population	SPMS	SPMS	SPMS	SPMS	SPMS	SPMS	SPMS
Baseline EDSS range	3.0 to 6.5	≤ 6.5	3.0 to 6.5	**3.5 to 6.5**	3.0 to 6.5	3.0 to 6.5	3.0 to 6.5
Age range	18 to 60	18 to 65	**18 to 55**	18 to 60	18 to 65	**18 to 55**	**18 to 58**
Prior IFN therapy	Allowed	**No prior IFN use**	**No prior IFN use**	**No prior IFN use**	**No prior IFN use**	**No prior IFN use**	No prior IFN use 4 weeks prior to study[a]
No relapses in certain number of months prior	3 months	2 months	2 months	NR	2 months	1 month	3 months
Recently documented progression	For ≥ 6 months in past 24 months	For ≥ 6 months in past 4 years	For ≥ 6 months in past 2 years	In the past 1 year	For ≥ 6 months in past 2 years	Progression in past 2 years or ≥ 2 relapses in past 2 years	In the past 1 year
History of RRMS	Required	Required	Required	NR	Required	Required	NR
Duration of MS	No restriction	**≥ 1 year**	NR	NR	**≥ 2 years**	**≥ 2 years**	NR
Duration of SPMS	No restriction	NR	NR	NR	NR	NR	**≥ 2 years**
MS severity score	No restriction	NR	NR	NR	NR	NR	**Score of 4 or higher**
T25-FW test	No restriction	NR	NR	NR	NR	NR	**< 30 seconds**
Outcome definitions							
Definition of ARR	Number of total relapses per PY	Number of total relapses per PY	Number of total relapses per PY	Number of total relapses per PY	Number of total relapses per PY	Number of total relapses per PY	Number of total relapses per PY
Definition of time to CDP-3	1-point increase in EDSS score: 3.0 to 5.0	NR	1-point increase in EDSS score: 3.0 to 5.0	*1-point increase in EDSS score: 3.0 to 5.5*	NR	*1-point increase in EDSS score: 3.0 to 5.5*	NR

	EXPAND	Nordic study	SPECTRIMS	IMPACT	North American study	European study	ASCEND
	Siponimod	IFN beta-1a	IFN beta-1a	IFN beta-1a	IFN beta-1b	IFN beta-1b	Natalizumab
	0.5-point increase in EDSS score: 5.5 to 6.5		0.5-point increase in EDSS score: 5.5 to 6.5	*0.5-point increase in EDSS score: 6.0 to 6.5*		*0.5-point increase in EDSS score: 6.0 to 6.5*	
Definition of time to CDP-6	1-point increase in EDSS score: 3.0 to 5.0 0.5-point increase in EDSS score: 5.5 to 6.5	1-point increase in EDSS score: 3.0 to 5.0 0.5-point increase in EDSS score: 5.5 to 6.5	NR	NR	*1-point increase in EDSS score: 3.0 to 5.5* *0.5-point increase in EDSS score: 6.0 to 6.5*	NR	*1-point increase in EDSS score: 3.0 to 5.5* *0.5-point increase in EDSS score: 6.0 to 6.5* *Increase of ≥ 20% in T25-FW* *Increase of ≥ 20% in 9-HPT*
Duration and placebo response							
Study duration	3 years	**3 years**[b]	3 years	**2 years**	**3 years**[c]	**3 years**[d]	**96 weeks**
Placebo response: ARR	0.16	0.27	0.71	0.30	0.28	0.57	0.17
Placebo response: Annualized discontinuation rate	0.084	0.60	0.057	0.142	0.093	0.132	0.186

9-HPT = 9-hole peg test; ARR = annualized relapse rate; CDP-3 = confirmed disability progression at three months; CDP-6 = confirmed disability progression at six months; EDSS = Expanded Disability Status Scale; IFN = interferon; IM = intramuscular; MAIC = matching-adjusted indirect comparison; MS = multiple sclerosis; NR = not reported; PY = per year; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test.

Note: Shaded cells indicate that differences exist between trials and either matching is not possible (i.e., EXPAND patient population is narrower) or the individual patient data required to match patients may not be available. Bold text indicates that differences exist between trials and the EXPAND population is broader; thus, matching may be possible. Italicized text highlights differences in outcome definitions between EXPAND and comparator trials.

[a] The EXPAND study allowed IFN treatment with no restriction, but in ASCEND, prior IFN therapy was allowed as long as it was stopped more than four weeks prior. Although the trials could not be matched on the four-week IFN restriction, this difference was considered of minor importance by the MAIC authors. ASCEND also excluded patients who had received natalizumab in the past.

[b] The Nordic study was stopped early due to non-significant results reported for the SPECTRIMS study (which tested a higher dose of IFN beta-1a). Mean treatment duration was 32 months and 31.1 months in the placebo and IFN groups, respectively.

[c] The North American study was stopped early with a mean duration of follow-up ranging from 32.8 months to 33.3 months.

[d] The European study was terminated at 33 months with a mean duration of follow-up ranging from 34.7 months to 35.1 months.

Source: CADTH Common Drug Review submission for Mayzent.[15]

Active SPMS Subgroup

The indication for siponimod has changed since the MAIC was conducted and submitted to CADTH. The revised indication is limited to those patients with active SPMS evidenced by relapses or imaging features characteristic of MS inflammatory activity. All trials enrolled a mixed population that included patients with and without active SPMS and there were no data reported for the subpopulation of patients with active SPMS. Post-hoc subgroup analyses suggest that fewer than half the patients in EXPAND would meet the criteria for active SPMS.

Table 27 summarizes baseline data on the proportion of patients with relapses or inflammatory lesions, which may be used to identify patients with active SPMS. The proportion of patients with relapses in the past two years ranged from 29% (ASCEND) to 70% (European study), or with relapses in the past year was 16% (ASCEND) and 39% (IMPACT); no information was available for the Nordic study. Data on the proportion of patients with Gd-enhancing lesions on T1-weighted images were 24% (ASCEND), 36% (IMPACT), and 21% (EXPAND). Except for the European study, it appears that a minority of patients enrolled in the comparator trials may have active SPMS.

Table 27: Comparison of Patient Characteristics Indicative of Active SPMS

	EXPAND	Nordic study	SPECTRIMS	IMPACT	North American study	European study	ASCEND
	Siponimod	IFN beta-1a	IFN beta-1a	IFN beta-1a	IFN beta-1b	IFN beta-1b	Natalizumab
Intervention dosage	2 mg daily	22 mcg SC weekly	22 mcg and 44 mcg SC 3 times weekly	60 mcg IM once weekly	250 mcg SC every 2 days	250 mcg SC every 2 days	300 mg IV every 4 weeks
Baseline characteristics that may identify patients with active SPMS[a]							
Proportion of patients with relapses in past year, n (%)	22	NR	NR	39	NR	NR	16
Proportion of patients with relapses in past 2 years, n (%)	36	NR	47	NR	45	70	29
Mean number of relapses per patient in past year	0.2	NR	NR	0.6	NR	NR	NR
Mean number of relapses per patient in past 2 years	0.7	NR	0.9	NR	0.8	NR	NR
Proportion of patients with Gd-enhancing lesions of T1-weighted images, n (%)	21	NR	NR	36	NR	NR	24

Gd = gadolinium; IFN = interferon; IM = intramuscular; NR = not reported; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis.

[a] Summary of baseline data related to relapse frequency or proportion of patients with recent history of relapses or inflammatory lesions detected through imaging. All trials enrolled a mixed population that included patients with and without active SPMS. No data were reported for the subpopulation of patients with active SPMS.

Source: CADTH Common Drug Review submission for Mayzent.[15]

Siponimod Versus Interferon Beta-1a (Rebif)

Two trials evaluated interferon beta-1a in patients with SPMS. These included the Nordic study that compared interferon beta-1a 22 mcg subcutaneous (SC) weekly to placebo, and the SPECTRIMS study that evaluated interferon beta-1a 22 mcg SC three times weekly, and 44 mcg SC three times weekly, to placebo.

Time to Confirmed Disability Progression

Interferon Beta-1a 22 mcg or 44 mcg SC Three Times Weekly

The population from the EXPAND study were matched to those in the SPECTRIMS study by excluding patients over 55 years of age, with an EDSS score of less than 3 or greater than 6.5, and those with prior interferon beta therapy. No matching was possible for the number of relapses prior to enrolment as the SPECTRIMs criteria were broader than EXPAND. No matching was possible for the duration of MS or SPMS, MS severity score, or timed walk test as there were no criteria related to these factors in the SPECTRIMS study. Based on matching, the sample size for EXPAND was reduced from 1,638 to 455 for CDP outcome. After adjustment for age, EDSS score, MS duration since diagnosis, duration of SPMS, number of relapses in the past two years, and sex, the effective sample size was reduced to 237 patients (14.5% of total EXPAND population or 52% of the matched population). Adjustment was not possible for normalized brain volume, Gd-enhancing lesions on T1-weighted images, or total volume of T2 lesions on T2-weighted images. Table 28 shows the patient characteristics before and after matching and adjustment. The matched and adjusted population for EXPAND had mean age, EDSS score, MS duration, and proportion of females that were similar to the SPECTRIMS study. No data were presented on other patient characteristics.

Table 29 provides a summary of the trial results on disability progression from the published studies, as well as the MAIC. For the matched and adjusted analysis (scenario A), the HR and 95% CI for the time to CDP-3 was 0.8 (95% CI, 0.46 to 1.38) for siponimod versus interferon beta-1a 22 mcg three times weekly and 0.84 (95% CI, 0.49 to 1.47) for interferon beta-1a 44 mcg three times weekly.

Table 28: Results of Population Matching and Adjustment for CDP — Siponimod vs. Interferon Beta-1 22 mcg or 44 mcg Three Times Weekly

Variables	SPECTRIMS	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F
N (Neff)	618	1638	455	237	239	253	268	325	350
Age (mean years [SD])	42.8 (7.1)	48.03 (7.84)	46.43 (6.81)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)
EDSS score at screening (mean [SD])	5.4 (1.1)	5.42 (1.06)	5.19 (1.11)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	-
MS duration since diagnosis (mean years [SD])	13.3 (7.1)	12.62 (7.77)	11.06 (7.91)	13.3 (7.11)	13.3 (7.11)	13.3 (7.11)	13.3 (7.11)	-	-
Duration of SPMS (mean years [SD])	4 (3)	3.77 (3.51)	3.42 (3.19)	4 (3)	4 (3)	4 (3)	-	-	-
Number of relapses in prior 2 years (mean [SD])	0.9 (1.3)	0.67 (1.19)	0.71 (1.08)	0.9 (1.3)	0.9 (1.3)	-	-	-	-
Sex (proportion female)	63.0%	60.01%	60.22%	63.0%	-	-	-	-	-

CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; IFN = interferon; MS = multiple sclerosis; Neff = effective sample size; SD = standard deviation; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

Note: Matched sample excludes patients over 55 years of age, with an EDSS score of less than 3 or greater than 6.5, and those with prior IFN beta therapy. Scenario A adjusts for all available ranked characteristics. Subsequent scenarios drop the lowest ranked factor.

Source: Reproduced from sponsor-submitted indirect treatment comparison.[15]

Table 29: Indirect Comparison Results for the Time to Confirmed Disability Progression

Comparator	Comparator study	Published results[a] HR or OR (95% CI)				MAIC results[b] HR or OR (95% CI)		
		N	Comparator vs. placebo	N	Siponimod vs. placebo	Neff	Siponimod vs. comparator	Siponimod vs. placebo
Time to CDP-6								
IFN beta-1b 250 mcg SC every 2 days	North American study	[redacted]	HR 0.92 (0.71 to 1.20)[c]	[redacted]	**HR 0.74 (0.60 to 0.92)**	[redacted]	**HR 0.55 (0.33 to 0.91)**	**HR 0.50 (0.32 to 0.78)**
IFN beta-1a 22 mcg SC weekly	Nordic study	[redacted]	HR 1.13 (0.82 to 1.57)			[redacted]	**HR 0.43 (0.20 to 0.93)**	**HR 0.48 (0.24 to 0.98)**
Natalizumab 300 mg IV every 4 weeks	ASCEND	[redacted]	OR 1.06 (0.74 to 1.53)	[redacted]	**OR 0.77 (0.61 to 0.97)**	[redacted]	OR 0.76 (0.44 to 1.30)	OR 0.80 (0.53 to 1.21)
Time to CDP-3								
IFN beta-1a 22 mcg SC 3 times weekly	SPECTRIMS	[redacted]	HR 0.88 (0.69 to 1.12)[c]	[redacted]	**HR 0.79 (0.65 to 0.95)**	[redacted]	HR 0.80 (0.46 to 1.38)	HR 0.70 (0.43 to 1.15)
IFN beta-1a 44 mcg SC 3 times weekly	SPECTRIMS	[redacted]	HR 0.83 (0.65 to 1.07)			[redacted]	HR 0.84 (0.49 to 1.47)	HR 0.70 (0.43 to 1.15)
IFN beta-1a 60 mcg IM weekly	IMPACT	[redacted]	HR 0.977 (0.68 to 1.41)			[redacted]	**HR 0.42 (0.20 to 0.88)**	**HR 0.41 (0.21 to 0.78)**
IFN beta-1b 250 mcg SC every 2 days	European study	[redacted]	**HR 0.74 (0.60 to 0.91)[c]**			[redacted]	HR 0.82 (0.42 to 1.63)	HR 0.61 (0.32 to 1.16)

CDP-3 = confirmed disability progression at three months; CDP-6 = confirmed disability progression at six months; CI = confidence interval; HR = hazard ratio; IFN = interferon; IM = intramuscular; MAIC = matching-adjusted indirect comparison; Neff = effective sample size; OR = odds ratio; SC = subcutaneous; vs. = versus.

Note: Results in bold had a 95% CI that excluded the null.

[a] Outcomes reported as time to CDP-6 for the comparisons with IFN trials and as the OR of CDP-6 at 96 weeks for the comparison with natalizumab.

[b] The target population is the comparator trial.

[c] The HR or CI were not reported in the publication. Missing values were estimated using either the HR and P value, the reported Kaplan–Meier curve through curve-fitting, as appropriate.

Source: Adapted from the sponsor-submitted indirect treatment comparison.[15]

Interferon Beta-1a 22 mcg SC Once Weekly

The patients from the EXPAND study were matched to those in the Nordic study by excluding any with a baseline EDSS score of more than 6.5 points, those who had received prior interferon therapy, or whose duration of MS was of less than one year. It was not possible to match on age, recent relapse-free time frame, or progression, as the criteria in the Nordic study were broader than in EXPAND. It was also not possible to match on the duration of SPMS, MS severity score, or T25-FW test score, as these were not specified in the inclusion criteria for the Nordic study. Matching reduced the sample size of EXPAND to 578.

Data were then adjusted based on age, EDSS score, duration of MS and SPMS, and sex. No adjustment was possible for normalized brain volume, Gd-enhancing lesions on T1-

weighted images, total volume of T2 lesions on T2-weighted images, and number of relapses in the two years prior. [redacted] (Table 30).

In the matched and adjusted base-case analysis, the HR for time to CDP-6 for siponimod versus interferon beta-1a 22 mcg once weekly was 0.43 (95% CI, 0.20 to 0.93) (Table 29).

