CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209884Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209884
Priority or Standard	Priority
Submit Date(s)	July 26, 2018
Received Date(s)	July 26, 2018 (Rolling Review)
PDUFA Goal Date	March 26, 2019
Division/Office	Division of Neurology Products
Reviewer Name(s)	David E. Jones, MD
Review Completion Date	3/12/2019
Established/Proper Name	Siponimod
(Proposed) Trade Name	Mayzent
Applicant	Novartis Pharmaceuticals Company
Dosage Form(s)	0.25 mg and 2 mg tablets
Applicant Proposed Dosing Regimen(s)	After titration, 2 mg by mouth daily
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with secondary progressive multiple sclerosis (SPMS)
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Relapsing forms of multiple sclerosis, including clinically isolated syndrome (CIS), relapsing remitting MS (RRMS), and active secondary progressive MS (SPMS)

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
ARR	Annualized relapse rate
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDP	Confirmed Disability Progression
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
CNS	Central Nervous System
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case report form
CRO	Contract research organization
CRT	Clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CUAL	Combined Unique Active Lesions
DMC	data monitoring committee
DP	disability progression
ECG	electrocardiogram
eCTD	electronic common technical document
EDSS	Expanded Disability Status Scale
ETASU	Elements to assure safe use
ECM	Expanded Cardiac Monitoring
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
IA	Interim Analysis
ICH	International Council for Harmonization
IND	Investigational New Drug Application

IR	Information Request
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MCP-mod	Multiple Comparisons Procedure with Modelling
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMRM	Mixed Model for Repeated Measures
MS	Multiple Sclerosis
MSSS	Multiple Sclerosis Severity Score
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NME	New Molecular Entity
OCS	Office of Computational Science
OLE	Open Label Extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PPMS	Primary progressive multiple sclerosis
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
RCT	Randomized Clinical Trial
REMS	risk evaluation and mitigation strategy
RMS	Relapsing Multiple Sclerosis
S1P	Sphingosine-1-phosphate
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SPMS	Secondary Progressive Multiple Sclerosis
T25FW	Timed 25 Foot Walk
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Siponimod (BAF312) is an oral sphingosine-1-phosphate (S1P) receptor modulator that binds to the S1P1 and S1P5 subtypes of the five known S1P receptors. The S1P receptors are ubiquitous in the body and have protean biologic functions, as per Table 1. Presumably, modulating S1P1 to limit the egress of lymphocytes from secondary lymphoid tissue at least partially explains the efficacy of this class of medications in preventing relapses in patients with relapsing MS. Siponimod is purportedly more selective than the currently approved S1P receptor modulator for relapsing forms of multiple sclerosis (fingolimod), which interacts with S1P1, S1P3, S1P4, and S1P5; therefore, siponimod may hypothetically mitigate some of the safety concerns with fingolimod, some of which are presumed to be at least partially modulated by S1P3 (Horga and Montalban, 2008).

Table 1. Reviewer Table. Distribution and biological activity of S1P receptors

Subtype	Locations	Proposed Effects
$S1P_1$	Lymphocytes	Regulate lymphocyte egress from lymphoid tissue
	Thymocytes	Regulate thymocyte egress from thymus
	Mast cells	
	Eosinophils	
	Vascular smooth muscle	Modulate vasomotor tone
	Endothelial cells	Increased endothelial permeability
	Atrial myocytes	Cardiac conduction[1]
	Gastric smooth muscle	
	Neurons	Neurogenesis
	Astrocytes	Astrocyte migration
	Oligodendrocytes	Oligodendrocyte progenitor differentiation / survival
$S1P_2$	Vascular smooth muscle	Modulate vasomotor tone
	Gastric smooth muscle	Gastric smooth muscle contraction
	Neurons	Neuronal excitability
$S1P_3$	Endothelial cells	Increased endothelial permeability
	Vascular smooth muscle	Vasomotor tone regulation
	Atrial myocytes	Cardiac conduction
	Neurons	
	Astrocytes	
$S1P_4$	Lymphocytes	Cell shape and motility
$S1P_5$	Oligodendrocytes	Oligodendrocyte progenitor differentiation / migration

Adapted from Table 1 in Horga and Montalban (2008). [1] S1P1 is expressed on atrial myocytes (Camm et al 2014).

Siponimod is presented as sipominod fumaric acid (co-crystal). The molecular formula of the free form is $C_{29}H_{35}F_3N_2O_3$, with a molecular mass of 516.61 g/mol. The molecular formula of the drug substance is $C_4H_4O_4 \bullet 2C_{29}H_{35}F_3N_2O_3$ with a molecular mass of 1149.2 (b) (4) g/mol. The drug substance is achiral. Siponimod shows no significant light absorption in the sunlight range between 290 and 700 nm and therefore has no phototoxic potential. The CAS No. for siponimod fumaric acid is 1234627-85-0 and the CAS name is 1-[[4-[(1E)-1-[[[4-Cyclohexyl-3-(trifluoromethyl)phenyl] methoxy]imino] ethyl]-2-ethylphenyl]methyl]-3-azetidinecarboxylic acid (2E)-2-butenedioate (2:1).

Siponimod is provided as 0.25 mg and 2 mg film-coated tablets for oral use. Each film coated tablet contains 0.25 mg or 2 mg siponimod, equivalent to 0.2 (b) (4) mg or 2.22 (b) (4) mg as siponimod fumaric acid co-crystal, respectively. Siponimod film-coated tablets contain the following inactive ingredients: microcrystalline cellulose, crospovidone, glyceryl behenate, lactose monohydrate, colloidal silicon dioxide with a film coating containing lecithin (soy), iron oxides (red and black iron oxides for the 0.25mg strength and red and yellow iron oxides for the 2 mg strength), polyvinyl alcohol, talc, titanium dioxide, xanthan gum.

The placebo tablets used in the studies described in this NDA have the same composition and configuration as the 0.25 mg and 2 mg drug products but do not contain siponimod.

1.2. Conclusions on the Substantial Evidence of Effectiveness

A single randomized, placebo-controlled trial (CBAF312A2304) performed in subjects deemed to have secondary progression multiple sclerosis (SPMS) meets its prespecified primary endpoint, time to 3-month confirmed disability progression (CDP) on the EDSS, and thus is a positive study. Despite that, it is very concerning that this study failed to meet its first "key" secondary endpoint, time to 3-month confirmed 20% worsening on the Timed 25 Foot Walk (T25FW), since the median EDSS of the population was 6.0, a value at which ambulatory dysfunction is the primary determinant of the EDSS. This reviewer also has concerns about the conduct of the study because attestations that subjects had SPMS were not collected, adjudication of subjects not having clinical documentation of EDSS progression in the prior two years did not consistently occur before randomization, and a "dual database access issue" may have resulted in the unblinding of 101 subjects and affected the outcome of the trial. Although CBAF312A2304 met its primary endpoint, the treatment effect was relatively modest (relative risk reduction of 21.2%, p=0.013), and the statistical strength of the effect is arguably insufficient for a single trial to support an indication of SPMS, especially given the aforementioned concerns.

Further analysis suggests that siponimod's treatment effect on 3-month CDP is driven by the subsets of subjects who experienced relapses in the 2 years prior to randomization, demonstrated gadolinium-enhancing lesions on a baseline MRI, or had an overall disease duration of less than 10 years. This suggests that siponimod has a greater treatment effect on

the “inflammatory” aspects of the disease, i.e., relapses and MRI activity in subjects with relapsing forms of multiple sclerosis, than it does on the “progressive” aspect of the disease, for which the pathophysiology is poorly defined and raises the question of whether there is sufficient evidence to support the approval of siponimod with an indication for relapsing forms of MS.

CBAF312A2304 utilizes a hierarchical analysis to deal with issues with multiplicity, and the second endpoint in this hierarchy (T25FW) failed to achieve statistical significance. Although this raises questions about the interpretability of subsequent endpoints, siponimod achieves large effect sizes with very low nominal p-values on multiple MRI metrics. Annualized relapse rate (ARR) is a “non-key” secondary endpoint and is not included in the hierarchical analysis of CBAF312A2304. Despite that and the observation that only a small percentage (13.1%) of subjects in CBAF312A2304 experienced confirmed MS relapses, the ARR result is nominally highly statistically significant ($p<0.0001$), supporting a potential role of siponimod in relapsing MS, especially given its robust effect on MRI outcomes.

CBAF312A2201 is a Phase 2, two-tiered, six-armed, dose-finding study in subjects with relapsing-remitting MS (RRMS) that utilizes dose-response on an MRI metric, combined unique active lesions (CUAL), as its primary endpoint. Although CBAF312A2201 was not powered to show an effect on ARR, it narrowly achieves a nominally statistically significant treatment effect on relapses ($p=0.0408$) at the 2 mg dose; however, the 0.5 and 10 mg arms of this study do not achieve nominal statistical significance. The results of CBAF312A2201 may also support role for siponimod in relapsing MS.

This reviewer has concerns about whether this circuitous route (including relaxing a hierarchical analysis, relying on secondary endpoints from a large SPMS trial and a small dose-finding study in RRMS, and minimizing concerns regarding the conduct of the Phase 3 study) provides substantial evidence of effectiveness to support approval of siponimod with an indication of relapsing forms of MS for siponimod. It is reassuring that many drugs that have a modulatory or suppressive effect on the immune system have been shown to have a benefit in relapsing MS, including a related S1P receptor modulator (fingolimod) that is approved for relapsing forms of MS. Considering this more global view of MS therapeutics convinces this reviewer that there is just enough evidence to be considered substantial and to support siponimod’s approval with an indication of relapsing forms of MS.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator that is being developed for multiple sclerosis. Siponimod is purportedly more selective that fingolimod, an S1P receptor modulator that was approved for relapsing forms of multiple sclerosis in 2010 given robust effects on relapse rates and new MRI activity in its clinical development program. Siponimod's development program includes a Phase 2, dose-finding study in subjects with RRMS and one Phase 3 study in subjects who were classified as having SPMS.

A single Phase 3 study to assess the effect of siponimod 2 mg daily on confirmed EDSS disability progression in 1651 adults who were classified as having SPMS meets its primary endpoint, time to 3-month confirmed disability progression (CDP) with a relative risk reduction 21% (p=0.013). The median duration of participation in this time-to-event study is almost 18 months, and the absolute risk reduction in 3-month CDP is almost 5.5% with siponimod; therefore, this study suggests that number needed to treat (NNT) to prevent one 3-month CDP over 18 months is approximately 19. Conversely, the study fails to achieve a statistically significant result on the first "key" secondary endpoint (time to 3-month confirmed worsening on the Timed 25 Foot Walk) in its prespecified hierarchical analysis, a finding that may not be congruent with the positive EDSS result in this population. The data supporting the utility of siponimod in non-relapsing SPMS are not persuasive and suggest that this more selective S1P modulator does not have a significant treatment effect on disability progression that is independent of relapse reduction.

The aforementioned Phase 3 study of siponimod shows a strong treatment effect on MRI metrics. Although only a small subset of subjects (13.1%) experienced relapses in this study of subjects deemed to have SPMS, CBAF312A2304 also shows a positive treatment effect on ARR; the adjusted ARR with siponimod is 0.071, and that with placebo is 0.160. A dose-finding, Phase 2 study in subjects with relapsing-remitting multiple sclerosis (RRMS) supports these results by showing a robust effect of siponimod on MRI metrics; however, only the 2 mg dose of siponimod achieved nominal statistical significance in reducing relapses in this study, which admittedly was not powered to show an effect on relapses. Considering this data and the data supporting the use of other immune-modulators (including an approved S1P modulator) in relapsing MS, siponimod should offer a benefit in relapsing forms of MS.

As per the safety review by Dr. Paul Lee, siponimod appears to have a modest and manageable safety profile. Although one might think that a

more selective S1P modulator like siponimod (especially one that does not bind S1P3) would mitigate some of the safety concerns with fingolimod, the data does not support this, so a 6-day titration is necessary to reduce the risk of bradyarrhythmia when starting siponimod. (Because S1P3 is also involved with endothelial permeability, one might assume that the risk of macular edema would be reduced with siponimod compared with fingolimod, but the safety data confirm a similar risk of macular edema with siponimod.) Further, the CYP2C9 genotype needs to be assessed before starting siponimod to determine the maintenance dose of siponimod (1 mg vs. 2 mg). CYP2C9 inducers or inhibitors alter circulating levels of siponimod, thus potentially requiring siponimod dose adjustments or restrictions on the use of these inducers/inhibitors.

Overall, the risk / benefit assessment for siponimod appears favorable when used in individuals with relapsing forms of MS.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The pathophysiology of MS consists of a clear inflammatory component (i.e., disease relapses and new MRI lesions) and another component that is termed "degenerative" (i.e., disease progression) but is poorly understood. Overall, it appears that MS becomes less "inflammatory" and more "degenerative" over time; however, both processes can contribute to increasing disability. Worsening disability from "inflammatory" disease is due to incomplete recovery from inflammatory events; conversely, disability progression from "degenerative" disease is insidious but of unclear etiology. With current metrics, distinguishing disability progression due to "degeneration" from disability worsening from "inflammation" is very	The pathophysiology of progressive MS is not understood but appears to differ from the inflammatory aspect of the disease that is prominent in relapsing MS. Despite this, many of the trials for progressive MS have utilized agents that have shown efficacy in relapsing MS, but unfortunately, most of these trials failed to achieve their primary endpoint. Although some have attributed these failures to inadequate outcomes measures (EDSS) or study duration, this reviewer agrees that the issues with trials for progressive MS also involve a difference in disease pathology and the difficulty in disentangling worsening disability from relapses from disease progression. Because there is not a biomarker for SPMS and because MS represents a continuum in which 2 processes, "inflammation"

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	difficult. • Approximately 85% of people diagnosed with MS initially have relapsing remitting MS (RRMS), which is an active inflammatory process characterized by relapses and the development of new MRI lesions, some of which lead to worsening disability. • Over time, many people with RRMS will exhibit a slow progression of disability that appears independent of inflammatory disease, heralding a transition to secondary progressive MS (SPMS). Although it is less common than in RRMS, active inflammatory disease can occur in SPMS (relapsing SPMS) but eventually relapses become rare as the disease transitions to non-relapsing SPMS. In relapsing SPMS, it is hard to disentangle worsening disability due to relapses from disability progression due to the "degenerative" process in SPMS.	and "degeneration," occur simultaneously, it is very difficult to adequately define a population of SPMS, especially relapsing SPMS, for a clinical trial. Issues to consider when attempting to do so include specifying the amount of time without relapses before the study, the period of time over which disability must increase during the study, and an algorithm to accurately disentangle disability worsening due to relapses from disability progression due to "degeneration." Other issues to consider when designing SPMS trials include the effect of previously (or currently) used MS drugs, the sensitivity of the disability scale to change at the level of disability of the population, and the necessary duration of the trial.
Current Treatment Options	• There are over a dozen agents approved for relapsing forms of MS. Data for these agents strongly suggest that they reduce both relapse rates and MRI activity; however, the efficacy of some of these agents in reducing disability progression at 12 or 24 weeks is questionable given less robust results and conflicting results among trials.	There are multiple agents approved to reduce the "inflammatory" component of the disease (relapses, new MRI lesions), but the development of an agent to alter the slow progression that occurs independent of inflammatory events ("progressive disease") remains a significant area of unmet need. The studies of the two agents approved for progressive MS (ocrelizumab and mitoxantrone) appear to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There are currently only two agents that are approved for progressive MS: ocrelizumab for primary progressive multiple sclerosis (PPMS) and mitoxantrone for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis. Mitoxantrone's effect is likely on inflammatory (i.e., relapsing) disease, and its clinical use is limited due to its risks of cardiotoxicity and leukemia.	have included subjects with more inflammatory disease and seem to have more of a treatment effect on inflammatory / relapsing MS than true progressive MS.
Benefit	• In CBAF312A2304, siponimod achieved an absolute risk reduction in 3-month CDP of almost 5.5% over placebo, giving a number needed to treat (NNT) to prevent one 3-month CDP event over 18 months of approximately 19. This treatment effect was driven by siponimod's effect on a subset of patients with relapses and inflammatory disease. • It is not clear that the CBAF312A2304 population had SPMS, because investigator attestations of SPMS were not collected, adjudication of 2-year disability progression was not consistently performed before randomization, and the Kaplan-Meier analyses suggest that almost 70% of subjects would not accrue 6-month confirmed disability progression in 3 years. • In addition to reducing new MRI activity, siponimod has a positive treatment effect on ARR: in CBAF312A2304,	Regardless of whether the subject population actually had SPMS, CBAF312A2304 does not support a benefit of siponimod in a population with predominantly progressive disease, e.g., non-relapsing SPMS, because siponimod's treatment effect on 3-month confirmed disability progression appears to be much greater for reducing worsening disability (from relapses and new MRI lesions) than for reducing disability progression (independent of inflammatory activity). Siponimod's effect on relapses and MRI metrics suggest that it may offer a benefit to people with relapsing MS, although it should be noted that only 13.1% of subjects in CBAF312A2304 experienced a relapse, that only the 2mg arm of CBAF312A2201 achieved nominal statistical significance on its ARR endpoint, that ARR was a secondary endpoint in both trials, and that MRI is not a measure of how a subject

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the adjusted ARR in subjects on siponimod was 0.071, and that in subjects on placebo was 0.160. CBAF312A2201 also demonstrates that siponimod has a beneficial treatment effect on MRI metrics and may have a potential benefit of reducing ARR. • The mis-assignment of study database privileges ("dual database access" issue) potentially compromised the blinding of 101 subjects in the single Phase 3 study of siponimod (CBAF312A2304).	"functions, feels, or survives." A sensitivity analysis removing the 101 subjects affected by the dual database access issue in CBAF312A2304 does not achieve statistical significance on CBAF312A2304's primary endpoint.
Risk and Risk Management	See the review of Safety by Dr. Paul Lee.	See the review of Safety by Dr. Paul Lee

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	☒ Clinical outcome assessment (COA) data, such as	See Sec 6.1 Study endpoints
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	☒ Clinician reported outcome (ClinRO)	See Sec 6.1 Study endpoints
	☒ Performance outcome (PerfO)	See Sec 6.1 Study endpoints
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS) that likely occurs when a genetically susceptible individual is exposed to an environmental trigger. MS is one of the most common causes of non-traumatic neurologic disability in young adults, and recent estimates suggest that almost one million people in the Unites States have this disease; therefore, the economic impact of MS (estimated at $10 billion annually in the US in 2013) is huge (Reich et al., 2018, Wallin et al., 2019). The International MS Genetics Consortium (IMSGC) has identified over 200 genetic loci that contribute to the risk of developing MS, and most of these genes are associated with the function of the immune system. The environmental triggers for MS are less well defined, although vitamin D deficiency and later exposure to the Epstein-Barr Virus (EBV) are considered to be risk factors for MS. The pathophysiology of MS includes a well-described inflammatory (or immune-mediated) component, which seems predominant earlier in the disease, and what is termed a "degenerative" component, which is less well understood but is felt to predominate later in the disease (Compston and Coles, 2008). The currently recognized clinical phenotypes of the disease include relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and primary progressive multiple sclerosis (PPMS); the modifier "active" can be used to indicate relapses or MRI activity, and the modifier "progression" can be used to indicate disability progression not attributable to relapses. Conversely, the term "worsening" should be reserved for disability progression attributable to relapses (Lublin et al. 2014).

About 85% of people who develop MS begin with RRMS, with an average age of diagnosis of approximately 30 years (Weinshenker et al., 1989). RRMS is characterized by recurrent inflammatory episodes, termed "relapses," in which auto-reactive lymphocytes marginate across the blood-brain barrier (BBB) and enter the CNS, leading to acute injury to myelin, oligodendrocytes, and axons, and potentially causing new or worsening neurologic deficits. Potential targets of acute inflammatory injury include the subcortical white matter, brainstem, optic nerve, and spinal cord; however, recent data suggests that the grey matter and neurons can also be a target of this inflammatory attack and that these cortical lesions may correlate better with disability (Compston and Coles, 2008). The diagnostic criteria for RRMS require clinical or imaging evidence of dissemination of clinical events "in time and space," meaning that a patient must experience at least two clinically or radiologically distinct episodes to be diagnosed with RRMS (Polman et al., 2011). Although early relapses may be followed by complete recovery, over time, relapses are associated with an accumulation of residual deficits and increasing disability (Confavreux et al., 1980; Weinshenker et al., 1989).

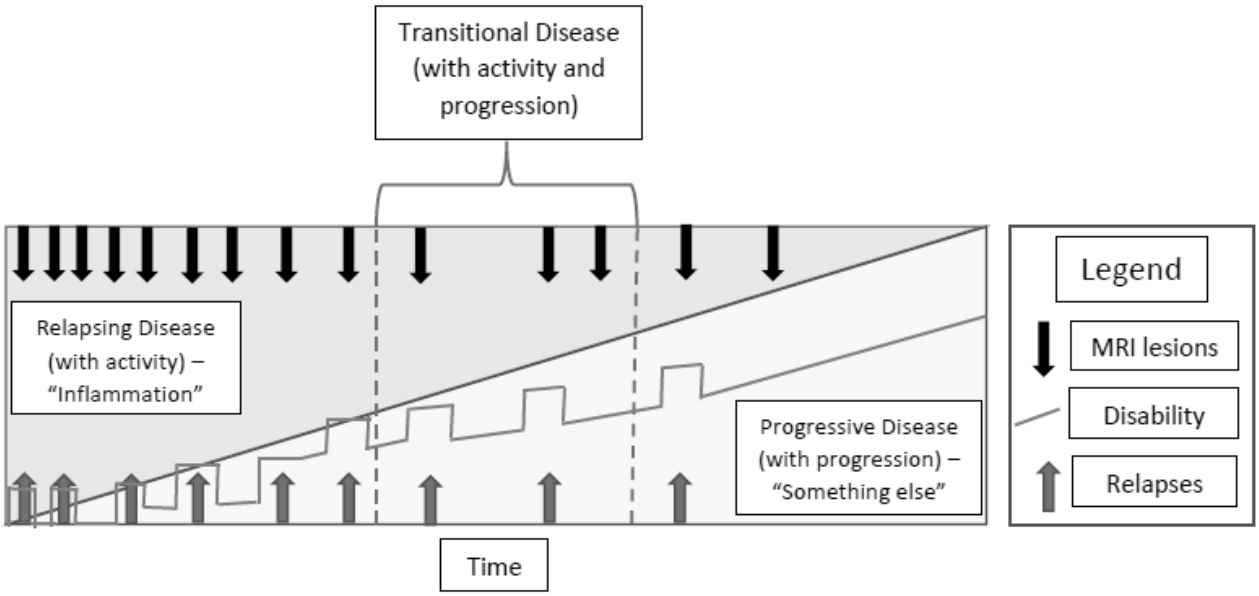
Over time (on average, ~15 years after the diagnosis of RRMS), a slow, insidious progression of disability--that appears to be independent of the occurrence of relapses--is seen in many patients with RRMS (Weinshenker et al., 1989, Confavreux et al., 2000). This phase of the disease is termed SPMS, and the progression of disability in this phase is felt to be driven by the poorly understood "degenerative" aspect of the disease. Given the nature of this progression, a diagnosis of SPMS is made retrospectively. Hypotheses regarding the pathophysiology of this "degenerative process" in SPMS include a bioenergetic deficit from mitochondrial dysfunction, compartmentalized inflammation behind an intact blood-brain barrier, increased free radicals, or simply "neurodegeneration." Relapses and new MRI lesions can still occur in SPMS but are less frequent, especially later in this phase of the disease (Correale et al., 2017).

About 15% of people with MS have PPMS, in which patients accumulate disability from the onset of the disease, typically with few if any relapses (Weinshenker et al., 1989). Like SPMS, it is also felt to be driven by more of a "degenerative process"; interestingly, the typical age of onset (mid-40's) of SPMS and PPMS is similar (Mahad et al., 2015, Antel et al., 2012). "Progressive Relapsing" MS (PRMS) refers to PPMS with occasional relapses, although this phenotype was removed from the most current phenotypic classification of MS and is now referred to as PPMS "with activity" (Lublin et al., 2014).

Two meta-analyses of clinical trials in relapsing MS (Sormani et al, 2009; Sormani and Bruzzi, 2013) suggest that the development of new MRI lesions may be a surrogate for relapses, so siponimod's robust effect on disease activity on MRI supports the effect of siponimod in reducing relapses. A similar meta-analysis (Sormani et al, 2010) suggests that the correlation between new MRI activity and disability worsening on EDSS was significantly weaker, perhaps explaining the discordant results in the trials of siponimod (and several other RMS therapies including fingolimod) between disability metrics and inflammatory activity, as measured by MRI activity and relapses. It is well established that there is not a good correlation between the burden of MRI disease and current disability, a phenomenon referred to as the "clinico-radiological paradox" (Barkhof 1999).

Unfortunately, there is not a biomarker for SPMS. Further, the transition from a primarily inflammatory disease (RRMS) to a predominantly "degenerative" disease (SPMS) likely occurs over a long period of time, during which both processes likely make a significant contribution to the pathophysiology of the disease in parallel (Katz-Sand et al, 2014). Recognition of this is illustrated by the use of terms such as "relapsing SPMS," "non-relapsing SPMS," and "transitional MS," and with the addition of the "with activity" and "with progression" modifiers to the updated description of the MS phenotypes (Lublin et al., 2014). During the transitional stage of the disease, having an effect on either the inflammatory or the "degenerative" phase of the disease is likely to slow the progression of disability from the disease (See Figure 1).

Figure 1. Reviewer Figure. Transition from relapsing to secondary progressive MS.



Although it remains unclear whether SPMS is an evolutionary outcome of the chronic inflammation caused by relapsing MS or is a separate pathological neurodegenerative process (Scott, 2017), effective prevention of relapses does not translate into prevention of disability in progressive MS (D'Amico et al., 2016). Although disability can result from residual deficits following relapses (Lublin et al., 2003), relapses are not the dominant factor resulting in severe and permanent disability in SPMS (Paz Soldan et al., 2015). Relapses are associated with a mean increase of 0.75 on the EDSS scale; however, in most patients, the disability incurred at the onset of a relapse improves significantly within two to three months (Lublin et al., 2003). Relapse-related EDSS increases that meet generally accepted criteria for confirmed progression of disability for three or six months are typically not sustained when patients are examined one or two years later (Liu et al., 2000); however, clinical trials in MS do not typically follow patients for sufficient duration to note this recovery (Wingerchuk & Weinshenker, 2016). It is therefore evident that damage from relapses alone cannot account for the timing and the quantity of permanent disability in SPMS, and that any clinical investigation of disability in SPMS must disentangle ephemeral disability due to relapses from disability due to the progressive disease.

The Federal Food, Drug, and Cosmetic Act of 1962 (FD&C) requires that drug manufacturers "demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies" to obtain marketing approval for a drug. Generally, this has been interpreted as a requirement for "at least 2 adequate and well controlled studies," although on occasion, "a single multicenter study of excellent design" that provides "highly reliable and statistically strong evidence of an important clinical benefit" have been accepted, especially after the FD&C was amended by the FDA Modernization Act of 1997. Further, clinical

endpoints, especially those that measure how a person "feels, functions, or survives," are preferable to surrogate markers of effect, which generally require post-marketing confirmatory studies. For these reasons, FDA gives more weight to relapses and disability progression (as measured by EDSS) endpoints than to MRI measures in MS clinical trials, especially given the relatively weak correlation between MRI and disability and the aforementioned "clinico-radiologic paradox."

The terms "relapsing MS" (RMS) or "relapsing forms of MS" include individuals with RRMS and relapsing SPMS. There are currently over a dozen approved medications that are indicated for relapsing forms of MS; however, non-relapsing SPMS is a significant unmet need in the therapeutic armamentarium for MS. Distinguishing relapsing from non-relapsing SPMS can be difficult, especially in individuals who are already taking one of the approved medications for RMS because any medication with efficacy in preventing relapses could be contributing real, but unmeasurable, benefit to patients by preventing new relapses and relapse-related disability.

Therapies approved for RMS with demonstrable reductions in relapse rates have not proven effective for SPMS. There have been randomized, placebo-controlled clinical trials with interferon beta-1a (Li et al., 2001; Andersen et al., 2004) and natalizumab (Kapoor et al., 2018) that show no reduction of disability progression in SPMS. A trial of interferon beta-1b by the European Study Group demonstrated a benefit on 3-month confirmed disability progression in SPMS, but the studied population appears to have an earlier, relapsing SPMS or "transitional MS." Conversely, an analogous North American study in an SPMS population did not demonstrate a benefit of interferon beta-1b on 6-month confirmed disability progression, although the population "may have tended toward the less inflammatory" (Panitch et al., 2004). Other clinical trials of plausible therapies for SPMS including pooled immunoglobulins (Hommes et al., 2004), a synthetic myelin basic protein sequence called MBP 8298 or dirucotide (Freedman et al., 2011; Warren et al., 2006), and Δ(9)-tetrahydrocannabinol (Zajicek et al., 2013) similarly showed no clinical benefit on disability progression. A clinical trial of mitoxantrone for SPMS demonstrates a significant positive treatment effect on EDSS and ambulation index, although the patient population is also suggestive of relapsing SPMS or "transitional MS" (Hartung et al., 2002). The data from this trial served as the basis for the approval of mitoxantrone for the indications of "reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, and worsening relapsing-remitting multiple sclerosis" in October of 2000.

Similar to the experience with SPMS, several randomized clinical trials for PPMS showed no overall benefit, including ones with glatiramer acetate (Wolinsky et al., 2007), rituximab (Hawker et al., 2009), and fingolimod (Lublin et al., 2016). A *post-hoc* analysis of the glatiramer acetate trial suggests a benefit of this drug in men with PPMS, and a subgroup analysis of the rituximab study suggested efficacy in a younger, more inflammatory population. Based on the results of the ORATORIO study, ocrelizumab was FDA-approved for PPMS in March of 2017,

although this study also seemed to include a more "inflammatory" population given its requirement for increased intrathecal immunoglobulin synthesis (Montalban et al., 2017).

2.2. Analysis of Current Treatment Options

As shown in Table 2, there are over a dozen MS drugs that are approved for the treatment of relapsing forms of MS, an indication that includes relapsing-remitting MS and relapsing SPMS, based on their effects on relapses and supported by their effect on MRI metrics. Many of these MS drugs do not have consistently positive data regarding disability progression; indeed, two of the three Phase 3 RRMS trials of a medication (fingolimod) in the same pharmacologic class as siponimod did not meet their disability endpoint. Although not supported by strong data, many providers will continue using one of these medications after subjects have transitioned from RMS to non-relapsing SPMS; however, the distinction between RMS and non-relapsing SPMS is admittedly very challenging, especially in individuals who are being treated with an MS drug.

Table 2. Reviewer Table. Approved treatments for relapsing MS

Approved Drug	Product Name	Approved Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Major Safety Concerns
Interferon beta-1b	Betaseron	Relapsing MS	1993	SC every other day	34% reduction in ARR	None
Interferon beta-1a	Avonex	Relapsing MS	1996	IM weekly	18% reduction in ARR	None
Glatiramer acetate [1]	Copaxone	Relapsing MS	1996	SC daily [2]	29% reduction in ARR	None
Mitoxantrone	Novantrone	Progressive relapsing and worsening relapsing- MS	2000	IV every 3 months	60% reduction in ARR	Cardiotoxicity, Leukemia
Interferon beta-1a	Rebif	Relapsing MS	2002	SC 3x/week	32% reduction in ARR (44mcg)	None
Natalizumab	Tysabri	Relapsing MS	2004	IV every 4 weeks	68% reduction in ARR	PML
Interferon beta-1b	Extavia	Relapsing MS	2009	SC every other day	34% reduction in ARR	None
Fingolimod	Gilenya	Relapsing MS	2010	PO daily	48-54% reduction in ARR	First dose bradycardia, transaminase elevation, macular edema, PML
Teriflunomide	Aubagio	Relapsing MS	2012	PO daily	32-36% reduction in ARR	Hepatotoxicity, teratogenicity
Dimethyl fumarate	Tecfidera	Relapsing MS	2013	PO twice daily	44-53% reduction in ARR	Lymphopenia, PML
Pegylated interferon beta	Plegridy	Relapsing MS	2014	SC Every 2 weeks	36% reduction in ARR	None
Alemtuzumab	Lemtrada	Relapsing MS	2015	2 courses twelve months apart	49% reduction in ARR in treatment-experienced subjects (compared with Rebif)	REMS for autoimmune conditions, serious infusion reactions, increased risk of

						malignancies
Ocrelizumab	Ocrevus	Relapsing MS	2017	IV every 2 weeks x 2 then IV every 6 months	46% reduction in ARR (compared with Rebif)	Potential increased risk of malignancies
[redacted]						(b) (4)

[1] Glatopa and other generic versions of the glatiramer acetate are now available.
[2] Daily and 3 times weekly formulations of glatiramer acetate are now available.
[redacted] (b) (4)

NOVANTRONE (mitoxantrone) is the only approved therapy indicated for the treatment of SPMS. The major safety concerns with mitoxantrone are cardiotoxicity and secondary leukemia, especially acute myeloid leukemia (AML). The lifetime maximum dose of mitoxantrone is 140mg/m^2, often limiting the duration of treatment with this medication to less than 3 years. OCREVUS (ocrelizumab), a monoclonal antibody directed against CD20, is the only approved therapy for Primary Progressive MS. Ocrelizumab is also approved for relapsing forms of MS, but there are no data to support its use in non-relapsing SPMS. The most significant safety concerns associated with ocrelizumab are infusion reactions, infections, and a possible increased risk of malignancy, especially breast cancer. Although off-label, some providers use intermittent high dose steroids, often monthly pulses of methylprednisolone, to treat SPMS. Effective treatments for non-relapsing SPMS that reduce long-term disability progression remain areas of significant unmet medical need. See Table 3.

Table 3. Reviewer Table. FDA Approved Treatments for Progressive Forms of MS

Approved Drug	Product Name	Approved Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Major Safety Concerns
Mitoxantrone	Novantrone	Secondary Progressive, Progressive Relapsing	2000	IV every 3 months	60% reduction in ARR 64% reduction in disability (SPMS)	Cardiotoxicity, Leukemia
Ocrelizumab	Ocrevus	Primary Progressive MS	2017	IV every 2 weeks x 2 then IV every 6 months	24% reduction in disability progression (PPMS)	Potential increased risk of malignancies

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Siponimod is a selective S1P receptor modulator with a similar mechanism of action to fingolimod (GILENYA), which is approved for RMS in adults in 2010 and in patients ages 10 and up in 2018. Siponimod is not currently marketed in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

Original IND Submission: September 15, 2006

The initial protocol for IND 076122 was a trial in 63 healthy volunteers comparing single and multiple doses across dose ranges from 2.5 mg to 500 mg.

Partial Clinical HOLD: March 26, 2009

The HOLD issue was the lack of nonclinical studies to support exposures of 3 to 6 months. Studies with exposure durations that were supported by the submitted nonclinical studies could continue.

Remove Partial Clinical Hold: May 19, 2009

Two 26-week studies in rats and monkeys addressed concerns with the duration of exposure in the proposed Phase 2 trial.

(b) (4)

(b) (4)

Special Protocol Assessment (SPA) Initial Submission: November 21, 2011

Two identical RRMS protocols were submitted.

SPA No Agreement: January 08, 2012

Two identical RRMS protocols

SPA Submission: April 24, 2012

CBAF312A2304 study in SPMS

SPA No Agreement: June 08, 2012

CBAF312A2304 study in SPMS

SPA Re-submission: July 09, 2012

CBAF312A2304 Study in SPMS

SPA Agreement: August 31, 2012

CBAF312A2304 study in SPMS

(b) (4)

Fast Track Designation #2: September 24, 2012

Indication: Treatment of patients with SPMS

SPA Amendment #1: July 19, 2014

This amendment proposed changes to the study's cardiac monitoring after initial data review and altered the trial epoch settings.

SPA Amendment #1 Agreement: May 5, 2015

SPA Amendment #2: March 27, 2015

This amendment proposed the rule and timing of the study's planned futility analysis (b) (4).

SPA Amendment #2 No Agreement: May 05, 2015

FDA agreed with planned interim analysis for futility (b) (4)

(b) (4)

Type C Meeting, March 7, 2017

Novartis requested this meeting to discuss the ability of the available evidence to serve as a basis of approval for siponimod for the treatment of SPMS. The FDA minutes for this meeting state "We note a nominally highly significant effect of siponimod on the annualized relapse rate in Study CBAF312A2304, suggesting efficacy on relapsing forms for MS … Your subgroup analysis of disability progression in patients without superimposed relapses in the 2 years prior to study start failed to reach nominal statistical significance … Study 2304 does not appear to provide sufficient evidence that siponimod slows progression independent of relapses … CBAF312A2304 may contribute evidence to support an effect of siponimod on relapsing forms of MS."

Type C Meeting (Written Responses Only), September 8, 2017

The Sponsor requested this meeting to discuss and gain agreement that the data from the pivotal Phase III study CBAFA2304 along with the Phase II study CBAF312A2201 is sufficient to support filing for a proposed indication of SPMS. FDA minutes for this meeting include the statement, "The study results, overall, suggest that most, and possibly all, of the effect of disability progression arose from an effect on active disease manifested by clinical relapses, i.e., from an effect on a relapsing form of MS."

Pre-NDA meeting, October 10, 2017

FDA meeting minutes state that submitting an NDA for siponimod with a labeled indication for SPMS would not be a refuse to file (RTF) issue and that the indication would be determined after completion of the review.

Rolling Review Granted: January 25, 2018

NDA Submission completed: June 28, 2018, with proposed indication of SPMS

CSR Amendment submitted to NDA: July 26, 2018

Reviewer comment: The regulatory history, (b) (4) *the FDA's responses to the Type C meetings in March and September of 2017, show that FDA clearly raised concerns that siponimod's effect on disability in CBAF312A2304 was due to its effect on relapses and thus whether this single study (CBAF312A2304) provided sufficient and substantial evidence to support an indication for SPMS. Despite these concerns, this NDA was submitted with a proposed indication of SPMS.*

3.3. Foreign Regulatory Actions and Marketing History

Siponimod received orphan designation from the European Medicines Agency for the treatment of polymyositis and dermatomyositis on November 19, 2014.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An inspection of the sponsor found that eighty-two sites in the CBAF312A2304 study experienced issues with "dual database access" in which 32 users of the main database had inappropriate access to a first dose database, potentially affecting outcome measures in 101 subjects. A sensitivity analysis performed in response to an Information Request dated January 3, 2019, revealed that exclusion of disability ratings for these 101 patients from the primary outcome measure analysis reduced the risk reduction in 3-month confirmed disability progression (CDP) for siponimod relative to placebo to 17.1% (p=0.062). Further, this inspection found that the investigator notes of attestation that subjects had SPMS were not collected and thus are not available for review and that some of the adjudications of 2-year disability progression occurred post-randomization. See the review by OSI team for further discussion of these issues.