Table 30: Results of Population Matching and Adjustment for CDP — Siponimod vs. Interferon Beta-1a 22 mcg SC Once Weekly

Variables	Nordic Study [a]	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E
N (Neff)	364	1642	578	157	159	298	399	450
Age (mean years [SD])	45.7 (7.1)	48.02 (7.86)	49.29 (7.75)	45.7 (7.11)	45.7 (7.11)	45.7 (7.11)	45.7 (7.11)	45.7 (7.11)
EDSS score at screening (mean [SD])	4.8 (1.1)	5.42 (1.06)	5.26 (1.11)	4.8 (1.1)	4.8 (1.1)	4.8 (1.1)	4.8 (1.1)	-
MS duration since diagnosis (mean years [SD])	14.3 (7.1)	12.61 (7.76)	12.23 (8.44)	14.3 (7.11)	14.3 (7.11)	14.3 (7.11)	-	-
Duration of SPMS (mean years [SD])	5.4 (3)	3.76 (3.51)	3.69 (3.48)	5.4 (3.01)	5.4 (3.01)	-	-	-
Sex (proportion female)	60.0%	59.99%	60.38%	60.0%	-	-	-	-

CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; IFN = interferon; MS = multiple sclerosis; Neff = effective sample size; SC = subcutaneous; SD = standard deviation; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

Note: Matched sample excludes patients with EDSS greater than 6.5, MS duration of less than one year, and those with prior IFN beta therapy. The Nordic study did not report standard deviations for adjusting factors. Results use imputed values from SPECTRIMS. Scenario A adjusts for all available ranked characteristics. Subsequent scenarios drop the lowest ranked factor.

Source: Reproduced from the sponsor-submitted indirect treatment comparison.[15]

Annualized Relapse Rate

Of the five factors selected for adjustment of ARR data, adjustment was only possible for the number of relapses per patient in the two years prior for the analysis comparing to the SPECTRIMS study. After matching and adjustment, the EXPAND effective sample size was reduced to 436 patients (26.7% of total N or 95% [436/457] of the matched population) (Table 31). After matching and adjustment for prior relapses, the rate ratio for the ARR was 0.73 (95% CI, 0.40 to 1.31) and 0.73 (95% CI, 0.40 to 1.32) for siponimod versus interferon beta-1a dosages of 22 mcg three times weekly and 44 mcg three times weekly, respectively (Table 32).

Only matching was possible for the ARR analysis that included the Nordic study. The sample size of the EXPAND study was 579 patients after matching, which was 35.3% of the 1,645 patients included in the trial. The rate ratio for the ARR was 0.59 (95% CI, 0.32 to 1.07) for siponimod versus interferon beta-1a 22 mcg SC once weekly in the matched analysis (Table 32).

Table 31: Results of Population Matching and Adjustment for ARR — Siponimod vs. Interferon Beta-1a 22 mcg or 44 mcg Three Times Weekly

Variables	SPECTRIMS	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A
N (Neff)	616	1641	457	436
Mean number of relapses in prior 2 years (SD)	0.9 (1.3)	0.67 (1.19)	0.71 (1.07)	0.9 (1.3)

ARR = annualized relapse rate; Neff = effective sample size; SD = standard deviation; vs. = versus.

Note: Matched sample excludes patients over 55 years of age, with an EDSS score of less than 3 or greater than 6.5, and those with prior interferon beta therapy. Scenario A adjusts for number of relapses in prior two years.

Source: Reproduced from the sponsor-submitted indirect treatment comparison.[15]

Table 32: Indirect Comparison Results for the Annualized Relapse Rate

Comparator	Comparator study	Published results[a] Rate ratio (95% CI)				MAIC results[b] Rate ratio (95% CI)		
		N	Comparator vs. placebo	N	Siponimod vs. placebo	Neff	Siponimod vs. comparator	Siponimod vs. placebo
Annualized relapse rate								
IFN beta-1b 250 mcg SC every 2 days	North American and European study (pooled)	[redacted]	0.65 (0.48 to 0.88)	[redacted]	**0.45 (0.34 to 0.59)**	[redacted]	0.90 (0.51 to 1.59) [c]	**0.59 (0.36 to 0.95)[c]**
IFN beta-1a 22 mcg SC weekly	Nordic study	[redacted]	0.90 (0.64 to 1.27)			[redacted]	0.59 (0.32 to 1.07) [c]	**0.53 (0.33 to 0.87)[c]**
IFN beta-1a 22 mcg SC 3 times weekly	SPECTRIMS	[redacted]	**0.69 (0.56 to 0.84)**			[redacted]	0.73 (0.40 to 1.31)	**0.50 (0.29 to 0.87)**
IFN beta-1a 44 mcg SC 3 times weekly	SPECTRIMS	[redacted]	**0.69 (0.56 to 0.85)**			[redacted]	0.73 (0.40 to 1.32)	**0.50 (0.29 to 0.87)**
IFN beta-1a 60 mcg IM weekly	IMPACT	[redacted]	**0.67 (0.49 to 0.90)**			[redacted]	0.997 (0.46 to 2.18)	0.67 (0.33 to 1.37)
Natalizumab 300 mg IV every 4 weeks	ASCEND	[redacted]	**0.45 (0.32 to 0.63)**			[redacted]	1.43 (0.78 to 2.61)	0.65 (0.39 to 1.06)

CI = confidence interval; IFN = interferon; IM = intramuscular; MAIC = matching-adjusted indirect comparison; Neff = effective sample size; SC = subcutaneous; vs. = versus.

Note: Results in bold had 95% CI that excluded the null.

[a] From comparator trials (IFN or natalizumab) or EXPAND study (siponimod).

[b] The target population is the comparator trial.

[c] Matched only; no adjustment was possible.

Source: Adapted from the sponsor-submitted indirect treatment comparison.[15]

Siponimod Versus Interferon Beta-1a (Avonex)

Patients from the EXPAND trial were matched to patients in the IMPACT study by removing those with baseline EDSS scores of less than 3 points and greater than 6.5 points, and those with prior interferon treatment experience. Matching was not possible on the documented progression criteria as the necessary data were not available in EXPAND. Patients could not be matched for duration of MS or SPMS, MS severity score, T25-FW test score, or recent relapse-free time frame as the IMPACT study had no criteria for these parameters.

Time to Confirmed Disability Progression

EXPAND patient data were adjusted for age, EDSS score, duration of MS, Gd-enhancing lesions on T1-weighted images, number of relapses in two years prior, and sex. Weighting was not possible for normalized brain volume, duration of SPMS, and total volume of T2 lesions on T2-weighted images. The effective sample size was 113 patients, which was 20% of the matched population from EXPAND.

The HR for the time to CDP-3 for siponimod versus interferon beta-1a 60 mcg intramuscular weekly was 0.42 (95% CI, 0.20 to 0.88) in the matched and adjusted analysis (see Table 29).

Table 33: Results of Population Matching and Adjustment for CDP — Siponimod vs. Interferon Beta-1a 60 mcg IM weekly

Variables	IMPACT	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F
N (Neff)	436	1590	563	113	113	322	354	520	534
Age (mean years [SD])	47.55 (7.95)	48.05 (7.87)	49.31 (7.81)	47.55 (7.97)	47.55 (7.97)	47.55 (7.96)	47.55 (7.96)	47.55 (7.96)	47.55 (7.96)
EDSS score at screening (mean [SD])	5.2 (1.1)	5.41 (1.07)	5.33 (1.03)	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	-
MS duration since diagnosis (mean years [SD])	16.45 (9)	12.68 (7.79)	11.76 (8.57)	16.45 (9.02)	16.45 (9.02)	16.45 (9.01)	16.45 (9.01)	-	-
1 Gd-enhancing T1 lesion (proportion)	16.5%	10.88%	11.37%	16.5%	16.5%	16.5%	-	-	-
2 Gd-enhancing T1 lesions (proportion)	5.8%	3.4%	2.84%	5.8%	5.8%	5.8%	-	-	-
3 Gd-enhancing T1 lesions (proportion)	3.6%	2.2%	1.78%	3.6%	3.6%	3.6%	-	-	-
≥4 Gd-enhancing T1 lesions (proportion)	10.3%	5.47%	5.68%	10.3%	10.3%	10.3%	-	-	-
Number of relapses in prior 1 year (mean [SD])	0.55 (1)	0.26 (0.55)	0.26 (0.51)	0.55 (1.01)	0.55 (1.01)	-	-	-	-
Sex (proportion female)	64%	60.25%	61.81%	64%	-	-	-	-	-

CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; Gd = gadolinium; IM = intramuscular; MS = multiple sclerosis; Neff = effective sample size; SD = standard deviation; vs. = versus.

Note: Matched sample excludes patients with baseline EDSS less than 3 or greater than 6.5 and those with prior interferon beta therapy. Scenario A adjusts for all available ranked characteristics. Subsequent scenarios drop the lowest ranked factor.

Source: Reproduced from the sponsor-submitted indirect treatment comparison.[15]

Annualized Relapse Rate

For the analysis of ARR, patient data from EXPAND were adjusted for time since onset of most recent relapse, number of relapses per patient in one year prior, and Gd-enhancing lesions on T1-weighted images (see Table 34). There was no adjustment for relapses in two years prior to enrolment or total volume of T2 lesions on T2-weighted images. The effective sample size was 119 patients (22% of the matched population).

The rate ratio for the ARR was 0.997 (95% CI, 0.46 to 2.18) for siponimod versus interferon beta-1a 60 mcg intramuscular weekly, based on the matched and adjusted analysis (Table 32).

Table 34: Results of Population Matching and Adjustment for ARR — Siponimod vs. Interferon Beta-1a 60 mcg IM Weekly

Variables	IMPACT	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C
N (Neff)	436	1550	547	119	122	482
Years since most recent relapse (mean [SD])	3.7 (5.1)	4.96 (5)	5.1 (5.55)	3.7 (5.11)	3.7 (5.11)	3.7 (5.11)
Number of relapses in prior 1 year (mean [SD])	0.55 (1)	0.27 (0.56)	0.27 (0.52)	0.55 (1.01)	0.55 (1.01)	-
1 Gd-enhancing T1 lesion (proportion)	16.5%	11.03%	11.33%	16.5%	-	-
2 Gd-enhancing T1 lesions (proportion)	5.8%	3.42%	2.93%	5.8%	-	-
3 Gd-enhancing T1 lesions (proportion)	3.6%	2.13%	1.83%	3.6%	-	-
≥4 Gd-enhancing T1 lesions (proportion)	10.3%	5.61%	5.85%	10.3%	-	-

ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; Gd = gadolinium; IM = intramuscular; Neff = effective sample size; SD = standard deviation; vs. = versus.

Note: Matched sample excludes patients with baseline EDSS less than 3 or greater than 6.5 and those with prior interferon beta therapy. Scenario A adjusts for all available ranked characteristics. Subsequent scenarios drop the lowest ranked factor.

Source: Reproduced from the sponsor-submitted indirect treatment comparison.[15]

Siponimod Versus Interferon Beta-1b (Betaseron)

The North American study and the European study evaluated interferon beta-1b 250 mcg every two days in patients with SPMS.

In both studies, patients were matched by excluding those with a baseline EDSS score of less than 3 points or greater than 6.5 points, and prior interferon therapy in the EXPAND study. To match the European study, those who were over 55 years of age were also excluded. The EXPAND population could not be matched on prior relapse-free period as the criteria in the European study was broader than in EXPAND. The matched population included 455 patients. For the comparison with the North American study data, patients could not be matched based on age as the population in the North American study was

broader than in EXPAND. Patients with a duration of MS of less than two years were excluded as matches to the North American study, which left 543 patients in the matched population. Details on inclusion criteria in the trials are listed in Table 26.

Time to Confirmed Disability Progression

For the comparison with the North American and European studies for the CDP outcomes, adjustment was possible for age, EDSS score, duration of MS and SPMS, number of relapses in the prior two years, and sex. No adjustment was possible for normalized brain volume, Gd-enhancing lesions on T1-weighted images, and total volume of T2 lesions of T2-weighted images. The effective sample size was reduced to 140 patients for the time to CDP-3 analysis (European study), and to 410 for the time to CDP-6 analysis (North American study), which represented 31% and 76% of the matched populations from EXPAND, respectively.

Prior to matching, the patients enrolled in the European study were younger (mean age of 41 years, SD = 7.2) than those in the North American study (mean age of 46.8, SD = 8.1) or the EXPAND study (mean age of 48.0, SD = 7.8), and were more likely to have had one or more relapses in the two years prior to enrolment. The results of population matching and adjustment for the time to CDP-3 and CDP-6 outcomes are shown in Table 35 and Table 36.

Table 35: Results of Population Matching and Adjustment for CDP-3 — Siponimod vs. Interferon Beta-1b, European Study

Variables	European Study	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F
N (Neff)	718	1638	455	140	141	163	205	274	274
Age (mean years [SD])	41 (7.2)	48.03 (7.84)	46.43 (6.81)	41 (7.22)	41 (7.22)	41 (7.21)	41 (7.21)	41 (7.21)	41 (7.21)
EDSS score at screening (mean [SD])	5.15 (1.1)	5.42 (1.06)	5.19 (1.11)	5.15 (1.1)	5.15 (1.1)	5.15 (1.1)	5.15 (1.1)	5.15 (1.1)	-
MS duration since diagnosis (mean years [SD])	13.1 (7.06)	12.62 (7.77)	11.06 (7.91)	13.1 (7.08)	13.1 (7.08)	13.1 (7.08)	13.1 (7.08)	-	-
Duration of SPMS (mean years [SD])	2.15 (2.3)	3.77 (3.51)	3.42 (3.19)	2.15 (2.31)	2.15 (2.31)	2.15 (2.3)	-	-	-
Relapse-free in prior 2 years (mean [SD])	30.4%	64.04%	59.78%	30.4%	30.4%	-	-	-	-
Sex (proportion female)	61.1%	60.01%	60.22%	61.1%	-	-	-	-	-

CDP-3 = confirmed disability progression at three months; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; Neff = effective sample size; SD = standard deviation; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

Note: Matched sample excludes patients over 55 years of age, with an EDSS score of less than 3 or greater than 6.5, and those with prior interferon beta therapy. Scenario A adjusts for all available ranked characteristics; subsequent scenarios drop the least important characteristic from adjustment.

Source: Reproduced from the sponsor-submitted indirect treatment comparison.[15]

Table 36: Results of Population Matching and Adjustment for CDP-6 — Siponimod vs. Interferon Beta-1b, North American Study

Variables	North American Study	EXPAND (un-matched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F
N (Neff)	939	1638	543	410	411	427	432	479	489
Age (mean years [SD])	46.83 (8.14)	48.03 (7.84)	49.4 (7.74)	46.83 (8.15)	46.83 (8.15)	46.83 (8.15)	46.83 (8.15)	46.83 (8.15)	46.83 (8.15)
EDSS score at screening (mean [SD])	5.13 (1.18)	5.42 (1.06)	5.27 (1.11)	5.13 (1.18)	5.13 (1.18)	5.13 (1.18)	5.13 (1.18)	5.13 (1.18)	-
MS duration since diagnosis (mean years [SD])	14.66 (8.32)	12.62 (7.77)	12.92 (8.24)	14.66 (8.33)	14.67 (8.33)	14.67 (8.33)	14.66 (8.33)	-	-
Duration of SPMS (mean years [SD])	4.03 (3.48)	3.77 (3.51)	3.84 (3.53)	4.03 (3.48)	4.03 (3.48)	4.03 (3.48)	-	-	-
Number of relapses in prior 2 years (mean [SD])	0.83 (1.32)	0.67 (1.19)	0.65 (1.1)	0.83 (1.32)	0.83 (1.32)	-	-	-	-
Sex (proportion female)	62.6%	60.01%	60.41%	62.6%	-	-	-	-	-

CDP-6 = confirmed disability progression at six months; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; Neff = effective sample size; SD = standard deviation; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

Note: Matched sample excludes patients with a duration of MS of less than two years, baseline EDSS of less than 3 or greater than 6.5, and those with prior interferon beta therapy. Scenario A adjusts for all available ranked characteristics; subsequent scenarios drop the least important characteristic from adjustment.

Source: Reproduced from the sponsor-submitted indirect treatment comparison.[15]

The analysis of time to CDP-3 reported an HR of 0.82 (95% CI, 0.42 to 1.63) for siponimod versus interferon beta-1b 250 mcg every two days, based on the population that was matched and adjusted to the European study. The HR for time to CDP-6 was 0.55 (95% CI, 0.33 to 0.91) for siponimod versus interferon beta-1b, based on the population matched and adjusted to the North American study (see Table 29).

Annualized Relapse Rate

The authors stated that no adjustment was possible for the analysis of ARR for the North American or European studies. Data from the two trials were pooled (total N = 1,343) and were compared with the matched and unadjusted population for EXPAND (effective sample size = 606, 36.8%). No comparison of baseline patient characteristics was presented. The rate ratio for ARR was 0.90 (95% CI, 0.51 to 1.59) for siponimod versus interferon beta-1b 250 mcg every two days (Table 32).

Siponimod Versus Natalizumab (Tysabri)

The ASCEND study compared natalizumab to placebo in patients with SPMS (Table 26). Patients from the EXPAND study were matched to those in ASCEND by excluding those older than 58 years of age, with baseline EDSS scores of less than 3 points or greater than 6.5 points, SPMS onset within the two years prior to enrolment, MS severity score of less than 4, most recent relapses within three months, and patients with T25-FW test results of more than 30 seconds during the screening period. The ASCEND study excluded patients who had received interferon in the past four weeks, or had received natalizumab at any time, but matching was not possible for these parameters. Moreover, no matching was possible for criteria related to the progression time frame because relevant data on time since disability progression were not captured in the EXPAND study. The matched population included 608 patients (38%) of the total EXPAND study population (Table 37).

There were important differences between trials in the definition of disability progression. In the ASCEND study, CDP-6 was a composite of three measures (change in EDSS, T25-FW test, or 9-HPT scores), and was measured at 96 weeks. In contrast, the time to CDP-6 in the EXPAND study was based on the EDSS score only and patients were followed for three years. In order to draw comparisons between the trials, the proportion of patients who experienced CDP-6 at 96 weeks was calculated using individual patient data from the EXPAND study (assuming patients with missing data experienced CDP-6). These data were compared to disaggregated data on EDSS-specific CDP-6 outcomes reported in the ASCEND study.

Table 37: Results of Population Matching and Adjustment for CDP-6 — Siponimod vs. Natalizumab, ASCEND Study

Variables	ASCEND	EXPAND (un-matched)	EXPAND (matched and un-adjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F	Scenario G	Scenario H	Scenario I	Scenario J
N (Neff)	887	1584	608	516	518	522	531	543	544	553	564	571	588
Age (mean years [SD])	47.25 (7.61)	48.07 (7.84)	47.77 (6.82)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)
EDSS score at screening (mean [SD])	5.6 (0.9)	5.41 (1.07)	5.75 (0.83)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	-
MS duration since diagnosis (mean years [SD])	12.14 (6.88)	12.69 (7.8)	13.28 (6.93)	12.14 (6.89)	12.15 (6.89)	12.14 (6.89)	12.15 (6.89)	12.14 (6.89)	12.14 (6.89)	12.14 (6.89)	12.14 (6.89)	-	-
Prior DMT (proportion)	77.0%	78.41%	83.55%	77.0%	77.0%	77.0%	77.0%	77.0%	77.0%	77.0%	-	-	-
Normalised brain volume (mean cm³ [SD])	1423.37 (82.95)	1422.95 (86.76)	1429.17 (83.49)	1423.37 (83.02)	1423.37 (83.02)	1423.37 (83.02)	1423.37 (83.02)	1423.37 (83.02)	1423.37 (83.02)	-	-	-	-
No Gd-enhancing T1 lesions (proportion)	76.2%	78.09%	78.12%	76.2%	76.2%	76.2%	76.2%	76.2%	-	-	-	-	-
Duration of SPMS (mean years [SD])	4.8 (3.37)	3.77 (3.51)	5.2 (3.32)	4.8 (3.38)	4.8 (3.38)	4.8 (3.37)	4.8 (3.37)	-	-	-	-	-	-
Total volume of T2 lesions (mean mm³ [SD])	16793.21 (17003.8)	15231.14 (15942.01)	14961.27 (16181.56)	16793.2 (17018.97)	16793.24 (17018.96)	16793.21 (17018.86)	-	-	-	-	-	-	-
Relapse-free in prior 2 years (mean [SD])	70.7%	63.83%	68.91%	70.7%	70.7%	-	-	-	-	-	-	-	-
Sex (proportion female)	62.0%	60.29%	59.05%	62.0%	-	-	-	-	-	-	-	-	-

CDP-6 = confirmed disability progression at six months; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis; Neff = effective sample size; SD = standard deviation; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test; vs. = versus.

Note: Matched sample excludes patients over 58 years of age, SPMS onset within previous two years of enrolment, baseline EDSS of less than 3 or greater than 6.5, MS severity score of less than 4, most recent relapses within three months, and patients with T25-FW test of more than 30 seconds during screening period. Scenario A adjusts for all available ranked characteristics; subsequent scenarios drop the least important characteristic from adjustment.

Source: Reproduced from the sponsor-submitted indirect treatment comparison.[15]

Confirmed Disability Progression

For the analysis of the proportion of patients with CDP-6, adjustment was possible for 10 criteria, which resulted in an effective sample size of 516 patients (85% of matched population) (Table 37). The odds ratio of CDP-6 at 96 weeks was 0.76 (95% CI, 0.44 to 1.30) for siponimod versus natalizumab (Table 29) for the matched and adjusted scenario A.

Annualized Relapse Rate

The population included in the MAIC for relapse frequency was adjusted for three factors as shown in Table 38, but not for the number of relapses in the past year or past two years. The effective sample size was 594, which was 97% of the matched EXPAND population.

The matched and adjusted ARR for siponimod versus natalizumab was 1.43 (95% CI, 0.78 to 2.61) (Table 32).

Table 38: Results of Population Matching and Adjustment for ARR — Siponimod vs. Natalizumab

Variables	ASCEND	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C
N (Neff)	887	1551	611	594	604	604
Years since most recent relapse (mean [SD])	4.75 (4.25)	4.96 (5)	5.26 (4.76)	4.75 (4.25)	4.75 (4.25)	4.75 (4.25)
No Gd-enhancing T1 lesions (proportion)	76.2%	77.76%	77.91%	76.2%	76.2%	-
Total volume of T2 lesions (mean mm^3 [SD])	16793.21 (17003.8)	15191.29 (15907.14)	14975.87 (16159.57)	16793.20 (17017.93)	-	-

ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis; Neff = effective sample size; SD = standard deviation; SPMS = secondary-progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk Test; vs. = versus.

Note: Matched sample excludes patients over 58 years of age, SPMS onset within previous two years of enrolment, baseline EDSS score of less than 3 or greater than 6.5, MS severity score of less than 4, most recent relapses within three months, and patients with T25-FW test of more than 30 seconds during screening period. Scenario A adjusts for all available ranked characteristics; subsequent scenarios drop the least important characteristic from adjustment.

Source: Reproduced from the sponsor-submitted indirect treatment comparison.[15]

Critical Appraisal of Sponsor-Submitted ITC

The sponsor-submitted ITC had a number of limitations that threatened the internal and external validity of the findings. The methods used to identify and select the studies would not meet the criteria for a systematic literature review. There was insufficient information provided on the primary literature search, which was conducted by the sponsor, to evaluate the rigour of the process. The supplemental search would not meet the criteria of a systematic literature search, as it only included a limited grey literature search, and screening was not conducted independently in duplicate. Although there were limitations to the methods used to select studies, the trials identified were the same as those included in a recent Institute for Clinical and Economic Review report on siponimod for patients with SPMS; thus, it is unlikely that relevant studies were missing.[53] Of note, there was no assessment of study quality or discussion of how any potential biases in the trials may impact the results of the MAIC.

The authors conducted a thorough review of the study design, inclusion and exclusion criteria, patient population characteristics, and outcomes measured in the clinical trials and identified a number of differences between studies that could potentially threaten the validity of an NMA or unadjusted ITC. Based on this review and the study data presented, the authors provided an adequate rationale for conducting the MAIC. The assessment of clinical heterogeneity by the Institute for Clinical and Economic Review was also in agreement that standard NMA techniques were not appropriate and they stated that due to differences in study design, study eligibility criteria, baseline characteristics of study

populations, and outcomes assessment, no quantitative indirect analyses could be conducted.[53] MAIC analyses were feasible because individual patient data were available for EXPAND, the EXPAND study and the comparator trials had sufficiently similar study designs and outcome definitions, and the inclusion criteria in the EXPAND study was broader or similar to the natalizumab and interferon trials.

The ITC authors stated that the population matching methods used were consistent with the *NICE Decision Support Unit Technical Support Document 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE*.[16] The matching criteria were based on the inclusion criteria for the EXPAND study and availability of comparable data from other trials. Clinical experts (number not specified) from Europe and Canada were consulted to identify the effect modifiers that were used as adjustment factors for CDP and ARR outcome measures. The clinical experts consulted for this Formulary Review agreed that the adjustment factors and their ranking appeared reasonable. However, it was not possible to fully match or adjust for all factors; therefore, not all differences could be accounted for. Data were limited for some of the adjustment factors, particularly for the ARR analyses. Two ARR analyses could not be adjusted and the others were adjusted for one of three parameters. The authors used a propensity score model based on generalized method of moments to determine weighting, as per NICE technical guidance. The results were reported as HRs, odd ratios, or rate ratios, and 95% CI, but the actual model used for parameter estimation was not specified.

The authors presented data on the patient demographics before and after weighting and adjustment for those variables that were included in the adjustment. The populations were well balanced for the adjustment variables, but it is unclear how well balanced populations were for other variables that may be clinically relevant but could not be adjusted due to lack of data, or those variables that were not part of the planned adjustment. Moreover, unmeasured effect modifiers cannot be controlled in an MAIC analysis. This is of concern considering that the interferon trials were published 15 years ago or more, and the management of MS has changed over time as new disease-modifying treatments have become available. Considering the time gap, it is possible that even after population-weighting, that systematic differences exist between the patients in the siponimod and interferon trials. Poor overlap between the trial populations is a concern because in most analyses, the effective sample size was substantially reduced. As all the interferon trials enrolled only treatment-naive patients, based on this criterion alone, less than one-third of the patients enrolled in EXPAND were potentially eligible for inclusion in the model. Adjustment further reduced the effective sample size, which in four analyses included 20% to 31% of matched patients (effective sample size of 113 to 157). The distribution of weights was not reported, but the small effective sample size suggests that there were substantial differences in the patients between trials. As a result, some patients may be assigned extreme weights, which could make the estimates unstable.

The authors provided the results of the base-case analyses (for the matched and fully adjusted population) as well as several exploratory analyses, which included an unadjusted ITC (Bucher method), matched only, univariate adjustment, as well as different adjustment scenarios that sequentially dropped the least important adjustment factor from the analysis. These analyses showed variation in treatment effect estimates, depending on the analysis methods or adjustment factors. Although some analyses showed statistically significant differences between treatments, given the limitations of these data, there is substantial uncertainty in the MAIC results.

The external validity of the results is limited given that the analyses comparing siponimod to interferon were restricted to patients who were interferon-naive. According to the experts consulted for this review, most patients in Canada diagnosed with SPMS would have previously received DMT for RRMS; thus, the findings of the MAIC may not be generalizable. Also, in all but one study, most patients included in the analyses did not have active SPMS. A further limitation is the comparators. Although interferon beta-1a and interferon beta-1b are the only other drugs in Canada with a Health Canada indication for SPMS, the clinical experts stated that these are not relevant comparators for the treatment of SPMS. As shown in Table 29, only the European study showed a benefit in terms of disability progression for interferon relative to placebo, but this trial enrolled a younger population that was more likely to have active disease than those enrolled in other trials. Although data comparing siponimod to natalizumab was summarized, this drug is not approved for use in Canada for patients with SPMS and its impact on disease progression is uncertain. The clinical experts consulted stated that other than siponimod, there are no disease-modifying treatments for patients with SPMS that have been shown to delay progression of disability but that most patients would continue on their current therapies in the absence of other effective treatments for SPMS. In summary, considering that the target population for these analyses is not clinically relevant to the patients who may be treated with siponimod in Canada, the utility of the findings is unclear.

Summary

The sponsor submitted an MAIC that compared siponimod to interferon beta-1a and interferon beta-1b and to natalizumab in patients with SPMS. The trials enrolled a mixed population of patients with active and non-active SPMS. Individual patient data from the EXPAND trial were used to match and adjust patients to those included in the comparator trials. An MAIC was deemed necessary due to differences across trials in the patient populations enrolled and changes in the treatment paradigm. The interferon trials, which were published between 1998 and 2004, included patients who were interferon-naive whereas in the EXPAND study, most of the included patients had received DMTs including interferon. There were also differences between trials in the age of patients enrolled, disease duration, EDSS score, and relapse frequency. Based on the clinical heterogeneity between trials, the Institute for Clinical and Economic Review[53] also concluded that ITC using standard methods was not appropriate.

Pairwise comparisons between siponimod and natalizumab, as well as siponimod and different interferon beta products and dosages, were conducted using MAIC methods. The results of some analyses suggest that disability progression may be delayed for siponimod versus interferon beta, while other analyses found no differences. No differences were found between siponimod and natalizumab in terms of disability progression. In addition, no differences were found between treatments for the analyses of relapse rates, which showed wide CIs, suggesting there was considerable uncertainty in the results.

Although the methods used to conduct the MAIC follow technical guidance,[16] the analyses have a number of limitations that impact the internal and external validity. There are concerns regarding the overlap between the comparator and siponimod trial populations, and the availability of data to allow for matching and adjustment. Matching was not possible for all criteria, and for some analyses, no or limited adjustment to balance potential effect modifiers was feasible. The small effective sample size of many analyses confirms that substantial differences exist between the patient populations in the siponimod and comparator trials. For the comparison between natalizumab and siponimod, only 38% of

EXPAND study patients were included after matching, and the effective sample size was further reduced after adjustment. There were also important differences between natalizumab and siponimod trials on the definition of CDP-6, requiring the use of imputed data to create comparable outcomes. Given these issues, there is substantial uncertainty in the MAIC results. Moreover, most patients included in the analyses did not have active SPMS, and the treatment effects reported for siponimod versus interferon apply to an interferon-naive patient population. Thus, the results may have little relevance to the population of interest to Canadian decision-makers as the analyses were not specific to patients with active SPMS — the approved indication for siponimod — and most patients who have developed SPMS would have previously received DMT. The relevance of interferon and natalizumab as a comparator is also limited; thus, the utility of these data is poor from a Canadian decision-making perspective.