4.2. Product Quality

See the review by the Chemistry, Manufacturing, and Control (CMC) reviewers. This review was not completed at the time of this review.

4.3. Clinical Microbiology

See CMC/Microbiology review, which was not completed at the time of this review.

4.4. Nonclinical Pharmacology/Toxicology

See the Nonclinical Pharmacology review. This was not completed at the time of this review.

4.5. Clinical Pharmacology

See the Clinical Pharmacology review, which was not completed at the time of this review.

4.6. Devices and Companion Diagnostic Issues

A need for an in vivo diagnostic companion device was identified during review. See the consult provided by CDRH.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

See Table 4 for a list of clinical trials of siponimod that are relevant to the MS indication.

Table 4. Reviewer table. Clinical Trials Relevant to MS Indication

Trial Identity	NCT no.	Trial Design	Dose / route	Study Endpoints	Duration/ Follow Up	No. of subjects	Populati on	Sites
		Studies to Support Efficacy and Safety						
A2304 Core	NCT01665144	Double blind RCT; Comparator: placebo	2 mg oral daily	3mCDP, 6mCDP, ARR	Variable (up to 37 months)	1651	SPMS	294 sites in 31 countries
A2304 Extension		Open-label	2 mg oral daily	3mCDP, 6mCDP, ARR	Up to 16 months	1220	SPMS	294 sites in 31 countries
A2201 Core	NCT00879658	Double blind RCT; Comparator: placebo	0.25 mg, 0.5 mg, 1.25 mg, 2 mg, 10 mg	ARR	3 and 6 months	297	RMS	73 sites in 12 countries
A2201E1 Extension		Dose blind phase and Open-label	(Dose-blind) 0.25 mg, 0.5 mg, 1.25 mg, 2 mg, 10 mg (Open) 2 mg	ARR, 3mCDP, 6mCDP	up to 5 years	184	RMS	73 sites in 12 countries
		Studies to Support Safety						
See Review of Safety by Dr. Lee								
		Other studies pertinent to the review of efficacy or safety						
CBAF312X2206	NCT02029274	Double blind RCT; Comparator: placebo	0.5 mg, 2 mg, 10 mg	MMT24, safety	48 weeks	17	dermato myositis	10 sites in 3 countries
CBAF312X2205	NCT01801917	Double blind RCT; Comparator: placebo	2 mg, 10 mg	MMT24, serum CK, safety	24 weeks	14	polymyo sitis	8 sites in 5 countries
CBAF3122202		Double blind RCT; Comparator: placebo	10 mg	Quality of life measures	24 weeks	18	dermato myositis and polymyo sitis	4 sites in 4 countries

5.2. Review Strategy

SPMS indication: The review for the indication of treatment of SPMS is limited to the large, time to event, Phase 3 study of siponimod in SPMS (CBAF312A2304) and the supportive 3- to 6-month Phase 2, dose-finding study of siponimod in RRMS (CBAF312A2201). Although the comparator was the same in both trials (placebo), the design and execution of these two trials was very different.

RMS indication: Although the application was submitted with a proposed indication of SPMS, this review also considers whether the data supports an indication of RMS, especially because some of the subjects from CBAF312A2304 were still having relapses and because CBAF312A2201 is a study of patients with RMS.

Safety: This review focuses on efficacy. See the clinical safety review by Dr. Paul Lee.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. 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

6.1.1. Study Design

Overview and Objective

Study CABF312A2304 is a Phase 3 clinical trial designed to assess the efficacy in reducing the time to 3-month confirmed disability progression (CDP) as well as the tolerability and safety of siponimod 2 mg daily compared to placebo in subjects with SPMS.

Trial Design

The A2304 study is a 1651-patient, randomized (2:1 ratio, siponimod:placebo), double-blind, parallel-group, placebo-controlled, time to event trial designed to evaluate the efficacy, tolerability, and safety of siponimod compared to placebo in subjects deemed to have SPMS. The primary endpoint is time to 3-month CDP as measured by the Expanded Disability Status Scale (EDSS).

Subjects completing the Core part of the study had the option to enter a single arm, active

treatment Open Label Extension (OLE) study if they fulfilled the eligibility criteria for the OLE. Subjects in the OLE study may receive siponimod for up to approximately seven years. Because it is a single-arm, open-labeled study, the OLE data is not considered in this efficacy review.

The Core study of Study A2304 consists of three "epochs" defined as follows:

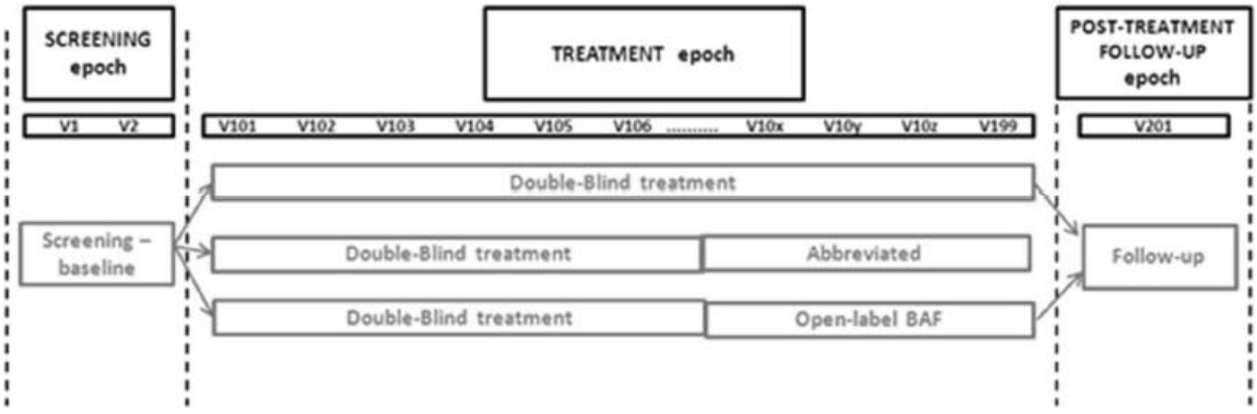
1. Screening Epoch
    - Screening (Day -45 to Day -8) for the determination of eligibility
    - Baseline (Day -7 to Day 1 until the first dose of study drug administration) for baseline assessments and confirmation of eligibility

2. Treatment Epoch
    - Study medication titration Day 1 to Day 7
    - Study Visit Day 28
    - Subsequent 3-month visits schedule thereafter with a time-to-event endpoint of time to 3-month CDP that determined when Treatment Epoch would end

3. Follow-up Epoch applies to subjects who:
    - Prematurely discontinued from double-blind study drug or from open-label siponimod and did not want to remain in the study (Note: these patients were not eligible to enter the OLE)
    - Completed the study on double-blind treatment or open-label siponimod and chose not to enter the OLE
    - Completed the study on double-blind treatment or open-label siponimod and planned to enter the OLE but would not be able to do so within one month.

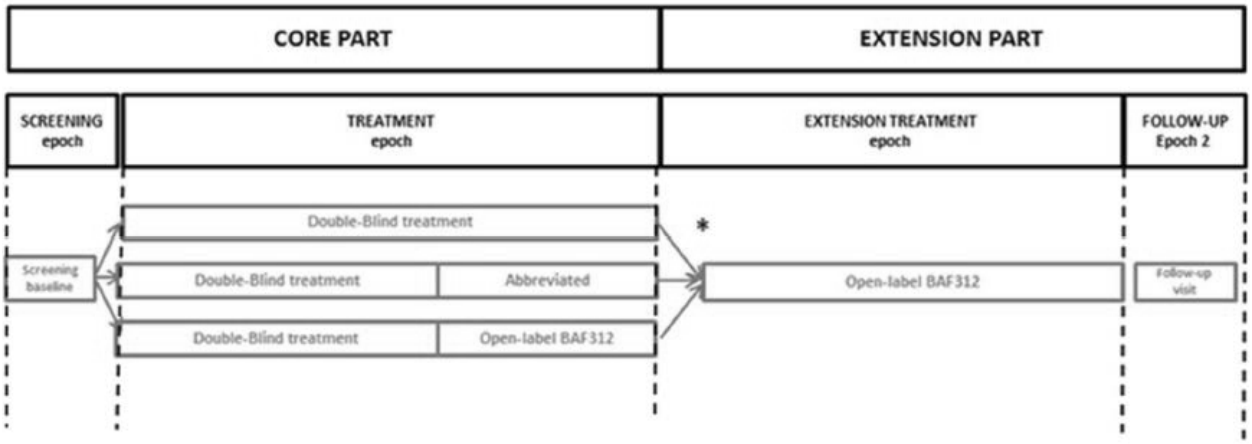
The study design is summarized in the figures below.

Figure 2. Sponsor Figure. CBAF312A2304 Core 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

Figure 3. Sponsor Figure. CBAF312A2304 Core and Extended Study Design



Randomization was 2:1 siponimod:placebo.

Blinding

Study A2304 employed a double-blind design. Subjects, investigator staff, persons performing the assessments, and the sponsor were to remain blinded to the identity of the treatment from the time of randomization until the database lock for the Core Part of the study.

To prevent unblinding during the double-blind treatment period, the Sponsor implemented the following procedures:

- Randomization data were kept strictly confidential until the time of the database lock and were not accessible by anyone else involved in the study with the following exceptions:
    - DMC members, Independent Statisticians, and Independent Programmers
    - PK analysts had access to the randomization codes associated with patients from whom PK samples were taken but PK results remained confidential until database lock.
- Per the CSR, "The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, appearance, taste, and odor."
- EDSS assessments were conducted by independent raters. EDSS assessments occurred per protocol every 3 months and in the case of a suspected MS relapse. The independent rater had access to prior EDSS scores for comparison.
- Two separate databases were set-up for the main clinical data and the first dose administration data because the dose initiation data may provide a viewer with clinical data that could reveal treatment assignment.
- Subjects received the first dose of study treatment under the supervision of an independent First-Dose Administrator who would not reveal the results of the monitoring to the patient or to anyone else associated with the clinical study unless there was medical justification for such notice. Adverse events associated with first dose such as bradycardia and AV block were recorded but not revealed to the study team except when necessary to ensure subject safety.
- There were restrictions on reporting of certain hematology results during blinded treatment because reduced lymphocyte counts were expected, given the mechanism of action for siponimod. Specifically, after the baseline visit, only the absolute counts for eosinophils, basophils and monocytes were communicated to sites by the central laboratory. The absolute total white blood cell, neutrophil and lymphocyte counts were measured at each visit by the central laboratory (and were blinded from the sponsor and the investigator) and were only communicated to the site in case of a notable abnormality that could have required a dose change.

Unblinding was permitted in the case of patient emergencies and at the conclusion of the Core Part of the study.

Reviewer comment: The planned procedures to maintain blinding seem reasonable and appropriate, especially the utilization of First Dose Administrators and a separate First

Dose database, because the occurrence of a bradyarrhythmia after the first dose of siponimod would be a potential source of unblinding. Unfortunately, as will be discussed later in this review, some users had inappropriate access to both the main clinical and the first dose database, introducing a potential source of unblinding into the study.

The restriction on reporting of lymphocytes (except in case of an abnormality significant enough to require consideration of a dose change) was a reasonable procedure to attempt to maintain the blind.

The EDSS evaluator's access to the prior EDSS scores is a potential source of bias, as the previous score could affect the disability evaluation and the calculation of subsequent EDSS scores, although careful rigor when performing the EDSS should minimize this issue.

Key Eligibility Criteria

Key Inclusion Criteria (Extracted from study protocol)

- Subjects aged 18 through 60 years of age at screening
- Prior history of relapsing-remitting MS (RRMS) according to the 2010 revised McDonald criteria (Polman et al., 2011)
- Secondary progressive course of MS (SPMS), defined by a progressive increase in disability (of at least 6 months duration) in the absence of, or independent of, relapses
    - Attestation by the investigator in a written statement that the disease had entered the progressive stage (according to the study definition) at least 6 months prior to enrollment
- Disability status at Screening with an EDSS score of 3.0 to 6.5 (inclusive)
- Documented EDSS progression in the 2 years prior to study of ≥1 point for subjects with EDSS <6.0 at screening, and ≥0.5 point for patients with EDSS ≥6.0 at screening. Should documented EDSS scores not be available, a written summary of the clinical evidence of disability progression in the previous 2 years, and retrospective assessment of EDSS score from data up to 2 years prior to screening had to be submitted for central review.
        - Note: A central review of the available clinical evidence of disability progression was required for patients without documented pre-trial EDSS assessments. This was completed by submitting a disability progression form for central adjudication. The central adjudication was led by

(b) (4) and team located at the (b) (4)

- No evidence of relapse or corticosteroid treatment within 3 months prior to randomization

  Reviewer Comment: While the inclusion criteria above seem reasonable, it should be recognized that there is no widely accepted biomarker to distinguish SPMS from RRMS. The clinical distinction between RRMS and SPMS is difficult, especially because relapses can occur in SPMS, worsening of disability can occur in RRMS; furthermore, there is an unknown period of time (estimated to be 2.9 years by Katz-Sand et al., 2014) in which the disease transitions from RRMS to SPMS. The distinction between RRMS and SPMS may be even more difficult in potential subjects who are taking a medication for MS.

  To distinguish siponimod's effect on disability progression from its effect on disability worsening attributable to relapses (and to have a better chance of selecting a population of non-relapsing SPMS), it would have been ideal to stipulate a lack of evidence of relapses for 36 months, although at least 12 (or preferably 24) months may be more realistic from a clinical trial design point of view It is recognized that there is not an accepted period of time without relapses that defines non-relapsing SPMS, even in patients who are not taking an approved therapy for relapsing MS.

  In clinical practice, the criterion for SPMS is often "in the eye of the beholder." In Study A2304, this clinical judgment was represented partially by the inclusion criterion stipulating the necessity of written attestation by the investigator that the subject had entered the "progressive phase" of the disease, as defined by at least 6 months of a progressive disability increase. With that said, OSI's inspections could not locate these attestations at several sites. On January 18, 2019, the sponsor noted in a response to an Information Request that "a specific attestation form for inclusion criterion 4 was not implemented for collection centrally as part of the study protocol," but "believes that the standard documentation practice for this and other eligibility criteria were appropriate." Because of the clinical judgement required to make a diagnosis of SPMS, the fact that these attestations were not collected and thus were not available for review erodes confidence in the claim that the subjects in the study population actually had SPMS, especially as the Kaplan-Meier analyses suggests that over 70% of subjects (even those randomized to placebo) would not experience 6-month CDP after 3-years in the study.

  Subjects also needed to have clinical documentation of EDSS progression in the 2 years prior to the study, although this also was not collected. If this clinical documentation did not exist in the medical record, a written summary of the evidence supporting disability progression over the prior 2 years was to be submitted to (b) (4) *for adjudication; however, OSI found that some of these summaries were not submitted for*

adjudication until after subjects had enrolled in the study. This finding further degrades confidence that CBAF312A2304 enrolled a population of subjects having SPMS.

Key Exclusion Criteria (Extracted from study protocol)

- Subjects with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS or with a known immunodeficiency syndrome.
- Pregnant or nursing (lactating) women.
- Women of child-bearing potential, unless they were using highly effective methods of contraception during dosing and for 30 days after the last dose of siponimod.
- History of malignancy (other than localized basal cell carcinoma of the skin) within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.
- Diabetes mellitus, unless well controlled and without known organ complications such as reduced renal function, significant retinal pathology, or neuropathy.
- Diagnosis of macular edema during pre-randomization phase. Subjects with a history of macular edema were allowed to enter the study provided that they did not have macular edema at the ophthalmic examination at the Screening Visit.
- Subjects with active systemic bacterial, viral, or fungal infections, or known to have acquired immune deficiency syndrome (AIDS) or positive human immunodeficiency virus (HIV) antibody.
- Positive results of screening period testing for serological markers for hepatitis A, B, C, and E indicating acute or chronic infection.
- Negative for varicella-zoster virus IgG antibodies at Screening.
- Received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 2 months prior to randomization.
- Treated with any of the medications listed below (Note: no wash-out period was required in the case of prior treatment with interferon-β or glatiramer acetate):
    - siponimod at any time
    - fingolimod within 2 months prior to randomization, or received fingolimod treatment for more than 6 months

- intravenous immunoglobulin within 2 months prior to randomization
- dimethyl fumarate within 2 months prior to randomization
- natalizumab within 6 months prior to randomization
- immunosuppressive/chemotherapeutic medications (e.g., e.g., azathioprine, methotrexate) within 6 months prior to randomization
- cyclophosphamide within 1 year prior to randomization
- rituximab, ofatumumab, ocrelizumab or cladribine within 2 years prior to randomization
- alemtuzumab at any time
- any mitoxantrone during previous 2 years prior to randomization or evidence of cardiotoxicity following mitoxantrone or a cumulative life-time dose of more than 60 mg/m^2
- teriflunomide within 2 years prior to randomization (unless teriflunomide plasma concentration was zero or without relevant biological significance) OR within 2 weeks prior to randomization following successful accelerated elimination procedure as described in the product label
- lymphoid irradiation, bone marrow transplantation or other immunosuppressive treatments with effects potentially lasting over 6 months, at any time

- Any medically unstable condition as determined by the investigator.
- Any of the following conditions or treatments that may affect cardiovascular function:
  - history of or current significant cardiac disease including cardiac failure (NYHA functional class II-IV), myocarditis, cardiomyopathy, angina pectoris or myocardial infarction (within 6 months), unstable angina (within 6 months), stroke (within 6 months), transient ischemic attach (TIA) (within 6 months), decompensated heart failure requiring hospitalization (within 6 months) or uncontrolled arterial hypertension.
  - cardiac conduction or rhythm disorders including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz Type II second degree AV block or higher-grade AV block (either history or observed at screening), unless patient had a functioning

pacemaker.

- cardiac arrhythmias requiring treatment or a history of cardiac syncope.
- treatment with Class Ia or III antiarrhythmic drugs.
- conditions requiring treatment with medication that may have caused AV block and suppressed AV conduction with the exception of beta-blockers
- patients receiving at randomization (or treatment initiation) heart-rate slowing calcium channel blockers, or other substances that may have decreased heart rate.
- PR interval >230 msec. Long QT syndrome or QTc prolongation (>450 msec in males or >470 msec in females) on screening ECG
- severe autonomic nervous system dysfunction
- cardiac condition requiring catheter ablation
- other cardiovascular conditions or treatments that may have significantly impacted the safety of the patient as determined by the investigator

- Any of the following pulmonary conditions:
  - history of or active severe respiratory disease, including chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis within 6 months prior to randomization
  - tuberculosis, except for history of successfully treated tuberculosis or history of prophylactic treatment after positive PPD skin reaction
  - severe asthma or asthma requiring regular treatment with oral steroids
- Any of the following hepatic conditions prior to randomization:
  - history of alcohol abuse, chronic liver or biliary disease
  - total or conjugated bilirubin greater than 1.5 times upper limit of normal (ULN) range, unless in the context of Gilbert's syndrome
  - alkaline phosphatase (ALP) greater than 1.5 times the ULN range
  - aspartate aminotransferase (AST), alanine aminotransferase (ALT) or

gammaglutamyl-transferase (GGT) >3 times ULN

- Any of the following abnormal laboratory values prior to randomization:
    - serum creatinine >1.7 mg/dL (150 µmol/L)
    - white blood cell (WBC) count <3,500/mm3 (<3.5 x 10^9/L)
    - lymphocyte count <800/mm^3 (<0.8 x 10^9/L)
    - serum potassium > ULN
    - other clinically significant laboratory assessment (i.e., hypomagnesemia or hypokalemia)
- Any of the following neurologic/psychiatric disorders prior to randomization:
    - score "yes" on item 4 or item 5 of the Suicidal Ideation section of the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS), if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for Non-Suicidal Self-Injurious Behavior (NSSI), if this behavior occurred in the past 2 years (if met, the patient was to be referred immediately to a mental health care professional for further assessment and/or treatment);
    - history of substance abuse (drug or alcohol) or any other factor (i.e., serious psychiatric condition) that may have interfered with the patient's ability to cooperate and comply with the study procedures;
    - progressive neurological disorder, other than MS, which may affect participation in the study or require the use of medications not allowed by the protocol
- Patients unable to undergo MRI scans
- Use of other investigational drugs at the time of enrollment or within the prior 30 days, or five elimination half-lives, or until the expected pharmacodynamic effect had returned to baseline, whichever was longer.
- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
- Homozygosity for CYP2C9*3 (tested at Screening) or refusal to test for CYP2C9*3 haplotype
- Use of concomitant medications that are potent inducers of CYP2C9 within four weeks

of the initial dosing.

- Any other disease or condition which could interfere with participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with the study procedures.

Reviewer Comment: These exclusion criteria appear appropriate to guard patient safety. It is concerning that this highly selected population may not represent "real world" people with MS and may underestimate the safety of the drug in a "real world" setting unless similar restrictions on the use of siponimod are adhered to in this setting. For more information on the safety of siponimod, refer to the safety review by Dr. Paul Lee.

The short "washout" for many of the preceding MS drugs (that reduce relapses and new MRI lesions) may mask ongoing inflammatory disease activity and lead to misclassification of late RRMS subjects as having non-relapsing SPMS, thus potentially enriching the study population with subjects with late RRMS and relapsing SPMS.

Treatment

Rationale for dose selection

The siponimod 2 mg dose used in CBAF312A2304 was chosen based on the results of CBAF312A2201, a Phase 2 dose-finding study of siponimod in subjects with RRMS that investigated the safety and efficacy of doses ranging from 0.25 to 10 mg. The primary outcome measure of CBAF312A2201 was the dose-response relationship among five doses of BAF312 and placebo during 3 months of treatment in patients with RRMS, as measured by the number of combined unique active [MRI] lesions (CUAL). To analyze dose-response, the investigators used the multiple comparison procedures with modeling (MCP-mod) statistical technique. Treatment with siponimod 10 mg reduced CUAL by over 80% compared with placebo. The 2 mg dose of siponimod had a similar response on this MRI endpoint, whereas the 0.5 mg dose level showed less evidence of efficacy (reduction of approximately 50% CUAL vs. placebo). Lymphoid sequestration of lymphocytes with siponimod followed a similar dose-response curve. The annualized relapse rate (ARR) was nominally significantly lower with siponimod 2 mg vs. placebo: 0.20 vs. 0.58 (p=0.044). For 0.5 mg, there was no apparent treatment effect on relapses (ARR 0.61), nor was there greater efficacy on relapses seen at the 10 mg dose (ARR 0.30); hence, 2 mg appears to be the optimal treatment dose for the CBAF312A2304 study.

Reviewer Comment: The choice of selecting the 2 mg dose for CBAF312A2304 seems reasonable. It is notable that the 2 mg dose of siponimod in CBAF312A2201 had a statistically significant effect on relapses but the 0.5 and 10 mg doses did not; however, the relevance of these observations may be low as the study arms were not powered to demonstrate an effect on relapses.

First Dose Monitoring

As described above, to preserve blinding of treatment status, the initial dose of study treatment was administered by an independent First Dose Administrator. The First Dose Administrator monitored cardiovascular and pulmonary status and would not divulge findings to patients, the study staff, or the sponsor unless there was a significant medical need to do so.

The dose titration that was introduced in CBAF312A2201 due to the occurrence of bradyarrhythmic events was also used in CBAF312A2304 because this initial-dose titration scheme appeared to reduce the frequency of symptomatic bradyarrhythmic events and asymptomatic atrioventicular-blocks in CBAF312A2201. Patients started treatment in the Core Part with a 6-day titration regimen of siponimod or matching placebo by the schedule outlined in the Table 5 below. Missing a dose of study medication during the titration or missing four or more days of study medication after the titration necessitated a re-titration.

Table 5. Reviewer Table: Titration and Re-titration Regimens, CBAF312A2304

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

Based on prior experience with siponimod (and other S1P agents), higher grade lymphopenia was expected to occur in <10% of patients at the 2 mg/day dose. To potentially reduce the need for treatment interruptions, which would have had a negative impact on the treatment effect, the protocol allowed subjects with lymphocyte counts $<0.2 \times 10^9$/L at 2 consecutive visits on the 2 mg/day dose level to switch to 1 mg/day, albeit in a blinded fashion.

Siponimod (0.25, 0.5, 1, and 2 mg) and dose-matched placebo were provided as film-coated tablets that were identical in appearance. Study drug for titration was packaged in blister cards that were dispensed for initial titration and re-titration. Study drug to be used for maintenance dosing was supplied in bottles containing fifty-five tablets (1 mg, 2 mg, or placebo).

Patients with confirmed 6-month disease progression were offered open-label siponimod during the Core Part. The open-label drug supply also consisted of film-coated tablets. All subjects starting the open-label extension were required to repeat the dose titration. The 2 mg titration packs for open-label siponimod were blister packs containing the following dosage strengths: 0.25, 0.5, 1, and 2 mg, and the 1 mg titration packs contained tablets of 0.25, 0.5, and 1 mg. Open-label siponimod for maintenance dosing was supplied in bottles containing fifty-five tablets (1 or 2 mg).

Reviewer Comment: Even though siponimod is deemed to selectively modulate S1P-1 and S1P-5, some subjects developed bradyarrhythmias after starting siponimod, thereby necessitating a 6-day dose titration and initial cardiac monitoring, particularly in at risk subjects. Presumably, this suggests that the modulation of S1P-1 plays more of a role in cardiac dysrhythmias than initially thought and may make the initiation of siponimod somewhat more cumbersome than fingolimod, a non-selective S1P agent.

The attempt to make the appearance of the siponimod and placebo tablets identical is appreciated, as this was an important step in maintaining the integrity of study blinding.

Concomitant Medications

The investigator instructed subjects to notify the study site about any new medications taken or prescribed after enrollment. Recording of all medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after enrollment in the study was required.

The protocol allowed enrollment of subjects who were being treated with a stable dose of (dal)fampridine. Subjects were not to change or start treatment with (dal)fampridine while on double-blind study drug, except if discontinuing (dal)fampridine due to unmanageable adverse events (AEs), in which case it was recommended that this first be discussed with the Novartis Medical Advisor.

Starting treatment with QT-prolonging or heart rate-lowering medications during study treatment initiation (i.e., the first 10 days) was to be avoided. For subjects receiving a stable dose of beta-blocker, resting heart rate was considered before starting study drug:

- If the resting heart rate was >50 bpm under chronic beta-blocker treatment, study drug could be introduced according to procedures for the Expanded Cardiac Monitoring Group.

- If resting heart rate was ≤50 bpm on a beta-blocker, study treatment was not to be initiated. The investigator was to carefully evaluate the individual risk-benefit relationship and the established guidelines depending on the type of beta-blocker being used and consider potential interruption of this beta-blocker treatment until the resting heart rate was >50 bpm. If it was decided to interrupt beta-blocker treatment, the investigator was to proceed with caution. Once the resting heart-rate was >50 bpm, study drug could have been initiated, and beta-blockers could have been re-started after 2 weeks of treatment with the study drug. Monitoring was not only to be limited to the heart rate-related effects but also to include symptoms related to arrhythmia and bradycardia.

- Introduction of beta-blocker treatment was allowed in subjects who were receiving a

maintenance dose of study treatment (i.e., at steady state).

The use of medications listed in the Study A2304 exclusion criteria (see above) was prohibited while the subject was on study drug. Concomitant use of the following medications or therapies was prohibited or allowed with provisions as indicated:

Prohibited, requiring discontinuation of study treatment:

- Immunosuppressive/chemotherapeutic medications or procedures, including cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, lymphoid irradiation and hematopoietic stem cell transplantation

- Monoclonal antibodies targeting the immune system, including natalizumab, rituximab, ofatumumab, ocrelizumab and alemtuzumab

Required interruption of study treatment and increased monitoring for infection:

- Any other immunomodulatory or disease-modifying MS treatment including, but not limited to: fingolimod, interferon beta, glatiramer acetate or systemic corticosteroids (except when given for MS relapse treatment)

Discouraged, but if used required ECG and clinical status assessment:

- Any concomitant medication that inhibits cardiac conduction (e.g., verapamil-type and diltiazem-type calcium channel blockers or cardiac glycosides)

Could be given without further action:

- Potent inducers of CYP2C9, such as barbiturates, rifampin, carbamazepine, phenytoin, phenobarbital, and St John's wort.

Reviewer Comment: The restrictions on concomitant medications seems reasonable, although treatment of comorbidities and initiation of exercise or rehabilitative programs may also influence disability outcomes (Berrigan et al, 2016, Petajan et al 1996, Haselkorn et al, 2015).

Treatment of Relapses

The protocol allowed treatment for a relapse consisting of a standard course of intravenous corticosteroids (up to 1000 mg/day methylprednisolone for three to five days), as clinically warranted. Standard of care procedures were to be followed during treatment. Tapering with oral corticosteroids was not allowed.

Reviewer Comment: In some cases, steroids appear to have been given for unconfirmed

relapses (experienced by 8.7% of the CBAF312A2304 study) or even worsening symptoms in the setting of fever or infection (Uhthoff's phenomenon). Decisions to treat confirmed relapses (or give steroids for unconfirmed relapses) may depend on relapse severity as well as differences in practice style and subject preferences. This would not be expected to influence the time-to event primary endpoint of CBAF312A2304 (time to 3-month CDP progression). See the section on "Rescue Medication Use" below.

Assessments

The visit schedule of assessments for all subjects is summarized in the table below.

Table 6. Sponsor Table. CBAF312A2304 Visit Assessments

Epoch	Screening		Treatment																	Follow up
Visit[1]	SCR D-45 to -8[2]	BL D-7 to D1[3]	D1	D7	D28	M3	M6	M9	M12	M15	M18	M21	M24	M27	M30[4]	M33[5]	M36[6]	EOT	EOS	FO
Visit No.	1	2	101	103	104	105	106	107	108	109	110	111	112	113	114	115	116	2900.1	199	201
Incl/Excl	X	X																		
IVRS call	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug[7]			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EDSS	X	X[8]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
T25W, 9-HPT	X	X[8]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PASAT, SDMT, LCVA		X[8]	X				X		X		X		X		X		X	X	X	
BVMT-R		X					X		X		X		X		X		X	X	X	
MRI		X							X				X				X	X	X	X
Physical exam, MS relapse, vital signs, medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X					X		X		X		X		X		X	X	X	
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab samples[9,10]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]
ECG	X		X[3]	X[3]		X			X				X				X	X	X	
Ophtha +OCT, PFTs	X					X			X				X				X	X	X	

Dermatology Exam	X								X				X				X	X	X	
Pop PK Samples[12]					X	X			X				X							
Biomarkers[3]		X				X							X					X	X	
PRO[13]		X[8]	X				X		X		X		X		X		X	X	X	
eC-SSRS	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

LCVA=low contrast visual acuity; PRO=patient-reported outcome
Procedures greyed out were not required for patients following the abbreviated schedule.
1 Visit windows were allowed for: ±1 day for Day 7, ±7 days for Day 28 and the Follow up (FO) visit, and ±14 days for the every 3 month visits during the Treatment Epoch
2 Screening (SCR) also included informed consent, demography, medical history, prior treatments, serology testing, CYP2C9 haplotype
3 Baseline (BL) (pre-treatment), M24, EOT and EOS also included HRCT assessments for approximately 100 patients enrolled and not requiring expanded pulmonary monitoring, but not required if the patient was following the abbreviated schedule. A pharmacogenetic blood sample was also taken at BL visit.
4 Repeat for Month 42 and Month 54
5 Repeat for Month 39, Month 45, Month 51, and Month 57
6 Repeat for Month 48
7 Study drug dispensed and unused medication retrieved. Study drug could also have been dispensed at unscheduled visit if indicated.
8 Assessments conducted at either the Baseline OR the Day 1 visit before the first dose of study treatment
9 Patients were required to be fasting for 12 hours (for fasting lipids and or biomarker studies) at SCR, M24, End of Treatment (EOT) and End of Study (EOS); and for 4 hours at Baseline and Month 3 (biomarker studies).
10 Serum pregnancy tests at SCR, EOT, and EOS visits for female patients of childbearing potential. Urinary pregnancy tests on Day 1 prior to dosing, at all other scheduled visits through EOS, and monthly between clinic visits (recorded in patient diary).
11 Laboratory assessments were repeated at FO visit if abnormal values were detected at the EOT or EOS visit.
12 PK sampling: dose administered at the site. Day 28 and Month 12 required pre-dose samples. For Month 3 and Month 24, 3 hours post dose were requested. Post-dose PK samples were also performed when all confirmatory lymphocyte level assessments (i.e., 1 week after a dose change, at the 'post-dose switch' visit).
13 PRO scales included MSIS-29, MSWS-12, EQ-5D. A PRO completion form was also completed at these visits.

Expanded Cardiac Monitoring

Subjects were assigned to a Cardiac Standard group or an Expanded Cardiac Monitoring Group based on the presence of risks for cardiovascular disease or AV conduction slowing (including treatment with beta-blockers) on their medical history or screening assessments. Expanded cardiac monitoring (ECM) included hourly vital signs for the first 6 hours and an EKG 3 and 6 hours after the first dose of the study medication was administered. ECM also included mobile cardiac telemetry (or a Holter monitor) until study day #7, on which an EKG was done 3 and 6 hours after that day's dose of study medication. ECM was initially performed in all subjects; however, amendment 1 altered the protocol so ECM was only necessary in subjects who met certain criteria (Expanded Cardiac Monitoring group). Despite that, most subjects had extensive cardiac assessments. See Table 7.

Table 7. Reviewer Table: Titration and Re-titration Regimens, CBAF312A2304

Subgroup type **Patient Characteristic**	**Siponimod N=1099** **n (%)**	**Placebo N=546** **n (%)**
Cardiac		
Expanded Cardiac Monitoring Group	358 (32.6%)	174 (31.9%)
Cardiac Standard Group		
Patients with extensive cardiac assessments	628 (57.1%)	311 (57.0%)
Patients with standard cardiac assessments	113 (10.3%)	61 (11.2%)

Reviewer Comment: Most subjects in CBAF312A2304 had expanded cardiac monitoring, including mobile cardiac telemetry (or Holter monitoring) during the first week of study drug. This seems appropriate given the risk of bradyarrhythmias with siponimod.

Study Endpoints

The study protocol specifies that the primary endpoint and two "key" secondary endpoints were to be tested in hierarchical order.

Primary Efficacy Endpoint

The primary endpoint of this study was the time to 3-month confirmed disability progression (CDP) as measured by the EDSS in subjects with SPMS. The study defined 3-month disability progression as a 1.0-point increase in EDSS from baseline for subjects with an EDSS between 3.0 and 5.0 (or 0.5-point increase for subjects with an EDSS of 5.5 – 6.5) that persisted until a scheduled visit 3 months after the initial disability progression (DP). Although disability progression could begin with a relapse, the confirmatory 3-month EDSS could not be done during an MS relapse; however, one could question how long a relapse lasts and whether recovery from some relapses can take over 3 months.

> *Reviewer Comment: This is a time to event analysis. This is a reasonable design, although the event in question (CDP) can occur due to a relapse (inflammatory event) or progression ("degenerative" event) as discussed in the Analysis of Condition section of this review.*

"Key" Secondary Endpoints

The first "key" secondary endpoint in the prespecified hierarchical analysis is the time to a 3-month confirmed 20% worsening on the timed 25-foot walk (T25FW) test. The Timed 25 Foot Walk (T25FW) is one of the three components of the Multiple Sclerosis Functional Composite (MSFC). Its value is the average of two 25-foot walk trials (timed in seconds), and a difference of 20% or more is deemed to be clinically significant. The T25FW was assessed every 3 months in the core part of this study.

The second "key" secondary endpoint in the prespecified hierarchical analysis is change from baseline in T2 lesion volume. Annual brain MRI scans were performed according to prespecified protocols and quality requirements that were outlined in the site MRI Manual. These scans included T1-weighted images (with and without gadolinium) and T2-weighted proton density and FLAIR sequences. A local neuro-radiologist reviewed the study for pathology that was not related to MS. A blinded centralized reading center assessed the quality of the scans and analyzed the MRI per prespecified protocols. The MRI was not to be performed within 30 days of the administration of steroids for an MS relapse.

> *Reviewer Comment: Given the emphasis that the EDSS places on ambulation in the middle of the scale (between 4 and 7) and the correlation between SPMS and ambulatory dysfunction (Confavreux et al, 2000), the inclusion of T25FW as a "key"*

secondary endpoint seems very appropriate. As the incidence of new T2 lesions decreases in SPMS (especially later SPMS or non-relapsing SPMS), the value of the change in T2 lesion volume "key" secondary endpoint is less clear for an SPMS study.

Other Secondary Endpoints (Extracted from study protocol)

1. To evaluate the efficacy of BAF312 relative to placebo in delaying the time to 6-month CDP
2. To evaluate the efficacy of BAF312 relative to placebo in reducing the frequency of confirmed relapses as evaluated by the annualized relapse rate (ARR), and to evaluate time to first relapse and proportion of relapse-free patients
3. To evaluate the effect of BAF312 compared to placebo on the patient reported outcome Multiple Sclerosis Walking Scale (MSWS-12)
4. To evaluate the efficacy of BAF312 compared to placebo with respect to inflammatory disease activity and burden of disease, as measured by conventional MRI (T1 Gd-enhancing lesions, new or enlarging T2 lesions, brain volume).
5. To evaluate the efficacy of BAF312 relative to placebo on 3-month confirmed disability progression as measured by EDSS in the following subgroups:
    a. SPMS patients with or without superimposed relapses
    b. Rapidly evolving patients, defined as 1.5 point or greater EDSS change in the 2 years prior to study start, and in those not meeting this criterion
    c. Patients with moderate and severe disease course, as defined by Multiple Sclerosis Severity Score (MSSS) of 4 or more at baseline, and in those not meeting this criterion
6. To evaluate the safety and tolerability of BAF312 vs. placebo

Relapses are a secondary endpoint of interest. CBAF312A2304 defined relapses as "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 must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or known infection." Study subjects were instructed to notify the treating neurologist of new symptoms potentially meeting this definition and to be evaluated and treated, ideally within 7 days of the onset of these symptoms. If this assessment suggested that the symptoms may represent a relapse, a blinded EDSS was performed by the evaluating neurologist to confirm the relapse. Relapse confirmation required an increase of at least 0.5 points from the previous (non-relapse) EDSS or an increase of 1 point on two (or 2 points on one) EDSS functional system(s), excluding changes in the bowel/bladder and cerebral functional systems. ARR was calculated for each subject as the number of relapses X 365.25 (days/year) ÷ time on study (days).