Other Relevant Studies

Long-Term Extension Studies

The long-term open-label extension phase (the extension part) of the EXPAND study is ongoing. No results from the extension part of the study were available at the time of this review.

Discussion

Summary of Available Evidence

The EXPAND study was the only study that met the criteria for the CADTH systematic review. The core part of the study was a double-blind, parallel-group, multi-centre, placebo-controlled, event-driven, exposure-driven, phase III RCT and was the focus of this review. A history of RRMS and a current diagnosis of SPMS, defined by a progressive increase in disability for at least six months, in the absence of relapses or independent of relapses, were required for inclusion in the study. Patients also had to have an EDSS score of between 3.0 and 6.5 (inclusive) at screening, and documented progression in the two years prior to enrolment. A total of 1,651 patients were randomized 2:1 to siponimod (n = 1,105) or placebo (n = 546). Treatment with siponimod or matched placebo began with a six-day titration period starting with 0.25 mg and progressing up to 1.25 mg on day 5, followed by a maintenance dose of 2 mg daily beginning on day 6. The primary objective was to demonstrate the superiority of siponimod relative to placebo in delaying the time to three-month CDP based on the EDSS score, for patients with SPMS. The definition of disability progression was based on the MID for the EDSS score, i.e., increase of 0.5 in the EDSS score for patients with a baseline score of 5.5 to 6.5 and an increase of 1.0 for a baseline score of 3.0 to 5.0. The two key secondary outcomes were time to three-month confirmed worsening of at least 20% from baseline in the T25-FW, and change from baseline in T2 lesion volume. The EXPAND study examined several other efficacy outcomes related to HRQoL, mobility and functional outcomes, cognitive function, relapse-related outcomes, and imaging outcomes, as well as harms.

Subgroup analyses were conducted for the primary and key secondary outcomes of the EXPAND study as part of the original protocol. The subgroups of particular interest to this review following the indication for siponimod approved by Health Canada are those related to disease activity (i.e., patients with or without relapses, and patients with or without T1 Gd-enhancing lesions). In addition, a set of sponsor-submitted, exploratory, post-hoc

analyses of patients with active SPMS, defined as patients with relapses in the two years prior to screening and/or at least one T1 Gd-enhancing lesion at baseline, was also included and summarized for this review. The post-hoc analyses included the primary and secondary efficacy outcomes of the EXPAND study, in addition to ARR, MSWS-12, and other imaging outcomes.

A younger patient population (mean age of 46.6 years) that was mostly female (63.8%) was included in the active SPMS subgroup of patients in the EXPAND study. On average, patients were diagnosed with MS approximately [redacted] prior to enrolment in the trial and had converted to SPMS 3.2 years prior to enrolment. More than half of patients (55.6%) were severely disabled based on an EDSS score at baseline of 6.0 to 6.5; the remainder were moderately to severely disabled (17% and 26% had an EDSS score of 5.0 to 5.5 and 3.0 to 4.5, respectively). Overall, the characteristics of disease were consistent with a population that has moderate-to-severe disability and SPMS.

In addition, one sponsor-submitted ITC was included that used MAIC methods to conduct pairwise comparisons between siponimod and interferon beta-1a and interferon beta-1b, and natalizumab, in patients with active and non-active SPMS.

Interpretation of Results

Efficacy

The EXPAND study sought to demonstrate efficacy of siponimod in delaying time to disability progression based on the EDSS in patients with SPMS. This was achieved based on the statistical significance of the primary outcome. In the FAS, there was a statistically significant difference in the time to three-month CDP for patients treated with siponimod compared with placebo, corresponding to a 21.2% risk reduction with siponimod in the overall study population. The magnitude of this effect was greater in the post-hoc analysis of patients with active SPMS, which showed a 30.7% risk reduction. [redacted] The planned subgroup analyses revealed that treatment with siponimod was associated with a risk reduction in time to three-month CDP in patients with and without relapses in the two years prior to study start, but the treatment effect was more pronounced in those with relapses. Treatment with siponimod had the same effect in patients with and without T1 Gd-enhancing lesions at baseline, and the treatment effect was more pronounced in patients with lesions. Further, the risk reduction associated with each of the two subgroups of patients with relapses and T1 Gd-enhancing lesions was more evident than in the overall population.

HRQoL was assessed using three self-reported outcome measures and was identified as an outcome important to patients in this review, none of which were included in the statistical testing hierarchy. [redacted] According to the clinical experts, patients treated with siponimod would not be expected to show improvement in HRQoL because the therapy under review is intended to delay or slow progression. However, HRQoL would be expected to decline in patients treated with placebo, but this

was not observed. In summary, no conclusions regarding the potential benefit of siponimod on HRQoL can be made. Patient input for this review also indicated that fatigue is an outcome of interest; however, this was not reported as an efficacy outcome in the EXPAND study.

Mobility was measured by the time to three-month confirmed worsening of at least 20% from baseline in the T25-FW, which was a key secondary outcome and was analyzed in the active SPMS subgroup. For patients with active SPMS, treatment with siponimod did not affect time to three-month confirmed worsening on the T25-FW, and no differences were observed between the subgroups analyzed. These results are aligned with the results of the FAS population, where no difference was observed between patients treated with siponimod and placebo. Since this outcome did not reach statistical significance in the FAS, subsequent testing of other secondary outcomes in the overall study population of EXPAND should have stopped. Although improvements in T25-FW were not expected with siponimod, patients treated with placebo would be expected to exhibit deterioration on this measure, according to the clinical experts consulted by CADTH. This was not observed in the current trial.

The analysis of ARR suggest that siponimod was associated with a reduction in the rate of confirmed ARR in both the active SPMS subgroup and the overall population; however, the magnitude of this reduction was greater in the active SPMS subgroup. Despite the magnitude of the treatment effect, it is important to acknowledge that this outcome was not included in the statistical hierarchy and details of the statistical analysis for the active SPMS subgroup were not available. The clinical experts on this review noted the potential for siponimod to affect the prevention of relapses while targeting disease progression. The evidence suggests that siponimod may provide benefit for reducing relapses in patients with SPMS and is particularly relevant to patients with the active form of the disease. This is reflected by the approved Health Canada indication for siponimod, as well as the FDA[28] and EMA[29] recommendations for the use of siponimod in patients with relapsing forms of MS (including CIS, RRMS, and active SPMS) and active SPMS, respectively. Based on input from the clinical experts consulted by CADTH, patients transitioning to SPMS who still have active inflammatory disease would likely continue to receive treatment, and physicians may consider using siponimod.

Several imaging outcomes were measured in the EXPAND study. The change from baseline in T2 lesion volume was a key secondary outcome of the EXPAND study. In the active SPMS subgroup, the difference between siponimod and placebo in the change from baseline in T2 lesion volume at month 12 was in favour of the siponimod treatment group. The corresponding results in the overall population were also in favour of siponimod; however, [redacted] The following imaging outcomes at month 12 were also assessed in the post-hoc active SPMS subgroup analysis and considered relevant to the CADTH review: the number of new or enlarging T2 lesions, the number of T1 Gd-enhancing lesions, and the percentage change in brain volume. [redacted] The analysis of imaging outcomes in the overall population was consistent with patients with the active SPMS subgroup analyses. Statistical testing was performed for this outcome, but this violated the statistical hierarchy as per the failure of the previous

secondary outcome to reach statistical significance. As per feedback from the clinical experts consulted for this review, the use of MRI outcomes is gaining importance in clinical practice, with a focus on the number of new lesions used to guide treatment recommendations. Further, siponimod is indicated for patients with evidence of imaging features indicative of inflammatory activity. It was also noted that a measure of brain volume is informative, but typically not available in clinical practice.

Overall, based on the results from the planned subgroup analyses and on the observed treatment effect of siponimod on relapsing and imaging outcomes, Health Canada concluded that the results of the EXPAND study:

> "suggested that the efficacy of siponimod for progression of disability in SPMS may not be independent of an effect on inflammatory disease activity. It remains uncertain whether there is an effect on disability progression, which is independent of the effect on inflammatory disease activity. These results could only be considered to support an indication for treatment of patients with active SPMS, characterized by the presence of relapses and/or imaging features that are consistent with MS inflammatory activity."[43]

The sponsor submitted an MAIC that compared siponimod to natalizumab, and interferon beta-1a and interferon beta-1b, in patients with SPMS. The results of some pairwise comparisons suggest that disability progression may be delayed for siponimod versus interferon beta, while other analyses found no differences. No differences were found between siponimod and natalizumab in terms of disability progression. In addition, no differences between treatments were found for the analyses of relapse rates, which showed wide CIs suggesting there was considerable uncertainty in the results. Moreover, most patients included in the analyses did not have active SPMS, and the treatment effects reported for siponimod versus interferon apply to an interferon-naive patient population. Thus, the results may have little relevance to the population of interest to Canadian decision-makers, as the analysis was not specific to patients with active SPMS (the approved indication), and most patients who have developed SPMS would have previously received DMT. The relevance of interferon and natalizumab as a comparator is also limited; thus, the utility of these data is poor.

As siponimod is not meant to be a curative treatment, one can assume that patients would continue to take siponimod long term or until it no longer offers benefit. The core part of the study aimed to follow patients receiving the study drug for up to 36 months, but data were not available for the majority of patients beyond month 18 or month 24 as a result of the event-driven study design. Although there is currently an ongoing study to evaluate the long-term efficacy, safety, and tolerability of siponimod (N = 1,220) that is expected to be completed in 2023, the lack of information available at this time is a limitation to the assessment of this treatment. Further, it is an open-label extension of the overall population and is not limited to patients with active SPMS. The EMA guidance for industry document noted that it is desirable to evaluate the effect on progression on a long-term basis as disability in MS is slow.[51] Five years or longer was recommended, but it was noted that this could be generated post-approval.

The clinical experts consulted by CADTH acknowledged that there is an unmet need in this treatment area as siponimod is the only treatment intended to target progression of SPMS. The available evidence and approved indication for siponimod suggest that siponimod is likely more effective for the treatment of patients with active disease. Considering this, it is difficult to identify whether the benefit of siponimod is the result of the impact on inflammatory activity related to relapses and/or imaging, or if the improved relapse and

imaging outcomes are the result of an impact on disease progression. A direct comparison of siponimod to DMTs that is currently used for patients with RRMS and patients with active SPMS is not available at this time and is a substantial limitation to a comprehensive, comparative analysis of the efficacy of siponimod. Moreover, the indirect evidence that is available is limited to comparisons with interferon beta and natalizumab that are associated with significant uncertainty.

As per feedback from the clinical experts on this review, there is currently a hesitation in clinical practice to diagnose patients with SPMS while knowing they do not have a treatment to offer patients. The fear of progressing from RRMS to SPMS was also noted in the patient input submission. The clinical experts also acknowledged that the availability of siponimod may lead physicians to diagnosis SPMS sooner. Despite this, diagnosing patients with SPMS was identified as a challenge during this review. The diagnosis is typically made clinically and retrospectively. It is also unclear whether siponimod will fully address this gap as it is specifically indicated for patients with active SPMS. In addition, the clinical experts on this review agreed that siponimod is unlikely to offer benefit for patients who are fully dependent (with an EDSS score of 8.0 or higher), but may be efficacious in patients with an EDSS score of less than 8.0. A limitation of the EXPAND study is that the evidence is only available for patients with a maximum EDSS score of 6.5.

About 78% of patients in the EXPAND study had prior experience with an MS DMT, but the clinical experts consulted by CADTH for this review thought this number was lower than what is true for patients in Canada. Data regarding previous treatment experience was not available for the active SPMS subgroup. A study is underway that is designed to assess the early phase safety and tolerability of converting patients from approved oral and injectable DMTs for relapsing forms of MS to siponimod. The EXCHANGE study is a six-month open-label, multi-centre phase IIIb study. It is expected to be completed in 2020 and should provide information on switching patients to siponimod.

Harms

The safety associated with the use of siponimod in patients with active SPMS is uncertain due to a lack of safety analyses specific to this population. The safety results for the broader population of patients with SPMS (both active and non-active) in the EXPAND study was used to inform the assessment of safety for the use of siponimod.

On average, patients were exposed to the study drug for approximately 18 months. During the EXPAND study, a greater proportion of patients treated with siponimod reported at least one AE compared to placebo. The most common AEs were headache, nasopharyngitis, and urinary tract infection. Approximately 18% and 15% of patients in the siponimod and placebo arms, respectively, reported experiencing a serious AE. The occurrence of specific AEs and serious AEs were similar between treatment groups with no major safety signals. The number of patients who stopped treatment due to AEs was also relatively low, with a rate for withdrawal due to AEs of 7.6% and 5.1% for siponimod and placebo, respectively. Four deaths were reported in each treatment group.

Siponimod is an immunomodulator that works by preventing immune cells, namely T cells and B cells, from being activated and released from the lymph nodes, thus preventing their circulation in the brain and spinal cord where they cause inflammation. As an immunomodulator, there is a risk of AEs related to immunosuppression, such as the development of opportunistic or serious infections. The occurrence of progressive multifocal leukoencephalopathy and cryptococcal meningitis were included as notable harms in this

review, although no cases were reported in the core part of the EXPAND study. According to the product monograph, one case of cryptococcal meningitis was reported during the extension of the EXPAND study.[13] The overall number of lymphocytopenia AEs reported was minimal (0.8% for siponimod, none for placebo). In summary, it is important that patients treated with siponimod are effectively monitored for risk of infection.

Siponimod is from the same drug class as fingolimod, another S1P receptor modulator that is indicated for RRMS, which has been known to cause bradycardia.[35] Bradyarrhythmia is listed as a warning in the product monograph for siponimod as well.[13] As such, bradycardia was also listed as a notable harm in the review of siponimod, and was more common among patients treated with siponimod compared to placebo (4.5% versus 2.6%), but infrequent overall. It was noted in the FDA review that the implementation of a six-day titration appeared to sufficiently reduce the risk of serious bradyarrhythmia,[28] which was reflected in the harms data from the EXPAND study.

Upon review of siponimod, the FDA concluded that the risks associated with siponimod are consistent with the safety profile of fingolimod, and that the risks of treatment-emergent AEs can be mitigated through screening and discontinuation of therapy as needed. Overall, the safety profile of siponimod was not a concern and did not preclude approval of this drug.[28] Details of the EMA's review were not available at the time of this review. Of note, upon reviewing a list of known common AEs associated with siponimod, 35% of patients from the patient input submission said they would not take siponimod due to the lack of post-market long-term data, and 28% were unsure about whether or not they would take siponimod.

Other Considerations

According to the product monograph, siponimod is contraindicated in patients with known hypersensitivity, and homozygous for CYP2C9*3*3 genotype (poor metabolizers). The genotype for CYP2C9 was determined for all patients included in the EXPAND study at screening, and patients with the CYP2C9*3*3 genotype were excluded. Patients who refused to test for the CYP2C9*3 haplotype were also excluded. The draft product monograph also recommends that patients should be genotyped to determine the CYP2CP metabolizer status prior to initiation of treatment with siponimod.[13] The clinical experts consulted for this review relayed that determining metabolizer status is not easily done in clinical practice; however, as part of the patient support program, the sponsor has agreed to provide genotype testing prior to initiation with siponimod as well as cover all costs related to siponimod "onboarding" (the term used by the sponsor; it is not clear what such costs would include).