Reviewer Comment: These additional secondary endpoints seem reasonable.

Statistical Analysis Plan

Below is this reviewer's interpretation of the statistical analysis plan (SAP). See the Biometrics review by Dr. Xiang Li for a more detailed discussion of the SAP.

Analysis population

Efficacy analyses were performed on the population (Full Analysis Set or FAS) of randomized subjects who received at least one dose of study medication. Subjects who stopped the assigned study medication were encouraged to continue to be followed in the study.

Endpoints

CBAF312A2304 is a time to event trial. It utilizes a hierarchical analysis for its primary and two secondary endpoints that were classified as "key."

The primary endpoint is the time to 3-month confirmed disability progression (CDP), expressed as a hazard ratio and analyzed by a Cox proportional hazards model with treatment, country, baseline EDSS, and SPMS subgroup (subjects with or without superimposed relapses) as covariates. Kaplan-Meier curves and log rank tests were also performed. Data were not imputed for subjects who discontinued the study after a disability event but before 3-month confirmation of that event, although a sensitivity analysis was performed in which it was assumed that these subjects would have had 3-month CDP. Subjects who did not experience a 3-month CDP event during the study were censored on the date of the last EDSS assessment.

The first "key" secondary endpoint was time to 20% worsening on the Timed 25 Foot Walk (T25FW) test. Analysis of this "key" secondary endpoint also utilized a Cox proportional hazards model with treatment, country, baseline EDSS, and SPMS subgroup as covariates.

The second "key" secondary endpoint was an MRI endpoint, namely the change in T2 lesion volume from baseline. Analysis of this "key" secondary endpoint used a mixed model for repeated measures (MMRM) with visit as a categorical variable and an unstructured covariance matrix.

Other secondary endpoints were assessed with an alpha = 0.05 significance level. There was no correction for multiplicity for these "non-key" secondary endpoints.

Power

Per the CSR:

> "The study was designed to have 90% power to detect a 30% reduction in the risk of 3-month CDP (hazard ratio of 0.70), using a log-rank test with 2-sided alpha level of 5% and 2:1 randomization of siponimod to placebo.

> Assuming a 2-year proportion with disability progression of 0.30 in the placebo group, a 2-year drop-out rate of 20%, and an enrollment rate of 100 patients per month, 1530 patients and an overall study duration of approximately 42 months were required to observe at least 374 patients with disability progression, which would give the required power. In this calculation, exponential distribution assumptions were used for the event and drop-out rates.
>
> The protocol was amended to update the criterion for stopping the Core Part of the study from 374 patients with 3-month CDP had been observed (original plan) to approximately 3 years after randomization of the first patient and at least 374 events observed. At approximately 3 years, it was expected that more than 374 patients with 3-month CDP had been observed. This was expected to compensate for the slight power loss due to the alpha adjustment for the interim analysis and a power of at least 90% was expected at the end of the Core Part."

Interim Analyses

The sponsor states that an unblinded interim analysis (IA) for futility was performed by a group (b) (4) that was independent of the study and by "independent programmers from Novartis all bound by a confidentiality agreement.". This IA was presented to the Data Monitoring Committee (DMC) in July of 2015, after which the DMC recommended continuation of CBAF312A2304 because the futility criterion was not reached (the 3-month CDP HR was 0.71). A planned blinded sample size re-estimation (BSSR) was performed in November of 2014, after which the DMC recommended not increasing the sample size.

Efficacy was reportedly not considered in the futility IA, and no further IAs were performed other than the two mentioned above. The DMC minutes from meetings before the futility IA mention (b) (4)

> *Reviewer Comment: An IR was received from the sponsor on 9/4/2018 regarding interim analyses. This IR includes the statements, "no stopping for efficacy based on the IA results was considered, although the protocol includes a p-value criterion for an early stopping for efficacy," "the set of futility IA results delivered to the DMC also included analyses by treatment group for the following efficacy variables: 6mCDP, relapse, MRI variables, timed 25-foot walk test," and "3mCDP HR=0.71 in overall population." Despite that response,* (b) (4)

Protocol Amendments

There were four protocol amendments to the original CABF312A2304 protocol.

Table 8. Reviewer Table: Synopsis of Protocol Amendments, CABF312A2304

Amendment	Release Date	Major Changes	Number of Subjects
1	05/26/2014	• Discontinue 6-hour first-dose observation requirement in subjects with a normal cardiovascular status • Reduce number of study epochs to 3 (Screening, Treatment, and Follow-up) • Permit the use of beta-blockers in the study • Contraception should be used for 30 days after the last dose of siponimod (increased from 7 days) • Add conditions for dimethyl fumarate and teriflunomide to the exclusion criteria • Remove exploratory cognitive sub-study	>1200 screened
2	03/05/2015	• Update the rule and timing of the planned futility analysis	>1500 randomized
3	10/06/2015	• Add open-label Extension Part added to study • Modify study stopping criteria to at least 374 3-month CDP events AND at least 95% of subjects having been assigned to treatment for at least 12 months • Analysis of change in T2 lesion volume changed to a repeated-measures mixed effects model	1651 randomized
4		• Clarify and justify the study duration (up to 84-month Extension Part) • Remove reference to electronic EDSS	1651 randomized

Data Quality and Integrity

A sponsor representative reviewed the study protocol and CRFs with study staff site at the site initiation visit or an investigator's meeting. Site monitors periodically visited study sites to review the completeness and accuracy of the collected data, adherence to the protocol and Good Clinical Practice (GCP), and study medication handling.

EDSS raters were trained and required to achieve Level C certification (the highest level) on a computerized assessment (Neurostatus eTest). Validation algorithms were utilized by the data entry system to improve the quality of the data.

> *Reviewer Comment: Many MS studies utilize the Neurostatus program to certify EDSS raters, and a pilot study suggests that Neurostatus e-Scoring (NESC) improves the*

consistency of EDSS assessments (D'Souza et al, 2016).

6.1.2. Study Results

Compliance with Good Clinical Practices

In Section 5.2 ("Ethical conduct of the study"), the sponsor states "this clinical study was designed, implemented, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki." The study protocol and the 4 amendments were to be approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each site before study initiation. An informed consent document (ICD) was to be completed for each subject before that subject engaged in any study procedures. Subject reconsent was required for subjects who experienced 6-month disability progression, a severe relapse, or 2 confirmed MS relapses. Consents were also required from subjects entering the extension study, participating in the pharmacogenetic component, or agreeing to a sub-study.

The CSR also states, "audits were conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs [Standard Operating Procedures], and are performed according to written QA [Quality Assurance] SOPs."

Financial Disclosure

Module 1, Section 1.3.4 of the NDA includes information regarding financial certification and disclosure. This section includes Form FDA 3454 indicating there were no financial arrangements with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR54.2(a). A list of investigators with any financial interest in the outcome of the study is included in this section of the NDA: almost all disclosures were "significant payments of other sorts," although one investigator disclosed that his wife is an employee of Novartis and holds stock options below $50,000.

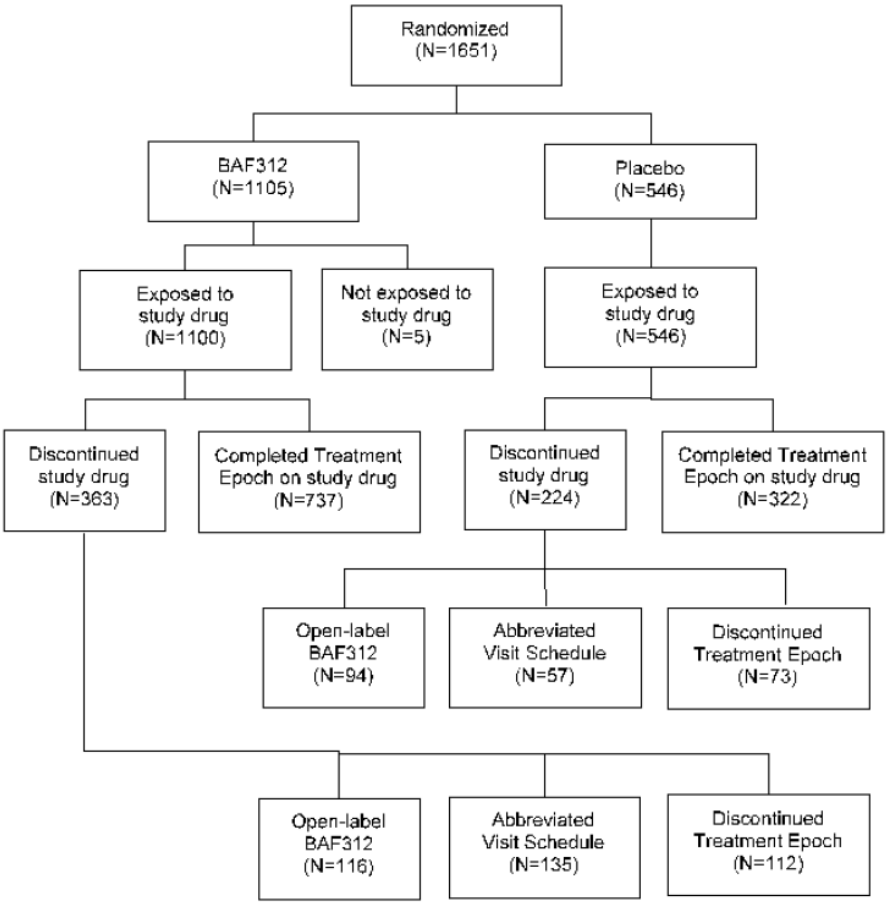
Patient Disposition

First subject randomized: 02/05/2013
Last subject randomized: 06/02/2015
Study completion date (Core Part): 4/29/2016

2092 subjects were screened to participate in CBAF312A2304 and 1651 were enrolled and randomized. The primary analysis was performed on the Intent to Treat (ITT) population, which

consisted of all randomized subjects who received one or more doses of the study medication. Five subjects were randomized to siponimod but not treated, and one subject did not provide informed consent; therefore, the ITT population or Full Analysis Set (FAS) included 1645 subjects. The disposition of subjects is summarized in Figure 4.

Figure 4. Sponsor Figure: Patient Disposition during Treatment Epoch, CBAF312A2304



More subjects remained on the study treatment assigned at randomization during the treatment epoch in the siponimod (66.7%) arm compared with the placebo (59.0%) arm. Of those who prematurely discontinued the assigned study treatment, many (32.0% in the siponimod arm, 42.0% in the placebo arm) transitioned to open label siponimod, which was allowed after a subject experienced 6-month CDP. Some of the others who stopped the assigned study treatment (37.2% in the siponimod arm, 25.4% in the placebo arm) continued to be followed in an abbreviated visit schedule, in which they did not take study medication but could take a commercially available MS medication. 10.1% of subjects randomized to siponimod (and 13.4% of those randomized to placebo) discontinued the Treatment Epoch and the study.

Reviewer Comment: The percentage of subjects who completed the treatment epoch on the study treatment assigned at randomization seems quite low, although a significant percentage of these subjects transitioned to open-label siponimod or the abbreviated visit schedule, in which they could take another available MS drug. Despite that caveat, the number of subjects who discontinued the study drug assigned at randomization in CBAF312A2304 is higher than that in other MS clinical trials of comparable scope. These low rates of completion on the study treatment assigned at randomization decreases confidence in the study results. In the FREEDOMS trial of fingolimod (Kappos et al, 2010), 81% of subjects completed the study on active drug (72% on placebo). Similarly, 74% of subjects in the TEMSO study (O'Connor et al, 2011) completed the study on teriflunomide (71% for placebo). In the studies of dimethyl fumarate (Gold et al, 2012, Fox et al, 2012), the completion rates on active drug (69% for DEFINE, 71% for CONFIRM) and placebo (65% for DEFINE, 64% for CONFIRM) were also higher than those in CBAF312A2304 (67% siponimod, 59% placebo).

All 5 subjects who were randomized but not exposed to study drug were in the siponimod arm.

The sponsor disposition analysis states that 81.7% of subjects randomized to siponimod (and 77.7% of subjects randomized to placebo) completed the Treatment Epoch, but this seems independent of the therapy subjects were taking when they completed the Treatment Epoch. With the caveat that the reason given for dropping out of a study may be inaccurate, the most common reasons for discontinuing the Treatment Epoch (per the sponsor's definition) were "Subject / Guardian Decision," "Adverse Event," and "Lack of Efficacy." See Table 9.

Table 9. Sponsor Table: Patient Disposition at end of Treatment Epoch

	BAF312 N=1105 n (%)	Placebo N=546 n (%)	Total N=1651 n (%)
Completed Treatment Epoch	**903 (81.7)**	**424 (77.7)**	**1327 (80.4)**
Discontinued Treatment Epoch	**202 (18.3)***	**122 (22.3)**	**324 (19.6)**
Primary reason for not completing Treatment Epoch			
Subject/guardian decision	96 (8.7)	77 (14.1)	173 (10.5)
Adverse event	45 (4.1)	18 (3.3)	63 (3.8)
Lack of efficacy	16 (1.4)	11 (2.0)	27 (1.6)
Physician decision	13 (1.2)	1 (0.2)	14 (0.8)
Pregnancy	0	0	0
Lost to follow-up	9 (0.8)	8 (1.5)	17 (1.0)
Progressive disease	8 (0.7)	4 (0.7)	12 (0.7)
Non-compliance with study treatment	5 (0.5)	0	5 (0.3)
Protocol deviation	3 (0.3)	1 (0.2)	4 (0.2)
Death	3 (0.3)	1 (0.2)	4 (0.2)
Technical problems	2 (0.2)	0	2 (0.1)
New therapy for study indication	2 (0.2)	1 (0.2)	3 (0.2)

* Includes 5 patients who were not exposed to study drug.

Reviewer Comment: Analyzing all subjects who discontinued the study treatment assigned at randomization and trying to identify the precise reason for discontinuing this treatment would have been much more beneficial. Although seemingly common practice, inclusion of "Subject / Guardian Decision" in the list of potential reasons to discontinue the Treatment Epoch lessens the utility of this analysis, especially as it was by far the most common reason for not completing this epoch. Further, subject / guardian decisions may be influenced by physician preference, which may be informed by a spectrum of factors ranging from intuition to unblinding.

Protocol Violations/Deviations

There were 1,951 protocol deviations in 1,028 subjects.

Table 10. Reviewer Table: Protocol deviations, CBAF312A2304

Category	N
GCP-related deviation	541
Key procedures not performed as per protocol	993
Prohibited concomitant medication	123
Selection criteria not met	151
Subject not withdrawn as per protocol	5
Treatment deviation	138

Source: DVCAT field of updated dv.xpt (CSR Amendment 1)

The "Selection Criteria Not Met" protocol deviation is of special interest. There were 39 codes (DVSPID) used to stratify this type of deviation, although their free text descriptions suggest significant overlap between these codes. Prohibited concomitant medication had its own category and was a subcategory of selection criteria deviations. With these analytic complications, the most common and relevant protocol deviations in regard to subject selection criteria are shown in Table 11.

Table 11. Reviewer Table: Protocol deviations with selection criteria, CBAF312A2304

Category	Criterion	Siponimod	Placebo	Total
Inclusion	Did not meet disability progression	8 (0.7%)	3 (0.5%)	11 (0.7%)
Exclusion	Prohibited medication before / at randomization	41 (3.7%)	12 (2.2%)	53 (3.2%)
Exclusion	Positive hepatitis serologies	15 (1.4%)	7 (1.3%)	21 (1.3%)

Source: updated dv.xpt (CSR Amendment 1)

Reviewer Comment: Somewhat surprisingly given the challenges in distinguishing late RRMS from relapsing (or non-relapsing) SPMS (Katz-Sand et al., 2014), there were very few deviations (<1%) regarding subjects who did not meet the criterion for disability

> *progression. Although this may be attributable to the SPMS attestations (and the adjudication of 2-year disability progression in subjects who did not have clinical documentation of EDSS progression over this time), it is very concerning that the sponsor did not collect (and thus is unable to provide) the notes of attestation supporting SPMS and that some of the adjudications occurred after randomization. These issues raise serious questions about whether the study population in this single trial supporting an indication of SPMS actually had SPMS.*

Because a reduction in heart rate after the first dose of siponimod could negatively affect study blinding, an independent team performed the first dose observations, and the "First Dose" database was separate from the "Main" study database. Before the database lock of the Core Part of the Study, it was learned that study personnel at 48 sites were inadvertently granted access to both databases (dual database access). Affected subjects were assigned a GCP01 ("Not following per protocol blinding procedures but integrity of the study is not compromised (Dual database access") protocol deviation. After initial submission of the NDA, the sponsor learned of more study personnel with dual database access, so an amendment to the NDA was submitted on 7/26/2018. This amendment updated the numbers of dual database access PDs and divided them into GCP01 (dual database access by the primary team) and GCP10 (dual database access by the first dose team). See Table 12.

Table 12. Reviewer Table: Dual Database Access Deviations, CBAF312A2304

PD Code	Description	Siponimod N (%)	Placebo N (%)	Total N (%)
GCP01	Dual database access by the Primary Team	107 (9.7%)	54 (9.9%)	161 (9.8%)
GCP10	Dual database access by the First Dose Team	69 (6.2%)	37 (6.8%)	106 (6.4%)

Source: Updated dv.xpt (CSR Amendment 1)

In addition, the following text was struck out in the CSR amendment: "~~In the electronic audit trail maintained for these systems there was no evidence of site staff accessing/ modifying the 'incorrect' database.~~" Because of this, an IR was sent to the sponsor inquiring why this text was deleted: the sponsor's response states that inappropriate modifications by "First Dose" users were made to the "Main" database in 11 subjects, 9 of whom were randomized. Users of the "Main" database modified data in the "First Dose" database for 10 patients. This IR also requested a copy of the database audit logs; however, the sponsor stated that an audit log of database access was no longer available but that an audit log for database modifications was available and allowed the inappropriate data modification analysis. An audit trail of the 1082 inappropriate edits (by 5 users) to the "Main" database was provided as an Excel spreadsheet. Further exploration (and OSI's inspection of the sponsor) revealed that eighty-two sites in the CBAF312A2304 study experienced issues with "dual database access" in which 32 users of the

main database had inappropriate access to a first dose database, potentially affecting outcome measures for 101 subjects.

> *Reviewer Comment: This "Dual Database Access" issue is very concerning. Although inappropriate data modifications seem to have made in only a few instances, the possibility that an investigator could access the database to determine treatment assignment raises concerns about the integrity of treatment blinding at the affected sites. The reported lack of a user access audit trail does not allow analysis of the scope of potential unblinding caused by this dual database access issue or provide assurance that this issue did not influence study data or outcomes.*
>
> *Although the sponsor provided a sensitivity analysis suggesting that the results of the Timed 25-foot walk were not affected by this dual database access issue, this is not very reassuring, as multiple other clinical considerations besides the T25FW measurement, up to recommending that a subject discontinue the trial, can be influenced by the degradation of the study blind. For the same reason, the analyses (annualized relapse rate, symbol digit modality test, and MRI metrics in the subset of subjects affected by the dual database access issue) included in the "impact analysis" received on 1/15/2019 do not negate the unblinding concerns raised by the dual database access issue.*

Table of Demographic Characteristics

The treatment groups appear balanced for baseline key demographic characteristics. Approximately 60% of the subjects are women, which is typical for MS (either RRMS or SPMS) trials. Because SPMS is typically thought to occur about 15 years after RRMS is diagnosed, which is commonly around age 30, the population's median age of 49 years is consistent with SPMS, albeit early SPMS because MS only reduces one's lifespan by an average of 7 years compared with the general population (Marrie et al, 2015). Over 90% of the subjects are Caucasian. Less than 10% of the subjects are from the US. See Table 13.

Table 13. Reviewer table: Baseline Demographic Characteristics, CBAF312A2304

Demographic Parameters	Siponimod (n=1105[1])	Placebo (n=546)
Sex		
Male	436 (39%)	223 (41%)
Female	669 (61%)	323 (59%)
Age (years)		
Mean (SD)	48.0 (7.8)	48.1 (7.9)
Median	49	49
Min, max	22,61	21,61
Age group		
≤45 years	394 (35.7%)	199 (36.5%)

Demographic Parameters	Siponimod (n=1105[1])	Placebo (n=546)
>45 years	711 (64.3%)	347 (63.6%)
Race		
White	1050 (95.0%)	513 (94.0%)
Black or African American	7 (0.6%)	3 (0.5%)
Asian	31 (2.8%)	18 (3.3%)
Other / Unknown	17 (1.5%)	12 (2.2%)
Ethnicity		
Hispanic or Latino	74 (6.7%)	32 (5.9%)
Not Hispanic or Latino	829 (75.0%)	410 (75.1%)
Other / Unknown	202 (18.3%)	104 (19.1%)
Region		
United States	102 (9.2%)	52 (9.5%)
Rest of the World	1003	494
Canada	32 (2.9%)	15 (2.7%)
South America	20 (1.8%)	10 (1.8%)
Europe	810 (73.3%)	401 (73.4%)
Asia	117 (10.6%)	56 (10.3%)
Australia	24 (2.2%)	12 (2.2%)

Source: ADSL

[1] Five subjects randomized to siponimod never took study medication. Another subject randomized to siponimod never signed the informed consent. These 6 subjects are excluded from the subsequent analyses.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

As per Table 14, the treatment groups are balanced for key disease characteristics at baseline, including EDSS, years since diagnosis, and previous treatment for MS. They are also balanced for the MS Severity Score (MSSS), a decile scale rating of disease severity derived from a subject's EDSS and years of disease duration (Roxburgh et al, 2005).

Table 14. Reviewer table: Other Baseline Characteristics, CBAF312A2304

Other Characteristics	Siponimod	Placebo
Baseline EDSS		
Mean (SD)	5.4 (1.1)	5.2 (1.0)
Median	6.0	6.0
<4 (%)	110 (10.0%)	51 (9.3%)
≥4 (%)	995 (90.0%)	495 (90.7%)
Baseline T25FW (seconds)		
Mean (SD)	17.1 (20.8)	16.0 (22.1)
Median	10.3	9.6
Baseline MS Severity Score (MSSS)		
Mean (SD)	5.83 (1.87)	5.95 (1.81)

Other Characteristics	Siponimod	Placebo
Median	5.99	6.24
Years since MS Diagnosis[1]		
Mean (SD)	12.9 (7.9)	12.1 (7.5)
Median	11.9	11.2
<5 years	190 (17.2%)	106 (19.4%)
5-10 years	268 (24.3%)	140 (25.6%)
>10 years	645 (58.5%)	300 (55.0%)
Relapses in previous 2 years[2]		
0 relapses	712 (64.4%)	343 (62.8%)
1 relapse	199 (18.0%)	104 (19.0%)
2 relapses	108 (9.8%)	57 (10.4%)
3 relapses	50 (4.6%)	24 (4.4%)
≥4 relapses	33 (3.0%)	17 (3.1%)
Baseline gadolinium-enhancing lesions[3]		
0 enhancing lesions	833 (75.4%)	415 (76.0%)
≥1 enhancing lesions	237 (21.4%)	114 (20.9%)
Previous treatment for MS		
Interferon	691 (62.5%)	348 (63.7%)
Any MS medication	860 (77.8%)	432 (79.1%)
Use of important concomitant medications		
Fampridine (and similar meds)	238 (21.5%)	114 (20.9%)

Source: ADBS

[1] Data missing for 2 subjects in siponimod arm. [2] Data missing for 4 subjects. [3] Data missing for 52 subjects.

Reviewer Comment: The groups appear relatively well matched. The mean number of years since diagnosis (12.9 years in the siponimod arm, 12.1 years in the placebo arm) suggests a population of subjects with late relapsing-remitting or early SPMS. A significant number of subjects in this trial exhibited clinical evidence of an inflammatory phenotype (relapsing disease), because over 1/3 of subjects had a relapse in the two years before the trial, and almost 25% of subjects had a gadolinium-enhancing lesion at baseline. This seems somewhat higher than expected for an SPMS population, because relapses and MRI activity are thought to be less common in this stage of the disease. Further, almost 80% of subjects had been on a previous MS medication, which may alter the degree of observable inflammatory disease in some subjects, depending on the prior MS drug and the time between cessation of that agent and entry into CBAF312A2304. It is reassuring the rates of the use of dalfampridine are balanced in this study.

Exposure

The number of days that subjects remained on study drug was similar in the siponimod and placebo arms of the study, as per Table 15 .

Table 15. Reviewer table: Number of Days before stopping study treatment, CBAF312A2304

Treatment Arm	Total study exposure	Mean subject exposure	Stddev subject exposure	Median subject exposure	Minimum subject exposure	Maximum subject exposure
Siponimod (Days)	611713	556.1	251.5	541.5	1	1103
Placebo (Days)	295510	541.2	233.0	530	6	1083

Source: ADTTE.PARAMCD = TTRTDIS

Treatment Adherence, Concomitant Medications, and Rescue Medication Use

Treatment Adherence

A response to an IR regarding treatment adherence to the initially assigned study treatment was received from the sponsor on 9/14/18 and included a dataset entitled "ADHQEXP." Table 16 suggests good adherence to the study treatment.

Table 16. Reviewer table: Adherence rates to study treatment, CBAF312A2304

Treatment Arm	Mean (%)	Stddev (%)	Median (%)
Siponimod	99.0	5.2	100
Placebo	99.6	2.4	100

Source: ADHQEXP

Reviewer Comment: Treatment adherence to the assigned study medication seemed very high, at least until subjects transitioned to another medication. 27 subjects in the siponimod arm (2%) but only 4 in the placebo arm (<1%) had adherence rates less than 90%. This difference may suggest an issue with tolerance to the study medication, but this reviewer defers this discussion to the safety reviewer.

Concomitant Medications

Table 17 lists the common concomitant medications used by subjects in the study.

The analysis on the use of concomitant steroids is complicated by the number of steroid formulations and the potential indications for which steroids can be given. Besides the many non-MS indications for steroids, short courses of steroids can be prescribed to treat an MS relapse and pulse steroids can be used to reduce relapse rates and the progression of MS. It was assumed that topical, intraocular, and epidural steroids are unlikely to be used for MS, so these were excluded from the analysis below. Many of the reported uses of steroids in the study seem to be for an MS relapse, a suspected relapse, or a symptom potentially attributable to a relapse; a few steroids courses were seemingly given for a pseudo-relapse, which

represents worsening symptoms in the setting of fever or infection (Uhthoff's phenomenon).

Table 17. Reviewer table: Common concomitant medications, CBAF312A2304

Standardized Medication Name	Siponimod # subjects (%)	Placebo # subjects (%)	Totals # subjects (%)
Baclofen	349 (31.6%)	180 (33.0%)	529 (32.2%)
NSAIDS (ibuprofen, diclofenac, naproxen, indomethacin)	281 (25.4%)	159 (29.1%)	440 (26.7%)
Steroids (Methylprednisolone, Prednisolone, Dexamethasone)	256 (23.2%)	165 (30.2%)	421 (25.6%)
Vitamin D	256 (23.2%)	120 (22.0%)	376 (22.9%)
Fampridine	238 (21.5%)	114 (20.9%)	352 (21.4%)
Acetaminophen	220 (19.9%)	128 (23.4%)	348 (21.2%)
Pregabalin	110 (10.0%)	44 (8.1%)	154 (9.4%)
Gabapentin	101 (9.1%)	65 (11.9%)	166 (10.1%)
Aspirin	84 (7.6%)	38 (7.0%)	122 (7.4%)
Ciprofloxacin	73 (6.6%)	36 (6.6%)	109 (6.6%)

Source: ADCM

Reviewer comment: Not surprisingly, many of these concomitant medications are commonly used in people with MS, including steroids, vitamin D, fampridine, pregabalin, and gabapentin. The use of steroids was higher in the placebo group, which may suggest that this group had more relapses and inflammatory disease activity than those randomized to siponimod. Presumably, the relatively high use of ciprofloxacin is attributable to urinary tract infections, which are not uncommon in individuals with MS and were common in CBAF312A2304.

Rescue Medication Use

MS relapses are inflammatory events heralded by the onset of new or worsening neurologic symptoms lasting at least 24 hours and occurring in the absence of fever or infection. Because this definition may be considered somewhat subjective, confirmed relapses are defined as relapses that result in a clinically significant change on the EDSS, i.e., an increase of 0.5 points in the overall EDSS, an increase of 1 point in two functional systems of the EDSS, or an increase of 2 points in one EDSS functional system.

Reviewer Comment: The EDSS is highly dependent on ambulation at scores around 6, so it is very conceivable that some bone fide relapses would not be confirmed because of this characteristic of the scale.

Corticosteroids were commonly given to treat a confirmed MS relapse in the study, although a few confirmed relapses were not treated with steroids. Table 18 shows the number of confirmed relapses that were treated with steroids in this study.

Table 18. Reviewer table: Confirmed relapses treated with corticosteroids, CBAF312A2304

# of Confirmed Relapses	Siponimod	Placebo	Totals
Treated with steroids	123	136	259
Not treated with steroids	11	7	18

Source: ADMSREL where OCCURCE = 'Y' by TRTP01P and CCTRTTK

Reviewer Comment: Taking the 2:1 randomization into account, confirmed relapses were substantially more common in the placebo arm of the study. Most confirmed relapses were treated with high-dose steroids. As per Table 17 (Concomitant Medications), just over 25% of subjects received significant doses of steroids (methylprednisolone, prednisolone, dexamethasone); however, the number of confirmed relapses treated with steroids (Table 18) is much less. Although high-dose steroids can be given for many indications other than a confirmed MS relapse, the frequency of steroid administration in CBAF312A2304, like in many other MS studies, suggests that a substantial number of subjects may have been given steroids for unconfirmed relapses, worsening MS symptoms, or other reasons.

Subjects who experienced 6-month CDP during the study were allowed to remain in the study but change from the assigned study treatment to open label siponimod or another MS therapy. 241 subjects changed to open label siponimod or another MS drug, mostly to open label siponimod. See Table 19. Despite this treatment change, these subjects remained in the Treatment Epoch.

Table 19. Reviewer table: Subjects who changed from the study treatment to another therapy, CBAF312A2304

Subjects who changed from study drug	Siponimod	Placebo
To open-label siponimod	117 (10.6%)	96 (17.6%)
To another MS therapy	18 (1.6%)	10 (1.8%)

Source: ADTTE.PARAMCD='TTRTDIS' and CNSR='0' group by TRT02A and TRTP01P

Reviewer Comment: Many subjects who experienced 6-month CDP and were thus eligible to change to either open-label siponimod or another MS drug decided to change to open-label siponimod. This is not surprising given the paucity of agents available for SPMS.

This ability of subjects who experienced a 6-month CDP event to change from the assigned treatment group to open-label siponimod or another MS therapy is very

reasonable from a subject point of view; however, having these subjects remain in the Treatment Epoch complicates the analysis of non-time-to-CDP endpoints including relapses and MRI changes. Because most of the changes were to open-label siponimod, the biggest concern would be subjects switching from placebo to siponimod, a switch that would not be expected to increase the risk of a Type I error on these non-CDP endpoints.

Efficacy Results – Primary Endpoint

Time to 3-month Confirmed Disability Progression

Disability progression was measured by Kurtzke Expanded Disability Status Scale (EDSS), a 10-point ordinal scale. Table 20 contains descriptive statistics performed by this reviewer to show the change in EDSS from baseline to study completion.

Table 20. Reviewer Table. Overall EDSS change, CBAF312A2304.

Treatment Group	Mean change in EDSS (SD)	Median change in EDSS	Minimum change in EDSS	Maximum change in EDSS
Siponimod	0.17	0	-3	+3.5
Placebo	0.27	0	-3	+3

Source: (ADEDSS.AVAL WHERE AVISITN = 200) – (ADBS.AVAL WHERE PARAMCD = 'BLEDSS')

Reviewer Comment: With the caveat that the EDSS is often criticized for being a non-linear scale that is relatively insensitive to change between 4 and 7, the mean change in EDSS from baseline to completion of study drug was quite small, even in the placebo arm of the study. Although there are many potential explanations for this observation, one is that not all of the subjects had progressive disease.

The primary endpoint of CBAF312A2304 is the difference between siponimod and placebo in the time to 3-month confirmed disability progression (CDP).

Table 21. Reviewer table: Subjects with Disability Progression (DP) event, CBAF312A2304

Disability progression (DP) events	Siponimod	Placebo
Subjects with DP *(anl03fl ='Y')*	437(39.8%)	258 (47.3%)
Subjects with DP assessed during a relapse *(anl02fl ='Y')*	156(14.2%)	125(22.9%)
Subjects with 3-month CDP *(anl05fl ='Y')*	290 (26.4%)	173 (31.7%)
Subjects with unconfirmed DPs *(Row 1 – Row3)*	147 (13.4%)	85 (15.6%)

Source: ADEDSS

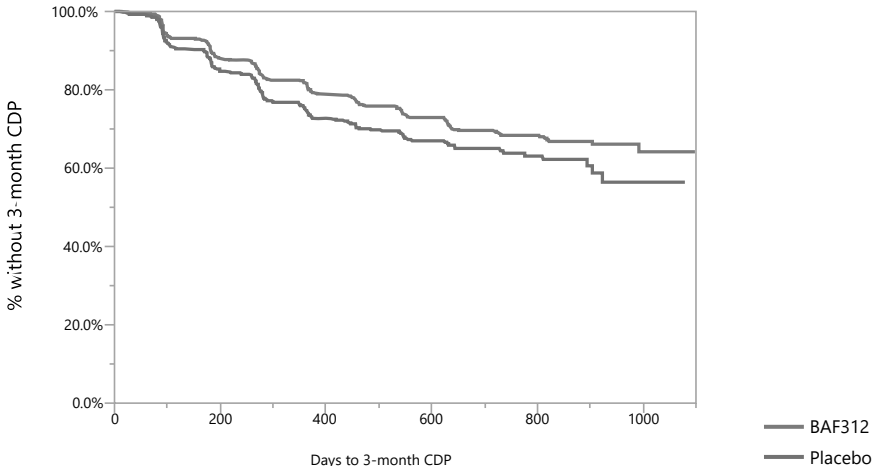
Reviewer Comment: The number of subjects with a 3-month CDP event is lower than the

number of subjects who discontinued the study drug assigned at randomization in the Treatment Epoch, although some subjects switched to open-label siponimod after experiencing 6-month CDP. (See Figure 4 and Table 9 in Patient Disposition Section above). This is a potential source of bias (because subjects may stop the assigned study drug after experiencing a DP event but before its 3- month confirmation) that might raise questions about the validity of the study results; however, the sponsor performed several sensitivity analyses to address this issue, and all of these achieved statistical significance. (See Table 25 of sensitivity analyses.)

This reviewer's Kaplan-Meier analysis for this endpoint (Figure 5) shows that siponimod reduces the time to 3-month CDP in the full analysis set (FAS) with a hazard ratio of 0.79, a 95% CI from 0.65-0.95, and a relative risk reduction 21.2% (p=0.013).

Figure 5. Reviewer Figure: Time to 3-month CDP (FAS), CBAF312A2304

(Source: ADTTCDP.PARAMCD='T3MCDPF')



3-month CDP in subjects in Full Analysis Set (FAS)

Treatment Group	Number	3-month CDP	No 3-month CDP
BAF312	1099	289 (26.2%)	810 (73.7%)
Placebo	546	173 (31.7%)	373 (68.3%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.1792	1	0.0129*
Wilcoxon	6.9448	1	0.0084*

Reviewer comment: This reviewer's analysis nearly reproduces that of Dr. Xiang Ling from the FDA Division of Biometrics (and that of the sponsor) and suggests a reduction in 3-month CDP with siponimod. Although statistically significant (albeit with a p-value

that is not much less than 0.05), the relative risk reduction of 21.2% (and absolute difference of 5.5%) in 3-month CDP seems quite modest, especially given the potential for siponimod's relapse rate reduction to impact the 3-month CDP result, the number of individuals who did not remain on the assigned study drug throughout the Core Part of the study, and the potentially unblinding "dual database access" issue.

Primary endpoint by subgroups

Table 22 demonstrates this reviewer's analysis of the influence of specific baseline characteristics on the time to 3-month CPD. The efficacy of siponimod on this study endpoint seems to be greater in women aged 45 years or less and in subjects with a disease duration of 10 years or less. Because most of the subjects were white (95%), were from outside the US (91%), had an EDSS of ≥4 (90%), and were in the per protocol set, the apparent benefit of these characteristics is likely driven by power.

The differential benefit of siponimod in subjects who had not previously been on an interferon is difficult to explain but may relate to a difference in disease severity (subjects initially started on a "more aggressive" therapy like natalizumab or mitoxantrone) or a shorter disease duration (in which oral medications were a potential alternative to injectable therapies like the interferons).

Table 22. Reviewer table: Time to 3-month CDP by baseline disease factors, CBAF312A2304

	Siponimod		Placebo		
	CPD n/N	% with CDP	CDP	% with CDP	Log Rank
Gender					
M, 40%	129/435	30%	75/223	34%	0.140
F, 60%	160/664	24%	98/323	30%	0.042
Age					
≤45, 36%	111/393	28%	74/199	37%	0.026
>45, 64%	178/706	25%	99/347	29%	0.173
Region					
OUS, 91%	289/1099	26%	173/546	32%	0.013
US, 9%	26/101	26%	8/52	15%	0.142
Race					
White, 95%	276/1046	26%	168/513	33%	0.005
Black, 1%	2/7	29%	0/3	0%	0.442
Asian, 3%	6/30	20%	4/18	22%	0.851
Other / UNK, 2%	5/16	31%	1/12	8%	0.089
Baseline EDSS					
<4, 10%	31/110	28%	17/51	33%	0.380
≥4, 90%	258/989	26%	156/495	32%	0.019

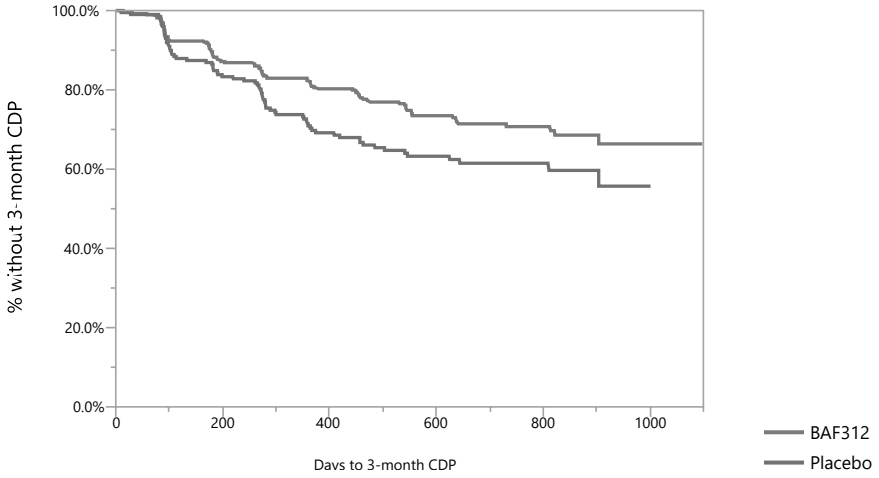
	Siponimod		Placebo		
	CPD n/N	% with CDP	CDP	% with CDP	Log Rank
Duration of Disease Since Diagnosis					
≤10, 43%	129/458	28%	90/246	37%	0.019
>10, 57%	160/641	25%	83/300	28%	0.284
Previous Treatment with Interferon Beta					
Yes, 63%	185/689	27%	102/348	29%	0.354
No, 37%	104/410	25%	71/198	36%	0.003
Per Protocol Population Flag					
Yes, 95%	268/1037	26%	165/523	32%	0.009
No, 5%	21/62	34%	8/23	35%	0.918

Reviewer Comment: The apparently differential effect of siponimod in delaying 3-month CDP in younger individuals with a shorter disease duration raises the question of whether siponimod's treatment effect is primarily evident in earlier, more inflammatory disease (i.e., relapsing multiple sclerosis), as occurred in prior positive trials in SPMS, including the MIMS study of mitoxantrone (Hartung et al., 2002) and the European interferon beta-1b study (1998). A similar effect on younger subjects with more inflammatory disease was also seen in the subgroup analysis of rituximab in the OLYMPUS trial of PPMS (Hawker et al., 2009). The possibility that this effect on disability is driven by siponimod's effectiveness on earlier, more-inflammatory disease (i.e., relapses and new MRI lesions) will be explored in more detail in the following analyses.

The SPMS phenotype is typically described as a slow, inexorable worsening of disability with fewer (or the absence of) relapses. The more recent description of the SPMS phenotype (Lublin et al, 2014) uses the modifier "active" to specify the presence (or absence) of concurrent relapses, although the occurrence of these may be influenced by treatment with an MS drug. With this caveat, this reviewer analyzed the time to 3-month CDP in subjects with and without relapses in the 2 years before the study (Figure 6 and Figure 7, respectively) because the lack of relapses in the previous 2 years may better identify subjects with less inflammatory disease.

Figure 6. Reviewer Figure: Time to 3-month CDP in subjects with relapses in the 2 prior years, CBAF312A2304

(Source: Join ADBS.PARAMCD='NRLLST2Y' WHERE AVAL>1 with ADTTCDP.PARAMCD='T3MCDPF')



3-month CDP in subset of subjects with relapses in the 2 years before the study

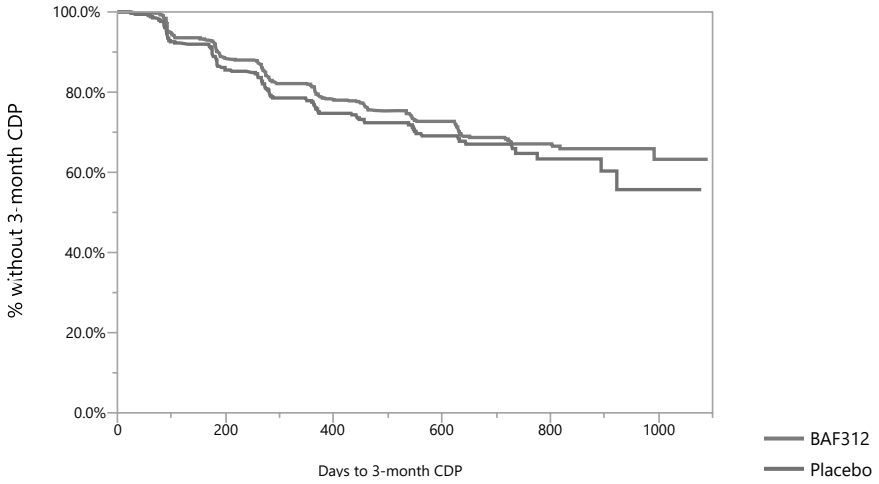
Treatment	Subjects with relapses 2 years before study	3-month CDP in this subset	No 3-month CDP in this subset
BAF312	388 (35.3%)	98 (25.3%)	290 (74.7%)
Placebo	202 (37.0%)	72 (35.6%)	130 (64.4%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.4862	1	0.0109*
Wilcoxon	6.7708	1	0.0093*

Figure 7. Reviewer Figure: Time to 3-month CDP in subjects without relapses in the 2 prior years, CBAF312A2304.

(Source: Join ADBS.PARAMCD='NRLLST2Y' WHERE AVAL=0 with ADTTCDP.PARAMCD='T3MCDPF')



3-month CDP in subset of subjects without relapses in the 2 years before the study

Treatment	Subjects without relapses 2 years before study	3-month CDP in this subset	No 3-month CDP in this subset
BAF312	708 (64.4%)	190 (26.8%)	518 (73.2%)
Placebo	343 (62.8%)	101 (29.4%)	242 (70.6%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	1.4709	1	0.2252
Wilcoxon	1.7549	1	0.1853

Reviewer Comment: This reviewer's analysis suggests similar findings to those shown in the pre-study relapses section of the forest plot displaying hazard ratios for 3-month CDP by subgroup (Figure 11-5 of the sponsor's Clinical Study Report, replicated in Figure 14 below). In this forest plot, the confidence interval (CI) for the hazard ratio of 3-month CDP crosses 1 for the subgroup without relapses in the prior 2 study, but the CI does not cross 1 (i.e., favors siponimod) in the subgroup with relapses in the 2 years before enrolling in the study.

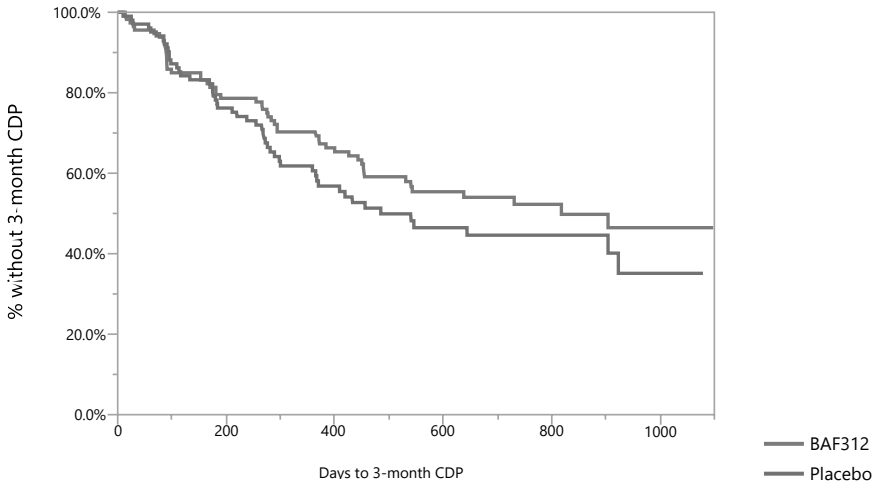
It is recognized that subjects can relapse after going for 2 years without a relapse (particularly subjects who were previously on an MS drug), so the predictive power of pre-study relapses for non-relapsing SPMS is incomplete. That said, this reviewer's analyses shown in Figure 6 and Figure 7 show that the reduction in 3-month CDP is

driven more by the subjects who experienced a relapse in the 2 years before the study than those who did not have a relapse in the 2 years before screening, suggesting that siponimod's treatment effect on 3-month CDP in this population is driven in part by its evident treatment effect on the inflammatory component of the disease.

The initial EDSS worsening could occur in the setting of a relapse but did not have to do so; however, the 3-month confirmation of this disability progression could not occur during an acute MS relapse. Because recovery from relapses may be incomplete, the number of MS subjects who experienced both a relapse and 3-month CDP event during the study is of interest. As shown in the secondary endpoint analysis later in this review (and as demonstrated by the approved S-1-P functional antagonist, fingolimod), siponimod appears quite effective at reducing relapses. Given this, it is unclear whether siponimod's effectiveness on reducing time to 3-month CDP is driven by relapse rate reduction (i.e., inflammatory events) or by altering the pathophysiology of the progressive phase of the disease (which is admittedly less well defined). The literature takes varying stances on the effect of reducing relapses in reducing disability; Lublin et al (2003) suggest that disability persists after almost 40% of relapses, but Tremlett et al (2009) suggest that the impact of relapses may be less in SPMS. Considering a topographical model of MS (Krieger et al, 2016), one might assume that recovery from relapses may depend on the degree of functional reserve (enabling recovery) and the clinical threshold to exhibit signs / symptoms. To clarify the effect of relapse reduction in CBAF312A2304, this reviewer performed time to 3-month CDP analyses in the subset of subjects with and without relapses during the study (Figure 8 and Figure 9, respectively).

Figure 8. Reviewer Figure: Time to 3-month CDP in subjects with confirmed relapses during the study, CBAF312A2304

(Source: Join [GROUP USUBJID OF (ADMSREL WHERE OCCURCE='Y')] with ADTTCDP.PARAM='T3MCDPF')



3-month CDP in subset of subjects with relapses during the study

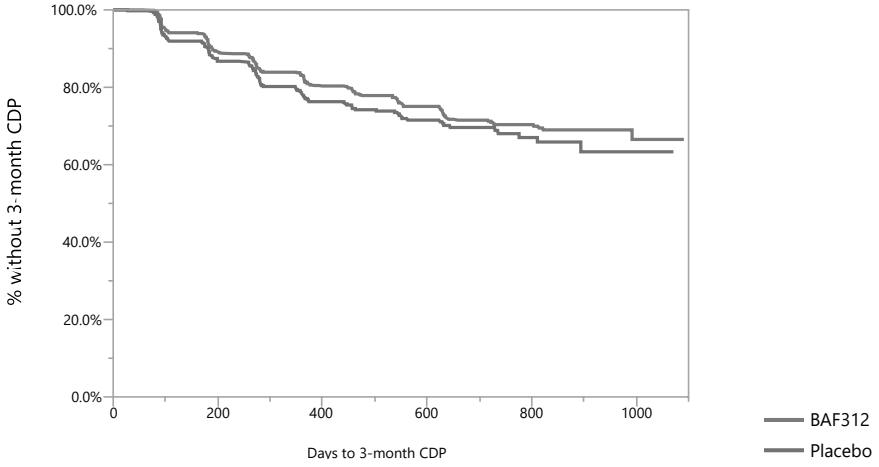
Treatment	Subjects with relapses during the study	3-month CDP in this subset	No 3-month CDP in this subset
BAF312	113 (10.3%)	51 (45.1%)	62 (54.9%)
Placebo	102 (18.7%)	51 (50.0%)	51 (50.0%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	1.5082	1	0.2194
Wilcoxon	1.1302	1	0.2877

Figure 9. Reviewer Figure: Time to 3-month CDP in subjects without confirmed relapses during the study, CBAF312A2304

(Source: Join subset of subjects not contained in ADMSREL WHERE OCCURCE='Y' with ADTTCDP.PARAM='T3MCDPF')



3-month CDP in subset of subjects without relapses during the study

Treatment	Subjects without relapses during the study	3-month CDP in this subset	No 3-month CDP in this subset
BAF312	986 (89.7%)	238 (24.1%)	748 (75.9%)
Placebo	444 (81.3%)	122 (27.5%)	322 (72.5%)

Group Comparison

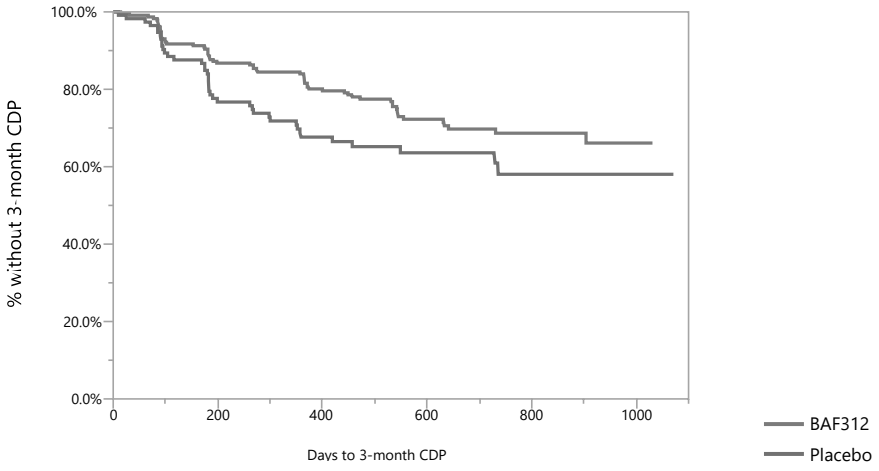
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	1.9845	1	0.1589
Wilcoxon	2.5802	1	0.1082

Reviewer Comment: Although the differences in this reviewer's Kaplan-Meier curves above are visually suggestive of a differential benefit of siponimod on the time to 3-month CDP in subjects who experienced relapses during the study, these differences do not meet statistical significance; however, this may relate to insufficient power because only a small minority of subjects experienced a relapse during CBAF312A2304. The graphs also suggest that subjects who experienced relapses during the trial were more likely to have disability progression that those who did not, which is not surprising given data that recovery from relapses is often incomplete (Lublin et al., 2003). It is recognized that analysis of an event (especially one open to interpretation, such as a relapse) occurring after randomization is subject to confounding and is fraught with difficulty. In sum, this analysis does not contribute much to the question of whether siponimod's effect on delaying 3-month CDP relates to its treatment effect on inflammatory disease.

The development of a gadolinium-enhancing lesion heralds the onset of an inflammatory event (relapse) in MS and represents a break-down of the blood brain barrier, allowing the margination of auto-reactive lymphocytes into the CNS (Lassman, 2008). As gadolinium enhancing lesions occur up to 10 times as frequently as relapses, measurement of these lesions is commonly used as a primary endpoint in Phase 2 studies in RMS. The average lesion enhances for 3-6 weeks; persistently enhancing lesions are quite rare in MS (Cotton et al 2003). Gadolinium-enhancing lesions are less common in SPMS, although "smoldering plaques" can be seen in SPMS (Frischer et al, 2015). This reviewer's Kaplan-Meier analyses of the time to 3-month disability progression in subjects who had or did not have a gadolinium-enhancing lesion at baseline follow (Figure 10 and Figure 11, respectively). Of note, data for the number of gadolinium-enhancing lesions at baseline was missing for 52 subjects.

Figure 10. Reviewer Figure: Time to 3-month CDP in subjects with gadolinium enhancing lesions at baseline, CBAF312A2304.

(Source: join ADBS.PARAMCD='BLT1GDN' WHERE AVAL>0 with ADTTCDP.PARAM='T3MCDPF')



3-month CDP in subset of subjects with gadolinium-enhancing lesions at baseline

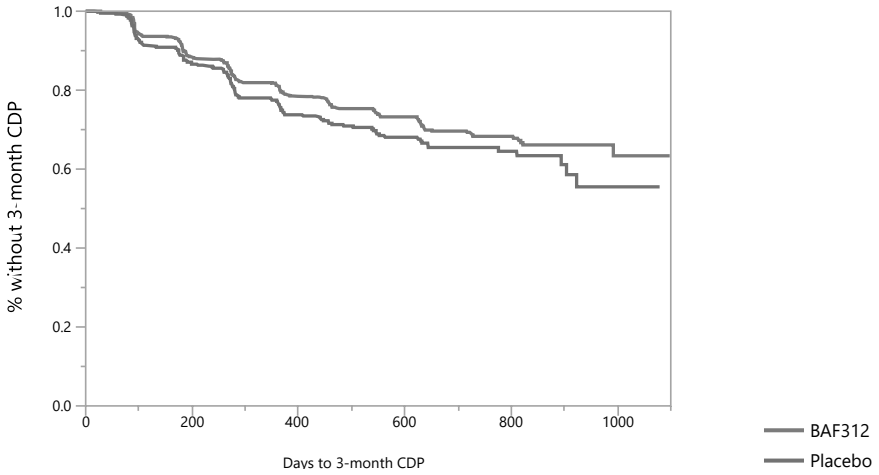
Treatment	Subjects with enhancing lesions at baseline	3-month CDP in this subset	No 3-month CDP in this subset
BAF312	236 (21.5%)	62 (26.3%)	174 (73.7%)
Placebo	114 (20.9%)	40 (35.1%)	74 (64.9%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.2389	1	0.0395*
Wilcoxon	5.3762	1	0.0204*

Figure 11. Reviewer Figure: Time to 3-month CDP in subjects without gadolinium enhancing lesions at baseline, CBAF312A2304

(Source: Join ADBS.PARAMCD='BLT1GDN' WHERE AVAL=0 with ADTTCDP.PARAM='T3MCDPF')



3-month CDP in subset of subjects without gadolinium-enhancing lesions at baseline

Treatment	Subjects without enhancing lesions at baseline	3-month CDP in this subset	No 3-month CDP in this subset
BAF312	828 (75.3%)	219 (26.4%)	609 (73.6%)
Placebo	415 (76.0%)	128 (30.8%)	287 (69.2%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.99919	1	0.0837
Wilcoxon	3.1127	1	0.0777

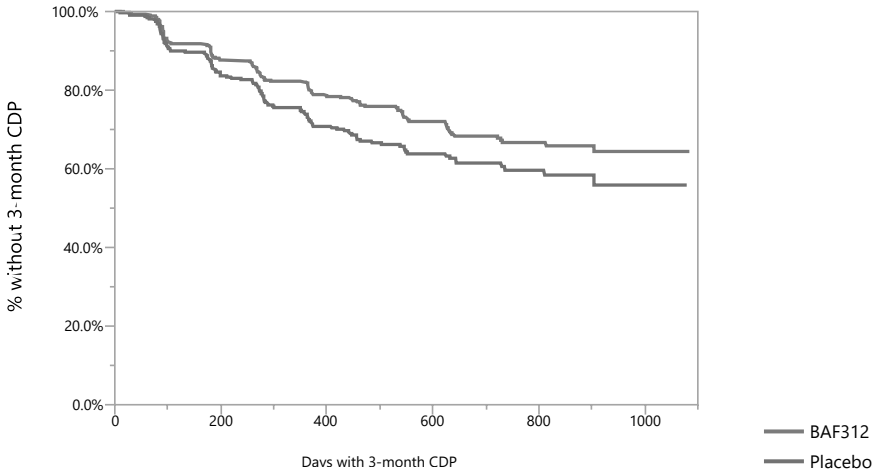
Reviewer Comment: The analyses shown in Figure 10 and Figure 11 suggest that the reduction in time to 3-month CDP appears to be partially driven by the subpopulation

who had enhancing lesions at baseline. This further supports the observation that siponimod's effect on 3-month CPD progression may be primarily due to its impact on the relapsing / inflammatory component of MS.

In addition to relapses and enhancing lesions, the development of new new/enlarging T2 lesions also represent sequelae of the inflammatory component of MS. The development of clinically silent lesions may represent relapses occurring in a "non-eloquent" location of the CNS (or those for which the CNS can rapidly compensate for the damage); indeed, a large meta-analysis of randomized clinical trials in MS (Sormani 2009, Sormani and Bruzzi, 2013) suggests that new MRI lesions may be a surrogate for relapses with an R(2)=0.71. In addition to relapse rate reduction, S-1-P functional antagonists (including siponimod as discussed in the secondary endpoint analyses below) are effective at reducing new MRI lesions. As most T2 hyperintensities exhibit persistence over time, this reviewer's analyses of the primary endpoint in patients with and without new / enlarging T2 hyperintensities (Figure 12 and Figure 13, respectively) may help clarify how much of the effect of 3-month CDP is related to an effect on the inflammatory component of the disease.

Figure 12. Reviewer Figure: Time to 3-month CPD in subjects with new/enlarging T2 lesions during the study, CBAF312A2304

(Source: Join ADTTCDP.PARAM='T3MCDPF' with (GROUP By USUBJID[ADMR.PARAMCD='T2NNEWP' and ADMR.AVAL>0])



3-month CDP in subset of subjects with new / enlarging T2 lesions during the study

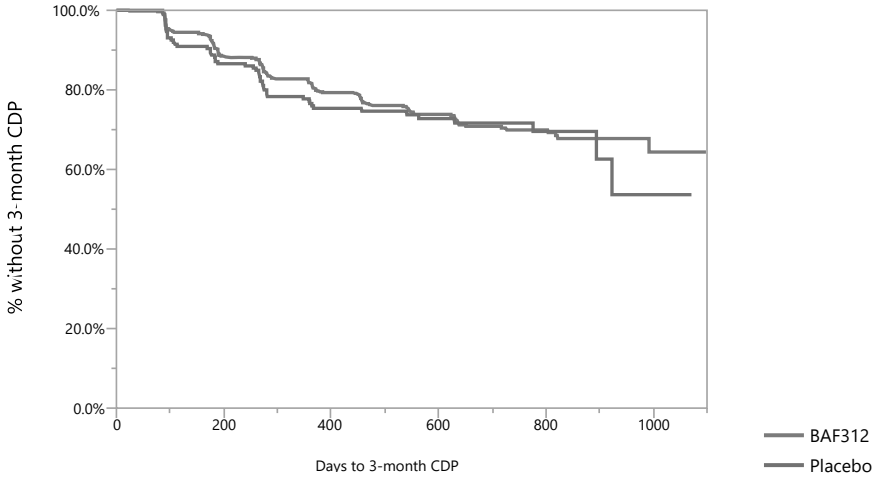
Treatment	Subjects with enhancing lesions at baseline	3-month CDP in this subset	No 3-month CDP in this subset
BAF312	442 (40.2%)	127 (28.7%)	315 (71.3%)
Placebo	320 (58.6%)	116 (36.3%)	204 (63.8%)

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.4174	1	0.0199*
Wilcoxon	5.8642	1	0.0155*

Figure 13. Reviewer Figure: Time to 3-month CPD in subjects without new/enlarging T2 lesions during the study, CBAF312A2304

(Source: Join ADTTCDP.PARAM='T3MCDPF' with (GROUP By USUBJID [ADMR.PARAMCD='T2NNEWP' WHERE SUM(ADMR.AVAL=0)])



3-month CDP in subset of subjects without new / enlarging T2 lesions during the study

Treatment	Subjects with enhancing lesions at baseline	3-month CDP in this subset	No 3-month CDP in this subset
BAF312	584 (53.1%)	154 (26.4%)	430 (73.6%)
Placebo	190 (34.8%)	52 (27.4%)	138 (72.6%)

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.4014	1	0.5264
Wilcoxon	0.6774	1	0.4105

Reviewer Comment: The analyses shown in Figure 12 and Figure 13 suggest that the reduction in 3-month CDP occurs in more subjects who experienced new / enlarging T2 hyperintensities during the study than those who did not, further suggesting that siponimod's treatment effect may be driven by its reduction in MRI evidence of inflammatory disease. Although these post-hoc *analyses consider a post-randomization event, the potential for bias with an imaging outcome is arguably less than that for a*

clinical outcome such as MS relapses, especially with the use of a blinded centralized reading facility.

Table 23 below summarizes the results of the above subgroup analyses for the primary endpoint of 3-month CDP.

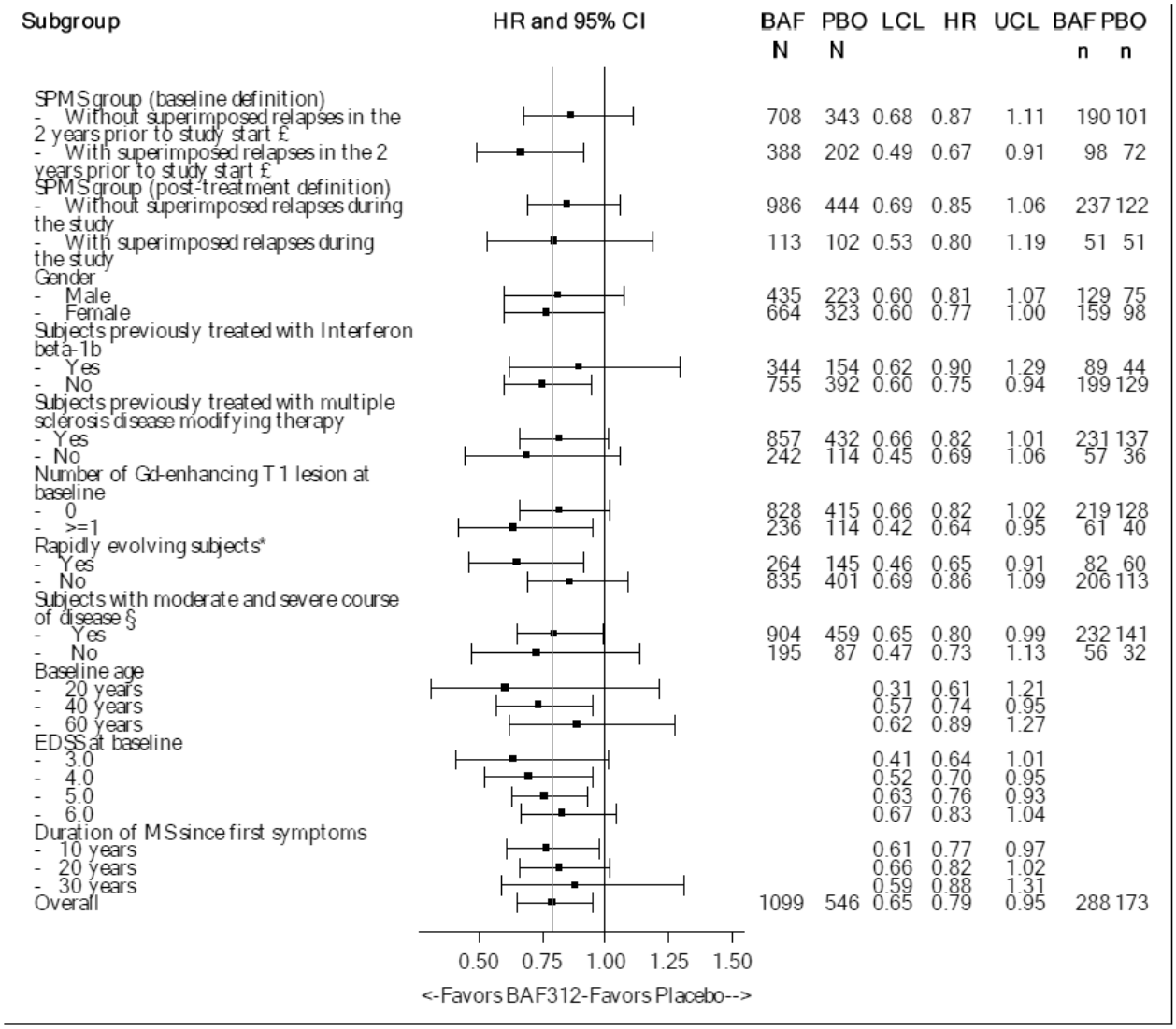
Table 23. Reviewer Table. Subgroup analyses of 3-month CDP

	3-month CDP				No 3-month CDP				
	Siponimod		Placebo		Siponimod		Placebo		
	#	%	#	%	#	%	#	%	p
Relapse w/in 2-yr of randomization									
Yes	98	8.9%	72	13.2%	290	26.4%	130	23.8%	0.01
No	190	17.3%	101	18.5%	518	47.1%	242	44.3%	0.22
Relapse during study									
Yes	51	4.6%	51	9.3%	62	5.6%	51	9.3%	0.22
No	238	21.7%	122	22.3%	748	68.1%	322	59.0%	0.16
Enhancing lesion at baseline[1]									
Yes	62	5.6%	40	7.3%	174	15.8%	74	13.6%	0.04
No	219	20.0%	128	23.4%	609	55.4%	287	52.6%	0.08
New T2 lesion during study[2]									
Yes	127	11.6%	116	21.2%	315	28.7%	204	37.3	0.02
No	154	14.0%	52	9.5%	430	39.1%	138	25.3%	0.53

[1] Data was missing for baseline gadolinium-enhancing lesions for 52 subjects.
[2] Data was missing for new T2 lesions for 106 subjects.

Figure 14 below is a snapshot of Figure 11-5 of the Clinical Study Report (CSR) that contains a forest plot of 3-month CDP hazard ratios for multiple subgroups. This forest plot includes 3 of the 4 subgroups (relapses before the study, relapses during the study, and baseline gadolinium-enhancing lesions) that were analyzed above, and it shows the subgroup results graphically with point estimates and 95% confidence intervals. It also suggests a differential benefit in women with a shorter disease duration, as suggested in Table 22 of this review, as well as a differential benefit in subjects with a moderate or severe course of disease and those with rapidly evolving disease. The sponsor's forest plot also shows the confidence interval of the hazard ratio for 3-month CDP crosses '1' for subjects with an EDSS of 6, which is notable because the median EDSS of the CBAF312A2304 population was 6.

Figure 14. Sponsor Figure. Time to 3-month CDP based on EDSS – forest plot displaying hazard rations, by subgroup (FAS)



N is the number of subjects in the subgroup; n is the number of subjects in the subgroup with confirmed disability progression. HR = hazard ratio. LCL/UCL = Lower/Upper limit of the HR 95% confidence interval

Results using a Cox proportional hazard model with treatment, country/region, baseline EDSS, SPMS group (with-/without superimposed relapses, baseline definition) and the subgroup (if other than SPMS group) as covariates.
£ Date of study start corresponds to the date of screening visit.

§ Moderate or severe course of disease is defined as Global MSSS of 4 or more at baseline.

* Rapidly evolving subjects are defined as subjects with 1.5 or greater EDSS change in the 2 years prior to or at study start and disability progression in the 2 years prior to study start was not adjudicated.

Subjects previously treated with Interferon beta-1b (IFNB)/disease modifying therapy (MS-DMT) are defined as subjects who received and stopped IFNB/MS-DMT prior to first dose of study treatment

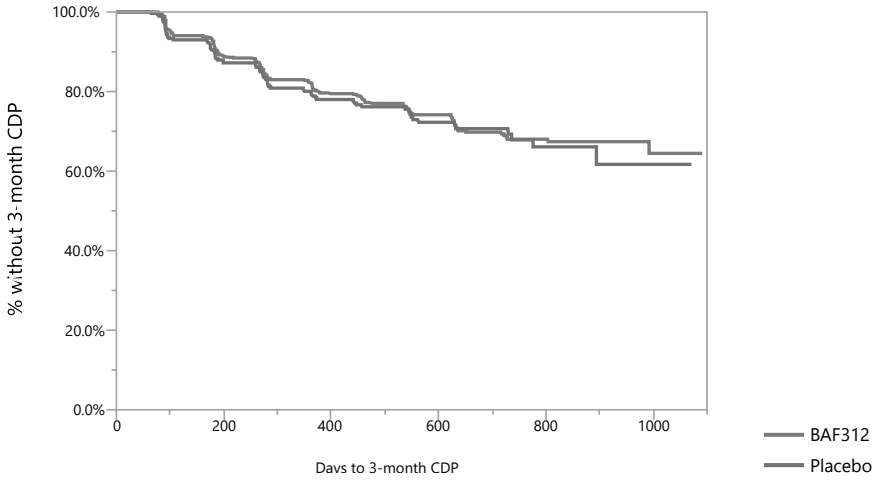
Reviewer Comment: Relapsing MS is considered an inflammatory process, and secondary progressive MS is often deemed "degenerative" with the caveat that the pathophysiology of this progressive stage of the disease is less well understood and may be partially explained by a bio-energetic deficit from mitochondrial dysfunction, an inappropriate innate immune response, compartmentalized inflammation behind an intake blood brain barrier, or increased free radicals. A biomarker for SPMS does not exist, and the distinction between relapsing and progressive MS is obscured because inflammatory events (relapses or new MRI lesions) may occur in progressive MS: the 2013 revisions to the progressive MS phenotype allows the "Active" modifier to denote this (Lublin et al, 2014). This distinction is further complicated in subjects who are currently on an MS medication to reduce inflammatory disease.

Two of the 3 Phase 3 RRMS trials of a medication (fingolimod) in the same pharmacologic class as siponimod did not meet their disability endpoint, nor did the INFORMS trial of fingolimod in PPMS (Lublin et al, 2016). The populations of the 2 positive SPMS trials (European interferon beta-1b, mitoxantrone) likely had late relapsing MS (or relapsing SPMS); therefore, the demonstrated benefit in these trials may have been driven by their effect on inflammatory disease, especially as the North American trial of interferon beta-1b in SPMS trial did not replicate this effect (Lancet 1998, Hartung et al 2002, Neurol 2004). Even if this siponimod study population truly has secondary progressive MS (and is not a population of late relapsing remitting MS, as this reviewer suspects), the above analyses support the hypothesis that the delay in 3-month CDP is more clearly related to the anti-inflammatory effect of siponimod (yielding a significant treatment effect on the relapsing or active aspect of the disease) than to an effect on the poorly understood "degenerative" process felt to dominant the pathophysiology of SPMS.

This reviewer performed a *post-hoc* time to-event analysis for the primary endpoint in the 955 subjects who did not have a relapse in the 2 years before the trial or during the trial. Although there is not a biomarker for inactive (non-relapsing, non-inflammatory) SPMS, this cohort (some of whom did not have a relapse in almost 5 years) may provide the best insight into whether siponimod's effect on 3-month CDP relates to its activity on relapsing / inflammatory disease or on the progressive / "degenerative" aspect of the disease.

Figure 15. Time to 3-month CDP in subjects without relapses in the 2 years before the study or during the study, CBAF312A2304

(Source: ADTTCDP.PARAM='T3MCDPF' in subset of subjects continued in both ADBS WHERE PARAMCD='NRLLST2Y' AND AVAL=0 AND ADTTCR WHERE PARMACD='TCFRLFAS' AND CNSR=1**)**



3-month CDP in subset of subjects without relapses in the 2 years before the study or during the study

Treatment	Subjects in subset without relapses	3-month CDP in this subset	No 3-month CDP in this subset
BAF312	664 (60.4%)	169 (25.5%)	494 (74.4%)
Placebo	292 (53.5%)	76 (26.0%)	216 (74.0%)

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.1978	1	0.6565
Wilcoxon	0.2958	1	0.5865

Reviewer Comment: Siponimod does not appear to offer a significant benefit on 3-month CDP in the subset of subjects who did not have relapses in the 2 years before the study or during the study. Given this result, and the above analyses suggesting that the effect of siponimod on 3-month CDP is driven by its effect on relapsing (inflammatory) disease, there may be a role for siponimod in individuals with relapses and active inflammation even though siponimod's capability of treating progressive disability in non-relapsing SPMS appears dubious.

As previously noted, the written attestations that subjects had SPMS defined by a progressive increase in disability (of at least 6 months duration) in the absence of, or independent of,

relapses, were not collected. The inclusion criteria also required either clinical documentation of EDSS progression or a written summary of evidence of disability progression in the two years before the study. The clinical documentation was not collected for adjudication, but the written summaries were adjudicated, although not always before randomization. An Information Request was sent to analyze the time to 3-month CDP in subjects with documented EDSS progression and those with adjudicated written summaries. As per Figure 16, the results of this analysis were not statistically significant for those subjects who lacked documentation of EDSS progression but had adjudicated written summaries of disability progression. The response, received on 3/4/2019, also states "Review of the demographic and baseline MS disease characteristics for the two subgroups revealed that patients included in the study based on adjudicated disability progression had longer disease duration, were slightly older, more severely disabled (based on EDSS) and had less inflammatory disease activity (Gd-enhancing lesions at baseline and pre-study relapses) compared to patients with documented EDSS progression, suggesting that this subgroup had more advanced SPMS."

Figure 16. Time to 3-month CDP by EDSS documentation or written summary of progression

Table 2-3 Time to 3-month confirmed disability progression based on EDSS - Cox proportional hazards model, by assessment of inclusion 6 (Full analysis set - A2304 Core Part)

			Comparison: BAF312 vs Placebo #		
Subgroup Treatment	n/N'	(%)	Risk reduction	Hazard ratio	95% CI
Documented EDSS progression					
BAF312 (N=643)	167/641	(26.1)	33.9%	0.66	0.52; 0.84
Placebo (N=341)	119/341	(34.9)			
Adjudicated disability progression					
BAF312 (N=448)	119/447	(26.6)	10.2%	0.90	0.65; 1.25
Placebo (N=200)	54/199	(27.1)			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates).
Using a Cox proportional hazards model with treatment, country, baseline EDSS, and SPMS group (with/without superimposed relapses, baseline definition) and race as covariates. Risk reduction is derived as (1-hazard ratio) * 100.

Reviewer Comment: The response to this Information Request (and the contents of Figure 16) reinforces that siponimod's treatment effect on the primary endpoint, 3-month CDP, in CBAF312A2304 is driven by subjects who had a shorter disease duration, less disability, and more evidence of inflammatory activity (relapses, MRI activity), i.e., subjects with late RRMS or "transitional MS."

Data Quality and Integrity

Per the BAF312A2304 study protocol (page 62), EDSS assessments were performed by independent EDSS raters who were to "remain blinded to adverse events, concomitant medications, laboratory data, and any other data that have the potential of treatment assignment." In addition to scheduled EDSS assessments, unscheduled assessments were performed in the event of a potential MS relapse. When possible, the same EDSS rater performed subsequent assessments on the same subject, although this rater had access to the results of prior assessments. EDSS raters had to be trained and certified in the administration and scoring of the EDSS by achieving a Level C rating on the Neurostatus eTest. An electronic version of the EDSS could be used, as this tool could cross-check data input and identify inconsistencies; however, reference to this tool was removed in Amendment 4 of the protocol.

As the primary endpoint is 3-month CDP as measured by the EDSS, the baseline EDSS should occur just before or at randomization. As per Table 24, the baseline EDSS occurred after randomization in 143 subjects, so most had an EDSS assessment before or at randomization.

Table 24. Reviewer Table: Subjects with baseline EDSS after randomization, CBAF312A2304

Test	N	Mean Delay (Days)	Median Delay (Days)
Siponimod	92	4.2	1
Placebo	51	2.8	1

Source: Compare ADSL.RANDDT to ADESS.ADT WHERE AVISIT="BASELINE"

Reviewer Comment: Most subjects had an EDSS recorded before or at randomization.