Conclusions

One double-blind, parallel-group, multi-centre, placebo-controlled, event-driven, exposure-driven, phase III RCT met the inclusion criteria for this review: the pivotal EXPAND study. The trial was conducted in patients with a broad range of SPMS phenotypes, but the indication approved by Health Canada is limited to patients with SPMS, defined as patients with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability. Data that were available to support efficacy of siponimod for this indication was limited to planned subgroup analyses based on disease activity and a post-hoc subgroup of patients with active SPMS, which was defined by having had relapses in the two years prior to screening and/or having at least one T1 Gd-enhancing lesion at baseline. These post-hoc subgroup analysis results of patients with active SPMS, representing 47% of the overall study population, constituted the main body of evidence in support of this review.

Patients treated with siponimod 2 mg daily demonstrated a clinical benefit compared to placebo in reducing the time to three-month CDP at month 12 based on a minimal clinically important change of EDSS score. Further, results of the study suggest that siponimod may provide benefit in preventing relapses and in improving imaging outcomes. However, no impact on patient's mobility was observed, and there is uncertainty regarding the improvement of disease-related symptoms and HRQoL. The observed benefits were generally consistent between the subgroup of active SPMS and the overall study population; however, the magnitude of the treatment effect of siponimod was more evident in the active SPMS subgroups. There were no major safety signals for siponimod based on the overall patient population, but this was limited by the lack of long-term data available at the time of this report. Results of the study are limited by issues with partial unblinding and high disproportional discontinuation. The subgroup analyses are subject to the same limitations, in addition to small sample size, potential for randomization that was not maintained, and results that may only be considered exploratory.

No direct evidence comparing siponimod to other DMTs for SPMS were identified in this review. No conclusions can be drawn from the sponsor-submitted ITC due to limitations that impact the internal and external validity of the findings. Key limitations included heterogeneity in the populations enrolled and the availability of data to allow for matching and adjustment of siponimod and comparator study populations. Moreover, the analyses were not specific to patients with active SPMS; thus, the utility of the results is limited.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	Oct 24, 2019
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(Mayzent* or siponimod* or baf 312 or baf312 or RR6P8L282I or Z7G02XZ0M6).ti,ab,ot,kf,hw,rn,nm.
2	1 use medall
3	*siponimod/
4	(Mayzent* or siponimod* or baf 312 or baf312).ti,ab,kw,dq.
5	or/3-4
6	5 use oemezd
7	6 not (conference review or conference abstract).pt.
8	2 or 7
9	remove duplicates from 8

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Mayzent OR siponimod OR baf 312
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: Mayzent OR siponimod OR baf 312

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	October 22, 2019
Keywords:	Mayzent, siponimod, baf 312
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics

Appendix 2: Excluded Studies

Table 39: Excluded Studies

Reference	Reason for exclusion
EXCHANGE Study (NCT03623243) Exploring the safety and tolerability of conversion to siponimod in patients with relapsing forms of multiple sclerosis: P1407 design of the 6 month prospective EXCHANGE study[poster] In: CDR submission: Mayzent (siponimod), 0.25 mg and 2 mg film-coated oral tablets) [**CONFIDENTIAL** sponsor's submission]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2019.	Study design (single-arm), poster
BOLD Study (Study A2201) Clinical Study Report: CBAF312A2201. A phase II, double-blind, randomized, multi-center, adaptive dose-ranging, placebo-controlled, parallel-group study evaluating safety, tolerability and efficacy on MRI lesion parameters and determining the dose response curve of BAF312 given orally once daily in patients with relapsing-remitting multiple sclerosis [**CONFIDENTIAL** internal sponsor's report]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2012 Mar 29.	Study design (phase II)
BOLD Extension Study (Study A2201E) Kappos L, Li DK, Stuve O, et al. Safety and Efficacy of Siponimod (BAF312) in Patients With Relapsing-Remitting Multiple Sclerosis: Dose-Blinded, Randomized Extension of the Phase 2 BOLD Study. *JAMA Neurology.* 2016;73(9):1089-1098.	Study design (phase II)

Appendix 3: Detailed Outcome Data

Exposure

An overview of commonly used concomitant medications by patients in the EXPAND study is summarized in Table 40.

Table 40: Commonly Used Concomitant Medications

	Siponimod N = 1,099	Placebo (N = 546)
Patients who took concomitant medication	1,022 (93.0)	507 (92.9)
Concomitant medication by: ATC level 1 ATC level 3 Preferred term		
Nervous system	[redacted]	[redacted]
Analgesics and antipyretics	[redacted]	[redacted]
Antidepressants	[redacted]	[redacted]
Anti-epileptics	[redacted]	[redacted]
Anxiolytics	[redacted]	[redacted]
Musculoskeletal system	[redacted]	[redacted]
Anti-inflammatory and antirheumatic products (non-steroids)	[redacted]	[redacted]
Muscle relaxants, centrally acting agents	[redacted]	[redacted]
Baclofen	[redacted]	[redacted]
Topical products for joint and muscular pain	[redacted]	[redacted]
Sensory organs	[redacted]	[redacted]
Anti-inflammatory agents	[redacted]	[redacted]

ATC = Anatomical Therapeutic Chemical.

Source: EXPAND Clinical Study Report.[14]

Patient Disposition

An overview of patient disposition after discontinuation of the study drug within the treatment epoch is summarized in Table 41.

Overall, about two-thirds (64.1%) of patients completed the treatment epoch on the study drug. A greater proportion of patients completed the treatment epoch on the study drug in the siponimod arm (66.7%) compared to placebo (59.0%). Of those who prematurely discontinued the study drug, 10.5% of patients assigned to siponimod and 17.2% of patients assigned to placebo continued with open-label siponimod, and [redacted]. A total of 11.2% of patients discontinued directly from the study drug.

The most common reasons for premature discontinuation from the study drug were [redacted] and AEs (7.4%). [redacted]

[redacted] Further, more patients in the siponimod group discontinued due to AEs (8.5% compared with 5.1%).

Table 41: Patient Disposition After Discontinuation of Study Drug During the Treatment Epoch — RAN

	EXPAND	
	Siponimod N = 1,105	Placebo N = 546
Received study drug, N (%)	1,100 (99.5)	546 (100)
Completed treatment epoch on study drug, n (%)	737 (66.7)	322 (59.0)
Prematurely discontinued study drug, n (%)	363 (32.9)	224 (41.0)
Continued with open-label siponimod	116 (10.5)	94 (17.2)
Continued in abbreviated schedule of assessment	[redacted]	[redacted]
Discontinued treatment epoch directly from study drug	[redacted]	[redacted]
Primary reason for premature discontinuation from study drug, n (%)		
Subject/guardian decision	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Adverse events	94 (8.5)	28 (5.1)
Lack of efficacy	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
As per protocol	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]
Dosing error	[redacted]	[redacted]
Technical problems	[redacted]	[redacted]

RAN = randomized analysis set.

Source: EXPAND Clinical Study Report.[14]

Sensitivity Analyses

Sensitivity Analyses for the Primary End Point (Time to Three-Month CDP Based on EDSS)

The primary analysis of time to three-month CDP was also conducted in the PPS and mFAS. [redacted] In addition, sensitivity analyses were performed for the primary efficacy variable using different assumptions. The reported risk reduction ranged from [redacted]

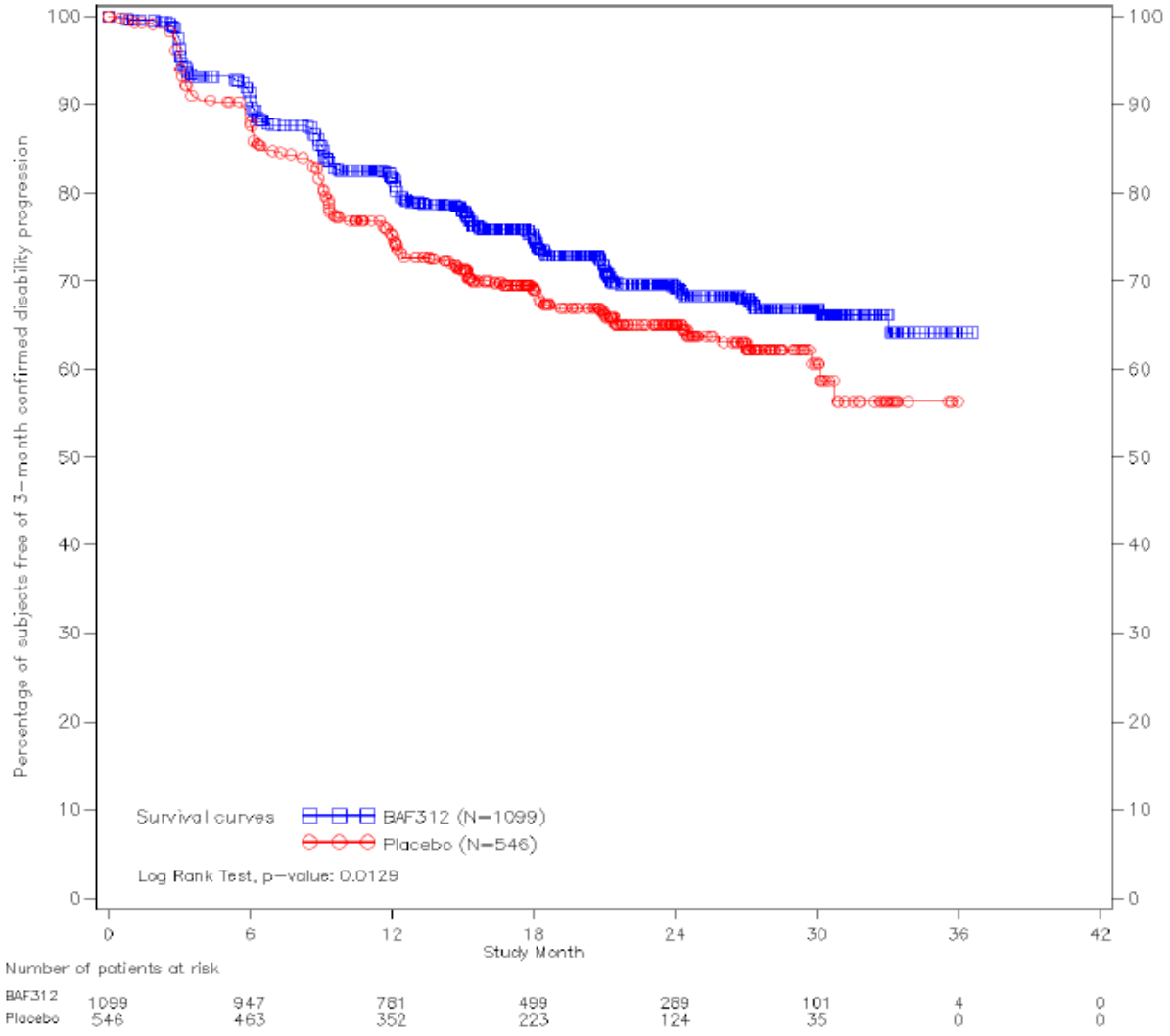
Sensitivity Analyses for the Key Secondary End Point (Time to Three-Month Confirmed Worsening in T25-FW of at Least 20% From Baseline)

A supportive sensitivity analysis of the T25-FW was conducted in the mFAS and PPS. [redacted]

Efficacy Results — Disease Progression or Improvement

A Kaplan–Meier curve for patients free of three-month CDP based on the EDSS score was provided as a supportive analysis for the primary efficacy outcome (see Figure 5). Briefly, a difference between siponimod and placebo begins between zero and six months, in favour of siponimod. The difference is sustained over the course of the study (until approximately 36 months). In addition, a log-rank test was performed for the survival curve, resulting in a P value of 0.0129.

Figure 5: Patients Free of Three-Month CDP Based on EDSS and Kaplan–Meier Curve — FAS



BAF312 = siponimod; CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; FAS = full analysis set.

Source: EXPAND Clinical Study Report.[14]

Efficacy Results — HRQoL

The EXPAND study assessed HRQoL using the MSWS-12, MSIS-29, and EQ-5D-3L. The results for the MSIS-29 and EQ-5D-3L at month 12 have been summarized in Table 42.

None of the HRQoL outcomes were included in the statistical hierarchy. The adjusted mean change from baseline at month 12 is presented in Table 42. [redacted] Further, the reported results for the HRQoL outcomes did not meet the MID described in Appendix 4.

Similarly at month 24, there was [redacted]

Table 42: EXPAND and HRQoL Outcomes Based on MSIS-29 and EQ-5D-3L — FAS

	Total N	n	Baseline	At month 12		Treatment group difference vs. control		
			Mean (SD)	Mean (SD)	Adjusted mean change from baseline (SE)	N	Mean difference (95% CI)	P value
MSIS-29, psychological impact item,[a] MMRM[b]								
Siponimod	[redacted]							
Placebo								
MSIS-29, physical impact item,[a] MMRM[b]								
Siponimod	[redacted]							
Placebo								
EQ-5D-3L, utility score,[a] MMRM[c]								
Siponimod	[redacted]							
Placebo								

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; FAS = full analysis set; HRQoL = health=related quality of life; MMRM = mixed-effects model for repeated measures; MSIS-29 = Multiple Sclerosis Impact Scale; SD = standard deviation; SE = standard error; vs. = versus.

Source: EXPAND Clinical Study Report.[14]

Efficacy Results — Mobility

Multiple Sclerosis Functional Composite: T25-FW and 9-HPT

The MSFC is a composite outcome derived from a combination of the 9-HPT, T25-FW, and PASAT. The results of the MSFC z score and mobility-related components (T25-FW and 9-HPT) at month 12 are provided in Table 43. The results of the PASAT subscale are

reported under the "cognitive function" efficacy outcomes. Of note, none of these outcomes were included in the statistical testing hierarchy and none of these outcomes were analyzed in an active SPMS patient subgroup.

[redacted]

[redacted]

[redacted]

Table 43: MSFC Based on z Score, T25-FW, and 9-HPT — FAS

	Total N		Baseline	At month 12		Treatment group difference vs. control		
		n	Mean (SD)	Mean (SD)	Adjusted mean change from baseline (SE)	N	Mean difference (95% CI)	P value
MSFC z score, change from baseline[a, b] (MMRM)								
Siponimod	[redacted]							
Placebo								
T25-FW, change from baseline[a, b] (MMRM)								
Siponimod	[redacted]							
Placebo								
9-HPT, change from baseline[a, b] (MMRM)								
Siponimod	[redacted]							
Placebo								

9-HPT = 9-hole peg test; CI = confidence interval; FAS = full analysis set; MMRM = mixed-effects model for repeated measures; MSFC = Multiple Sclerosis Functional Composite; SD = standard deviation; SE = standard error; T25-FW = Timed 25-Foot Walk Test; vs. = versus.

[a] Outcome was outside the statistical testing hierarchy.

[b] Model was adjusted for treatment and corresponding baseline score (i.e., MSFC z score, T25-FW score, or 9-HPT score).

Source: EXPAND Clinical Study Report [14]

Efficacy Results — Cognitive Function

Cognitive function was assessed in the EXPAND study via the SDMT, PASAT, and BVMT-R (total recall and delayed recall). The outcomes at month 12 are provided in Table 44. The outcomes related to cognitive function were not included in the statistical hierarchy and were not analyzed in an active SPMS patient subgroup.