Forty-two subjects (22 siponimod, 20 placebo) experienced an onset of disability progression but then dropped out of the study before a 3-month disability event could be confirmed and thus were not included in the primary endpoint (3-month CDP) analysis. Only 5 of these disability onset events were attributed to a relapse. The most common reason (n=27) for these drop-outs was "Subject / Guardian Decision," and only six were for "Adverse Event." In the sponsor's sensitivity analysis #1 (categorizing these drop-outs as having confirmed disability progression on the date of disability onset), siponimod achieves a 24.1% risk reduction in 3-month CDP (p=.0028). See Table 25.

As CBAF312A2304 is a time to event trial, it was possible for the study to end after some subjects had the onset of disability progression but before that disability progression could be confirmed 3 months later. This occurred in 81 subjects, 57 of whom were in the siponimod arm and 24 in the placebo arm. In the sponsor's sensitivity analysis #6 (subjects with disability onset that could not be confirmed at 3 months due to study completion), siponimod achieves a 23.1% risk reduction in 3-month CDP (p=0.0026). See Table 25.

Table 25. Sponsor Table: Primary analysis and sensitivity analysis for the 3-months CDP – Cox proportional hazards model

			Comparison: BAF312 vs Placebo	
Analysis	**BAF312 n/N'**	**Placebo n/N'**	**Risk reduction**	**p-value**
Primary analysis	288/1096	173/ 545	21.2%	0.0134
Sensitivity analysis #1	309/1096	192/545	24.1%	0.0028
Sensitivity analysis #6	351/1096	213/545	23.1%	0.0026
Sensitivity analysis #7	348/1096	209/545	22.3%	0.0041

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates).
Sensitivity analysis #1: subjects who discontinue Treatment Epoch prematurely and have a potential DP event at the end of the Core Part, were considered to have confirmed progression at the start date of this potential DP event.
Sensitivity analysis #6: subjects who have a potential DP event at the end of the Core Part were considered to have confirmed progression at the start date of this potential DP event.
Sensitivity analysis #7: Same as sensitivity analysis 6, but patients having potential DP with latest EDSS scores during relapse were not considered to have confirmed progression.

Reviewer Comment: Drop-outs were the subject of an Information Request (IR) sent to the sponsor on 7/19/2018. Even though dropouts after disability onset were more frequent in the placebo arm, sensitivity analysis #1 (which considered subjects who dropped out after a disability progression event to have 3-month CDP) suggests that these drop-outs did not significantly affect the results of this trial. Although the number of siponimod subjects with unconfirmed disability progression at the end of the study is somewhat higher than expected (compared with placebo), sensitivity analysis #6 and 7 suggest that this higher dropout rate for patients with unconfirmed disability progression did not impact the outcome of the trial either. Obviously, one caveat to acceptance of these sensitivity analyses is the potentially unblinding "dual database access issue."

To ensure accuracy, a possible MS relapse should be confirmed with an unscheduled visit for an EDSS (and laboratory assessment to rule out pseudo-exacerbation in the setting of an infection) soon after the onset of the relapse symptoms, ideally within a week. Table 26 below shows the mean times to relapse confirmation.

Table 26. Reviewer Table: Time between relapse onset and confirmation, CBAF312A2304

Test	Confirmed Relapses	Mean (Days)	Std Dev (Days)	Min (Days)	Max (Days)	Median (Days)
Siponimod	132	12.6	17.7	0	98	6
Placebo	143	11.5	15.2	0	89	5.5

Source: ADMSRRL.CFCEDTC – ADMSREL.ASTDT where ADMSREL.OCCURCE='Y'

Reviewer Comment: The mean time interval between the onset of relapse symptoms and the confirmatory EDSS is suboptimal, although this is not unusual in other MS clinical trials and may relate to delayed notification of the investigator that the subject was having new symptoms concerning for a relapse or a delayed relapse evaluation after a subject reported these symptoms. The median number of days suggests that half of relapses were confirmed in a reasonable amount of time (<7 days).

Subjects could also drop out of the study after experiencing a relapse, whether confirmed or unconfirmed. As per the aforementioned 7/19/2018 IR, this occurred 71 times, 43 of which were in the placebo arm and 28 in the siponimod arm. Most of these drop-outs were for "Lack of Efficacy," "Subject / Guardian Decision," or "Progressive Disease."

Reviewer Comment: Almost 8% of subjects in the placebo arm dropped out of the A2304 study after experiencing a confirmed or unconfirmed relapse, but only about 3% of the siponimod arm did so. These observations raise questions about the robustness of the study results, especially given that the rate of dropout in the placebo arm (~8%) is greater than the absolute difference in 3-month CDP (5.5%).

Quality assurance audits were performed on the study systems, investigator sites, and third-party vendors.

Efficacy Results – Secondary and other relevant endpoints

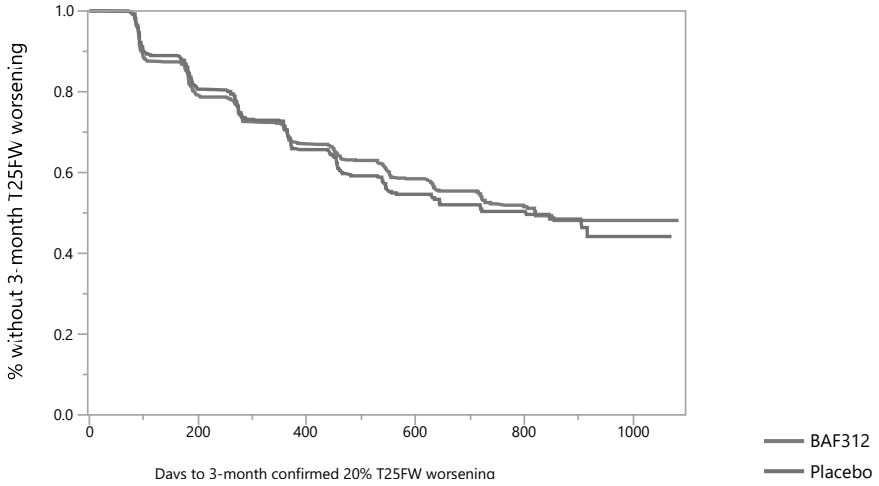
The two "key" secondary endpoints were time to 3-month confirmed 20% increase in the timed 25-foot walk (T25FW) and change in T2 lesion volume from baseline; the primary endpoint and these two key secondary endpoints were prespecified to be tested in hierarchical order.

Time to 20% worsening in Timed 25-foot Walk

As shown in Figure 17, siponimod did not achieve a statistically significant improvement in this reviewer's analysis of the first key secondary endpoint (difference in time to 20% worsening on T25FW compared to placebo), achieving only a 6.2% risk reduction in favor of siponimod.

Figure 17. Reviewer Figure: Time to 3-month confirmed 20% T25FW worsening (FAS), CBAF312A2304

(Source: ADTTCDP.PARAMCD='T3M25WF')



3-month confirmed T25FW worsening in subjects in Full Analysis Set (FAS)

Treatment Group	Subjects	3-mos T25FW worsening	No 3-mos T25FW worsening
BAF312	1099	436 (39.7%)	663 (60.3%)
Placebo	546	226 (41.4%)	320 (58.6%)

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.3945	1	0.5299
Wilcoxon	0.0925	1	0.7610

Reviewer Comment: As stated by the sponsor (and duplicated in this analysis), siponimod did not achieve a statistically significant improvement over placebo in the time to a 3-month confirmed 20% change in the T25FW. As per data by Confavreaux (2000), insidious progression is often apparent after a person with MS reaches an EDSS of 4.0, which is the point at which the EDSS becomes heavily biased to changes in ambulation. Because the median EDSS in CABF312A2304 was 6 and because EDSS change between 5 and 8 is entirely dependent on changes in ambulation, siponimod's failure to meet the T25FW endpoint potentially raises questions about the study's 3-month CDP result, although this discrepancy could be explained by hypothesizing that the T25FW is less sensitive to change than the EDSS. The results of the trial's primary outcome would seem more robust (and confidence in the results would be greater) if the study achieved a positive effect on both the time to EDSS progression and the time to

T25FW worsening, the first "key" secondary endpoint (and the second endpoint in the prespecified hierarchical analysis) in this trial.

Change in T2 lesion volume from baseline

The other key secondary endpoint was the differential change in T2 lesion volume from baseline in subjects on siponimod compared to those on placebo. Although it is recognized that a prior endpoint (difference in time to 3-month confirmed 20% worsening onT25FW) in the prespecified hierarchical analysis scheme did not achieve statistical significance, the large effect size and very low p-values (nominal p<0.0001) on this "traditional" MS clinical trial measure suggests that this finding should not be discounted, especially as the potential unblinding from the "dual database access issue" should not affect this endpoint given the use of a blinded, centralized reading center.

Reviewer Comment: With this caveat regarding the failure of a prior endpoint in the prespecified hierarchical analysis, the magnitude of the differences in the change in T2 lesion volume is noteworthy.

Because CBAF312A2304 is a time to event trial in which subjects were able to transition to open-label siponimod after experiencing 6-month CDP, the number of subjects decreases in the 24- and 36-month analyses below.

Table 27. Reviewer Table: Unadjusted change in T2 lesion volume (mm3) from baseline to month 12, by visit, CBAF312A2304

Treatment	Change in T2 lesion volume (mm^3) at 12 months					
	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	1025	196	1509	37	-15992	12942
Placebo	509	790	2141	203	-5654	22100

Source: Mean(CHG) in ADMR.PARAMCD='T2VOL', VISIT contains {Month12, EOT, EOS, FO}, ANL01FL='Y', and AVISIT = Month12

Table 28. Reviewer Table: Unadjusted change in T2 lesion volume (mm3) from baseline to month 24, by visit, CBAF312A2304

Treatment	Change in T2 lesion volume (mm^3) at 24 months					
	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	627	171	1398	32	-8266	13342
Placebo	305	881	2140	309	-6541	17405

Source: Mean(CHG) in ADMR.PARAMCD='T2VOL', VISIT contains {Month24, EOT, EOS, FO}, ANL01FL='Y', and AVISIT = Month24

Table 29. Reviewer Table: Unadjusted change in T2 lesion volume (mm3) from baseline to month 36, by visit, CBAF312A2304

Treatment	Change in T2 lesion volume (mm^3) at 36 months					
	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	133	-104	1485	-69	-4500	7863
Placebo	53	659	2714	292	-13156	8186

Source: Mean(CHG) in ADMR.PARAMCD='T2VOL," VISIT contains {Month36, EOT, EOS, FO}, ANL01FL='Y', and AVISIT = Month36

Reviewer Comment: This reviewer's analyses of the unadjusted change in T2 volumes at 12, 24, and 36 months is essentially mirror those provided by the sponsor (CSR BAF312A2304 page 502-3). As above, an earlier endpoint in the prespecified hierarchical analysis did not meet statistical significance. With that caveat, the demonstrated difference (although technically not statistically significant due to the prespecified hierarchical analysis) in reducing the change in T2 lesion volume in the siponimod arm is robust and suggests a marked anti-inflammatory effect of this agent, as new T2-lesions are felt to be inflammatory in etiology and may be a surrogate for relapses as per Sormani et al, 2009 and Sormani and Bruzzi, 2013.

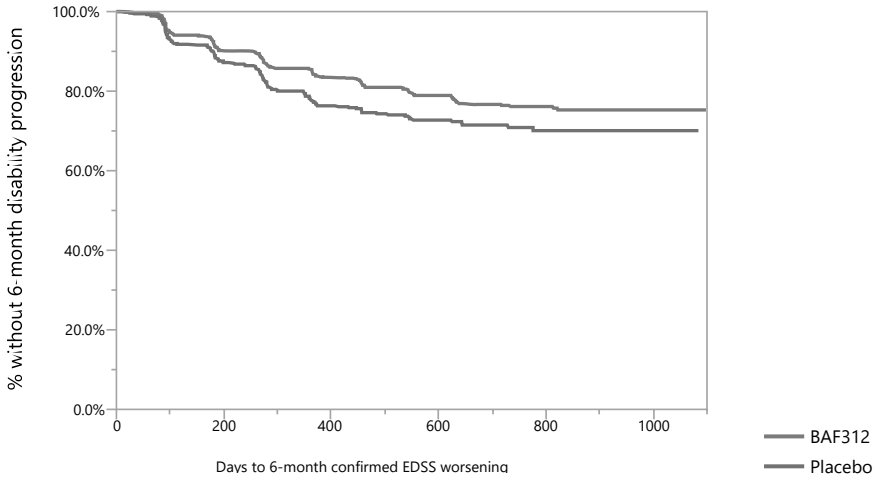
It is noted that some subjects experienced a decrease in T2 lesion volume, which certainly can be observed with improvement in the degree of inflammation (and associated edema) with effective therapies for MS. Atrophy of brain lesions (T2 hyperintensities) can also be seen in individuals with MS, especially progressive MS, an observation that was recently highlighted in Dwyer et al, 2018; however, the clinical implication of lesion atrophy is not yet clear.

Time to 6-month CDP

Six-month confirmed EDSS progression is often felt to be a more difficult endpoint to meet than 3-month CDP due to the potential confounder of recovery from relapses with shorter term disability endpoints; however, relapse recovery may be more difficult (and slower) for subjects deemed to have SPMS, especially in a population with a median EDSS of 6.0. Despite this, this reviewer's analysis suggests that siponimod reduces the time to 6-month (24-week) confirmed EDSS progression, a secondary endpoint that was not prespecified as "key" or as part of the pre-specified hierarchical analysis. The risk reduction was 26% (p=0.0068). See Figure 18.

Figure 18. Reviewer Figure: Time to 6-month CDP (FAS), CBAF312A2304

(Source: ADTTCDP.PARAMCD='T6MCDPF')



6-month CDP in subjects in Full Analysis Set (FAS)

Treatment Group	Subjects	3-month CDP	No 3-month CDP
BAF312	1099	219 (19.9%)	880 (80.1%)
Placebo	546	139 (25.5%)	407 (74.5%)

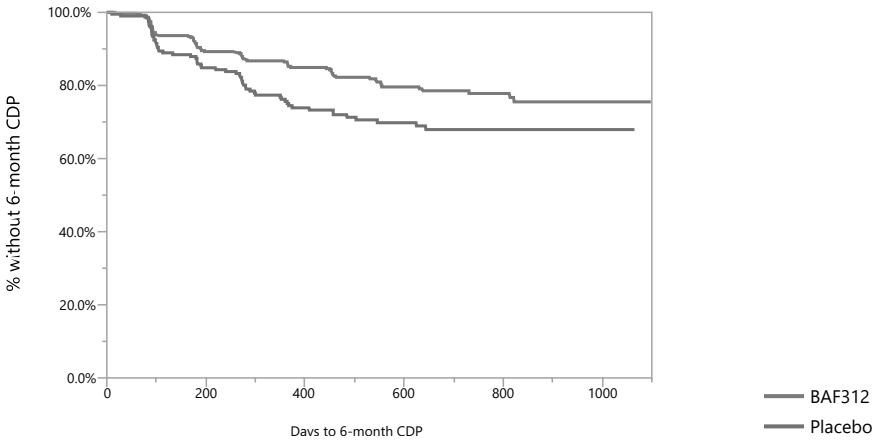
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	7.3338	1	0.0068*
Wilcoxon	8.7870	1	0.0030*

Reviewer comment: Although siponimod's treatment effect on 6-month CDP was statistically significant, the absolute reduction in 6-month CDP with siponimod was also quite modest at 5.6%. The Kaplan-Meier curve also suggests that over 70% of subjects (even those randomized to placebo) would not experience 6-month CDP after 3-years in the study, suggesting that the study population may not have been a prototypical SPMS population.

As per this reviewer's Kaplan-Meier graphs below, (Figure 19 and Figure 20), the effect on delaying 24-week confirmed EDSS progression appears to be driven by the subset of the population who experienced relapses in the 2 years before the study.

Figure 19. Reviewer Figure: Time to 6-month CDP in subjects with relapses in the 2 prior years, CBAF312A2304 (Source: Join ADBS.PARAMCD='NRLLST2Y' WHERE AVAL>0 with ADTTCDP.PARAMCD='T6MCDPF'**)**



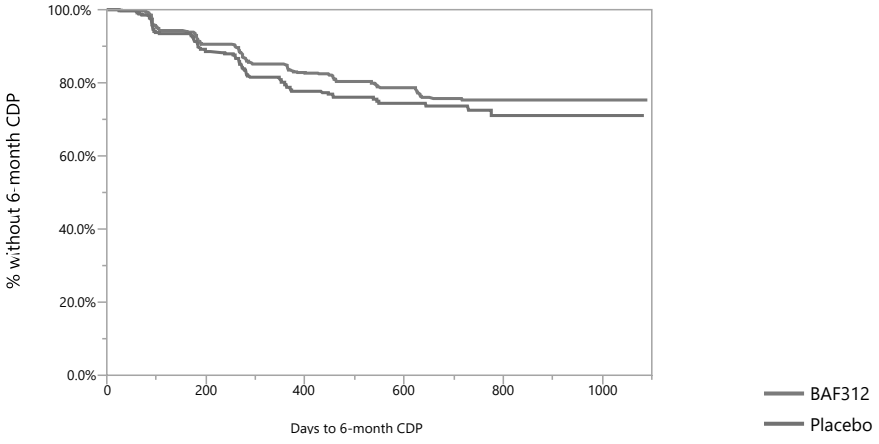
6-month CDP in subset of subjects with relapses in the 2 years before the study

Treatment	Subjects with relapses 2 years before study	6-month CDP in this subset	No 6-month CDP in this subset
BAF312	388 (35.3%)	74 (19.1%)	314 (80.9%)
Placebo	202 (37.0%)	58 (28.7%)	144 (71.3%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.9191	1	0.0085*
Wilcoxon	7.9760	1	0.0047*

Figure 20. Reviewer Figure: Time to 6-month CDP in subjects without relapses in the 2 prior years, CBAF312A2304 (Source: Join ADBS.PARAMCD='NRLLST2Y' WHERE AVAL=0 with ADTTCDP.PARAMCD='T6MCDPF')



6-month CDP in subset of subjects without relapses in the 2 years before the study

Treatment	Subjects without relapses 2 years before study	6-month CDP in this subset	No 6-month CDP in this subset
BAF312	708 (64.4%)	144 (20.3%)	564 (79.7%)
Placebo	343 (62.8%)	81 (23.6%)	262 (76.4%)

Group Comparison

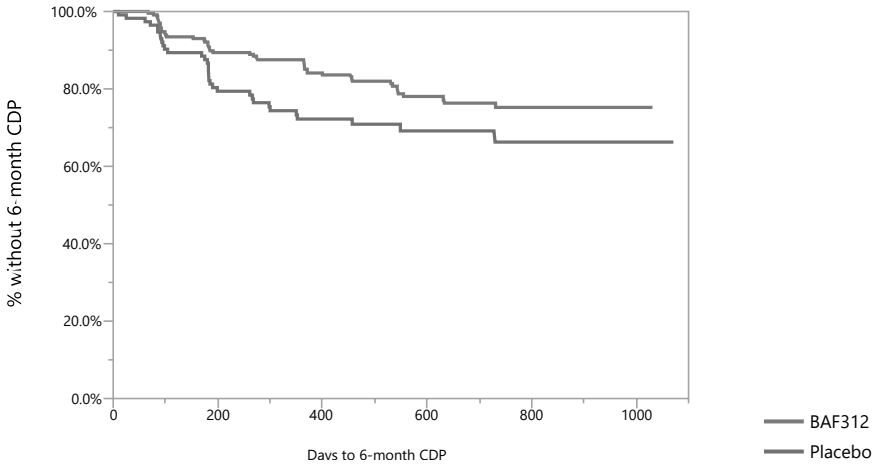
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.0242	1	0.1548
Wilcoxon	2.4925	1	0.1144

Reviewer Comment: Similar to the pre-specified analysis of relapses in the 2 years before the study on 3-month CDP, this post-hoc *analysis assessing the effect of pre-study relapses on 6-month CDP also suggests that the effect on siponimod on this end-point is driven by its treatment effect on the subset of subjects with continued relapses and inflammation in the 2-years before the study.*

As per this reviewer's Kaplan-Meier graphs below (Figure 21 and Figure 22), the effect on 6-month CDP also appears to be driven by the subset of the population who had gadolinium-enhancing lesions at baseline.

Figure 21. Reviewer Figure: Time to 6-month CDP in subjects with enhancing lesions at baseline, CBAF312A2304

(Source: join ADBS.PARAMCD='BLT1GDN' WHERE AVAL>0 with ADTTCDP.PARAM='T6MCDPF')



6-month CDP in subset of subjects with gadolinium-enhancing lesions at baseline

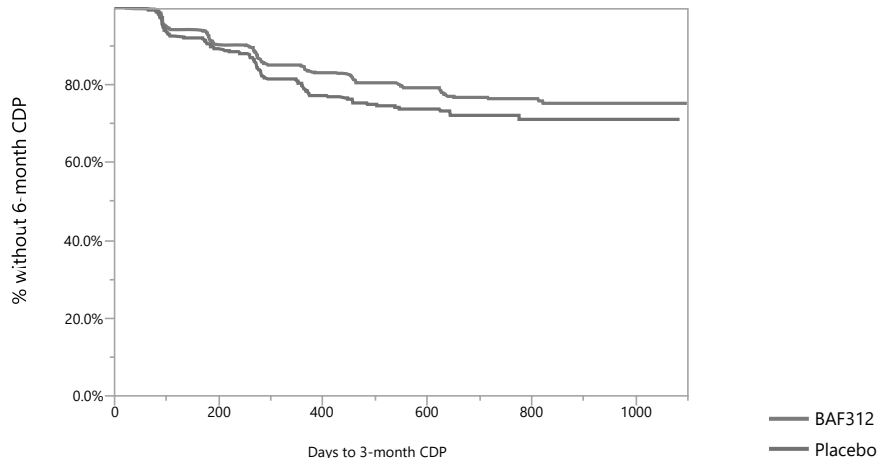
Treatment	Subjects with enhancing lesions at baseline	6-month CDP in this subset	No 6-month CDP in this subset
BAF312	236 (21.5%)	48 (20.3%)	188 (79.7%)
Placebo	114 (20.9%)	33 (29.0%)	81 (71.1%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.4968	1	0.0340*
Wilcoxon	5.7498	1	0.0165*

Figure 22. Reviewer Figure: Time to 6-month CDP in subjects without enhancing lesions at baseline, CBAF312A2304

(Source: join ADBS.PARAMCD='BLT1GDN' WHERE AVAL=0 with ADTTCDP.PARAM='T6MCDPF')



6-month CDP in subset of subjects without gadolinium-enhancing lesions at baseline

Treatment	Subjects without enhancing lesions at baseline	6-month CDP in this subset	No 6-month CDP in this subset
BAF312	828 (75.3%)	165 (20.0%)	663 (80.1%)
Placebo	415 (76.0%)	102 (24.6%)	313 (75.4%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.6994	1	0.0544
Wilcoxon	4.2131	1	0.0401*

Reviewer Comment: Similar to the pre-specified analysis of baseline gadolinium-enhancing lesions on 3-month CDP, this post-hoc analyses of baseline enhancing lesions

on 6-month CDP also suggests that the effect on siponimod on this end-point is driven by its effect on the subset of subjects with more inflammatory disease., i.e., those patients with gadolinium-enhancing lesions on a baseline MRI.

Annualized relapse rate

Another non-key secondary endpoint of interest was the annualized relapse rate (ARR) for confirmed relapses. As per Table 30, 215 subjects in Study A2304 experienced a total of 277 confirmed relapses during 691,980 days of observation.

Table 30. Reviewer Table: Subjects with a confirmed relapse during the study, FAS, CBAF312A2304

Treatment (Number of Subjects)	# of relapses	Subjects with ≥1 confirmed relapse(s)	Subjects with >1 confirmed relapses
Siponimod (n=1099)	134	113 (10.3%)	18 (1.6%)
Placebo (n=546)	143	102 (18.7%)	29 (5.3%)

Source: Subset of ADMSREL with ADMSREL.OCCURCE = 'Y'

Table 31 presents this reviewer's descriptive statistics of the subject-level ARR, while Table 32 calculates an ARR from the number of relapses and number of subject days in the study.

Table 31. Reviewer Table: Subject-based ARR (confirmed relapses), FAS, CBAF312A2304

Treatment	# of Subjects	Mean ARR	Std Dev ARR
Siponimod	1099	0.071	0.254
Placebo	546	0.175	0.463

Source: Mean(AVAL) of subset ADARR.PARAMCD = 'ARRRLPC' by TRTP01

Table 32. Reviewer Table: Number of confirmed relapses and number of subject days during study, FAS, CBAF312A2304

Treatment	# of Relapses	# Subject Days	Group-Based ARR
Siponimod	134	691980	.071
Placebo	143	343285	.152

Source: Sum ADARR.NCFRLSTY >0 / Sum ADARR.NBDYSTY * 365.25 by TRTP01

Reviewer Comment: As would be expected in a trial of subjects with SPMS, 986 (89.7%) of subjects randomized to siponimod and 444 (81.3%) of subjects randomized to placebo did not experience a relapse in this trial. The unadjusted subject- and group-based ARRs calculated above by this reviewer are essentially the same as those derived by the sponsor, representing a 59% and 53% reduction in the subject-based and group-based unadjusted ARR, respectively.

Table 33 below describes the sponsor's adjusted analysis of ARR for confirmed relapses in CBAF312A2304, which is confirmed in the Biometrics review by Dr. Xiang Ling.

Table 33. Sponsor Table: ARR for confirmed relapses – negative binomial regression (FAS), CBAF312A2304

		Between-treatment comparison BAF312 vs Placebo§		
Treatment	Adjusted ARR (95% CI)§	Rate reduction	ARR ratio (95% CI)	p-value
BAF312 (N=1099)	0.071 (0.055;0.092)	55.5%	0.445 (0.337;0.587)	<0.0001
Placebo (N=546)	0.160 (0.123;0.207)			

Analysis period: from first day of study drug up to end of core part.
§ Obtained from fitting a negative binomial regression model adjusted for treatment, country/region, baseline EDSS, baseline number of T1 Gd-enhancing lesions, and SPMS group (with/without superimposed relapses, baseline definition) (offset: time in analysis period in years).

Reviewer Comment: As per Table 33, the sponsor calculates an adjusted ARR reduction of 55.5%. This relapse rate reduction is similar to that for the approved S1P-modulator (fingolimod) and suggests that siponimod has treatment effect on relapses, which, as discussed above, appears to drive its effect on disability progression. Similar to my prior comments regarding the T2 lesion volume endpoint, the nominal p-value for this finding is very low (<0.0001) and suggests that the chance of a Type I error is almost nil, even if the first "key" secondary endpoint of the study did not achieve statistical significance.

Obviously, some relapses were not confirmed by an EDSS worsening. Although some of these may have represented pseudo-relapses in the setting of fever / infection (Uhthoff's phenomenon) or natural fluctuations in symptom severity, some may have been missed inflammatory events, because the EDSS is criticized for being a non-linear scale and relatively insensitive to change in the middle of the overall scale (and the middle of the functional system subscales). Table 34 below explores the incidence of unconfirmed relapses in CBAF312A2304.

Table 34. Reviewer Table: Subjects with an unconfirmed relapse during the study, FAS, CBAF312A2304

Treatment	# of unconfirmed relapses	Subjects with ≥1 unconfirmed relapse(s)	Subjects with >1 unconfirmed relapses
Siponimod (n=1099)	103	85 (7.7%)	11 (1.0%)
Placebo (n=546)	76	58 (10.6%)	31 (5.7%)

Source: Subset of ADMSREL with ADMSREL.OCCURCE = 'N'

Reviewer Comment: It is noted that the relapse rates in the placebo-treated arm of CBAF312A2304 are lower than those in many other MS clinical trials, which may indicate a reduction in relapses in subjects later in the disease course and / or with SPMS. Given the rates of non-confirmed relapses, another possibility is the difficulty in confirming relapses: the non-linearity of the EDSS (and functional systems) makes it more difficult to demonstrate progression around an EDSS of 6 (or a functional system score > 2).

Factoring relapse severity and relapse recovery into the analysis of relapses may offer more insight into the benefit of siponimod over placebo in this trial. Confirmed relapses treated with steroids or requiring hospitalization may suggest increased relapse severity, albeit with the caveat of potential confounders including subject and investigator preference, regional practice trends, and knowledge of treatment assignment due to ineffective blinding. The degree of recovery from a relapse may be confounded by the degree of existing MS pathology and the amount of remaining functional reserve. Table 35 and Table 36 report this reviewer's descriptive statistics of the subject-calculated ARR in the subset of subjects having a confirmed relapse requiring steroids or hospitalization, respectively.

Table 35. Reviewer Table: ARR in subjects with confirmed relapses requiring steroids, FAS, CBAF312A2304

Treatment	# of Subjects	Mean ARR	Std Dev ARR
Siponimod	104	0.066	0.249
Placebo	97	0.164	0.446

Source: Mean(AVAL) of subset ADARR.PARAMCD = 'ARRRSDC' by TRTP01

Table 36. Reviewer Table: ARR in subjects with confirmed relapses requiring hospitalization, FAS, CBAF312A2304

Treatment	# of Subjects	Mean ARR	Std Dev ARR
Siponimod	36	0.021	0.132
Placebo	38	0.065	0.307

Source: Mean(AVAL) of subset ADARR.PARAMCD = 'ARRRHOC' by TRTP01

Reviewer Comment: The above <u>unadjusted</u> analyses are similar to those performed by the sponsor and suggest that siponimod reduces the number of relapses requiring steroids (unadjusted 46.6% ARR reduction) and those requiring hospitalization (60.7% reduction) compared with placebo in this trial. These may suggest that siponimod also reduces relapse severity, although subject / investigator preference and regional practice trends may confound this analysis.

Table 37 reports this reviewer's descriptive statistics of the subject-calculated ARR in the subset of subjects having a confirmed relapse without complete recovery.

Table 37. Reviewer Table: ARR in subjects with confirmed relapses without complete recovery, Full analysis dataset, CBAF312A2304

Treatment	# of Subjects	Mean ARR	Std Dev ARR
Siponimod	58	0.034	0.167
Placebo	57	0.089	0.338

Source: Mean(AVAL) of subset ADARR.PARAMCD = 'ARRWCRC' by TRTP01

Reviewer Comment: The above analysis replicates that of the sponsor and suggests that siponimod reduces the number of relapses with incomplete recovery compared with placebo in this trial by 49.2% (unadjusted ARR). This may also suggest a reduction in relapse severity with siponimod, although pre-existing MS pathology and the lack of a functional reserve may confound this analysis. This reduction in relapse severity may further suggest siponimod's effect on the pathophysiology underlying the relapsing aspect of the disease.

Note that all of the ARR analyses performed above yielded a reduction of over 50%.

Enhancing T1 lesions

Another non-key secondary endpoint of interest in CBAF312A2304 is the number of gadolinium enhancing lesions. Many subjects did not experience an observed enhancing lesion during the trial, probably because of the studied population (SPMS) and the observation that the typical MS lesion enhances with gadolinium for an average of 3 weeks, even without treatment with steroids (Cotton et al, 2003). Because CBAF312A2304 is a time to event trial in which subjects were able to transition to open-label siponimod after experiencing 6-month CDP, the number of subjects decreases in the 24- and 36-month analyses below.

Table 38. Reviewer Table: Number of gadolinium-enhancing T1 lesions at 12 months, CBAF312A2304

		Number of Gadolinium-enhancing T1 lesions at 12 months				
Treatment	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	1020	0.1	1.1	0	0	30
Placebo	507	0.9	2.7	0	0	24

Source: Mean(AVAL) in ADMR.PARAMCD='T1GDN', VISIT contains {Month12, EOT, EOS, FO}, ANL01FL='Y', and AVISIT=Month12

Table 39. Reviewer Table: Number of gadolinium-enhancing T1 lesions at 24 months, CBAF312A2304

		Number of Gadolinium-enhancing T1 lesions at 24 months				
Treatment	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	623	0.1	0.6	0	0	12
Placebo	304	0.4	1.2	0	0	12

Source: Mean(AVAL) in ADMR.PARAMCD='T1GDN', VISIT contains {Month24, EOT, EOS, FO}, ANL01FL='Y', and AVISIT=Month24

Table 40. Reviewer Table: Number of gadolinium-enhancing T1 lesions at 36 months, CBAF312A2304

		Number of Gadolinium-enhancing T1 lesions at 24 months				
Treatment	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	132	0.1	0.3	0	0	2
Placebo	52	0.5	1.6	0	0	7

Source: Mean(AVAL) in ADMR.PARAMCD='T1GDN', VISIT contains {Month36, EOT, EOS, FO}, ANL01FL='Y', and AVISIT=Month36

Reviewer Comment: The number of gadolinium-enhancing lesions in this reviewer's analysis above is essentially the same as noted in Table 14.2-6.1 in the CSR. Similar to this study's treatment effect on relapses, the reduction in gadolinium-enhancing lesions is notable and, per the sponsor's analyses, is nominally highly statistically significant ($p<0.0001$) at 12 and 24 months. These analyses show siponimod's efficacy on reducing enhancing (active, inflammatory) lesions on MRI, further supporting this reviewer's hypothesis that siponimod's effect on disability progression is driven by its anti-inflammatory effect.

Dose/Dose Response

Dose vs. response was not assessed in this trial.

Durability of Response

Durability of response was not assessed in this trial. An open-label extension of CBAF312A2304 remains ongoing, but the lack of a comparator arm limits the ability to confidently assess the continued efficacy (or durability) of the response.

Persistence of Effect

Efficacy following withdrawal of treatment was not assessed in this trial. With that said, given the presumed mechanism of action of siponimod and fingolimod (sequestration of ~70% of circulating lymphocytes in lymph nodes and other lymphoid tissue), one could posit that the effect of the drug would last at least until these lymphocytes were released from the lymphoid

tissue (on average, about 2 weeks after cessation of siponimod). It should also be considered that lymphocyte-depleting therapies given after cessation of siponimod may not be effective until the sequestered lymphocytes have egressed from the lymphoid tissue.

Additional Analyses Conducted on the Individual Trial

As above, analysis of the primary endpoint suggests that much of siponimod's effect on 3-month CDP is driven by relapses and inflammatory disease. Review of the regulatory history for siponimod reveals that the Division expressed concerns that siponimod's effect on 3-month CDP was driven in part by relapse rate reduction and that it was unclear if siponimod had an effect on non-relapsing SPMS. (b) (4)

Siponimod's regulatory history supports the assertion that the relapsing population would be the population in which a treatment effect would be seen. FDA stated that the relapsing benefit in A2304 supported by A2201 might support the submission of an NDA for relapsing MS, (b) (4) This reviewer's analysis of 3-month CDP in CBAF312A2304 also suggests that siponimod may be effective in relapsing MS, as does its effects on the change in T2 lesion volume, ARR, and T1 enhancing lesions. It would not be surprising for siponimod to have a benefit on relapsing MS, as there are three positive Phase 3 trials supporting the use of another medication with a similar mechanism of action (fingolimod) for this indication.

The inclusion criteria for a "typical" Phase 3 trial in relapsing MS would select subjects with one relapse in the past year or 2 relapses in the past 2 years. To continue to explore the potential role of siponimod in relapsing disease, this reviewer performed some of the preceding analyses below in the subset of subjects in A2304 who would qualify for a "typical" RRMS trial. See Table 41.

Table 41. Reviewer Table: Number of Subjects who would qualify for a RRMS Trial

Criterion	Siponimod	Placebo
Subjects with one or more relapses in last year prior to screening	226 (20.6%)	129 (23.6%)
Subjects with two or more relapses in past 12-24 months prior to screening	94 (8.6%)	48 (8.8%)
Union of these two criteria [1]	252 (23.0%)	142 (26.0%)

Source: Subset of ADBS where (PARAMCD = 'NURLP12' and AVAL > 0) or (PARAMCD= 'NR12T24M' and AVAL > 1)
[1] 2 subjects without ARR data

Reviewer Comment: 24% (394) of subjects in A2304 would have qualified for a typical RRMS study given one or more relapses in the past 12 months or more than one relapse in the past 24 months. The following post-hoc *analyses in this section of the review will be performed on this subset of CBAF312A2304, which will be denoted as "**QualRRMS**." It is also recognized that the relatively small size of this cohort may cause the subsequent analyses to have insufficient power for definitive conclusions.*

ARR in QualRRMS

Table 41 contains descriptive statistics on the confirmed ARR in subjects in the QUALRRMS subset of CBAF312A2304 who would qualify for a typical RRMS study.

Table 41. Reviewer Table: Subject-based ARR (confirmed relapses) in QualRRMS, CBAF312A2304

Treatment	# of Subjects	Mean ARR	Std Dev ARR
Siponimod	252	0.132	0.361
Placebo	142	0.294	0.652

Source: Mean(AVAL) ADARR.PARAMCD = 'ARRRLPC' by TRTP01 in QualRRMS subset

Reviewer Comment: In this post-hoc *analysis, the subset of subjects who would qualify for a "typical" RRMS study exhibited a 55% reduction in unadjusted ARR (p=0.0035). This result aligns well with the results of the ARR analysis in the entire A2304 population as well as the placebo-controlled RMS study described on the labeling of a similar approved S1P receptor modulator (fingolimod) in which a reduction of over 50% in ARR was observed.*

Change in T2 lesion volume in QualRRMS

Table 42, Table 43, and Table 44 contain descriptive statistics on the T2 lesion volumes at 12, 24, and 36 months in subjects in the QUALRRMS subset of CBAF312A2304.

Table 42. Reviewer Table: Unadjusted change in T2 lesion volume (mm3) from baseline to month 12 in QualRRMS, CBAF312A2304

		Change in T2 lesion volume (mm^3) at 12 months				
Treatment	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	231	91.4	1906.7	33	-15992.0	12942.0
Placebo	136	1020.8	2734.3	243	-3814.0	22100.0

Source: Mean(CHG) in ADMR.PARAMCD='T2VOL," VISIT contains {Month12, EOT, EOS, FO}, ANL01FL='Y', and AVISIT = Month12 in QualRRMS subset

Table 43. Reviewer Table: Unadjusted change in T2 lesion volume (mm3) from baseline to month 24 in QualRRMS, CBAF312A2304

		Change in T2 lesion volume (mm^3) at 24 months				
Treatment	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	156	224.9	1874.8	-1.0	-5428.0	13342.0
Placebo	80	1084.4	2619.6	389.5	-2235.0	17405.0

Source: Mean(CHG) in ADMR.PARAMCD='T2VOL," VISIT contains {Month24, EOT, EOS, FO}, ANL01FL='Y', and AVISIT = Month24 in QualRRMS subset

Table 44. Reviewer Table: Unadjusted change in T2 lesion volume (mm3) from baseline to month 36 in QualRRMS, CBAF312A2304

		Change in T2 lesion volume (mm^3) at 36 months				
Treatment	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	34	-155.5	1941.8	-147.5	-3788.0	7863.0
Placebo	15	1031.1	1055.6	710.0	-352.0	2612.0

Source: Mean(CHG) in ADMR.PARAMCD='T2VOL', VISIT contains {Month36, EOT, EOS, FO}, ANL01FL='Y', and AVISIT = Month36 in QualRRMS subset

Reviewer Comment: In this post-hoc *analysis on the subset of subjects who would qualify for a typical RRMS study (QualRRMS subset), siponimod achieves a significant reduction in the change in T2 lesion volume over the course of the study. The difference between siponimod and placebo was 929.4mm^3 at 12 months (p=0.0003), 859.5mm^3 at 24 months (p=0.0051), and 1186.6 mm^3 at 36 months (p=0.0042). The high magnitude of the effect and the achieved statistical significance support a strong MRI treatment effect with siponimod; a similar approved S1P modulator (fingolimod) also achieved a significant MRI benefit in its clinical trial program.*

Enhancing T1 lesions in QualRRMS

Table 45, Table 46, and Table 47 contain descriptive statistics on the number of gadolinium-enhancing lesions at 12, 24, and 36 months in subjects in the QUALRRMS subset of CBAF312A2304.

Table 45. Reviewer Table: Number of gadolinium-enhancing T1 lesions at 12 months in QualRRMS, CBAF312A2304

		Number of Gadolinium-enhancing T1 lesions at 12 months				
Treatment	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	231	0.2	0.7	0	0	5
Placebo	134	1.4	3.6	0	0	22

Source: Mean(AVAL) in ADMR.PARAMCD='T1GDN', VISIT contains {Month12, EOT, EOS, FO}, ANL01FL='Y', and AVISIT=Month12 in QualRRMS subset

Table 46. Reviewer Table: Number of gadolinium-enhancing T1 lesions at 24 months in QualRRMS, CBAF312A2304

		Number of Gadolinium-enhancing T1 lesions at 24 months				
Treatment	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	159	0.1	0.4	0	0	3
Placebo	81	0.5	1.3	0	0	7

Source: Mean(AVAL) in ADMR.PARAMCD='T1GDN', VISIT contains {Month24, EOT, EOS, FO}, ANL01FL='Y', and AVISIT=Month24 in QualRRMS subset

Table 47. Reviewer Table: Number of gadolinium-enhancing T1 lesions at 36 months in QualRRMS, CBAF312A2304

		Number of Gadolinium-enhancing T1 lesions at 36 months				
Treatment	Subjects (n)	Mean	Std Dev	Median	Min	Max
Siponimod	34	0.1	0.3	0	0	1
Placebo	14	0.4	1.1	0	0	4

Source: Mean(AVAL) in ADMR.PARAMCD='T1GDN', VISIT contains {Month36, EOT, EOS, FO}, ANL01FL='Y', and AVISIT=Month36 in QualRRMS subset

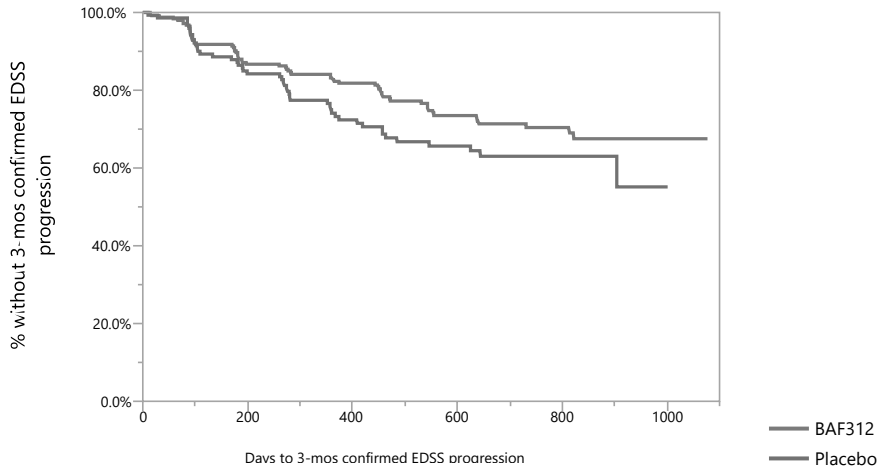
Reviewer Comment: In this post-hoc analysis of the QualRRMS subset of CBAF312A2304, siponimod achieved a significant reduction in the change in the number of gadolinium enhancing lesions at 12 (p=0.0001) and 24 months (p=0.003). The reduction was not statistically significant at 36 months (p=0.19); however, the number of patients remaining in this time to event trial at 36 months was quite low. These data are quite similar to the data reported for clinical trials with fingolimod.

Time to 3-month disability progression in the QualRRMS subset

Figure 23 shows the post-hoc Kaplan-Meier analysis for time to 3-month CDP in the QualRRMS subset of CBAF312A2304.

Figure 23. Reviewer Figure. Time to 3-month CDP in QualRRMS

(Source: ADTTCDP.PARAMCD='T3MCDPF' in QualRRMS subset)



3-month CDP in subjects in QUALRRMS subset

Treatment Group	Number	3-month CDP	No 3-month CDP
BAF312	252	64 (25.4%)	188 (74.6%)
Placebo	142	47 (33.1%)	95 (66.9%)

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.9398	1	0.0864
Wilcoxon	2.9850	1	0.0840

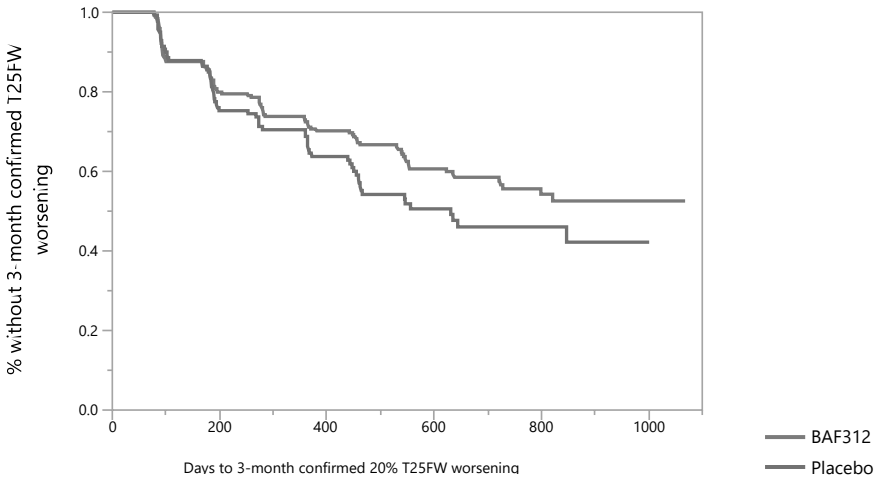
Reviewer Comment: Interestingly, siponimod did not achieve a statistically significant reduction in time to 3-months CDP in this post-hoc *analysis of the QualRRMS subset of CBAF312A2304, although a strong trend is noted.*

Time to 3-month 20% worsening on T25FW in QualRRMS subset

Figure 24 shows this reviewer's post-hoc Kaplan-Meier analysis for time to 20% T25FW worsening in the QualRRMS subset of CBAF312A2304.

Figure 24. Reviewer Figure. Time to 3-month 20% T25FW worsening, CBAF312A2304

(Source: ADTTCDP.PARAMCD='T3M25WF' in QualRRMS subset)



3-month confirmed 20% T25FW worsening in subjects in QUALRRMS

Treatment Group	Subjects	3-mos T25FW worsening	No 3-mos T25FW worsening
BAF312	252	95 (37.7%)	157 (62.3%)
Placebo	142	65 (45.8%)	77 (54.2%)

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.9948	1	0.0835
Wilcoxon	2.1460	1	0.1429

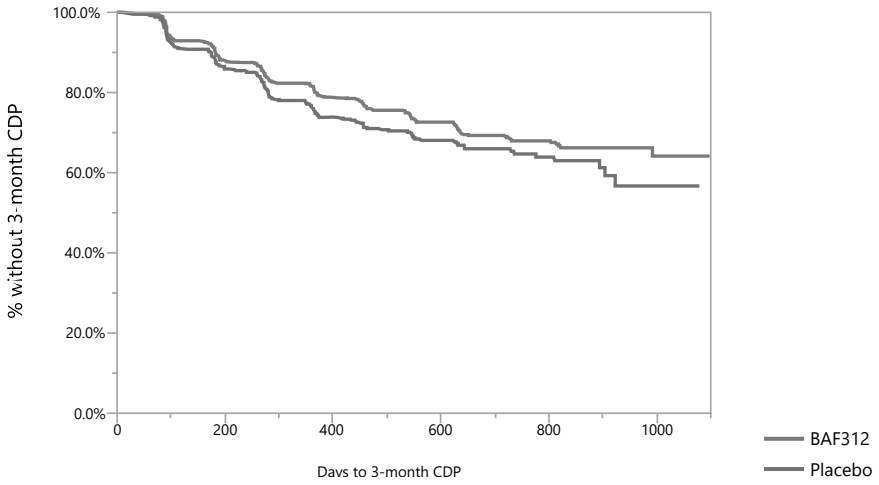
Reviewer Comment: In this post-hoc *analysis, siponimod did not achieve statistical significance in reducing the time to 3-month confirmed 20% worsening in the T25FW compared with placebo in the subset of subjects who would qualify for a typical RRMS study.*

Overall, these post-hoc analyses suggest an effect of siponimod on relapses and MRI metrics (active, inflammatory disease) in the subset of subjects in CBAF312A2304 who would qualify for a "typical" RRMS study. Siponimod's effects on 3-month CDP and 3-month confirmed T25FW worsening were not statistically significant; however, it is recognized that this subset of patients may not be powered to show an effect.

Subjects potentially unblinded due to dual database access

Reductions in heart rate were common after administration of the first dose of siponimod, so a separate team and database were used to collect safety information related to this first dose administration. Unfortunately, 34 users of the main study database for CBAF312A2304 were inadvertently granted access to the first dose database, a potential source of unblinding for 101 subjects. This reviewer repeated an unadjusted analysis of the primary endpoint for the 1544 subjects whose data was not compromised by this dual database issue - see Figure 25.

Figure 25. Reviewer Figure: Time to 3-month CDP in "unblinded" subjects



3-month CDP in "unblinded" subjects

Treatment Group	Number	3-month CDP	No 3-month CDP
BAF312	1034	275 (26.6%)	759 (73.4%)
Placebo	510	157 (30.8%)	353 (69.2%)

Group Comparison

Test	ChiSquare	Prob>ChiSq
Log-Rank	3.5754	0.0586
Wilcoxon	3.8715	0.0491

Reviewer Comment: When removing subjects that were potentially unblinded by the dual database access issue, this reviewer's unadjusted analysis of the primary endpoint did not meet statistical significance on the log-rank test. An Information Request was sent to the sponsor to perform a sensitivity analysis (adjusted for covariates) on the primary endpoint (3-month CDP) on the subset of 1544 subjects who were not potentially unblinded by this dual database access issue, and the result of their analysis was a risk reduction of 17.1% that was also not statistically significant (p=0.062).

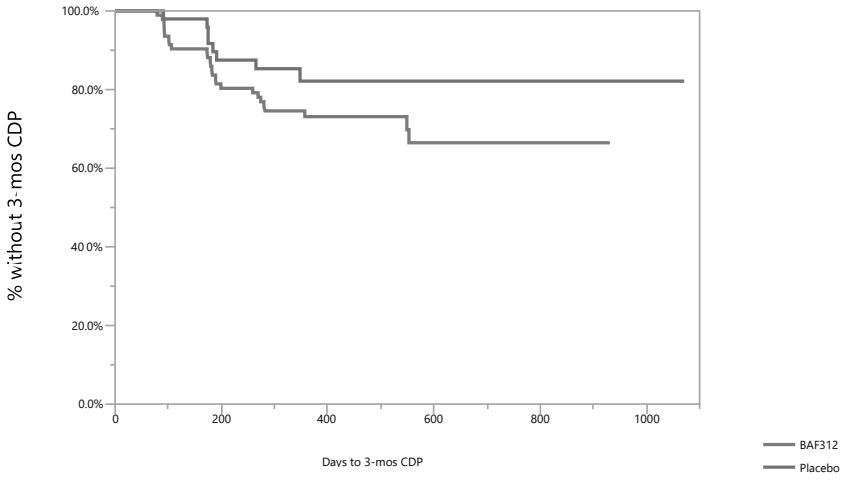
Given the realization that this change in statistical significance could have occurred by chance, this reviewer asked the Division's Biometric consultants to verify this analysis and run repeated simulations in which the primary analysis was performed on 5000 subsets of the Full Analysis set from which 101 subjects had been randomly removed. Their simulations show that the subset of subjects potentially unblinded by the dual database access issue may not be a representative sample of the CBAF312A2304 study population (p=0.028). (See Biometric analysis by Dr. Xiang Ling for further details on this analysis.)

The sponsor provided a sensitivity analysis suggesting that the results of the Timed 25-foot walk were not affected by this dual database access issue and an impact analysis suggesting that the ARR, symbol digit modality test, and MRI metric analyses were also not affected by this dual database access issue. Especially given the potential effect that the "dual database access" issue had on the 3-month CDP primary endpoint, this reviewer does not find these analyses reassuring, because multiple other clinical considerations, up to recommending that a subject discontinue the trial, can be influenced by the degradation of the study blind.

Time to 3-month CDP in subjects from USA

Because the sponsor is seeking approval for marketing in the United States, this reviewer's analysis of the primary endpoint (time to 3-mos CPD) was repeated on the subset of the subjects from the United States.

Figure 26. Reviewer Figure. Time to 3-mos CDP in subset of subjects from USA



3-month CDP in subjects in Full Analysis Set (FAS)

Treatment Group	Number	3-month CDP	No 3-month CDP
BAF312	101	26 (25.7%)	75 (74.3%)
Placebo	52	8 (15.4%)	44 (84.6%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.1564	1	0.1420
Wilcoxon	1.9308	1	0.1647

Reviewer Comment: As above, a post-hoc *analysis of the cohort of subjects from the US did not achieve a statistically significant difference on the primary outcome of time to 3-month CDP, although the effect size is similar. This lack of statistical significance could relate to power given the relatively low percentage of the study population that was from the US (<10%), or it could relate to the identified regional, ethnic, and genetic differences in the disease. The sponsor provides an analysis suggesting that the lack of efficacy may be driven by the relatively higher number of low-enrolling sites in the US. This reviewer agrees and suspects that with more robust study enrollment (or with post-marketing use of siponimod) in the US, the US experience with siponimod will converge on the results achieved by the European study sites.*

Time to 3-month CDP in white and non-white subjects

Outcomes in people with MS can vary by race, e.g., subjects of African descent often have a more aggressive MS phenotype, although MS remains more common in people of Caucasian descent. Even though most of the study population was white, the sponsor was asked to provide an analysis of the primary endpoint (time to 3-month confirmed disability progression) stratified by race into “white” and “non-white” subgroups. See Table 48.

Table 48. Sponsor Table. Time to 3-mos CDP in "white" and "non-white" subjects

			Comparison: BAF312 vs Placebo #		
Subgroup Treatment	n/N'	(%)	Risk reduction	Hazard ratio (95% CI)	p-value
White					
BAF312 (N=1046)	275/1043	(26.4)	24.5%	0.75 (0.62; 0.92)	0.0042*
Placebo (N=513)	168/512	(32.8)			
Non-white					
BAF312 (N=53)	13/53	(24.5)	-106.0%	2.06 (0.72; 5.86)	0.1755
Placebo (N=33)	5/33	(15.2)			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates).
Using a Cox proportional hazards model with treatment, country, baseline EDSS, and SPMS group (with/without superimposed relapses, baseline definition) and race as covariates. Risk reduction is derived as (1-hazard ratio) * 100.

Reviewer Comment: Unfortunately, the low number of "non-white" subjects and disability progression in this subgroup preclude the formation of meaningful conclusion about the effect of siponimod in a "non-white" population.

6.2 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

6.2.1 Study Design

Overview and Objective

Study CBAF312A2201 is a Phase 2 randomized clinical trial designed to assess the efficacy, safety, and tolerability of 5 different doses of daily siponimod compared to placebo in subjects with RRMS.

Trial Design

Study CBAF312A2201 is a 297-subject, randomized, double-blind, multi-center, adaptive dose-finding, placebo-controlled Phase 2 trial to evaluate the efficacy and safety of multiple doses of siponimod versus placebo in subjects with RRMS diagnosed by the 2005 McDonald criteria. The primary endpoint is the dose response relationship among five doses of siponimod and placebo on the monthly number of combined unique active lesions (CUAL) on MRI over 3-months of treatment. A major secondary objective of this study was to determine the safety and

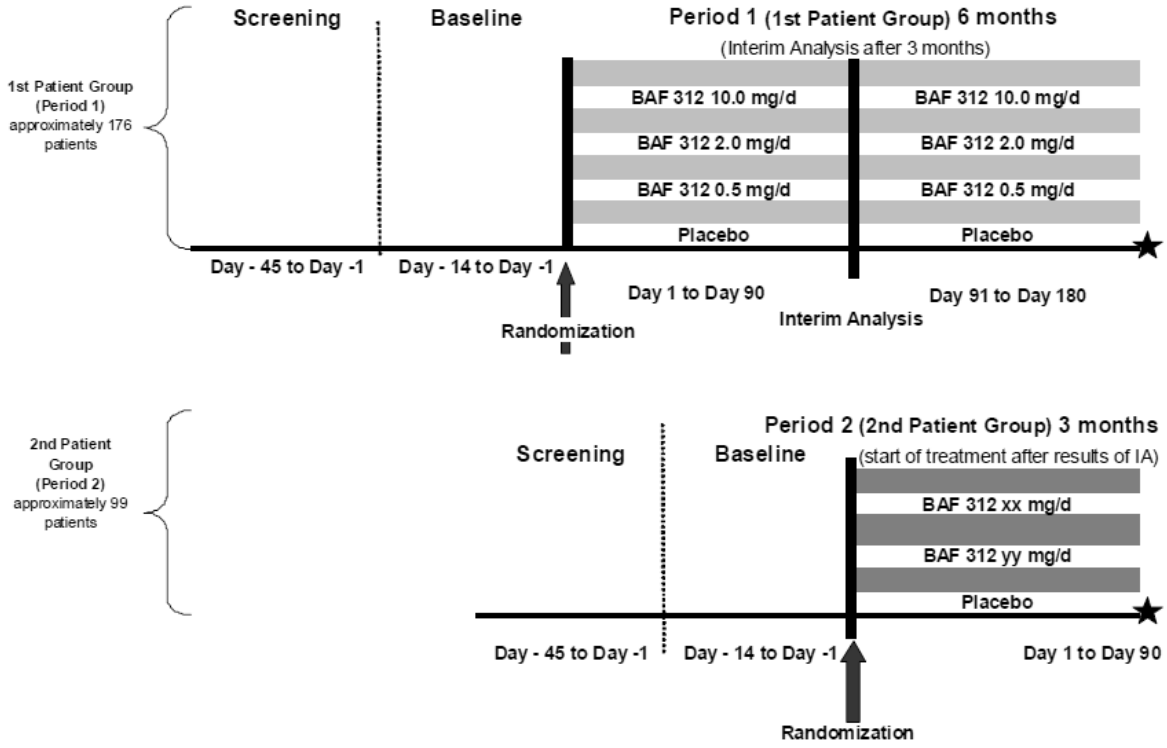
tolerability of siponimod, especially in regard to cardiac bradyarrhythmias, blood pressure, lymphopenia, infections, and ophthalmologic complications (macular edema) given the safety profile of a similar S1P receptor modulator (fingolimod).

This study utilized 2 sequential cohorts. The first cohort consisted of 188 subjects who were randomized 1:1:1:1 to siponimod 10 mg, siponimod 2 mg, siponimod 0.5 mg, or placebo once daily for 6 months. After a prespecified interim analysis to decide whether to continue the study and if so, to choose 2 additional doses of siponimod, a second cohort of 109 subjects were randomized 4:4:1 to siponimod 1.25 mg, siponimod 0.25 mg, or placebo and followed for 3 months. Subjects who completed the study were potentially eligible to receive siponimod in an open label extension study.

An external Data Monitoring Committee was used to allow independent risk / benefit and safety assessments during the study.

The study design is summarized in Figure 27 below.

Figure 27. Sponsor Figure: CBAF312A2201 study design



Blinding

Study CBAF312A2201 employed a double-blind design. Subjects, investigators, evaluators, and the sponsor (except for the data safety monitoring team, the data monitoring committee, and independent statisticians and programmers) remained blinded to the identity of the treatment from the time of randomization until database lock. Because bradycardia after the first dose of siponimod could lead to unblinding, study-independent first dose administrators were used. Total WBC and lymphocyte counts were not provided to the primary team unless there were "notable abnormalities." An independent team had access to the data for the interim analysis before initiation of the second cohort.

Unblinding was permitted in the case of patient emergencies and at the conclusion of the study.

Key Eligibility Criteria

Key Inclusion

- Patients had to give written informed consent before any assessment was performed.
- 18 through 55 years of age inclusive
- Male or female
- Females of childbearing potential:
  - Must have had a negative pregnancy test at baseline prior to entry into the double-blind treatment phase
  - Must have used simultaneously two forms of effective contraception (either partner) during the treatment and for one month or one menstrual cycle, whichever was longer after discontinuation of the study drug
  - If either post-menopausal for 12 months prior to randomization or surgically sterile (through hysterectomy or bilateral oophorectomy, if documented), were not required to use birth control
- Diagnosis of MS as defined by revised McDonald criteria
- A relapsing-remitting course of disease with
  - At least 1 documented relapse during the previous year, or
  - 2 documented relapses during the previous 2 years, or
  - A positive Gd-enhanced MRI scan at screening (in case the first MRI scan obtained at screening was negative, a second scan could be obtained 1 month later)
- An Expanded Disability Status Scale (EDSS) score of 0-5.0 inclusive at randomization
- Neurologically stable with no evidence of relapse or corticosteroid treatment within 30 days prior to randomization

- Patients who declined initiation or continuation of treatment with available disease modifying drugs for MS, for whatever reason, after having been informed about their respective benefits and possible AEs by the investigator
- Patient was willing to refrain from submersion in water (i.e. bathing or swimming) while wearing the Mobile Cardiac Telemetry (MCT) adherent device during dose titration

Key Exclusion

- A manifestation of another type of MS than RRMS
- History of chronic disease of the immune system other than MS, or a known immunodeficiency syndrome
- History or presence of malignancy (except for successfully-treated basal or squamous cell carcinoma of skin)
- A known, or 'new' diagnosis of diabetes mellitus (if screening blood glucose was suspicious for diabetes [≥ 126mg/dL or ≥ 7 mmol/L if fasting; ≥ 200mg/dL or 11.1 mmol/L if random testing] a patient was to be further evaluated for diabetes mellitus)
- Diagnosis of macular edema during pre-randomization phase (patients with a history of macular edema was allowed to enter the study provided that they did not have macular edema at the ophthalmic examination at the Screening Visit)
- Active systemic bacterial, viral or fungal infections, or diagnosis of AIDS, Hepatitis B, Hepatitis C infection defined as a positive HIV antibody, Hepatitis B surface antigen or Hepatitis C antibody tests, respectively
- Negative for varicella-zoster virus IgG antibodies at Screening
- Had received any live or live attenuated vaccines (including for varicella-zoster virus or measles) within 2 months prior to randomization
- Had received total lymphoid irradiation or bone marrow transplantation
- Had been treated with:
  - ACTH or oral or injected corticosteroids within 1 month prior to randomization
  - IFN-β or glatiramer acetate within 3 months prior to randomization
  - immunosuppressive medications such as azathioprine or methotrexate within 6 months prior to randomization
  - immunoglobulins and/or monoclonal antibodies (including natalizumab) within 6 months prior to randomization (this rule does not apply for alemtuzumab, rituximab, see below)
  - alemtuzumab, rituximab, cladribine, cyclophosphamide, mitoxantrone, or other immunosuppressive treatments with effects potentially lasting over 6 months, at any time

- Any medically unstable condition, as assessed by the primary treating physician
- Any of the following cardiovascular conditions:
  - History or presence of stable or unstable ischemic heart disease (IHD), myocardial infarction**,** myocarditis, or cardiomyopathy
  - history of Raynaud's disease
  - cardiac failure at time of Screening and/or Baseline (Class II - IV, according to NYHA Classification) or any severe cardiac disease as determined by the investigator
  - history of cardiac arrest
  - history of symptomatic bradycardia
  - resting pulse rate < 55 bpm prior to randomization
  - history or presence of a clinically relevant impairment of cardiac conduction including sick sinus syndrome, sino-atrial heart block
  - clinically significant AV block, bundle branch block or an increased QTc interval > 440 msec on screening electrocardiogram (ECG) prior to randomization
  - history or presence of symptomatic arrhythmia or arrhythmia requiring or being otherwise of clinical significance
  - arterial hypertension, uncontrolled by medication
  - requiring treatment with medication that impairs cardiac conduction (e.g., beta blockers, verapamil-type and diltiazem-type calcium-channel blockers, or cardiac glycosides)
  - history of syncope of suspected cardiac origin
  - history of catheter ablation
- Any of the following pulmonary conditions:
  - severe respiratory disease or pulmonary fibrosis
  - tuberculosis, except for history of successfully treated tuberculosis or history of prophylactic treatment after positive PPD skin reaction
  - abnormal chest High Resolution Computer Tomography (HRCT), chest X-Ray or chest MRI suggestive of active pulmonary disease
  - abnormal Pulmonary Function Tests: forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) values lower than 70% of predicted value
  - patients receiving chronic (daily) therapies for asthma
- Any of the following hepatic conditions:
  - chronic liver or biliary disease
  - total bilirubin greater than the upper limit of the normal range (ULN) unless in context of Gilbert's syndrome
  - conjugated bilirubin greater than the ULN
  - alkaline phosphatase (AP) greater than 1.5 x ULN

  - aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT) greater than 2 x ULN
  - gamma-glutamyl-transferase (GGT) greater than 3 x ULN
- Any of the following abnormal laboratory values:
  - potassium > ULN
  - serum creatinine > 1.7mg/dL (150 µmol/L)
  - white blood cell (WBC) count < 3,500/mm^3 (< 3.5 x 10^9/L)
  - lymphocyte count < 800/mm^3 (< 0.8 x 10^9/L)
- Any of the following neurological/psychiatric disorders:
  - history or presence of substance abuse (any use of illicit or prescription drugs or alcohol constituting an abuse pattern in the opinion of the investigator)
  - progressive neurological disorder, other than MS
- Unable to undergo MRI scans due to claustrophobia or metallic implants incompatible with MRI
- Unable to receive gadolinium-based MRI contrast agents due to a history of hypersensitivity to gadolinium-based contrast agents, or severe renal insufficiency
- Participation in any clinical research study evaluating another investigational drug or therapy within 3 months prior to randomization
- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
- Homozygosity for CYP2C9*3 (will be tested at Screening), and refusal to test for CYP2C9*3 haplotype
- Patients who used (or had used within four (4) weeks or 5 half- lives, whichever was greater before initial dosing) concomitant medications that were strong or moderate inhibitors or inducers of CYP2C9
- History of S1P receptor modulator therapy
- Any other disease of condition which would have interfered with the participation in the study according to the study protocol, or with the ability with the patients to cooperate and comply with the study procedures.
- Had an implantable device with an active minute ventilation sensor or active magnet features.
- Had a known allergy or hypersensitivity to adhesives or hydrogel.

Reviewer Comment: The inclusion and exclusion criteria seem reasonable and appropriate for a Phase 2 RRMS study. Although the intent of this lengthy list of exclusion criteria is probably attributable to an appropriate sense of caution, this list makes it cumbersome for investigators to find eligible subjects to enroll subjects in this study, potentially leading to slowed enrollment and protocol deviations. Even more concerning is that this highly selected population may not represent "real world" individuals with MS and may underestimate the safety of the drug in a "real world" setting unless the label specifies similar restrictions on the use of siponimod.

Treatment

Rationale for Dose Selection

CABF312A2201 was designed to explore the dose-response curves for siponimod. The highest dose of siponimod tested in the study was 10 mg daily, as this showed near-maximal (80%) reduction in lymphocyte counts in the Phase I study. It was predicted that siponimod 0.5mg daily would reduce lymphocytes by less than 50%. The first cohort randomized subjects to 10 mg, 2 mg, or 0.5 mg of siponimod (or placebo). The doses for cohort 2 (siponimod 1.25 mg daily, siponimod 0.25 mg daily, and placebo) were selected based on analysis of the dose-response data from the first cohort.

First Dose Monitoring

It is known that administration of the first dose of S1P functional antagonists like siponimod can cause temporary heart rate reductions or bradyarrhythmias, for which subjects were monitored in the study. In cohort 1, vitals were assessed pre-dose and for at least 6 hours after the first dose. Given an observed bradyarrhythmia signal in cohort 1, a 10-day dose titration was used in cohort 2 – vitals were checked before the first dose and for 6 hours after the first, 2nd, and 7th dose. EKGs were to be checked before the first dose and 2, 4, and 6 hours after the first dose in cohort 1. Mobile Cardiac Telemetry (MCT) was utilized during the dose titration in subjects in cohort 2.

To preserve blinding of treatment status, the initial dose of study treatment was administered by an independent First Dose Administrator, who monitored the subjects cardiovascular and pulmonary status after that dose of study medication was given. The First Dose Administrator would not divulge findings to patients, the study staff, or the sponsor unless there was a significant medical need to do so.

Concomitant Medication

The investigator instructed subjects to notify the study site about any new medications taken or prescribed after the subject was enrolled in the study. Recording of all medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after enrollment in the study was required.

Immunosuppressive medications, immunoglobulins, monoclonal antibodies, beta-interferons, glatiramer acetate, ACTH, oral / inhaled steroids (except for short courses of steroids for an MS relapse), plasma exchange, and medications that impair cardiac conduction were not to be used during the study unless the study drug was permanently discontinued. Live or live attenuated vaccines were not to be used during the study or until 3-months after cessation of the study drug. Medications that induce or inhibit CYP2C9 were not to be co-administered with siponimod.

The use of anticholinergics and beta-agonists was allowed for the treatment of symptomatic bradycardia associated with siponimod.

Treatment of Relapses

The protocol allowed treatment for a relapse consisting of a standard course of corticosteroids (up to 1000 mg/day methylprednisolone for three-five days), as clinically warranted. Tapering with oral corticosteroids was not allowed. Standard of care procedures were to be followed during treatment.

Assessments

Table 49. Sponsor Table: CBAF312A2201 Table of Visit Assessments

Phase	**Pre-randomization**		**Double-blind Treatment** Period 1: 6 months (Visit 3 to 10) Period 2: 3 months (Visit 3 to 6, and 10)								**Follow up**
Visit No. *	Screen-ing	Base-line	3	4	5	6	7	8	9	10	Follow Up Visit[2]
Study Month	-45 days	-14 days	Day 1	Day 7	Month 1	Month 2	Month 3	Month 4	Month 5	End of Treat-ment[1]	+ 3 months
							Visits 7 to 9 only applicable for patients in Period 1				
Informed Consent	X										

Background, Demography	X										
Inclusion/ Exclusion Criteria	X	X									
Medical history	X										
MS history/ MS treatment	X										
Physical examination[3]	X	X	X	X	X	X	X	X	X	X	X
Chest HRCT/ Chest X-ray[18]	X									X	
Vital Signs	X	X[17]	X	X	X	X	X[17]	X	X	X[17]	X
24 hours Holter Monitoring	X		X				X[14]			X[14]	
First dose administration			X								
ECG		X	X[15]								
24 hours Blood Pressure[19]		X					X[14]			X[14]	
Hematology, Blood chemistry[5]	X[6]	X		X	X		X			X	X[20]
Pregnancy Test (serum)[7]	X	X					X			X	
Urine Analysis	X	X		X	X		X			X	X[20]
Ophthalmologic examination[8]	X				X		X			X	
Pulmonary Function Tests	X				X					X	
Dermatology Examination (by a derma-tologist)	X									X	
MRI[10]	X	X[9]			X	X	X	X	X	X	
EDSS[11]	X						X			X	
MS Relapse[11]	X	X	X	X	X	X	X	X	X	X	X
Blood sample for PK					X		X			X	
Blood sample for DNA[12]	X	X									
Blood sample for plasma[16]		X			X		X			X	
Blood sample for DNA (safety)[21]	X										
Blood sample for RNA[16]		X			X		X			X	
FACS[4]		X					X			X	
PRIMUS[22,4]		X								X	
uFIS[22, 4]		X								X	
Study Drug Dispensation			X	X	X	X	X	X	X		
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adverse Event /Serious AE	X[13]	X[13]	X	X	X	X	X	X	X	X	X

1. For patients randomized in Period 1, End of Treatment Visit is at Month 6, for Patients randomized in Period 2, End of Treatment Visit is at Month 3.
2. Pa ients who prematurely discontinue study drug will be asked to complete the End of Treatment visit and continue in the study with an abbreviated visit schedule. Patients who prematurely discontinue study and do not want to continue in the study with the abbreviated visit schedule, or patients who complete he double-blind treatment phase but do not enter the Extension Phase will be asked to complete the 3-month follow up visit to monitor the safety of these patients using clinical assessments.
3. Physical examination will include a dermatologic examination by the treating physician.
4. This examina ion is done at selected study sites.
5. Laboratory results must be available prior to randomization to evaluate inclusion/exclusion criteria. Hematology results will be in part blinded to maintain the study blind. Additional Blood samples (3 mL) will be collected for exploratory analysis.
6. Serology testing will be performed as part of the Screening Visit labs to determine the patient's immune status with respect to the following viruses (in all cases IgG antibodies will be measured): Varicella-zoster virus, Herpes simplex virus-1, Herpes simplex virus-2, Measles. Patients who are negative for varicella zoster virus IgG antibodies at Screening are not eligible for randomization.
7. Serum pregnancy test to be performed by central laboratory. Pregnancy test can also be performed additionally at investigator's discretion during the study.
8. Ophthalmologic examination will include best corrected visual acuity, low contrast visual acuity, and dilated ophthalmoscopy. Central foveal thickness by OCT will be performed at each designated visit.
9. MRI scan must be performed within 30 days prior to randomiza ion. If the patient does not fulfill inclusion criteria on the basis of bout/relapse history (see Inclusion Criteria No. 5) and the first Gd-enhanced MRI scan is negative, a second scan may be obtained one mon h later to be eligible for the study participa ion.
10. The MRI scans will include: T2-weighted (T2 and proton density) images, fluid attenuated inversion recovery (FLAIR) images, 3DT1, and T1-weighted images before and after administration of Gd contrast medium (0.1 mmol/kg). Selected sites will also acquire MTR.
11. Unscheduled visits are required to confirm MS relapse and additional EDSS assessments may be conducted.
12. The blood draw(s) for Pgx assessments is only done after the separate informed consent is signed. The blood sample for DNA can be taken at Screening or Baseline.
13. According to Novartis procedure, before start of study drug administration, only SAE will be recorded
14. 24 hours Holter monitoring and 24 hours blood pressure monitoring is planned for the same study visit (at Visit 7 and at End of Treatment Visit. The assessments have to be done sequentially (patient have to come to the study site on 2 different days).
15. ECG to be obtained on Day 1 before BAF312 administration, and 2, 4 and 6 hour post-first dose. Data of the administration of the first dose of study drug will be captures on a paper CRF and will not be part of the eCRF.
16. The blood draws for Pgmx are only done after the separate informed consent is signed.
17. At Baseline Weight and Height will be measured. At End of Treatment and at visit 7 only weight.
18. For inclusion and End of Treatment Visit chest HRCT is preferred, but chest X-ray can be performed, if HRCT is not available. For safety monitoring of lung (i.e. in case of decrease of pulmonary function test values), chest HRCT has to be performed (due to higher resolu ion of HRCT).
19. Ambulatory Blood pressure Measurement should be done at the **non-**dominant arm (in right-handers mount device at the left arm).
20. Laboratory values and urine analysis will be only done at Follow up visit if abnormal values were measured at the End of Treatment visit.
21. At Screening patient will undergo genotyping for CYP2C9*3 haplotype identification for safety reasons (patients homozygous for this allele are not eligible for the study).
22. Quality of Life assessments are only applicable for patients participa ing in period 1.
23. This examination is done at selected study sites.

Study Endpoints

Primary Efficacy Endpoint

The primary objective of this study is to evaluate the dose response relationship among five doses of BAF312 and placebo during 3 months of treatment in patients with RRMS, as measured by the number of combined unique active [MRI] lesions (CUAL). CUAL requires a prior study for comparison, so techniques need to be followed to ensure image comparability, including similar sequences, slice thickness (without gap), and orientation (subcallosal line). T2 lesions in MS are typically persistent, although detection of small new lesions can be challenging in subjects who have already accrued a high burden of MRI disease. Enhancing lesions in MS typically enhance for 3-6 weeks and are relatively easy to identify, although it is necessary to ensure that the abnormal signal is not representative of a blood vessel or vascular anomaly. Enhancing lesions are typically hypointense on non-contrasted T1 scans. These T1 hypointense lesions ("black holes") can be persistent but are not necessarily so, especially if they appear less hypointense ("greyer"). At 6 months, almost 40% of T1 black holes will remain hypointense, and these persistent black holes are thought to correlate well with the degree of

axonal loss in the lesion and resultant disability (Cotton 2003, Sahraian 2010, van Waesberghe 1998).

Secondary Endpoints

- To evaluate the safety and tolerability (including cardiac events and blood pressure effects) of BAF312 during 6 months or 3 months of treatment in MS patients
- To evaluate the dose response relationship of BAF312 and placebo during 6 months of treatment in patients with RRMS, as measured by CUAL
- To explore the effect of BAF312 on the number of relapses and thereof derived measures (e.g. annualized relapse rate (ARR), proportion of relapse-free patients)
- To explore the correlation of the course of the lymphocyte count with paraclinical (MRI activity) and clinical course
- To determine the effect of BAF312 at 6 and 3 months treatment on additional MRI parameters:
    1. Total number of monthly *new* [Gd]-enhanced lesions (T1 weighted lesions)
    2. Total number of *all* [Gd]-enhanced lesions (T1 weighted lesions)
    3. Total number of monthly new or enlarging T2-weighted lesions
    4. Proportion of subjects without any new MRI disease activity
    5. MRI response in subjects with high disease activity at baseline (≥ 2 [Gd]-enhanced lesions)
- To determine the steady state plasma concentrations of BAF312 in RRMS patients

Statistical Analysis Plan

Below is this reviewer's interpretation of the statistical analysis plan (SAP). See the Biometrics review of Dr. Xiang Ling for a more detailed discussion of the SAP.