For the SDMT, in the siponimod and placebo groups, a between-groups difference of [redacted] A similar response was

observed at month 24 (treatment group difference of [redacted]

For the change from baseline in the PASAT score, which is a subscale of the MSFC, the between-groups difference [redacted] (Table 44). [redacted]

In terms of the total recall score for the BVMT-R at month 12 (Table 44), [redacted]

Table 44: Cognitive Function Outcomes Based on SDMT, PASAT, and BVMT-R — FAS

	Total N	Baseline		At month 12		Treatment group difference vs. control		
		n	Mean (SD)	Mean (SD)	Adjusted mean change from baseline (SE)	N	Mean difference (95% CI)	P value
SDMT (oral score),[a] MMRM[b]								
Siponimod	[redacted]							
Placebo								
PASAT,[a] MMRM[c]								
Siponimod	[redacted]							
Placebo								
BVMT-R (total recall score),[a] MMRM[b]								
Siponimod	[redacted]							
Placebo								
BVMT-R (delayed recall score),[a] MMRM[b]								
Siponimod	[redacted]							
Placebo								

BVMT-R = Brief Visuospatial Memory Test-Revised; CI = confidence interval; FAS = full analysis set; MMRM = mixed-effects model for repeated measures; PASAT = Paced Auditory Serial Addition Test; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SE = standard error; vs. = versus.

[a] Outcome was outside the statistical testing hierarchy.

[b] Model was adjusted for treatment, region and/or country, and corresponding baseline score.

[c] Model was adjusted for treatment and baseline score.

Source: EXPAND Clinical Study Report. [14]

Efficacy Results — Relapse-Related Outcomes

A Kaplan–Meier curve for the percentage of relapse-free patients in the FAS is shown in Figure 6. [redacted] This measure included all relapses (confirmed and unconfirmed).

Figure 6: Percentage of Relapse-Free Patients, Kaplan–Meier Curve — FAS

Figure 6 contained confidential information and was removed at the request of the sponsor.

BAF312 = siponimod; FAS = full analysis set.

Note: Relapses were measured up until the end of the core part of the study.

Source: EXPAND Clinical Study Report.[14]

Efficacy Results — Imaging Outcomes

At month 12, the proportion of siponimod-treated patients and placebo-treated patients who were free of new or enlarging T2 lesions was [redacted], respectively, relative to baseline. At month 24 (relative to month 12), [redacted] of patients from the siponimod and placebo treatment groups, respectively, were free of new or enlarging T2 lesions. Regarding T1 Gd-enhancing lesions, [redacted] of patients treated with siponimod and placebo, respectively, were free of lesions at month 12.

Table 45: Additional Imaging Outcomes at Month 12

	EXPAND (FAS)		EXPAND (active SPMS subgroup)	
	Siponimod (N = 1,099)	Placebo (N = 546)	Siponimod (N = 516)	Placebo (N = 263)
T2 lesions				
Proportion of patients free of new or enlarging T2 lesions (relative to baseline)[a]				
n/m (%)	[redacted]	[redacted]	NR	NR
T1 Gd-enhancing lesions				
Proportion of patients free of T1 Gd-enhancing lesions,[a] n/m (%)				
n/m (%)	[redacted]	[redacted]	NR	NR

FAS = full analysis set; Gd = gadolinium; m = number of subjects with result in this scan; n = number of patients free of lesions; NR = not reported; SPMS = secondary-progressive multiple sclerosis.

[a] Outcome was outside the statistical testing hierarchy.

[b] Model was adjusted for treatment, region and/or country, age, and baseline number of T1 Gd-enhancing weighted lesions (offset = time between visits).

Source: EXPAND Clinical Study Report.[14]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- EDSS
- MSFC
- T25-FW
- PASAT
- SDMT
- MSWS-12
- BVMT-R
- MSIS-29
- EQ-5D-3L
- MRI outcomes

Findings

Table 46: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
EDSS	A clinician-administered assessment scale evaluating the functional systems of the CNS in patients with MS	Moderate inter-rater or intra-rater reliability. The validity of EDSS has been established in numerous studies.	1.0-point change when the EDSS score was between the 0 to 5.0 range 0.5-point change when the EDSS score was between the 5.5 to 8.5 range
MSFC	A multi-dimensional clinical outcome measure for MS disability, consisting of T25-FW, 9-HPT, and PASAT	Excellent test-retest reliability. The construct and convergent validity of MSFC have been demonstrated.	A 20% change in scores on T25-FW and 9-HPT
T25-FW	A validated measure for walking ability in patients with MS. This is 1 component of MSFC	Strong reliability has been reported. The validity of this measure has been established in patients with MS.	A change of 20%
PASAT	An audiotaped measure for cognitive function. This is 1 component of MSFC	Adequate reliability. Its validity has been established in patients with MS.	NA

Outcome measure	Type	Conclusions about measurement properties	MID
SDMT	A validated measure of cognitive processing speed	Excellent test-retest reliability. Its validity has been demonstrated in patients with MS.	A raw score change of 4 points or a 10% change
MSWS-12	A patient-reported, 12-item measure to evaluate the impact of walking impairment in people with MS	High test-retest reliability. Convergent and discriminant construct validity have been demonstrated in patients with MS.	Ranged from 10.4 to 22
BVMT-R	A measure of visuospatial memory for patients with neuropsychological disorders, including MS	Reliable instrument. The validity of BVMT-R was also established.	NA
MSIS-29	A self-reported, disease-specific 29-item questionnaire to measure both the physical and psychological impact of MS	MSIS-29 version 1: Excellent reliability; validity (convergent and discriminant) was demonstrated, and there were strong correlations with other scales for MS, although weak correlations were observed in a subgroup. Note: version 2 of the MSIS-29 was used in the EXPAND study.	Physical subscale: 8 Psychological subscale: 6.25
EQ-5D-3L	A generic measure of HRQoL including a descriptive system and a VAS	Adequate test-retest reliability. Validity has been established in patients with MS.	Index score: 0.050 to 0.084 VAS: NA

9-HPT = 9-hole peg test; BVMT-R = Brief Visuospatial Memory Test-Revised; CNS = central nervous system; EDSS = Expanded Disability Status Scale; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; HRQoL = health-related quality of life; MID = minimal important difference; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSIS-29 = Multiple Sclerosis Impact Scale; MSWS-12 = Multiple Sclerosis Walking Scale; NA = not available; PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modalities Test; T25-FW = Timed 25-Foot Walk Test; VAS = visual analogue scale.

Expanded Disability Status Scale

The EDSS is a validated tool to assess the extent of disabilities in patients with MS.

The EDSS is an ordinal scale used to measure disability in MS. It addresses disability in eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation.[7] The EDSS score is a composite ranging from 0 to 10 (in increments of 0.5) that incorporates functional systems grades as well as the degree of functional disability and ambulation (see Table 47).[44] Scores from 0 to 4.5 represent normal ambulation, while scores of 5 and above represent a progressive loss of ambulatory ability.

The distribution of EDSS scores among patients with MS is typically biphasic, accumulating around 2 to 3 points, and 6 to 7 points, indicating that patients do not stay equally long at each step of the scale. There are many criticisms of the EDSS, such as the moderate intra-rater reliability of the scale (kappa values between 0.32 to 0.76 for the EDSS and between 0.23 to 0.58 for the individual functional systems) and these were reported in previous studies.[44] Other criticisms include poor assessment of upper limb and cognitive function, and the lack of linearity between score difference and clinical severity.[45-47] The validity of the EDSS has been examined. Some studies indicated that the EDSS has strong to very strong correlation with the Barthel Index, the London Handicap Scale, the Scripps Neurological Rating Scale, the Functional Independence Measure, and the physical functioning domain of the Medical Outcomes Study 36-item Short Form (36) Health Survey (SF-36), while EDSS has weaker correlation with the Ambulation Index. EDSS was also found to be poorly correlated with

neuropsychological impairment and the brain changes measured by MRI.[44] Other limitations include the fact that it relies heavily on the evaluation of motor function and the ability to walk; as such, a patient who might not be able to walk but maintains full dexterity is classified toward the severe end of the scale.

In published literature, the MID was determined to be a 1.0 point change when the score was between the EDSS range of 0 to 5.0, while it was determined that this value decreased to a 0.5 point change when the EDSS score was between the 5.5 to 8.5 range.[44,62]

Table 47: Scoring of EDSS

Normal neurological exam (all grade 0 in FS; Cerebral grade 1 acceptable)	
1	No disability, minimal signs in 1 FS (i.e., grade 1 excluding Cerebral grade 1)
1.5	No disability, minimal signs in more than 1 FS (more than 1 grade 1 excluding Cerebral grade 1)
2.0	Minimal disability in 1 FS (1 FS grade 2; other 0 or 1)
2.5	Minimal disability in 2 FS (2 FS grade 2; others 0 or 1)
3.0	Moderate disability in 1 FS (1 FS grade 3; others 0 or 1), or mild disability in 3 or 4 FS (3 or 4 FS grade 2; others 0 or 1), though fully ambulatory
3.5	Fully ambulatory but with moderate disability in 1 FS (1 grade 3) and 1 or 2 FS grade 2; or 2 FS grade 3; or 5 FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relative severe disability consisting of 1 FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 m
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 assistances; characterized by relatively severe disability, usually consisting of 1 FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 m
5.0	Ambulatory without aid or rest for about 200 m, and disability severe enough to impair full daily activities (e.g., to work a full day without special provisions). (Usual FS equivalents are 1 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 about 100 m, and disability severe enough to preclude full daily activities. (Usual FS equivalents are 1 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 about 100 m with or without resting. (Usual FS equivalents are combinations with more than 2 FS grade 3+.)
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 m without resting. (Usual FS equivalents are combinations with more than 2 FS grade 3+.)
7.0	Unable to walk beyond about 5 m even with aid, and essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone, and up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than 1 FS grade 4+; very rarely, pyramidal grade 5 alone.)
7.5	Unable to take more than a few steps, and restricted to wheelchair; may need aid in transfer, wheels self but cannot carry on in standard wheelchair a full day, and may require motorized wheelchair. (Usual FS equivalents are combinations with more than 1 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 and 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 arm(s) and retains some self-care functions. (Usual FS equivalents are combinations, generally 4+ in several systems.)
9.0	Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+)
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+.)
10.0	Death due to MS.

EDSS = Expanded Disability Status Scale; FS = functional system; MS = multiple sclerosis.

Source: National MS Society[63]

Multiple Sclerosis Functional Composite

The MSFC is a measure of MS disability that was developed in 1994 by a task force convened by the US National Multiple Sclerosis Society.[64] The MSFC assesses different clinical dimensions by including three quantitative, continuous tests that evaluate the upper extremity, lower extremity, and cognitive function: arm (the 9-HPT), leg (T25-FW), and cognition (PASAT).[64,65] The 9-HPT measures arm and hand function according to the time needed for the patient to insert and remove nine pegs from a board. Both hands are assessed and the final score is recorded as the mean time for both hands. The T25-FW assesses change in ambulatory function, and a time increase of 20% or greater indicates a clinically meaningful impairment in gait. The PASAT measures cognitive function in which patients listen to a series of spoken numbers, and each number must be added to the prior number. The final score is the number of correct additions in the series.[66] For T25-FW and 9-HPT, a higher test result means the patient worsened from baseline. For PASAT, a higher test result means that the patient improved from baseline. In order to ensure that all measures are in the same direction, a transformation is necessary. Therefore, raw scores for each component are converted to standard scores (z scores) in order to achieve a common metric, in SD units (e.g., mean of 0 and SD = 1). A z score reflects how far a given raw score falls above ($z > 0$) or below ($z < 0$) the mean of a reference population ($z = 0$). The z scores for each component are averaged to generate a single MSFC score.[67] However, the MSFC has been criticized based on its expression as a z score that is not intuitive for interpretation, its dependence on a reference population for z score calculation, and the weighting of the different MSFC components.[66,68]

In a study on a small cohort of patients (10 patients) where the MSFC was administered to each patient twice over a two-week period for a total of six assessments, inter-rater reliability and ICC coefficients were reported at 0.98 and 0.96, respectively.[44,67] Construct validity of MSFC was demonstrated when the scores were lower in more disabled patients (–0.4 in PPMS and –0.3 in SPMS versus +0.42 in RRMS).[66] Convergent validity of MFSC (correlation with EDSS) was established in the study by Ozakbas et al.[69] (N = 38), where a moderate to strong correlation between EDSS and MSFC was observed. In looking at individual components, the EDSS had the lowest correlation (r = 0.31) with the PASAT, and the authors suggested that this might confirm the observation of poor assessment of cognitive function by EDSS. The strongest correlation was between EDSS and T25-FW (r = 0.84) followed by 9-HPT (r = 0.51) (which was moderately correlated). Again, this is consistent with the observation of poor assessment of upper limb function by EDSS. A systematic review of MSFC found the correlation with EDSS to range from –0.41 to –0.83.[44] Moderate correlation was observed between MSFC scores and the MRI findings ($r < 0.50$).[66]

Based on data from 161 patients with PPMS, a 20% change in scores on T25-FW and 9-HPT are considered clinically meaningful; however, a clinically meaningful value for the PASAT or the overall MSFC score has not been determined.[65,66]

Timed 25-Foot Walk Test

The T25-FW, a test of maximum walking speed on a short distance, is commonly used to monitor ambulation status and to assess treatment outcomes in patients with MS. It is one of three components of the MSFC, a multi-dimensional measurement tool used in assessing patients with MS. During the test, the patient is instructed to walk as fast and safely as possible across a clearly marked, linear 25-foot course. An assistive device is

allowed. The patient is timed walking the 25-foot course twice and the T25-FW score is the average in seconds of the two successive tests.[68]

T25-FW has been validated in patients with MS and has been shown to be correlated to EDSS across disability severity and MS types. Construct validity of the T25-FW has been established when strong correlations of this measure with other measures of walking and lower extremity functioning were reported. For example, T25-FW scores strongly correlated with the 100-m timed walk test (r = 0.92), 6-minute walk test (r = –0.83), Timed Up and Go test (r = 0.85), and Six Spot Step Test (r = 0.92), as well as the MSWS-12 (r = 0.78).[68] Adequate reliability of T25-FW was observed in multiple studies with patients with MS, with a sample size ranging from 10 to 151. The intra-class correlation (ICC) coefficient ranged from 0.94 to 0.99.[68]

A change of at least 20% in the T25-FW is commonly cited as the MID for patients with MS.[68,70]

Paced Auditory Serial Addition Test

PASAT is a neuropsychological test and a measure of cognitive function. It was first developed to monitor the recovery of patients who had sustained mild head injuries, and was subsequently adapted for use in patients with MS. The PASAT is widely used in MS studies.[71] It presents a list of single-digit numbers to the patient every two seconds (PASAT2) or three seconds (PASAT3; this version was used in EXPAND). The patient must add each number to the one that immediately precedes it and state the result.[72] PASAT assessed patients' auditory information processing speed and flexibility, as well as their calculation ability. The number of correct answers from the PASAT test was recorded (the range possible is 0 to 60).[14] PASAT is one of the three components of the MSFC.