The primary and secondary analyses were performed on the Full Analysis Dataset (FAS), which consisted of all patients who were randomized to a study treatment and received at least one dose of that treatment.

The primary endpoint (dose-response relationship among five doses of BAF312 and placebo during 3 months of treatment in patients with RRMS, as measured by the CUAL) was analyzed by the multiple comparison procedure with modelling techniques (MCP-mod), adapted for count data. There was no imputation for missing data.

The secondary endpoints included analysis on other MRI variables, but confirmed relapse rates were also assessed. The annualized relapse rate (ARR) was calculated by either taking the mean of the ARR for each subject (subject level ARR) or dividing the total number of relapses by

the total number of study days for the group and multiplying by 365.25 (group level ARR). Group level ARR was compared between treatment groups using a negative binomial regression with treatment group and baseline number of relapses in the previous 2 years as covariates, and log (time on study in years) as the offset variable, using the log link.

Descriptive (summary) statistics were used for the safety analysis of siponimod.

Protocol Amendments

There was only one protocol amendment to the original CABF312A2201 protocol.

Table 50. Reviewer Table: Synopsis of Protocol Amendments, CABF312A2304

Amendment	Release Date	Major Changes	Number of Subjects
1	03/17/2010	• Dose titration in response to bradyarrhythmia seen with first dose of siponimod in cohort 1	188 randomized

Data Quality and Integrity: Sponsor's Assurance

A sponsor representative reviewed the study protocol and CRFs with study staff site at the site initiation visit or an investigator's meeting. Site monitors periodically visited study sites to review the completeness and accuracy of the collected data, adherence to the protocol and Good Clinical Practice (GCP), and study medication handling.

6.2.2 Study Results

Compliance with Good Clinical Practices

In section 11.1 ("Regulatory and Ethical Compliance"), the sponsor states "This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) harmonized tripartite guidelines for good clinical practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki." The study protocol (and the protocol amendment) was approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each site before study initiation. An informed consent document (ICD) was completed for each subject before that subject engaged in other study procedures.

Financial Disclosure

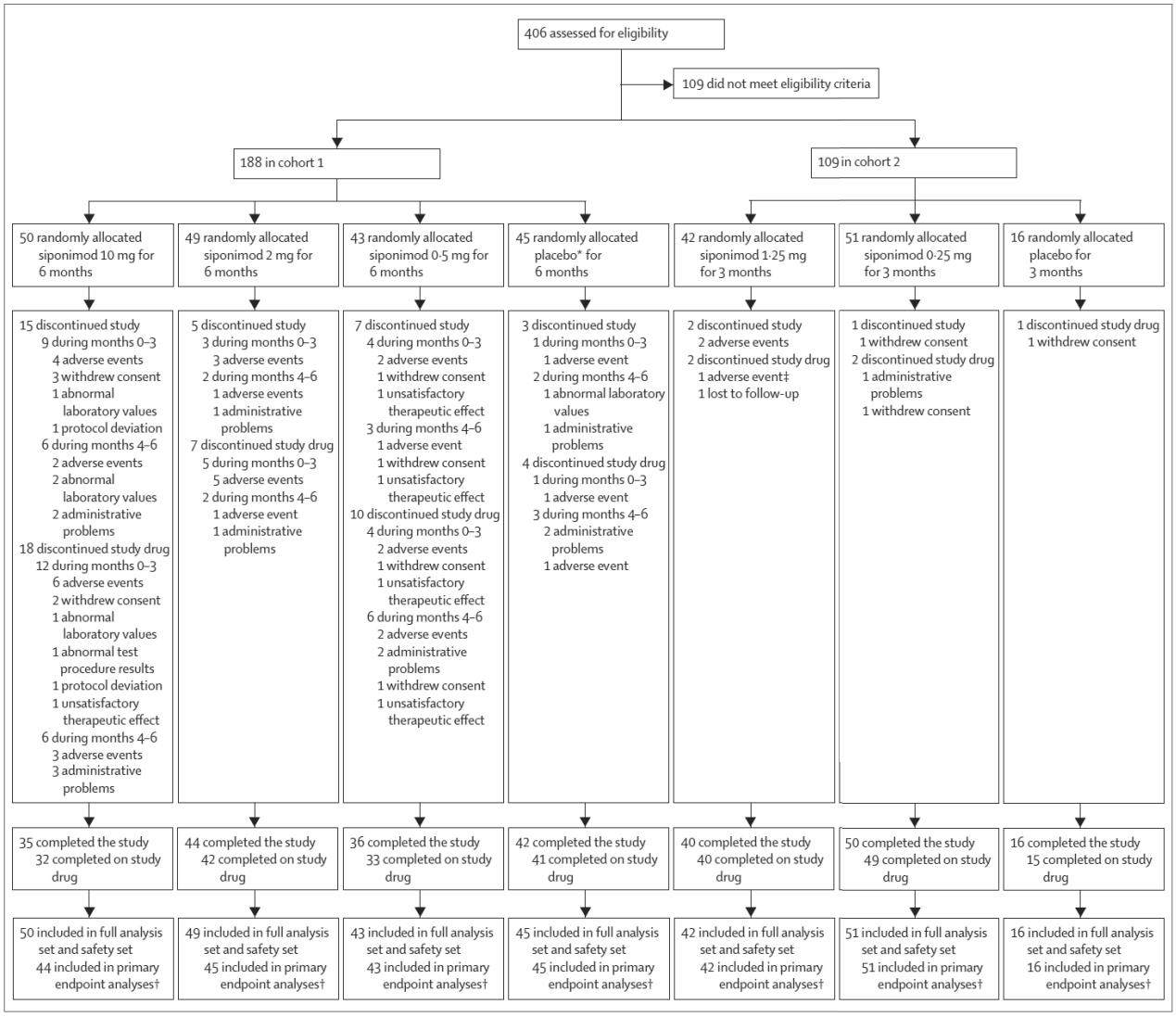
Module 1, Section 1.3.4 of the NDA includes information regarding financial certification and disclosure. The document in this section includes Form FDA 3454 indicating there were no financial arrangements with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR54.2(a). A list of investigators with any financial interest in the outcome of the study is included in this section of the NDA: almost all disclosures were "significant payments of other sorts," although one investigator disclosed that his wife is an employee of Novartis and holds stock options below $50,000.

Patient Disposition

First patient visit: 3/30/2009
Last patient visit: 5/4/2011

406 subjects with relapsing MS were screened and 297 were enrolled and randomized in A2201. 188 of these were in cohort 1, and 109 were in cohort 2. One subject in cohort 1 was misrandomized and never received study drug, so this subject was excluded from the full analysis set. In cohort 1, 148 (79%) of subjects completed the study on study drug. In the 3-month cohort 2 study, 104 (95%) of subjects completed the study on the assigned drug. The disposition of subjects is summarized in Figure 28.

Figure 28. Extracted from K Selmaj et al, 2013: Patient Disposition, CBAF312A2201



Reviewer Comment: A significant percentage (21%) of subjects did not complete CBAF312A2201 on the assigned study drug, including 32/50 (36%) of those randomized to siponimod 10 mg.

Protocol Violations / Deviations

Protocol deviations / violations were separated into those that involved the "first dose" administration of the drug and those that did not. There were 152 protocol deviations that were not directly related to the administration of the first dose. Table 51 delineates the most common of these protocol deviations.

Table 51. Reviewer table: Protocol Deviations, CBAF312A2201

Deviation	Siponimod 0.25 mg	Siponimod 0.5 mg	Siponimod 1.25 mg	Siponimod 2 mg	Siponimod 10 mg	Placebo
Not following blinding procedures	8	8	9	4	3	6
QTcF > 440msec or is missing	4	6	8	2	3	7
MRI performed within 14 days of steroids	2	6	1	1	2	11
Subject took a CYP2C9 inducer or inhibitor	0	0	0	3	0	10

Source: VIOPTO

Reviewer Comment: A higher proportion of subjects in the placebo arm had an MRI within 14 days of receiving systemic steroids than in the other arms of the study. Because steroids should not affect the burden of T2 lesions (and may decrease the number of enhancing lesions), the imbalance is unlikely to negatively impact the analysis of the primary endpoint of this trial (and may make it slightly harder for siponimod to "win"). The imbalance with the use of CYP2C9 inhibitors / inducers in the placebo arm should not impact the efficacy analysis of siponimod.

Most of the deviations regarding not following blinding procedures entailed a reduction in sitting pulse or missing pre- or post-dose EKGs.

Table of Demographic Characteristics

Table 52 outlines the demographic characteristics of the RRMS population in CBAF312A2201.

Table 52. Reviewer table: Baseline Demographic Characteristics, CBAF312A2201

Demographic Parameter	Siponimod 0.25 mg (n=51)	Siponimod 0.5 mg (n=43)	Siponimod 1.25 mg (n=42)	Siponimod 2 mg (n=49)	Siponimod 10 mg (n=50)	Placebo (n=62)
Sex						
Male	9	13	11	15	20	17
Female	42	30	31	34	30	45
Age (years)						
Mean (SD)	37.3 (8.4)	36.0 (8.8)	35.4 (8.9)	37.4 (8.9)	36.4 (8.4)	35.3 (8.6)
Median	36	35	35	37	37	35
Min, max	23,53	21,55	19,55	19,55	20,53	19,52
Race						
White	50	42	41	47	48	60

Demographic Parameter	Siponimod 0.25 mg (n=51)	Siponimod 0.5 mg (n=43)	Siponimod 1.25 mg (n=42)	Siponimod 2 mg (n=49)	Siponimod 10 mg (n=50)	Placebo (n=62)
Black	1	0	1	1	0	1
Other / Unknown	0	1	0	1	2	1
Ethnicity						
Hispanic or Latino	1	1	1	1	1	1
Mixed	0	3	1	0	2	1
Other / Unknown	50	39	40	48	47	60
Region						
United States	7	5	6	8	6	9
Canada	3	3	2	5	7	4
Europe	34	28	28	30	31	40
Russia	4	6	3	5	6	7
Turkey	3	1	3	1	0	2

Source: ADMG

Reviewer Comment: As expected in a trial of relapsing MS, the typical subject was a white woman in her thirties. Over half (191/297 or 64%) of the study population's subjects were from Europe.

Other Baseline Characteristics

Table 53 highlights the disease characteristics of the RRMS population in CBAF312A2201.

Table 53. Reviewer table: Other Baseline Characteristics, CBAF312A22011 [1]

Other Characteristics	Siponimod 0.25 mg	Siponimod 0.5 mg	Siponimod 1.25 mg	Siponimod 2 mg	Siponimod 10 mg	Placebo
Baseline EDSS						
Mean (SD)	2.3 (1.1)	2.2 (1.3)	2.0 (1.0)	2.4 (1.2)	2.3 (1.0)	2.3 (1.1)
Median	2	1.5	2	2	2	2
Years since MS Diagnosis						
Mean (SD)	4.6 (5.3)	5.6 (6.7)	4.1 (4.7)	4.4 (4.9)	3.9 (5.6)	4.9 (5.8)
Median	2.0	2.5	2.0	2.4	2.3	2.2
Number of relapses in previous 2 years						
0	1	0	0	0	1	0
1	14	20	19	14	14	24
2	22	14	14	21	21	28
3	11	5	9	10	11	8
≥4	3	4	0	4	3	1

Other Characteristics	Siponimod 0.25 mg	Siponimod 0.5 mg	Siponimod 1.25 mg	Siponimod 2 mg	Siponimod 10 mg	Placebo
Subjects with baseline gadolinium-enhancing lesions						
Present	23 (45%)	23 (53%)	22 (52%)	26 (53%)	22 (44%)	35 (56%)
Previous treatment(s) for MS						
Interferon	21	13	13	19	15	24
Glatiramer	11	7	9	8	6	12
Natalizumab	1	2	2	1	0	4
Other	6	2	4	3	1	6
None	23	26	23	28	32	30

Source: AHIS2, AHIS
[1] Data missing for one subject

Reviewer Comment: The baseline disease characteristics seem typical for a relapsing MS trial, and the population appears relatively well-matched in regard to disease characteristics. Given the number of subjects from Europe, I suspect that many of the subjects who selected a previous treatment of "Other" were referring to azathioprine, but this is not specified in the AHIS dataset.

Treatment Adherence, Concomitant Medications, and Rescue Medication Use

Treatment Adherence

The study coordinator or other study personnel assessed adherence to the study medication at each study visit. This was performed by pill counts, from which adherence feedback was given to the subject. Site-level drug accountability was assessed by study monitors at site visits and at the end of the study.

Reviewer Comment: Per the CSR, adherence data was transcribed on the Data Administration Record CRF. Because a clear way of calculating medication adherence is not obvious to this reviewer after review of the Dosage Administration Record CRF and the DAR dataset, an Information Request was sent to the sponsor to provide this information. See Figure 29.

Figure 29. Sponsor Figure. Percentage of days with dose interruption (CBAF312A2201)

Treatment	No. of patients missing dose	Precentage of days with missing dose n'/m (%)	Patient % of days with missing dose n(%) 0%	<=1%	<=5%	>5%
BAF312 0.25 mg (N=51)	1	1/4728 (0.02)	50 (98.0)	1 (2.0)	0	0
BAF312 0.5 mg (N=43)	3	11/7226 (0.15)	40 (93.0)	0	3 (7.0)	0
BAF312 1.25 mg (N=42)	0	0/3909 (0)	42 (100)	0	0	0
BAF312 2 mg (N=49)	10	111/8173 (1.36)	39 (79.6)	4 (8.2)	4 (8.2)	2 (4.1)
BAF312 10 mg (N=50)	6	42/7044 (0.60)	44 (88.0)	2 (4.0)	2 (4.0)	2 (4.0)
Placebo (N=61)	2	9/9594 (0.09)	59 (96.7)	1 (1.6)	1 (1.6)	0

Concomitant Medications

Table 54 lists the common concomitant medications used by subjects in the study. A significant number of subjects were also on birth control pills, whether femodene, drospirenone, desogestrel, progesterone, or other.

Table 54. Reviewer Table. Common concomitant medications, CBAF312A2201

Standardized Medication Name	Total # subjects	Siponimod 0.25 mg # subjects	Siponimod 0.5 mg # subjects	Siponimod 1.25 mg # subjects	Siponimod 2 mg # subjects	Siponimod 10 mg # subjects	Placebo # subjects
Paracetamol	70	2	21	6	11	17	13
Ibuprofen	69	6	11	4	13	15	20
Methylprednisolone	67	7 256	16 165	3	11	13	17
Vitamin D	30	5	5	3	5	7	5
Influenza vaccine	25	0	6	0	7	5	7
Pregabalin	19	4	3	1	2	2	7
Lorazepam	15	2	4	0	3	1	5
Aspirin	14	1	3	2	2	5	1
Ciprofloxacin	12	2	0	1	2	3	4

Source: ACMD

Rescue Medications

Corticosteroids were commonly given to treat a MS relapse in the study, although this was not required. Table 55 shows the number of confirmed relapses that were treated with steroids in this study.

Table 55. Reviewer table: Relapses treated with steroids, CBAF312A2201

	Siponimod 0.25 mg	Siponimod 0.5 mg	Siponimod 1.25 mg	Siponimod 2 mg	Siponimod 10 mg	Placebo
Relapses treated with steroids	6	8	2	4	8	10

Source: AMSR, where AMSR.AMSR.Rec1n < 2 and (AMSR.STOTHY3C=1 or AMSR.STOTHY6C=1)

Efficacy Results- Primary Endpoint

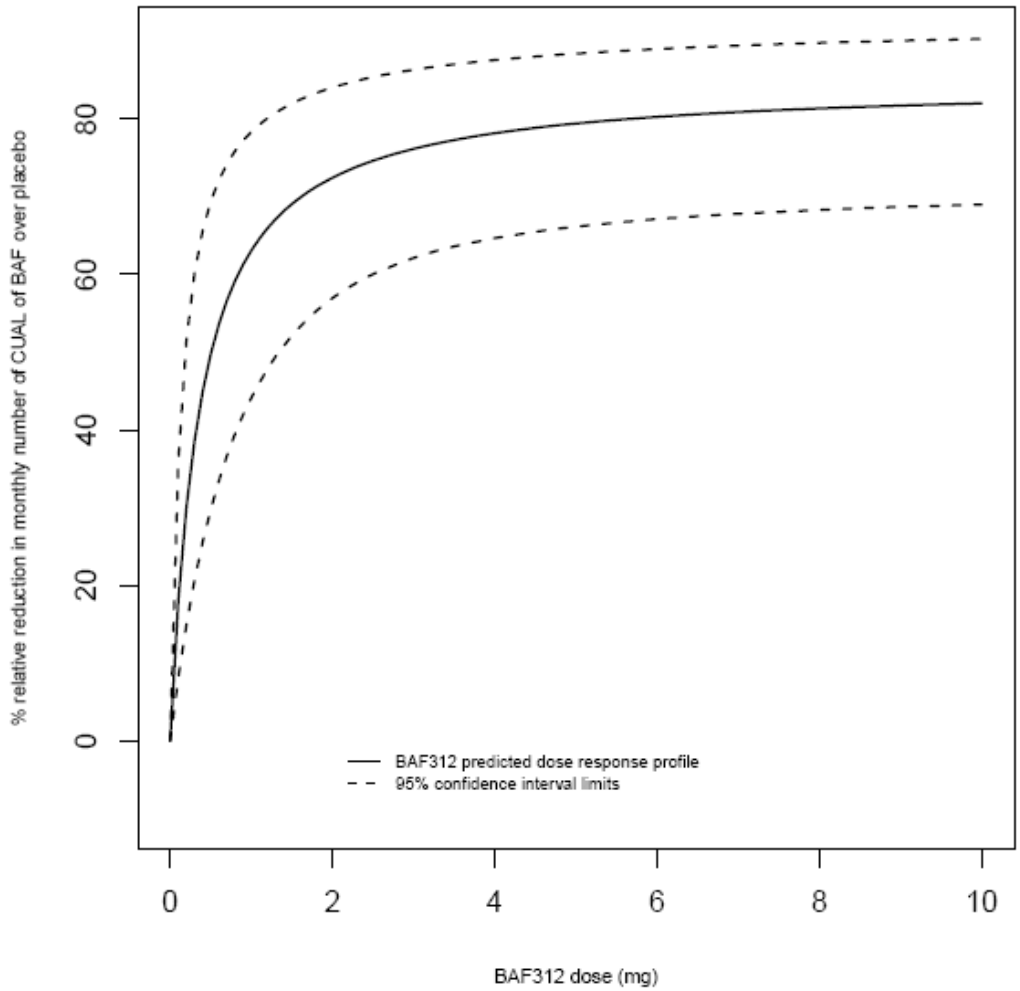
Dose-response reduction in monthly number of combined unique active lesions at 3 months

The primary endpoint of A2201 utilized the sum of new / enlarging T2 hyperintensities and T1 enhancing lesions on an MRI, a metric that is otherwise known as Combined Unique Active Lesions (CUAL).

As is typical in recent Phase 2 studies in relapsing MS, A2201 was a relatively short study that utilized frequent (monthly) MRI scans. As MRI lesions can occur up to 10 times as commonly as relapses in RMS, a drug's ability to reduce MRI activity may give some initial indication of its efficacy in MS; indeed, a large meta-analysis by Sormani et al 2009 (extended in Sormani and Bruzzi 2013) suggest a correlation between MRI and relapses. That said, the limited correlation between the degree of MRI disease and a subject's clinical status at a given point (clinico-radiographic paradox) and the relatively weak correlation between MRI activity and disability progression limit the utility of this potential surrogate (Barkhof 1999, Sormani et al 2010).

The first cohort of 188 subjects was treated for 6-months with either siponimod 10 mg, siponimod 2 mg, siponimod 0.5 mg, or placebo, randomized 1:1:1:1. The second cohort of 109 subjects was treated for 3-months with either siponimod 1.25mg, siponimod 0.25mg, or placebo (randomized 4:4:1). Monthly MRI were to be performed for all subjects in the study, and CUALs in the first 3 months were counted by subject. The MCP-mod methodology was adapted for count data and was used to evaluate the dose response relationship among 5 doses of siponimod and placebo during 3 months of treatment. The resultant dose-response curve at month 3 is copied from the CSR and shown in Figure 30.

Figure 30. Sponsor Figure. Dose response curve at Month 3 estimated by Bayesian longitudinal analysis (FAS)



Reviewer Comment: The CUAL dose response curve of five doses of siponimod compared to placebo is shown above and suggests the appropriateness of continuing to study the 2 mg dose, at least in regard to efficacy. This analysis was replicated by the Biometrics reviewer, Dr. Xiang Ling.

Efficacy Results – Relevant Secondary Endpoints

Annualized relapse rate

Annualized relapse rate (ARR) was a secondary endpoint of interest in A2201. As per Table 56, this reviewer's analysis suggests that CBAF312A2201 demonstrates that siponimod had a significant treatment effect on ARR, especially at the 2 mg dose.

Table 56. Reviewer table: Annualized Relapse Rate, cohort #1, FAS, CBAF312A2201

	Siponimod 0.5 mg n=43	Siponimod 2 mg n=49	Siponimod 10 mg n=50	Placebo n=45
# Confirmed relapses at 6 months	13	5	9	13
Time in Study (Days)	7408	8336	8557	8212
Group level ARR[1]	0.64	0.22	0.38	0.58
Subject level ARR	0.85	0.36	2.73[2]	0.57

Source: AMSR.RELNUM6C, INSTUDY6, and ARRPAT6C where AMSR.Period = 1 and AMSR.Rec1n < 2
[1] Group level ARR = (# relapses / # days in study) *365.25; subject level ARR is mean of subject ARRs
[2] One subject had a relapse just after entering the study and withdrew 3 days after randomization.

Reviewer Comment: This analysis duplicates that of the sponsor (CSR Table 11-6). Although this study was not powered to show a treatment effect on relapses, this analysis suggests that siponimod 2 mg may have a treatment effect on reducing relapses, which is not surprising given the expected class effect of S1P receptor modulators (including the approved drug, fingolimod) on relapse rates.

The sponsor also analyzed relapse rate reductions with a negative binomial regression model adjusted for treatment group, number of relapses in the prior 2 years, with log (time on study in years) as the offset variable. See Table 57.

Table 57. Sponsor Table: Analysis of annualized relapse rate for confirmed relapses up to 6 months (Period 1; Full Analysis Set)

	BAF312 10 mg N=50	BAF312 2 mg N=49	BAF312 0.5 mg N=43	Placebo N=45
Model based results				
- Group level ARR	0.30	0.20	0.61	0.58
- 95% CI of ARR	(0.151, 0.613)	(0.081, 0.478)	(0.351, 1.062)	(0.337, 1.002)
- ARR-ratio to placebo	0.524	0.340	1.051	
- 95% CI for ARR-ratio	(0.219, 1.257)	(0.121, 0.956)	(0.486, 2.273)	
- p-value	0.148	0.041	0.899	
- % relative reduction	47.6	66.0	-5.1	

Reviewer Comment: In this analysis, the 2 mg dose of siponimod showed an effect on reducing relapse rates, albeit with only marginally nominal statistical significance; however, CBAF312A2201 was not powered to show an effect on ARR, especially given the brief duration of treatment, and thus should not be considered an adequate and well-designed study necessary to show substantial evidence of effectiveness.

Durability of Response

Durability of response was not assessed in this trial.

Persistence of Effect

Efficacy following study completion was not assessed in this trial, although there was an open label extension phase.

Additional Analyses Conducted on the Individual Trial

The first cohort of 188 subjects was treated for 6-months with either siponimod 10 mg, siponimod 2 mg, siponimod 0.5 mg, or placebo, randomized 1:1:1:1. A monthly MRI was to be performed in subjects in the study, and the siponimod demonstrated significant reductions in CUAL compared to placebo. See Table 58.

Table 58. Reviewer table: CUAL, cohort #1, CBAF312A2201

CUAL	Siponimod 0.5 mg	Siponimod 2 mg	Siponimod 10 mg	Placebo
Sum	308	175	212	649
Mean / Subject (Std)	1.3 (3.5)	0.7 (1.5)	0.8 (2.6)	2.4 (4.2)
Relative reduction	53%	73%	67%	---
p-value	<0.001	<0.001	<0.001	---

Source: AMRI, where Period = 1, MRIRSL1A = 'CUAL' and AMRI.VIS1N <> 1

Reviewer Comment: This reviewer performed an analysis of CUAL reduction at 6-months in the first cohort of CBAF312A2201. This analysis is congruent with the dose-response analysis performed above (for the primary endpoint) and suggests that siponimod is effective at reducing CUAL and suggests that the 2 mg proposed marketing dose was appropriate for further study and is likely to be effective in reducing relapse rate.

The second cohort of 109 subjects was treated for 3-months with either siponimod 1.25mg, siponimod 0.25mg, or placebo (randomized 4:4:1), and monthly MRIs were performed. Given the very brief duration of this study cohort (especially if some period of time may be required for siponimod to become effective) and the small size of the placebo cohort, repeating the above analysis on cohort 2 is unlikely to be informative.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

An integrated assessment of efficacy is limited as the two clinical trials of siponimod in MS utilized different populations (RRMS vs. SPMS) and different primary endpoints (CUAL vs. 3-month CDP).

7.1.1. Primary Endpoints

The primary endpoint for the Phase 2 study in RRMS (CBAF312A2201) was a dose-response reduction in the number of combined unique active lesions (CUAL) on MRI among 5 doses of siponimod and placebo. As shown in Section 6.2, CBAF312A2201 achieves statistical significance on this endpoint.

The primary endpoint for the Phase 3 study of siponimod 2 mg daily in SPMS (CBAF312A2304) was time to 3-month confirmed disability progression (CDP). Although the effect appears to have been driven by an effect on inflammation and relapses, CBAF312A2304 achieved a statistically significant relative risk reduction of 21% (absolute risk reduction of 5.5%) on time to 3-month CDP (p=0.013), as shown in Section 6.1.

7.1.2. Secondary and Other Endpoints

Annualized relapse rate (ARR) is a secondary endpoint of interest in the CBAF312A2201 study. Although the study was not adequately powered to show a difference on ARR, the 2 mg dose did achieve nominal statistical significance in this study (p=0.0408).

CBAF312A2304 utilized a hierarchical analysis of the primary endpoint (time to 3-month CDP) and two secondary endpoints (time to confirmed 20% worsening on the Timed 25 Foot Walk and change in T2 lesion volume) that were identified as "key." The first "key" secondary endpoint (time to confirmed 20% worsening on T25FW) did not achieve statistical significance (relative risk reduction of 6%, p=0.44). Despite the failure of the first "key" secondary endpoint in the hierarchical analysis to achieve statistical significance, the second "key" endpoint (change in T2 lesion volume) in the hierarchy achieved a robust treatment effect with a nominally highly significant nominal p-value (<0.0001).

CBAF312A2304 also assessed the effect of siponimod on ARR, a "non-key" secondary endpoint (55% relative risk reduction, nominal p<0.0001); however, the absolute relapse rates were very low (0.07 in the siponimod arm, 0.16 in the placebo arm) in this

study.

7.1.3. Subpopulations

Sixty percent of the subjects in CBAFA2304 were women. As per the forest plot in Figure 14, the confidence interval for the analysis of the primary endpoint (3-month CDP) included '1' for both women and men. Almost 95% of the subjects in CBAF312A2304 were white.

7.1.4. Dose and Dose-Response

See Figure 29 for the dose-response curve of siponimod for the number of CUAL in CBAF312A2201. CBAF312A2304 only assessed one dose of siponimod (2 mg).

7.1.5. Onset, Duration, and Durability of Efficacy Effects

There were no dedicated onset, duration, or durability studies performed in the pivotal and support trial in this application.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In CBAF312A2304, much of the benefit of siponimod was due to its effect on relapses and inflammation, outcomes which research and clinical experience suggest do not provide significant clinical benefits in patients with SPMS who are not experiencing relapses. This reviewer is concerned that many people with non-relapsing SPMS will be treated with siponimod despite a lack of data to support a benefit in this population, leading to their potential exposure to the manifold risks associated with receiving a therapy lacking expectation of efficacy.

7.2.2. Other Relevant Benefits

This reviewer is not convinced by suggestions that S1P receptor modulators may stimulate oligodendrocyte progenitor cells (OPC), and the sponsor provides no clinical evidence to support that this alleged effect would be significantly different for siponimod than for other S1P modulator therapies (Zhang et al, 2015). This reviewer does not foresee any other potentially relevant benefits of siponimod at this time.

7.3. Integrated Assessment of Effectiveness

It is difficult to provide an across trial comparison as the two trials supporting the NDA for siponimod utilize different populations, different endpoints, and different study designs. CBAF312A2304 achieves statistical significance on its primary endpoint (time to

3-month CPD based on EDSS) in subjects classified as having SPMS; however, its failure to achieve statistical significance on the first "key" secondary endpoint (time to 3-month confirmed T25FW worsening) may not be congruent with this EDSS finding. Further, some issues with the conduction of the study were identified, including a "dual database access" issue affecting 101 subjects. A sensitivity analysis removing these subjects has a significant impact on the p-value of the 3-month CDP result, weakening it from almost 0.01 to over 0.05. Given these issues, this reviewer is not convinced that the statistical strength of this un-replicated 3-month CDP finding is sufficient to show substantial evidence of effectiveness to support the approval of siponimod with an indication of SPMS.

It is apparent that much (if not all) of siponimod's apparent treatment effect on increasing disability is derived from its effect on relapses and MRI lesions (i.e., inflammation) in subjects with relapsing SPMS (or late RRMS), raising the question of whether there is sufficient evidence of effectiveness to support an indication of relapsing forms of MS, especially given the support that CBAF312A2201 offers for this indication. This reviewer is bothered by the small number of subjects in CBAF312A2304 who experienced a relapse, the dose-finding design of CBAF312A2201, the marginal nominal significance (p=0.0408) of the single dose arm of CBAF312A2201 to achieve significance on ARR (although admittedly this study was not powered for ARR), and the designation of ARR as secondary in both trials. Despite these concerns, these studies provide evidence to support an indication of relapsing MS. The robust effect on MRI metrics in both trials is also supportive of a relapsing MS indication, although MRI is not a measure of how a person "functions, feels, or survives," and the relevance of MRI metrics is potentially questioned by their relatively poor correlation with clinical disability progression and the "clinico-radiologic paradox." Factoring in the efficacy of other immunomodulatory and immunosuppressive agents (including the approved S1P receptor modulator, fingolimod), this reviewer finds that there is likely substantial evidence of effectiveness to support the approval of siponimod with an indication for relapsing forms of MS.

8. Review of Safety

See the clinical review of safety by Dr. Paul Lee.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not convened for this NDA.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The label has not been finalized at the time of this review.

10.2. Nonprescription Drug Labeling

This section is not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

See the clinical review of safety by Dr. Paul Lee.

12. Postmarketing Requirements and Commitments

Postmarketing requirements and commitments for siponimod have not yet been finalized at the time of this review but will likely address a pregnancy registry, pregnancy outcomes, long-term effects on pulmonary function tests (PFTs), and enhanced pharmacovigilance for infections and malignancies. See the clinical review of safety by Dr. Paul Lee.

13. Appendices

13.1. References

Andersen O, Elovaara I, Färkkilä M, Hansen HJ, Mellgren SI, Myhr KM, Sandberg-Wollheim M, Sorsesen SP. 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.

Antel J, Antel S, Caramonos Z, Arnold DL, Kuhlmann T. Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity. Acta Neuropathol 2012, 123: 627-638.

Barkhof F. MRI in multiple sclerosis: Correlation with expanded disability status scale (EDSS). Mult Scler 1999; 5(4): 283-286.

Berrigan LI, Fisk JD, Patten SB, Tremlett H, Wolfson C, Warren S, Fiest JA, McKay KA, Marrie RA. Health-related quality of life in multiple sclerosis: Direct and indirect effects of comorbidity. Neurology 2016; 86: 1417-1424.

Camm J, Hla T, Bakshi R, Brinkmann V. Cardiac and vascular effects of fingolimod: Mechanistic basis and clinical implications. Am Heart J 2014; 168(5):632-644.

Compston A, Coles A. Multiple Sclerosis. Lancet 2008; 372: 1502-1517.

Confavreux C, Aimard, Devic M. Course and prognosis of multiple sclerosis assessed by the computerized data processing of 349 patients. Brain 1980; 103:281-300.

Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med 2000; 343:1430-8.

Correale J, Gaitan MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain 2017, 140: 527-546.

Cotton F, Weiner H, Jolesz F, Guttmann C. MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals. Neurology 2003; 60: 6460-646.

D'Amico E, Patti F, Zanghì A, Zappia M. A Personalized Approach in Progressive Multiple Sclerosis: The Current Status of Disease Modifying Therapies (DMTs) and Future Perspectives. Int J Mol Sci. 2016;17(10): E1725.

D'Souza M, Yaldizli O, John R, Vogt DR, Papadopoulou A, Lucassen E, Menegola M, Andelova M, Dahlke F, Schnyder F, Kappos L. Neurostatus e-Scoring improves consistency of Expanded Disability Status Scale assessments: A proof of concept study. MSJ 2017; 23(4):587-603.

Dwyer MG, Bergsland N, Ramasamy DP, Jakimovski D, Weinstock-Guttman B, Zivadinov R. Atrophied brain lesion volume: A new imaging biomarker in multiple sclerosis. J Neuroimaging 2018; 28(5): 490-495.

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

Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, Yang M, Raghupathi K, Novas M, Sweetser MT, Viglietta V, and Dawson KT. Placebo-controlled Phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012; 367: 1087-1097.

Freedman MS, Bar-Or A, Oger J, Traboulsee A, Patry D, Young C, Olsson T, Li D, Hartung HP, Krantz M, Ferenczi L, Verco T; MAESTRO-01 Investigators. A phase III study evaluating the efficacy and safety of MBP8298 in secondary progressive MS. Neurology. 2011;77(16):1551-60.

Frischer JM, Weigand SD, Guo Y, Kale N, Parisi JE, Pirko I, Mandrekar J, Bramow S, Metz I, Bruck W, Lassmann H, Lucchinetti CF. Clinical and pathological insights into the dynamic nature of white matter multiple sclerosis plaques. Ann Neurol 2015; 78: 710-721.

Gold R, Kappos L, Arnold DA, Bar-Or A, Giovannoni G, Selmaj K, Tornatore C, Sweetser MT, Yang M, Sheikh SI, and Dawson KT. Placebo-controlled Phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012; 367:1098-1107.

Hartung HP, Gonsette R, Konig N, Kwiecinski H, Guseo A, Morrissey SP, Krapf H, Zwingers T, Mitoxantrone in Multiple Sclerosis Study Group (MIMS). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicenter trial. Lancet 2002; 360: 2018-2025.

Haselkorn JK, Hughes C, Rae-Grant A, Henson LJ, Bever CT, Lo AC, Brown TR, Kraft KH, Getchius T, Gronseth G, Armstrong MJ, Narayanaswami P. Summary of comprehensive systemic review: Rehabilitation in multiple sclerosis. Neurology 2015; 85(21): 1896-1903.

Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, Hauser S, Waubant E, Vollmer T, Panitch H, Zhang J, Chin P, Smith CH, OLYMPUS study group. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol 2009, 66(4): 460-471.

Hommes OR, Sørensen PS, Fazekas F, Enriquez MM, Koelmel HW, Fernandez O, Pozzilli C, O'Connor P. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. Lancet. 2004 Sep 25-Oct 1;364(9440):1149-56.

Horga A and Montalban X. FTY720 (fingolimod) for relapsing multiple sclerosis. Expert Rev Neurotherapeutics 2018; 8(5): 699-714.

Kapoor R, Ho PR, Campbell N, Chang I, Deykin A, Forrestal F, Lucas N, Yu B, Arnold DL, Freedman MS, Goldman MD, Hartung HP, Havrdová EK, Jeffery D, Miller A, Sellebjerg F, Cadavid D, Mikol D, Steiner D; ASCEND investigators. 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.

Kappos L, Radue E-W, O'Connor P, Polman C, Hohlfeld R, Calabresi P, Selmaj K, Agoropoulou C, Leyk M, Zhang-Auberson L, Burtin P, FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362(5):387-401.

Katz-Sand I, Krieger S, Farrell C, Miller AE. Diagnostic uncertainty during the transition to secondary progressive multiple sclerosis. Mult Scler 2014; 20(12): 1654-1657.

Krieger SC, Cook K, De Nino S, Fletcher M. The topographical model of MS: A dynamic visualization of disease course. Neurol Neuroimmunol Neuroinflamm 2016; 3:e279.

Kurtzke JF. On the evaluation of disability in multiple sclerosis. Neurology 1961; 11:686-694.

Lassmann H. The pathologic substrate of magnetic resonance alterations in multiple sclerosis. Neuroimaging Clin N Am. 2008; 18: 563-576.

Li DK, Zhao GJ, Paty DW, the University of British Columbia MS/MRI Analysis Research Group and the SPECTRIMS Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. Neurology. 2001;56(11):1505-13.

Liu C, Blumhardt LD. Disability outcome measures in therapeutic trials of relapsing remitting multiple sclerosis: effects of heterogeneity of disease course in placebo cohorts. J Neurol Neurosurg Psychiatry 2000; 68:450-7.

Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology 2003; 61(11):1528-32.

Lublin F, Miller DH, Freedman MS, Cree BAC, Wolinsky JS, Weiner H, Lubetzki C, Hartung HP, Montalban X, Uitdehaag BMJ, Merschhemke M, Li B, Putzke N, Liu FC, Haring DA, Kappos L, INFORMS study investigators. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomized, double-blind, placebo-controlled trial. Lancet 2016; 387: 1075-1084.

Lublin FD, Reingold SC, Cohen JA, Cutter GR, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014; 83(3): 278-86.

Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol 2015; 14(2): 183-193.

Marrie RA, Elliott L, Marriott J, Cossoy M, Blanchard J, Leung S, and Yu N. Effect of comorbidity on mortality in multiple sclerosis. Neurology 2015; 85(3): 240-247.

Montalban X, Hauser SL Kappos L Arnold DA, Bar-Or A, Comi G, de Seze J, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Rammohan KW, Selmaj K, Traboulsee T, Sauter A, Masterman D, Fontoura O, Belachew S, Garren H, Mairon N, Chin P, Wolinsky JS, ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017; 376(3):209-220.

O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, Benzerdjeb H, Truffinet P, Wang L, Miller A, and Freedman MS. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011; 365:1293-1303.