The test-retest reliability of PASAT was adequate (reliability coefficients ranged from 0.70 to 0.87). PASAT was found to be moderately correlated with the Brief Repeatable Battery of Neuropsychological Tests and global cognitive function of z scores (validity coefficients ranged from 0.30 to 0.63), and strongly correlated with SDMT (validity coefficients ranged from 0.54 to 0.62).[73]

An MID for PASAT was not identified from the literature for patients with MS.

SDMT

Cognitive impairment is a significant potential consequence of MS. The SDMT is a commonly used neuropsychological test for screening cognitive impairment.[74] Like the PASAT, the SDMT measures information processing speed, which tends to decline with MS progression.[74,75] The patient was presented with a test instrument that included a row of single digits (1 to 9) with nine unique symbols at the top and an array of symbols paired with empty spaces below. The patient was required to match the number with each symbol as rapidly as possible. The scoring was calculated based on the number of correct answers in 90 seconds.

SDMT performance in screening patients with MS for cognitive impairment was evaluated in 359 patients with MS. At a specificity of 0.60, a high sensitivity was obtained (0.91), indicating the potential of the SDMT as a sentinel test for cognitive impairment.[76] In another study, the test-retest reliability coefficient was 0.97 in a sample of 34 patients with MS tested over two weeks, and the reliability was maintained at one-month and two-year intervals.[75] Validity (construct, predictive, discriminative, and criterion) was demonstrated in

patients with MS, showing that SDMT is a good measure of processing speed or efficiency. In addition, the SDMT was found to be strongly correlated to various MRI measures, such as atrophy, lesion burden, and microstructural pathology.[75]

A change of 4 points in the raw scores of the SDMT or a 10% change in magnitude was considered an MID in SDMT.[75]

Multiple Sclerosis Walking Scale

The MSWS-12 is a 12-item patient-reported questionnaire used to assess the impact of walking impairment in people with MS.[77] Twelve aspects of walking function and quality (walking, running, climbing stairs, standing, balance, distance, effort, support needed indoors, support needed outdoors, speed, smoothness, and concentration needed to walk) were identified as important by patients with MS.[70] The patient answers each of the 12 questions listed in Table 48 using a 5-point Likert scale where 1 = not at all, 2 = a little, 3 = moderately, 4 = quite a bit, and 5 = extremely. Items are summed to generate a total score (ranging from 12 to 60) and transformed to a scale with a range of 0 to 100. Higher scores indicate greater impact of MS on a patient's ability to walk.[70,77]

The literature suggests that the MSWS-12 is a valid measure of walking speed, endurance, and quality of gait in patients with MS. Based on data from 602 patients with MS, item test-retest reproducibility for MSWS-12 was high (≥ 0.78). In terms of validity, MSWS-12 was strongly correlated with the MSIS-29 physical subscale (Pearson's r = 0.74 to 0.79), SF-36 physical functioning domain (Pearson's r = –0.77 to –0.79), Functional Assessment of Multiple Sclerosis (FAMS) mobility subscale (Pearson's r = –0.70 to –0.76), EDSS (Pearson's r = 0.65) and moderately correlated with the T25-FW (Pearson's r = 0.46).[77] In a sample of 199 Italian patients with MS, the reliability of MSWS-12 was found to be excellent (0.94). Criterion validity of MSWS-12 was demonstrated when strong correlation between MSWS-12 and the EDSS score was observed, suggesting patients who reported lower walking ability on the scale also had a higher level of disability as rated by the clinicians.[78]

A range of 10.4 points to 22 points was reported to be an MID for MSWS-12 across studies, depending on the statistical approach and population studied.[79-81]

Table 48: Questions of the Multiple Sclerosis Walking Scale

In the past 2 weeks, how much has your multiple sclerosis…
1. limited your ability to walk?
2. limited your ability to run?
3. limited your ability to climb up and down stairs?
4. made standing when doing things more difficult?
5. limited your balance when standing or walking?
6. limited how far you are able to walk?
7. increased the effort needed for you to walk?
8. made it necessary for you to use support when walking indoors?
9. made it necessary for you to use support when walking outdoors?
10. slowed down your walking?
11. affected how smoothly you walk?
12. made you concentrate on your walking?

Source: Hobart, JC., *et al.* (2003)[77]

Brief Visuospatial Memory Test-Revised

The BVMT-R is a brief cognitive assessment tool used to assess visuospatial memory in patients with neuropsychological disorders, including MS.[48] During the assessment, the patients are shown a visual display of six simple figures for three consecutive 10-second tests. The same sheet of figures is used in the three tests. After each test, the patients are required to draw as many designs as accurately as they can and in the correct location. After completion of the three tests, the patients are asked to reproduce the designs in the exact layout after a 25-minute delay filled with other distractor tasks. Scoring of the tests are based on the accuracy of the drawings and the location of the figures. For each figure, one point is awarded to each satisfactory domain, resulting in a maximum of 12 points per test.[14,48]

In a group of 40 Brazilian patients with MS, moderate inter-rater coefficient (kappa = 0.62) and excellent ICC coefficient (0.85) were reported among three different raters. BVMT-R was also found to be strongly correlated with the SDMT, another instrument to assess cognitive function in patients with MS.[82] The criterion or discriminant validity of BVMT-R and the convergent validity were also established when comparing data between the MS group and healthy controls, as well as between BVMT-R and the California Verbal Learning Test — second edition (rho = 0.36) or between BVMT-R and the SDMT (rho = 0.60).[82]

An MID of BVMT-R for patients with MS was not identified in the literature.

Multiple Sclerosis Impact Scale (MSIS-29)

The MSIS-29 is a 29-item questionnaire that was developed at the Neurological Outcome Measures Unit of the UCL Queen Square Institute of Neurology and the National Hospital for Neurology and Neurosurgery in London, England.[83] This self-reported questionnaire is used to measure both the physical and psychological impact of MS on affected individuals. The physical component assesses 20 items including balance, gripping, movement, stiffness, and spasm (1 through 20), while the psychological component assesses nine items including social and/or leisure activities, work, mental fatigue, anxiety, and confidence (21 through 29).[84,85] Items in the original MSIS-29 (version 1) were rated using a five-category scoring system, including categories of "not at all," "a little," "moderately," "quite a bit," and "extremely."[85] MSIS-29 version 2 was used in the EXPAND study. Symptoms for each item are rated on a 4-point Likert scale: 1 = "not at all," 2 = "a little," 3 = "moderately," and 4 = "quite a bit." Items 1 to 20 and items 21 to 29 are summed respectively and transformed to scores from 0 (no problem) to 100 (extreme problems) to generate the total score for the physical impact subscale and the psychological impact subscale. Higher scores indicate greater impact on day-to-day life with a negative change on either of the subscales indicative of improvement.[83]

In order to assess the validity and reliability of the MSIS-29, Riazi et al. examined the MSIS-29 (version 1) along with three other self-reported measures — FAMS, SF-36, and the 12-item General Health Questionnaire — in 233 patients with confirmed MS.[86] They also assessed the EDSS in each patient. The patient population consisted of three hospital-based samples (a rehabilitation treatment sample, a corticosteroid treatment sample, and a PPMS sample). The authors determined that the MSIS-29 met the standard criteria for being a reliable and valid measurement. The estimates for Cronbach's alpha ranged from 0.87 to 0.95 for the physical and psychological subscales across all three samples. Correlations with other measures and variables demonstrated the convergent and discriminant validity of MSIS-29 as a measure of the physical and psychological impact of

MS. In general, the MSIS-29 physical subscale correlated strongly with the FAMS mobility subscale (correlations = –0.63 to –0.75) and SF-36 physical functioning subscale (correlations = –0.52 to –0.73), and the MSIS-29 psychological subscale correlated well with the SF-36 mental health subscale (correlations = –0.64 to –0.77), FAMS emotional well-being subscale (correlations = –0.67 to –0.75), and General Health Questionnaire subscale (correlations = 0.68 to 0.77). However, weak correlations were observed between the MSIS-29 physical subscale and EDSS (correlations = 0.27 to 0.69) or between the MSIS-29 psychological subscale and EDSS (correlations = 0.14 to 0.48), in particular in the rehabilitation sample. Similar results were obtained in the hospital setting when compared to the community setting.[86] In contrast to this, moderately strong correlations were observed in Costelloe et al. between changes in the MSIS-29 physical score and changes in the EDSS scores in the ranges of 0 to 8.5 and 5.5 to 8, whereas the correlation was weaker between the two with EDSS changes in the range of 0 to 5.[62] There were no psychometric tests performed for MSIS-29 version 2.

Using receiver operating characteristic curves in 214 patients with a range of MS disability (EDSS scores ranged from 0 to 8.5 and MSIS-29 scores ranged from 0 to 99), Costelloe et al. determined that a minimal change of 8 points in the MSIS-29 physical subscale was clinically significant.[62] A study by Phillips et al. also suggested a worsening of 7.5 points or more on the MSIS-29 physical subscale as a reasonable threshold for identifying patients with RRMS who have experienced a clinically significant change in the physical impact of MS.[87] A worsening of 6.25 points has been suggested as the MID for the psychological subscale based on the standard error of measurement in the ADVANCE trial.[88]

EuroQol 5-Dimensions 3-Levels

The EQ-5D-3L is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments.[89,90] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain and/or discomfort, and anxiety and/or depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems,” “some problems,” and “extreme problems,” respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value to self-reported health states (EQ-5D index score) from a set of population-based preference weights.[89,90] The second part of the EQ-5D is a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.” Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121 and 33211
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm).

Scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

One study assessed the EQ-5D as well as the validated Patient Determined Disease Steps scale and the MSWS-12 in patients with MS. Moderately strong correlations between the EQ-5D and the Patient Determined Disease Steps and MSWS-12 were observed (Spearman's r = –0.56 and –0.59, respectively; P < 0.0001 for both).[91] In addition, a review determined a lack of content validity for patients with MS for the EQ-5D as it was found to be missing certain domains (i.e., mobility, mood) that were important to the disease and showed difficulty in differentiating between levels of disability.[92] Test-retest reliability in the MS population was determined to be good (ICC coefficient = 0.81).[92]

Reported minimal clinically important differences for this scale in the general population ranged from 0.033 to 0.074.[93] For patients with MS, the MID ranged from 0.050 to 0.084.[91]

Magnetic Resonance Imaging Outcomes

MRI techniques play an important role in the diagnosis of MS and are valuable in monitoring treatment response and predicting disease progression. However, the correlation between the lesions observed on MRI scans and the clinical manifestations of the disease remains controversial.[94-96]

A series of MRI outcomes were included in the EXPAND study. The change from baseline in T2 lesion volume was used as a proxy for burden of disease. Inflammatory disease activity was measured by the number of new or enlarging T2 lesions, proportion of patients free of new or enlarging T2 lesions, number of T1 Gd-enhancing lesions, and proportion of patients free of T1 Gd-enhancing lesions. Gd-enhanced lesions are useful for identifying active inflammation, whereas the occurrence of T2 lesions requires interpretation based on a comparison with the number of T2 lesions observed in previous scans.[6] Percentage brain volume change from baseline was also reported.

Appendix 5: Pre-NOC CADTH Systematic Review Protocol

Table 49: Inclusion Criteria for the Systematic Review

Patient population	Adults with secondary-progressive multiple sclerosis. **Subgroups** • Age • EDSS at baseline • Disease activity (e.g., active, progressing)
Intervention	Siponimod administered orally once daily. **Siponimod administration** • Treatment initiation period: Dosing is titrated from 0.25 mg to 1.25 mg over a 5-day period • Maintenance period: 2 mg daily ○ 1 mg daily is recommended for the maintenance dose in patients with CYP2C9*2*3 or CYP2C9*1*3 genotype
Comparators	• Interferon beta-1a and interferon beta-1b • Placebo/best supportive care
Outcomes	**Efficacy outcomes** • Disability progression or improvement[a] • Health-related quality of life[a] • Mobility[a] • Cognitive function[a] • Symptoms (e.g., fatigue)[a] • Relapse • Imaging outcomes (e.g., MRI brain lesions, MRI brain volume) **Harms outcomes** • AEs • SAEs • WDAEs • Mortality • Notable harms: Cardiac effects (e.g., bradycardia), neoplasia, serious infections (e.g., progressive multifocal leukoencephalopathy), opportunistic infections (e.g., cryptococcal meningitis), lymphocytopenia, macular edema
Study design	Published and unpublished Phase III and IV RCTs

AE = adverse event; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

References

1. Olek M, Howard J. Clinical presentation, course, and prognosis of multiple sclerosis in adults. In: González-Scarano F, ed. Waltham (MA): UpToDate 2019: www.uptodate.com. Accessed 2019 Nov 27.
2. National Institute for Health and Care Excellence. Multiple sclerosis in adults: management. *(Clinical guideline CG186)* 2014; https://www.nice.org.uk/guidance/cg186. Accessed 2019 Dec 4.
3. Olek M, Mowry E. Pathogenesis and epidemiology of multiple sclerosis. In: González-Scarano F, ed. Waltham (MA): UpToDate; 2019: www.uptodate.com. Accessed 2019 Nov 27.
4. Public Health Agency of Canada. Canadian Chronic Disease Surveillance System (CCDSS). 2018; https://health-infobase.canada.ca/ccdss/data-tool/. Accessed 2019 Dec 4.
5. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014;83(3):278-286.
6. Freedman MS, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. *Can J Neurol Sci.* 2013;40(3):307-323.
7. Langeskov-Christensen D, Feys P, Baert I, Riemenschneider M, Stenager E, Dalgas U. Performed and perceived walking ability in relation to the Expanded Disability Status Scale in persons with multiple sclerosis. *J Neurol Sci.* 2017;382:131-136.
8. Betaseron (interferon beta-1b): lyophilized powder for subcutaneous injection 0.3 mg/vial [product monograph]. Mississauga (ON): Bayer Inc; 2016 Aug 8: https://pdf.hres.ca/dpd_pm/00036140.PDF. Accessed 2020 Jan 24.
9. Rebif (interferon beta-1a): 8.8 µg/0.2 mL, 22 µg/0.5 mL and 44 µg/0.5 mL solution for injection in pre-filled syringes; multidose 22 µg × 3 (66 µg/1.5 mL), multidose 44 µg × 3 (132 µg/1.5 mL) solution for injection in pre-filled cartridges [product monograph]. Mississauga (ON): EMD Serono, A Division of EMD Inc., Canada; 2016 Aug 22: https://pdf.hres.ca/dpd_pm/00036126.PDF. Accessed 2020 Jan 24.
10. Avonex (interferon beta-1a): liquid for injection [product monograph]. Mississauga (ON): Biogen Canada Inc.; 2016 Jun 27: https://pdf.hres.ca/dpd_pm/00035455.PDF. Accessed 2020 Jan 24.
11. La Mantia L, Vacchi L, Di Pietrantonj C, et al. Interferon beta for secondary progressive multiple sclerosis. *Cochrane Database Syst Rev.* 2012;1:Cd005181.
12. Olek M, Mowry E. Disease-modifying treatment of relapsing-remitting multiple sclerosis in adults. In: González-Scarano F, ed. Waltham (MA): UpToDate 2019: www.uptodate.com. Accessed 2019 Nov 10.
13. Mayzent (siponimod tablets): film coated tablets, 0.25 mg and 2 mg siponimod, oral [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2020 Feb 20.
14. Clinical Study Report: CBAF312A2304. A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312 [**CONFIDENTIAL** internal sponsor's report]. Basel (CH): Novartis Pharmaceutical Company; 2014 Jan 20.
15. CDR submission: Mayzent (siponimod), 0.25 mg and 2 mg film-coated oral tablets) [**CONFIDENTIAL** sponsor's submission]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2019 Oct 8.
16. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE Sheffield (GB): NICE Decision Support Unit; 2016: http://nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf. Accessed 2020 Jan 24.
17. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17(2):162-173.
18. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69(2):292-302.
19. Olek M, Howard J. Evaluation and diagnosis of multiple sclerosis in adults. In: González-Scarano F, ed. Waltham (MA): UpToDate 2019: www.uptodate.com. Accessed 2019 Nov 27.
20. Multiple Sclerosis Society of Canada. Progressive multiple sclerosis. https://mssociety.ca/hot-topics/progressive-multiple-sclerosis. Accessed 2019 Dec 20.
21. Plantone D, De Angelis F, Doshi A, Chataway J. Secondary progressive multiple sclerosis: definition and measurement. *CNS Drugs.* 2016;30(6):517-526.
22. Olek M, Mowry E. Treatment of progressive multiple sclerosis in adults. In: González-Scarano F, ed. Waltham (MA): UpToDate 2019: www.uptodate.com. Accessed 2019 Nov 10.
23. National Multiple Sclerosis Society. Secondary progressive MS (SPMS). https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS. Accessed 2019 Dec 18.
24. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler.* 2018;24(2):96-120.

25. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology.* 2018;90(17):777-788.

26. Olek M, Narayan R, Frohman E, Frohman T. Symptom management of multiple sclerosis in adults. In: González-Scarano F, ed. Waltham (MA): UpToDate 2019: www.uptodate.com. Accessed 2019 Dec 5.

27. Canadian physical activity guidelines for adults with multiple sclerosis. Ottawa (ON): Canadian Society for Exercise Physiology; 2018: https://www.csep.ca/CMFiles/Guidelines/specialpops/CSEP_MS_PAGuidelines_adults_en.pdf. Accessed 2019 Dec 5.

28. Center for Drug Evaluation Research. Medical review(s). *Mayzent (siponimod) tablets. Company: Novartis Pharmaceuticals Canada Inc.. Application No.: 209884. Approval date: 03/26/2019 (FDA approval package)*. Rockville (MD): U. S. Food and Drug Administration (FDA); 2019 Mar 12: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209884Orig1s000MedR.pdf. Accessed 2020 Jan 24.

29. European Medicines Agency. Mayzent (siponimod). 2020; https://www.ema.europa.eu/en/medicines/human/EPAR/mayzent. Accessed 2020 May 26.

30. Mavenclad (cladribine): 10 mg tablet [product monograph]. Mississauga (ON): EMD Serono, a Division of EMD Inc., Canada; 2017 Nov 29: https://pdf.hres.ca/dpd_pm/00042413.PDF. Accessed 2020 May 26.

31. Ocrevus (ocrelizumab for injection): concentrate for intravenous infusion 300 mg/10 mL (30 mg/mL) [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2019 Apr 9: https://pdf.hres.ca/dpd_pm/00050590.PDF. Accessed 2020 May 26.

32. Plegridy (peginterferon beta-1a): liquid for injection 125 µg [product monograph]. Mississauga (ON): Biogen Canada Inc; 2018 Aug 9: https://pdf.hres.ca/dpd_pm/00050016.PDF. Accessed 2020 May 26.

33. Lemtrada (alemtuzumab):12 mg/1.2 mL concentrate for solution for intravenous infusion [product monograph]. Mississauga (ON): Sanofi Genzyme, a division of sanofi-aventis Canada Inc.; 2020 Feb 18: https://pdf.hres.ca/dpd_pm/00055105.PDF. Accessed 2020 May 26.

34. Tecfidera (dimethyl fumarate): delayed-release capsules 120 mg and 240 mg [product monograph]. Mississauga (ON): Biogen Canada Inc; 2019 Nov 28: https://pdf.hres.ca/dpd_pm/00054126.PDF. Accessed 2020 May 26.

35. Gilenya (fingolimod): 0.25 mg and 0.5 mg capsules [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2019 Oct 30: https://pdf.hres.ca/dpd_pm/00053984.PDF. Accessed 2019 Dec 19.

36. Copaxone (glatiramer acetate injection): 20 mg / 1 mL and 40 mg / 1 mL pre-filled syringes for subcutaneous injection [product monograph]. Toronto (ON): Teva Canada Limited; 2018 Apr 25: https://pdf.hres.ca/dpd_pm/00045008.PDF. Accessed 2020 May 26.

37. Extavia (Interferon beta-1b): lyophilized powder for subcutaneous injection 0.3 mg/vial [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc; 2016 Sep 12: https://pdf.hres.ca/dpd_pm/00036353.PDF. Accessed 2019 Dec 19.

38. Tysabri (natalizumab): concentrate for solution for intravenous infusion 300 mg/15 mL [product monograph]. Mississauga (ON): Biogen Canada Inc; 2017 Jan 10: https://pdf.hres.ca/dpd_pm/00039755.PDF. Accessed 2020 May 26.

39. Aubagio (teriflunomide): tablets14 mg [product monograph]. Mississauga (ON) Sanofi Genzyme, a division of sanofi-aventis Canada Inc.; 2019 Sep 25: https://pdf.hres.ca/dpd_pm/00053291.PDF. Accessed 2020 May 26.

40. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.

41. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 Jan 24.

42. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet.* 2018;391(10127):1263-1273.

43. Health Canada reviewer's report: Mayzent (siponimod) [**CONFIDENTIAL** internal report]. Ottawa (ON): Therapeutics Products Directorate, Health Canada; 2020 Mar 2.

44. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol.* 2014;14:58.

45. Chapuis B, Helg C, Maurice P, et al. [Super intensive treatment followed by bone marrow autograft in cases of hematologic neoplasms and solid tumors]. *Schweiz Med Wochenschr.* 1988;118(10):341-346.

46. Ashton DS, Beddell CR, Cooper DJ, Lines AC. Determination of carbohydrate heterogeneity in the humanised antibody CAMPATH 1H by liquid chromatography and matrix-assisted laser desorption ionisation mass spectrometry. *Anal Chim Acta.* 1995;306(1):43-48.

47. Barkhof F. MR imaging in monitoring the treatment of MS: making good use of resources. *Advances in MRI Contrast.* 1996;4(2):46-53.

48. Tam JW, Schmitter-Edgecombe M. The role of processing speed in the Brief Visuospatial Memory Test - revised. *Clin Neuropsychol.* 2013;27(6):962-972.

49. Freedman M, Bar-Or A, Oger J, et al. A phase III study evaluating the efficacy and safety of MBP8298 in secondary progressive MS. *Neurology.* 2011; 77(16):1551–1560.

50. Gold R, Kappos L, Bar-Or A, et al. Efficacy of siponimod in secondary progressive multiple sclerosis patients with active disease: the EXPAND study subgroup analysis. Poster presented at: 35th congress of the European Committee for Treatment and Research in Multiple Sclerosis and 24th Annual Conference of Rehabilitation in MS, 11-13 September 2019, Stockholm, Sweden. 2019.

51. Committee for Medicinal Products for Human Use. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. *(European public assessment report)*. Amsterdam (NL): European Medicines Agency; 2015 Mar 26: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-multiple-sclerosis_en-0.pdf. Accessed 2020 Jan 24.

52. Samjoo IA, Worthington E, Haltner A, et al. Matching-adjusted indirect treatment comparison of siponimod and other disease modifying treatments in secondary progressive multiple sclerosis. *Curr Med Res Opin.* 2020:1-1.

53. Siponomod for the treatment of secondary progressive multiple sclerosis: effectiveness and value. Boston (MA): Institute for Clinical and Economic Review; 2019 Jun 20: https://icer-review.org/wp-content/uploads/2018/10/ICER_MS_Final_Evidence_Report_062019.pdf. Accessed 2019 Dec 17.

54. Andersen O, Elovaara I, Farkkila M, et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2004;75(5):706-710.

55. Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS) Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: clinical results. *Neurology.* 2001;56(11):1496-1504.

56. Li DK, Zhao GJ, Paty DW. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. *Neurology.* 2001;56(11):1505-1513.

57. Cohen JA, Cutter GR, Fischer JS, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology.* 2002;59(5):679-687.

58. Panitch H, Miller A, Paty D, Weinshenker B. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology.* 2004;63(10):1788-1795.

59. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European study group on interferon beta-1b in secondary progressive MS. *Lancet.* 1998;352(9139):1491-1497.

60. Kappos L, Polman C, Pozzilli C, Thompson A, Beckmann K, Dahlke F. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. *Neurology.* 2001;57(11):1969-1975.

61. Kapoor R, Ho PR, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurol.* 2018;17(5):405-415.

62. Costelloe L, O'Rourke K, Kearney H, et al. The patient knows best: significant change in the physical component of the Multiple Sclerosis Impact Scale (MSIS-29 physical). *J Neurol Neurosurg Psychiatry.* 2007;78(8):841-844.

63. Society NM. EDSS Form.

64. Drake AS, Weinstock-Guttman B, Morrow SA, Hojnacki D, Munschauer FE, Benedict RH. Psychometrics and normative data for the Multiple Sclerosis Functional Composite: replacing the PASAT with the Symbol Digit Modalities Test. *Mult Scler.* 2010;16(2):228-237.

65. Bosma LV, Kragt JJ, Brieva L, et al. Progression on the Multiple Sclerosis Functional Composite in multiple sclerosis: what is the optimal cut-off for the three components? *Mult Scler.* 2010;16(7):862-867.

66. Polman CH, Rudick RA. The Multiple Sclerosis Functional Composite: a clinically meaningful measure of disability. *Neurology.* 2010;74 Suppl 3:S8-15.

67. Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Mult Scler.* 1999;5(4):244-250.

68. Motl RW, Cohen JA, Benedict R, et al. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. *Mult Scler.* 2017;23(5):704-710.

69. Ozakbas S, Cagiran I, Ormeci B, Idiman E. Correlations between Multiple Sclerosis Functional Composite, Expanded Disability Status Scale and Health-Related Quality of Life during and after treatment of relapses in patients with multiple sclerosis. *J Neurol Sci.* 2004;218(1-2):3-7.

70. Hobart J, Blight AR, Goodman A, Lynn F, Putzki N. Timed 25-foot walk: direct evidence that improving 20% or greater is clinically meaningful in MS. *Neurology.* 2013;80(16):1509-1517.

71. Fischer JS, Jak AJ, Kniker JE, Rudick R. Multiple Sclerosis Functional Composite (MSFC): administration and scoring manual. New York (NY): National Multiple Sclerosis Society; 2001: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/10-2-3-31-MSFC_Manual_and_Forms.pdf. Accessed 2019 Dec 5.

72. Barker-Collo SL, Purdy SC. Determining the presence of reliable change over time in multiple sclerosis: evidence from the PASAT, Adjusting-PSAT, and Stroop Test. *Int J MS Care.* 2013;15(4):170-178.

73. Sonder JM, Burggraaff J, Knol DL, Polman CH, Uitdehaag BM. Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. *Mult Scler.* 2014;20(4):481-488.

74. Parmenter BA, Weinstock-Guttman B, Garg N, Munschauer F, Benedict RH. Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. *Mult Scler.* 2007;13(1):52-57.

75. Benedict RH, DeLuca J, Phillips G, et al. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Mult Scler.* 2017;23(5):721-733.

76. Van Schependom J, D'Hooghe M B, Cleynhens K, et al. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. *Eur J Neurol.* 2014;21(9):1219-1225, e1271-1212.

77. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology.* 2003;60(1):31-36.

78. Marengo D, Rosato R, Gamberini G, et al. Examining the validity of the Multiple-Sclerosis Walking Scale-12 with Rasch analysis: results from an Italian study. *Mult Scler Relat Disord.* 2019;36:101400.

79. Goldman MD, Ward MD, Motl RW, Jones DE, Pula JH, Cadavid D. Identification and validation of clinically meaningful benchmarks in the 12-item Multiple Sclerosis Walking Scale. *Mult Scler.* 2017;23(10):1405-1414.

80. Learmonth YC, Dlugonski DD, Pilutti LA, Sandroff BM, Motl RW. The reliability, precision and clinically meaningful change of walking assessments in multiple sclerosis. *Mult Scler.* 2013;19(13):1784-1791.

81. Baert I, Freeman J, Smedal T, et al. Responsiveness and clinically meaningful improvement, according to disability level, of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. *Neurorehabil Neural Repair.* 2014;28(7):621-631.

82. de Caneda MAG, Cuervo DLM, Marinho NE, de Vecino MCA. The reliability of the Brief Visuospatial Memory Test - Revised in Brazilian multiple sclerosis patients. *Dement Neuropsychol.* 2018;12(2):205-211.

83. Hobart J, Cano S. Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods. *Health Technol Assess.* 2009;13(12):iii, ix-x, 1-177.

84. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain.* 2001;124(Pt 5):962-973.

85. Bacci ED, Wyrwich KW, Phillips GA, Vollmer T, Guo S. Analysis of the psychometric properties of the Multiple Sclerosis Impact Scale-29 (MSIS-29) in relapsing-remitting multiple sclerosis using classical and modern test theory. *Mult Scler J Exp Transl Clin.* 2016;2:2055217316673235.

86. Riazi A, Hobart JC, Lamping DL, Fitzpatrick R, Thompson AJ. Multiple Sclerosis Impact Scale (MSIS-29): reliability and validity in hospital based samples. *J Neurol Neurosurg Psychiatry.* 2002;73(6):701-704.

87. Phillips GA, Wyrwich KW, Guo S, et al. Responder definition of the Multiple Sclerosis Impact Scale physical impact subscale for patients with physical worsening. *Mult Scler.* 2014;20(13):1753-1760.

88. Newsome S, Guo S, Altincatal A. Impact of peginterferon beta-1a and disease factors on quality of life in multiple sclerosis. *Mult Scler Relat Disord.* 2015:350-357.

89. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199-208.

90. Brooks R. EuroQol: the current state of play. *Health Policy.* 1996;37(1):53-72.

91. Kohn CG, Sidovar MF, Kaur K, Zhu Y, Coleman CI. Estimating a minimal clinically important difference for the EuroQol 5-Dimension health status index in persons with multiple sclerosis. *Health Qual Life Outcomes.* 2014;12:66.

92. Kuspinar A, Mayo NE. A review of the psychometric properties of generic utility measures in multiple sclerosis. *Pharmacoeconomics.* 2014;32(8):759-773.

93. Sinnott P, Joyce V, Barnett P. Guidebook: preference measurement in economic analysis. Menlo Park (CA): Health Economics Resource Center (HERC); 2007: https://www.herc.research.va.gov/files/BOOK_419.pdf Accessed 2019 Dec 5.

94. Rovira A AC, Alonso J. Magnetic resonance monitoring of lesion evolution in multiple sclerosis. *Ther Adv Neurol Disord.* 2013;6(5):298-310.

95. Klawiter EC. Current and new directions in MRI in multiple sclerosis. *Continuum (Minneap Minn).* 2013;19(4 Multiple Sclerosis):1058-1073.

96. Schaffler N, Kopke S, Winkler L, et al. Accuracy of diagnostic tests in multiple sclerosis--a systematic review. *Acta Neurol Scand.* 2011;124(3):151-164.