Panitch H, Miller A, Paty D, Weinshenker B, North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology. 2004;63(10):1788-95.

Paz Soldan MM, Novotna M, Abou Zeid N, et al. Relapses and disability accumulation in progressive multiple sclerosis. Neurology 2015; 84(1):81-8.

Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol 1996; 39(4): 432-441.

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.

Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. N Engl J Med 2018; 378:169-180.

Roxburgh RHSR, Seaman SE, Masterman T, Hensiek AR, Sawcer SJ, Vukusic S, et al. Multiple Sclerosis Severity Score: Using disability and disease duration to rate disease severity. Neurology 2005; 64(7): 1144-1151.

Scott TF. Understanding the impact of relapses in the overall course of MS; refinement of the 2 stage natural history model. J Neuroimmunol. 2017; 305: 162-166.

Sahraian MA, Radue E-W, Haller S, Kappos L. Black holes in multiple sclerosis: definition, evolution, and clinical correlations. Acta Neurol Scand 2010; 122:1-8.

Sormani MP, Bonzano L, Roccatagliata l, Cutter GR, Mancardi GL, and Bruzzi P. Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: A meta-analytic approach. Ann Neurol 2009; 65(3): 268-275.

Sormani MP, Bonzano L, Roccatagliata l, Mancardi GL, Uccelli A, and Bruzzi P. Surrogate endpoints for EDSS worsening in multiple sclerosis: A meta-analytic approach. Neurology 2010:

75(4) 302-309.

Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. Lancet Neurol 2013; 12: 669-676.

Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y. Impact of multiple sclerosis relapses on progression diminishes with time. Neurology 2009; 73(20): 1616-1623.

Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, et al. The prevalence of MS in the United States: A population-based estimate using health claims. Neurology 2019; 92:e1-e12. doi:10.1212/WNL.0000000000007035.

Warren KG, Catz I, Ferenczi LZ, Krantz MJ. Intravenous synthetic peptide MBP8298 delayed disease progression in an HLA Class II-defined cohort of patients with progressive multiple sclerosis: results of a 24-month double-blind placebo-controlled clinical trial and 5 years of follow-up treatment. Eur J Neurol. 2006; 13(8): 887-95.

Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain 1989;112 (Pt 1):133-46.

Wingerchuk DM, Weinshenker BG. Disease modifying therapies for relapsing multiple sclerosis BMJ. 2016;354: i3518.

Wolinsky JS, Narayana PA, O'Connor O, Coyle PK, Ford C, Johnson K, Miller A, Pardo L, Kadosh S, Ladkan D, PROMiSe Trial Study Group. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol 2007, 61: 14-24.

Zajicek J1, Ball S2, Wright D2, Vickery J2, Nunn A3, Miller D4, Cano MG2, McManus D4, Mallik S4, Hobart J2; CUPID investigator group. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. Lancet Neurol. 2013; 12(9): 857-865.

Zhang J, Zhang ZG, Li Y, Ding X, Shang X, Lu M, Elias SB, Chopp M. Fingolimod treatment promotes proliferation and differentiation of oligodendrocyte progenitor cells in mice with experimental autoimmune encephalomyelitis. Neurobiology of Disease 2015; 76: 57-66.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): CBAF312A2201, CBAF312A2304

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: CBAF312A2201 – 644; CBAF312A2304 - 4484		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): CBAF312A2201 – 0; CBAF312A2304 - 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): CBAF312A2201 –5; CBAF312A2304 - 21		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: CBAF312A2304 – 0; CBAF312A2201 - 1 Significant payments of other sorts: CBAF312A2304 – 21; CBAF312A2201 - 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Kurtzke Expanded Disability Status Scale

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory, and the precise step number is defined by the Functional System (FS) score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation, and usual equivalents in Functional System scores are provided.
Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS. Each step (e.g., 3.0 to 3.5) is still part of the DSS scale equivalent (i.e., 3). Progression from 3.0 to 3.5 should be equivalent to the DSS score of 3.

0 - Normal neurological exam (all grade 0 in FS).

1.0 - No disability, minimal signs in one FS (i.e., grade 1).

1.5 - No disability, minimal signs in more than one FS (more than on FS grade 1).

2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).

2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).

3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.

3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).

4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest 500 meters.

4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance: characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.

5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions): (usual FS equivalents are one grade 5 alone, others 0 or 1: or combinations of lesser grades usually exceeding specifications for step 4.0).

5.5 - Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities: (usual FS equivalents are one grade 5 alone, others 0 or 1: or combination of lesser grades usually exceeding those for step 4.0).

6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting: (usual FS equivalents are combinations with more than two FS grade 3 +).

6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting (usual FS equivalents are combinations with more than two FS grade 3 +).

7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (usual FS equivalents are combinations with more than one FS grad 4 +; very rarely pyramidal grade 5 alone).

7.5 - Unable to take more than a few steps; restricted to wheelchair, may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; (usual FS equivalents are combinations with more than one FS grade 4 +).

8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms; (usual FS equivalents are combinations, generally grade 4 + in several systems).

8.5 - Essentially restricted to bed much of the day; has some effective use of arm(s); 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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID E JONES
03/26/2019 12:53:48 PM

PAUL R LEE
03/26/2019 05:18:34 PM

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209884
Priority or Standard	Priority
Submit Date(s)	June 28, 2018
Received Date(s)	July 26, 2018, August 31, 2018
PDUFA Goal Date	March 26, 2019
Division/Office	Division of Neurology Products
Reviewer Name(s)	Paul R. Lee, M.D., Ph.D.
Review Completion Date	March 18, 2019
Established/Proper Name	Siponimod
(Proposed) Trade Name	Mayzent
Applicant	Novartis
Dosage Form(s)	0.25 mg and 2 mg tablets
Applicant Proposed Dosing Regimen(s)	2 mg by mouth daily
Applicant Proposed Indication(s)/Population(s)	MAYZENT is indicated for the treatment of patients with secondary progressive multiple sclerosis (SPMS)
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Relapsing forms of multiple sclerosis to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	Advisory Committee
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
AR	Adverse Reaction
AST	Aspartate Aminotransferase
AV	Atrioventricular
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BP	Blood Pressure
BPM	Beats Per Minute
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
CNS	Central Nervous System
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Clinical Review Template
CSR	Clinical Study Report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
eCRF	Electronic Case Report Form
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good Clinical Practice

GGT	Gamma-Glutamyltransferase
GRMP	Good Review Management Practice
HR	Heart Rate
HRS	Hours
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IR	Incidence Rate
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MS	Multiple Sclerosis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NME	New Molecular Entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OR	Odds Ratio
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PI	Prescribing Information or Package Insert
PK	Pharmacokinetics
PMC	Postmarketing Commitment
PML	Progressive Multifocal Leukoencephalopathy
PMR	Postmarketing Requirement
PP	Per Protocol
PPI	Patient Package Insert
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update report
PY	Patient-Years
REMS	Risk Evaluation and Mitigation Strategy
RMS	Relapsing (forms of) Multiple Sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGE	Special Government Employee
SMQ	Standardized MedDRA Query
SOC	Standard of Care

SPMS	Secondary Progressive Multiple Sclerosis
TEAE	Treatment Emergent Adverse Event
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal

1. Executive Summary

1.1. Product Introduction

Please refer to Dr. David Jones's Review of Clinical Efficacy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Please refer to Dr. David Jones's Review of Clinical Efficacy.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

In their NDA for siponimod, the applicant seeks approval for the treatment of patients with secondary progressive forms of multiple sclerosis (SPMS). The safety databases contain patients with relapsing multiple sclerosis and progressive multiple sclerosis, and this review analyzes the collective risks in all patients and when appropriate notes differences in findings between the two multiple sclerosis subtypes. This review evaluates the safety of siponimod. If efficacy is demonstrated and the benefits of siponimod outweigh the risks of multiple sclerosis, then I recommend that approval be accompanied by labeling language including warnings and a medication guide to mitigate the identified risks.

This document reviews the risk profile of siponimod. Use of siponimod is associated with the known class effects of S1P modulators such as lymphopenia, infections, bradyarrhythmias, macular edema, elevated liver transaminases, hypertension, and decreased pulmonary function tests. Some of these adverse reactions have the potential for more serious outcomes in the post marketing period in which there is less frequent monitoring of patients than in the setting of clinical trials. Warnings in the labeling and in a Medication Guide for patients may mitigate potentially serious outcomes of these adverse reactions. A recommendation regarding approval for an indication can only by made based on a consideration of benefit and of risk. I will provide an assessment of the risks and recommendations for labeling to mitigate the risk if efficacy is demonstrated. If the efficacy reviewer determines the benefits outweigh the risk, then siponimod would be approved for the treatment of multiple sclerosis.

Risk:

Siponimod is associated with a risk of infections because of a dose-dependent decrease in serum lymphocytes. Almost 50% of patients in controlled trials experienced infections, and while most were mild, there were cases of sepsis and deaths associated with infections. Opportunistic infections were not identified in association with siponimod in controlled trials, but, based on experience with other S1P modulators, it is expected that postmarketing experience will reveal opportunistic infection risk. Siponimod is associated with induction of bradycardia and can cause more serious atrioventricular block in some patients. Labeling will need to describe the titration scheme that reduces the risk for most patients, symptoms of concern for cardiovascular toxicity for all patients, and additional cardiac monitoring needed in higher risk patients. Siponimod is associated with macular edema and patients should obtain an ophthalmological examination for any visual change. Siponimod is associated with elevated blood pressure and a risk of hypertension; patients should be monitored and treated for hypertension. Siponimod is associated with decreased respiratory function testing and respiratory symptoms. Other S1P modulators have been associated severe exacerbation of multiple sclerosis after discontinuation, and this potential for severe disability after stopping should be

included on labeling for all S1P modulator therapies. Siponimod is processed by a specific cytochrome, CYP2C9, and patients with the *3/*3 variant of this enzyme should be contraindicated from taking siponimod because of their relative inability to metabolize it leading to exposures associated with higher risk of AEs. Determination of a patient's CYP2C9 genotype is necessary before starting therapy because maintenance dosing and co-administration of siponimod with inducers/inhibitors of the CYP2C9 pathway will need to be based on patient genotype.

Analysis and Recommendations Regarding Safety:

The risks associated with siponimod are minor, largely amenable to treatment, or end with discontinuation of the therapy. If the clinical efficacy review recommends approval, the rarity of serious, irreversible, or fatal events would not preclude approval of siponimod. I recommend Warnings and Precautions for infections, macular edema, bradyarrhythmia, liver injury, severe exacerbations after discontinuation, respiratory effects, and hypertension. I recommend describing epilepsy and thromboembolic event frequencies observed in the clinical trials in Section 6 of labeling. I recommend guidance for the initial titration of siponimod to mitigate the risk of cardiac conduction abnormalities and increased cardiac monitoring for patients rated as "higher risk" based on criteria used to stratify cardiac risk in clinical trials. Patients with significant cardiac disease or high degree atrioventricular blocks should not take siponimod because of the cardiac effects. I recommend genotype-based dosing for siponimod and for inhibitors and inducers of the CYP2C9 pathway. I recommend a Medication Guide to describe these risks and symptoms of concern. I recommend enhanced pharmacovigilance in post marketing for events of serious infections including opportunistic infections (b) (4) and for malignancies.

I recommend postmarketing requirements as follows: a prospective study of respiratory effects of siponimod, a pregnancy registry, a pregnancy outcomes study, a juvenile toxicology study, a pediatric study, and a postmarketing commitment to develop an assay for CYP2C9 genotype specific for siponimod.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Please refer to Dr. David Jones's Review of Clinical Efficacy	
Current Treatment Options	• Please refer to Dr. David Jones's Review of Clinical Efficacy	
Benefit	• Please refer to Dr. David Jones's Review of Clinical Efficacy	
Risk and Risk Management	Safety Database The safety database for siponimod contains a single Phase 3 placebo-controlled trial in adults with SPMS (Study CBAF312A2304) and its open label extension, a Phase 2 placebo-controlled trial in adults with relapsing multiple sclerosis, as well as supportive data from placebo-controlled trials in dermatomyositis and polymyositis. Drug exposure is adequate, was at or above proposed doses, and the demographics of the clinical trial subjects reflects the intended population for use. Safety Concerns • The most common AEs in the safety data from the controlled study portion of a Phase 3 trial in patients with secondary progressive multiple sclerosis (at least 5% and at least as frequent as placebo) were: headaches (14.5%), falls (11.6%), hypertension (10.5%), upper	Given the established relationship between initiation of other S1P modulators and bradycardias/bradyarrhythmias, the applicant instituted a 6-day titration schedule and categorized patients for cardiac monitoring purposes as having standard cardiac risk (no prior cardiac medical problems) and high risk (previous history of cardiac disease, especially bradycardia or rhythm disturbances) with more rigorous monitoring for the latter group. Labeling should define patients at high risk of developing significant symptomatic bradycardia or serious atrioventricular

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	respiratory tract infections (8.3%), dizziness (6.8%), nausea (6.7%), diarrhea (6.4%), AST increased (5.9%), and pain in extremities (5.5%). The most common AEs in the safety data from the controlled study portion of a Phase 2 trial in patients with relapsing multiple sclerosis (at least 5% and at least as frequent as placebo) were headaches (30.6%), vertigo (12.2%), cough (10.2%), dizziness (10.2%), alanine aminotransferase increased (8.2%), influenza (8.2%), atrioventricular block second degree (6.1%), and bradycardia (6.1%). • Sixteen deaths (0.6%, 0.35/100 PY) have occurred in siponimod-treated patients in controlled and open label studies of multiple sclerosis: 2 by myocardial infarctions with one patient having a lengthy smoking history and a family history of myocardial infarction, 1 due to craniocerebral injury after seizures causing traumatic falls, 1 completed suicide with a history of depression and recent antidepressant initiation with acute stress in his professional life, 1 of urosepsis over 50 days from last dose of siponimod and after receiving rituximab, 1 of septic shock in setting of end-stage metastatic cancer, 1 of malignant melanoma with multiple organ dysfunction syndrome 31 days after discontinuation of siponimod, 1 due to lung adenocarcinoma 4 months after discontinuation of siponimod and with a lengthy smoking history, 1 due to amyotrophic lateral sclerosis, 2 due to respiratory compromise in patients with advanced progressive multiple sclerosis 58 and 267 days after last doses of siponimod, 1 of unknown reasons who had	conduction block during initial dose titration and provide monitoring recommendations accordingly to mitigate these potential risks. Siponimod is associated with lymphopenia and a risk of infections, and uncertainty exists in whether the outcomes of infections would be more serious in an unmonitored outpatient setting or in patients with other risks of immunosuppression due to exposure to other multiple sclerosis therapies. Labeling infections as a Warning would highlight the need for awareness of the potential for infections and may mitigate the risk for serious outcomes. Based on postmarketing experience with another S1P modulator, siponimod will likely be associated with an increased risk of serious complications associated with prolonged immunosuppression such as progressive multifocal leukoencephalopathy. Labeling will need to warn of the potential for cryptococcal meningitis, progressive multifocal leukoencephalopathy, and other opportunistic infections.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	discontinued the study and siponimod approximately 100 days before due to testicular cancer, 1 due to an Acinetobacter pneumonia in a patient with existing respiratory compromise, 2 due to pulmonary embolism which occurred 100 and 170 days after last doses of siponimod, and 1 suspected sudden cardiac death 4 month after last dose of siponimod without autopsy to confirm. There were too few deaths in multiple sclerosis trials to support conclusions about relative mortality risk. • Siponimod appears to be associated with an increased risk of serious vascular events such as stroke and myocardial infarction. • Siponimod appears to be associated with an increased frequency of falls associated with serious injuries including concussions, bone fractures, and head trauma. These falls may be related to the increased frequency of dizziness reported by patients taking siponimod relative to placebo patients. • Siponimod maintenance dose requires knowing a patient's genotype of the cytochrome responsible for siponimod processing CYP2C9 with high metabolizer genotypes taking 2 mg daily and low metabolizing genotypes taking 1 mg daily maintenance, respectively. Siponimod is contraindicated for the CYP2C9 *3/*3 genotype. • Siponimod is associated with lymphopenia, hypertension, macular	Siponimod labeling should reflect Warnings established for other S1P modulators that are expected to occur with siponimod including unexpected neurological effects, severe exacerbations in multiple sclerosis after discontinuation, and posterior reversible encephalopathy syndrome. There was an imbalance in strokes associated with siponimod treatment during controlled trials despite equal risks of stroke risk factors between treatment groups. There were no clear risk factors that appeared to confer greater risk or predict events. There was an imbalance in AEs and SAEs related to falls and dizziness in both clinical trials in patients with multiple sclerosis. These events should be described in labeling. Patients with previous cardiac medical history are at higher risk of developing symptomatic bradycardia and atrioventricular blocks. Patients with existing high degree cardiac block should be contraindicated from

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	edema, decreased respiratory function testing, liver transaminase elevations, and hypersensitivity reactions. These AEs are known to be associated with another approved S1P modulator and were expected to be associated with siponimod therapy because of unavoidable drug class effects. • Given the cardiac effects associated with initiation of S1P modulator therapy, specifically severe bradycardia and atrioventricular conduction blockades, the applicant instituted a titration over 6 days and examined outcomes in patients deemed at high and low risk of cardiac events. Patients without conduction abnormalities or history of bradycardia at baseline tolerated the titration with a low risk of serious cardiac AEs. Patients at high risk still experienced first dose-related cardiac AEs and labeling should provide guidance for first dose monitoring in these higher risk patients. <u>Safety in the Postmarketing Setting</u> The risk for serious outcomes of adverse events such as infections and vascular events in the postmarketing setting when patients are likely to be observed less frequently by medical personnel is unknown. <u>Risk Management</u> Product labeling with Warnings and Precautions and a Medication Guide regarding the risks of infections, falls, vascular events, hypertension, liver injury, malignancies may mitigate the risks of serious outcomes of these events.	siponimod treatment. Higher risk patients require first dose monitoring when initiating siponimod. The labeling for siponimod needs to provide criteria for identifying higher risk patients and instructions for how to perform first-dose monitoring. Risk of cutaneous malignancy may rise in the postmarket setting as it did in association with use of another S1P modulator therapy in MS. Enhanced reporting of malignancies will help identify if there is a risk that needs to be addressed in labeling. Warnings and a Medication Guide with information regarding the main safety risks may help mitigate serious outcomes of these

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Titration to maintenance dose may mitigate risk of serious cardiac arrhythmias in most patients. Identification of patients at higher risk of cardiac conduction abnormalities with initiation of siponimod and observed first dose monitoring in these patients may mitigate risk of serious outcomes of adverse events in these patients. Genotype-based dosing may mitigate increased risks of serious adverse events associated with siponimod treatment due to relative differences in metabolism between genotypes. A postmarketing requirement for a pregnancy registry and outcomes study will help to evaluate the risks of siponimod exposure in pregnancy and prenatal development. Another postmarketing requirement will be a need for a trial to examine longitudinal effects of siponimod on respiratory testing and respiratory symptoms. A postmarketing commitment will direct the applicant to the develop an assay to determine patient genotype that is specifically for use with siponimod. Pediatric and supportive nonclinical in juvenile animal studies are postmarketing requirements to establish the safety of siponimod in children and adolescents with relapsing forms of multiple sclerosis.	risks in the postmarketing setting. Labeling will provide instructions for all patients to undergo electrocardiogram to determine baseline risk and for patients with existing or historical bradyarrhythmias to undergo first dose monitoring. A specific assay for siponimod genotyping is needed. There are genotype assays in widespread commercial use that may be used "off-label" for genotyping until the applicant validates a test specific for siponimod. Siponimod interferes with S1P receptors with a significant role in cardiac development and therefore represents a potential risk of association with cardiac birth defects. Because the risk of adverse outcomes in pregnancy has not been characterized fully, and because siponimod will be administered to women of childbearing potential, a pregnancy registry should be a postmarketing requirement.

1.4. Patient Experience Data

APPEARS THIS WAY ON ORIGINAL

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	▪ Clinical outcome assessment (COA) data, such as	[*e.g.,* Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	☒ Clinician reported outcome (ClinRO)	see Section 6
	☒ Performance outcome (PerfO)	see Section 6
	□ Qualitative studies (*e.g.,* individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[*e.g.,* Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (*e.g.,* submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[*e.g.,* Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Multiple Sclerosis (MS) is a chronic autoimmune disorder of the central nervous system characterized by neurologic deficits that are due to one of more areas of injury to myelin, oligodendrocytes, and neurons, specifically, the neuronal axon. Acute inflammation injury may occur in the subcortical white matter, brainstem, optic nerve, or the spinal cord. The diagnostic precepts used in establishing a diagnosis of MS require clinical or imaging evidence of a dissemination of neurological deficits and injuries "in space and time."[1]

Approximately 85% of patients diagnosed with MS initially have a form characterized by acute inflammatory attacks termed relapses.[2] This waxing and waning pattern of symptoms is the origin of the clinical subtyping of "relapsing and remitting" forms of MS as opposed to the rarer "progressive" forms of MS that may not have clearly identifiable periods of remission.

Although early relapses in relapsing MS may be followed by complete recovery, over time, in most patients, there is an accumulation of residual deficits and increasing disability.[2] In some patients, disability progression is occurs in parallel and seemingly independent of acute exacerbations, and this phase of the disease (which may be an entirely different disease) is termed "secondary progressive multiple sclerosis" (SPMS).[3] Patients with SPMS may or may not continue to experience discrete relapses and the overall appearance of their disease course is more consistent with a neurodegenerative process than a pulsatile relapse-remission history.[4]

With no clear consensus about the exact pathophysiology underlying SPMS, there are proposed classifications of SPMS that include specifying whether there is "active" disease, the referenced activity being evidence of clinical relapses and inflammation.[4] In the absence of a defining pathological mechanism, there are no accepted biomarkers to define SPMS with clinical certainty, and, as such, the diagnosis of SPMS remains a subject of continued debate and research.

With uncertainty about diagnosis comes difficulty in treatment. Despite much progress in the treatment of relapsing forms of MS, for which there are over a dozen approved therapies presently, there exists a paucity of effective treatments for SPMS. Presently, there is one approved therapy indicated for any defined form of SPMS, mitoxantrone, a therapy that is not often used in clinical practice because of significant toxicities. There exists an unmet medical need for effective therapies for SPMS that can be used longitudinally without an associated risk of potentially life-shortening or life-ending complications as exist with mitoxantrone.

2.2. Analysis of Current Treatment Options

The currently approved therapies for Relapsing forms of MS (RMS), Primary Progressive multiple sclerosis, and SPMS are shown in Table 1. Available therapies reduce the annualized relapse rate in patients with RMS by 30 to 50%. While a reduction in the number of relapses is desirable, it is unclear whether reducing relapse frequency results in a significant reduction in

long-term disability. Differences in methodology and in the populations studied limit interpretation of the full effect of these therapies on permanent disability. Several studies have shown a numeric reduction in some measure of disability that was confirmed 12 and/or 24 weeks after an initial significant increase in a given disability score. However, if a statistically significant reduction was seen in one trial, the result was usually not replicated in a second trial. Although most therapies approved for the treatment of RMS show a reduction in various Magnetic Resonance Imaging (MRI) findings associated with RMS, the interpretation of these neuroimaging changes in the context of patient function do not support the use of any of these MRI measures as primary criteria for the choice of therapy.

Because they were the earliest approved therapies and because there have been few major safety concerns, either a β-interferon or glatiramer acetate are often the initial choice for treatment for new onset typical RMS. Because the interferons share the same presumed mechanism of action and have similar efficacy, if the response is not adequate to one interferon then the choice of next therapy is usually not a different interferon and usually not glatiramer acetate. There are now several approved alternative therapies with efficacy at least comparable to the interferons and glatiramer acetate. The data available are not enough to conclude that the efficacy of any of the alternative therapies is superior to the older "first line" therapies.

Each approved therapy has unique benefits and risks. Unless there is strong evidence of superior efficacy and/or a notable lack of safety concerns, any new approved therapy will most likely be used for those who have not responded adequately to the interferons, glatiramer acetate, and possibly one of the approved oral therapies.

Table 1: FDA-approved treatments for Relapsing Forms of Multiple Sclerosis

Approved Drug	Product Name	Relevant Indication	Year Approved	Route & Frequency of Administration	Efficacy Information	Major Safety Concerns	Other Comments
Beta interferon 1b	Betaseron (Betaferon in EU)	Relapsing forms of MS	1993	subcutaneous every other day	32% reduction in ARR	None	
Beta interferon 1a	Interferon β-1a	Relapsing forms of MS	1996	IM weekly	32% reduction in ARR	hepatotoxicity	
Glatiramer acetate	Copaxone	Relapsing forms of MS	1996	subcutaneous daily	29% reduction in ARR	None	

Approved Drug	Product Name	Relevant Indication	Year Approved	Route & Frequency of Administration	Efficacy Information	Major Safety Concerns	Other Comments
Mitoxantrone	Novantrone	Secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis	2000	IV every 3 months	60% reduction in ARR 64% reduction in disability	Cardiotoxicity	Limited clinical use due to toxicity
Beta interferon 1a	Rebif	Relapsing forms of MS	2002	subcutaneous three times weekly	32% reduction in ARR	hepatotoxicity	
Natalizumab	Tysabri	Relapsing forms of MS	2004	IV every 4 weeks	61% reduction in ARR	Progressive Multifocal Leukoencephalopathy	
Beta interferon 1b	Extavia	Relapsing forms of MS	2009	subcutaneous every other day	30% reduction in ARR	None	
Fingolimod	Gilenya	Relapsing forms of MS	2010	orally once daily	55% reduction in ARR	1st dose bradycardia, macular edema, impaired pulmonary function tests, fetal risk	indicated for use ≥ 10 years old
Teriflunomide	Aubagio	Relapsing forms of MS	2012	orally once daily	31% reduction in ARR	black box warnings for hepatotoxicity and teratogenicity	
Dimethyl fumarate	Tecfidera	Relapsing forms of MS	2013	orally once daily	49% reduction in ARR	lymphopenia	
PEGylated Interferon Beta	Plegridy	Relapsing forms of MS	2014	subcutaneous every 2 weeks	36% reduction in ARR	None	
Alemtuzumab	Lemtrada	Relapsing forms of MS after inadequate responses to 2 or more other MS treatments	2015	2 courses 12 months apart	49% reduction in ARR	black box warning for serious/fatal autoimmune conditions thrombocytopenia and anti-glomerular basement membrane disease; serious and life-threatening infusion reactions, increased risk of malignancies	not indicated for use in patients less than 18 years of age due to safety concerns

Approved Drug	Product Name	Relevant Indication	Year Approved	Route & Frequency of Administration	Efficacy Information	Major Safety Concerns	Other Comments
Glatiramer acetate (generic)	various	Relapsing forms of MS	2015	subcutaneous daily	29% reduction in ARR	None	
Ocrelizumab	Ocrevus	Relapsing and Progressive forms of MS	2016	IV every 2 weeks x 2 then IV every 6 months	46% reduction in ARR (RMS) 24% reduction in disability progression (progressive MS)	infusion reactions, increased risk of breast cancer	

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Please refer to Dr. David Jones's Review of Clinical Efficacy.

3.2. Summary of Presubmission/Submission Regulatory Activity

Please refer to Dr. David Jones's Review of Clinical Efficacy.

3.3. Foreign Regulatory Actions and Marketing History

Please refer to Dr. David Jones's Review of Clinical Efficacy.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please refer to the review by OSI. A final report of OSI findings is not complete at the time of submission of this review.

4.2. Product Quality

Please refer to the review by the Chemistry, Manufacturing, and Control (CMC) reviewers. This review is not complete at the time of submission of this review.

4.3. Clinical Microbiology

Please refer to the review by the CMC/Microbiology reviewers. This review as not completed at the time of submission of this review.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the Nonclinical Pharmacology review. This review as not completed at the time of submission of this review.

4.5. Clinical Pharmacology

The mechanism of action of siponimod is modulation of sphingosine-1-phosphate (S1P) receptors. Siponimod selectively targets the S1P1 and S1P5 subtypes of the S1P receptor family. The interaction between siponimod and S1P receptors promotes rapid and long-lasting internalization of surface S1P receptors. Lymphocytes rely on S1P signaling to translocate from lymph nodes into the circulating serum. Reducing S1P receptors on lymphocytes' surfaces inhibits their egress from lymph nodes and reduces the number of lymphocytes in the peripheral blood. The siponimod-related reduction in circulating lymphocytes appears to inhibit the inflammatory autoimmune processes associated with MS.

The data below regarding pharmacokinetics and pharmacodynamics are from the Clinical Overview provided by the applicant and reflect the findings most relevant to safety.

- The effective half-life at steady state ranges between 22-36 hours.
- At the 2 mg dose, the typical female SPMS patient experiences a 79% reduction in absolute lymphocyte count (ALC) compared to baseline.
- After 2 mg chronic daily dosing, the median time for ALC recovery following drug discontinuation to 1.0×10^9/L is predicted to be 5 days for a typical female patient.

For further details regarding clinical pharmacology, please refer to the review by the Clinical Pharmacology team. This review is not complete at the time of submission of this review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Please refer to Dr. David Jones's Review of Clinical Efficacy.

5.2. Review Strategy

Please refer to Dr. David Jones's Review of Clinical Efficacy for his review strategy. My approach to the Review of Safety is described in Section 8 of this review.

6. Review of Relevant Individual Trials Used to Support Efficacy

Please refer to Dr. David Jones's Review of Clinical Efficacy.

7. Integrated Review of Effectiveness

Please refer to Dr. David Jones's Review of Clinical Efficacy.

8. Review of Safety

8.1. Safety Review Approach

My review strategy will be to focus this safety review on findings from clinical trials of patients with multiple sclerosis (MS) because the applicant seeks approval for siponimod as a treatment for the secondary progressive form of MS (SPMS). Although the applicant seeks approval for SPMS treatment in this NDA, the application also includes findings from clinical trials of siponimod in patients with relapsing forms of MS. The applicant included reports from trials in smaller populations of patients diagnosed with autoimmune diseases that have different primary manifestations from MS, dermatomyositis, and polymyositis, and these trials will support findings from the MS trials. The clinical pharmacology studies undertaken largely in

healthy subjects will further inform the findings in patients with MS exposed to siponimod but are not a primary focus of this review. I will confine the major discussions and conclusions of this review to safety findings in the indicated population, patients with MS, which includes safety data from patients with relapsing forms of MS and patients with SPMS.

In this application, the applicant seeks approval for the treatment of patients with SPMS. The protocol of the pivotal study in this application defined patients with SPMS as those with progression of disability "in the absence of relapses, or independent of relapses" and who have not had evidence of or corticosteroid treatment for a relapse in the three months prior to entering the trial. While this definition of SPMS is reasonable and was agreed upon by the Agency prior to trial initiation, it is important to note that there is no generally accepted clinical definition of SPMS, and there is debate about whether progressive and relapsing forms of MS represent a continuum of the same disease or are distinct, separate, pathological disease processes.

> *Reviewer Comment: The patient population in the pivotal trial in this application who experienced a significant treatment effect were patients who were continuing to experience relapses, despite the applicant's claim these were prototypical SPMS patients (who would not be expected to be experiencing relapses.) Therefore, the indicated population for whom benefit would be predicted would be described best as patients with active SPMS, which is a relapsing form of MS. I will provide a broad review encompassing both forms of MS because there is considerable overlap between these two populations.*

The MS clinical development program for siponimod includes two controlled, randomized clinical trials. The applicant conducted Study A2304 in patients with SPMS and Study A2201 in patients with RMS.

Study CBAF312A2304 (abbreviated as Study A2304) is a 1651-patient, randomized, double-blind, parallel group, placebo-controlled variable treatment duration Phase 3 study undertaken in patients with SPMS. In this study, patients followed a week-long titration to a maintenance dose (2 mg). The duration of the core portion of this study was variable and based on the number of confirmed disability events at 3-months, the primary efficacy endpoint. This study has an ongoing extension trial (CBAF312A2304EP or 2304EP) that has 1220 enrolled patients as of the safety update cut-off date of December 31, 2017.

Study CBAF312A2201 (abbreviated as Study A2201) is a 297-patient, randomized, double-blind, randomized, multi-center, adaptive, dose-ranging, placebo-controlled, parallel-group, two-period Phase 2 study undertaken in patients with RMS. In Study A2201, patients with RMS were exposed to several doses of siponimod for three- or six-months' duration. There were two

periods in Study A2201, and in Period 2, a titration schedule for siponimod was introduced to reduce side effects associated with starting treatment at maintenance dose. After completion of the controlled portion of this trial, patients could enroll in an open label extension trial of 2 mg siponimod for up to three more years. The extension of this study, A2201E enrolled 184 patients for up to five years of observation.

This review relies primarily on the safety data from Studies A2201 and A2304 because these safety data originated in patients with the desired indication for approval, multiple sclerosis. I refer to additional efficacy and safety data that were provided as part of the ongoing extension study of Study A2304 and the long-term extension study of Study A2201, Study CBAF312A2201E1. I discuss safety data from the single and multiple dose clinical pharmacology studies and controlled studies performed in patients with dermatomyositis and polymyositis (CBAF312A2202, CBAF312X2205, and CBAF312X2206) to provide additional support for the findings in the MS development program.

In this review, I summarize information from the applicant's presentations, and, when needed, supplement the Applicant's reported findings with analyses that I conducted using data provided in the Clinical Study Report, the Integrated Summary of Safety, Safety Updates, Addenda, and all other the data provided by the applicant in the application and in responses to formal Information Requests. I performed analyses using the JMP software program. For adverse events (AEs), I present the safety data from studies in other indications to demonstrate commonly reported events and infrequent events of potential concern to supplement and to inform the main presentation of AEs from the MS trials. Because there were several siponimod treatment doses used in clinical trials, I will focus most safety discussions on the proposed marketing dose of 2 mg.

To contextualize the subject of this review, siponimod is in the class of S1P receptor modulators--fingolimod being the prototypical member--that inhibit lymphocyte egress from lymph nodes. Chronic administration of S1P modulator therapies lowers the circulating lymphocyte count and presumably reduces the number of auto-reactive lymphocytes available to migrate to the CNS where they would contribute to the pathology associated with MS. The exact mechanism of action of siponimod is unknown but presumed proposed to be a decrease in CNS autoimmune injury resulting from a reduction in the circulating lymphocyte pool.

Prior experience with the S1P receptor modulator therapies has identified several AEs and risks associated the use of S1P modulators. These risks include initial dose bradycardia and cardiac conduction block, macular edema, serious infections including opportunistic infections seen in immune compromised patients, hypertension, increased liver enzymes (without liver failure), reduction in the Forced Expiratory Volume in one second (FEV1), reduction in the diffusing capacity of the lung for carbon monoxide (DLCO), and cutaneous malignancies. I interrogated the databases the applicant provided to assess whether there were any new safety issues both

related and unrelated to these known AEs. I will analyze studies performed in patients with any form of MS collectively and broken down by MS subtype in respective studies. The goal is to arrive at a comprehensive summary of safety risks associated with siponimod therapy in the indicated population.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Safety Population Exposure

In the original NDA submission (cut-off date May 31, 2017), the applicant stated a total of approximately 3278 unique subjects (1249 healthy subjects, 24 hepatic impaired subjects, 8 renal impaired subjects, 49 PM/DM patients and 1948 MS patients) have been enrolled into the siponimod clinical program (inclusive of Phase 1, Phase 2 and Phase 3). There were 2760 unique patients who had been exposed to at least one dose of siponimod, and of these patients, 1737 patients had been exposed to siponimod (any dose or duration) in Phase 2 and 3 controlled trials in MS. the applicant provided exploratory trial data from an additional 49 patients with polymyositis and dermatomyositis exposed to doses ranging from 0.5 mg-10 mg of siponimod. The cumulative exposure of patients with MS to siponimod since the development program's inception on March 5, 2009, until the cut-off date of May 31, 2017, was estimated to be 4048.6 patient-years (PY).

The 120-day Safety Update contained additional safety information available through December 31, 2017. The submission provided updates of AEs and safety findings in the only ongoing study, A2304EP, as well as an update of the analyses in the entire safety data set and errata to the original NDA safety data. In this update, the cumulative exposure estimate was revised to 4619.8 PY.

Table 2: Studies of Siponimod in Multiple Sclerosis Included in Integrated Summary of Safety

Study ID	Design	Duration	Treatment/Dose	Patients Randomized	Comments
Placebo Controlled Trials					
CBAF312A2201	Phase 2 double-blind randomized, placebo-controlled multi-center (with US sites), dose-	3 or 6 months	Siponimod 0.25, 0.5, 1.25, 2, 10 mg) daily	N=297 Men: 85 Women: 212 Siponimod: 235	Primary Endpoint: Dose response relationship between siponimod and the

Study ID	Design	Duration	Treatment/Dose	Patients Randomized	Comments
	ranging study in RMS		Placebo	Placebo: 62	number of combined unique active MRI lesions (CUAL)
CBAF312A2304	Phase 3, double-blind, randomized, placebo controlled, multicenter study (with US sites), efficacy and safety study in SPMS	Flexible, 11 to 37 months	Siponimod 1 or 2 mg daily Placebo	N=1651 Men: 659 Women: 992 Siponimod: 1105 Placebo: 546	Primary endpoint: 12-week CDP
Long Term Extension Trials					
CBAF312A2201E1	Extension study to the A2201 study with dose blinded and open-label phases	Dose blinded: 2 years Open Label: 3 years	Dose blinded: Siponimod 0.25, 0.5, 1.25, 2, 10 mg) daily Open label: 2 mg daily	N=184 (dose blinded) N=159 (Open label)	Study is complete
CBAF312A2304EP	Open-label in patients with SPMS from Study A2304	Ongoing, up to 84 months	Siponimod 2 mg daily	N=1220	Study is ongoing

Source: Tabular listing of all clinical studies, NDA 209884

Presently, the A2304EP trial is the only ongoing trial of siponimod for any indication. The applicant included updated safety information regarding AEs and findings in this study in the 120-day safety update.

The following table further summarizes patient exposure to siponimod in the controlled clinical trials undertaken in autoimmune patients in this application.

Table 3: Safety Population, Clinical Trials in Autoimmune Diseases

Clinical Trial Groups	Siponimod	Placebo
Multiple Sclerosis	N	N
Study A2201 Double-blind, randomized, multi-center, adaptive, dose-ranging, placebo-controlled, parallel-group, two-period Phase 2 study in patients with RMS	235	62
Study A2201E1 Open label extension trial in patients with RMS	184	-
Study A2304 (Core Part) Multi-center, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration Phase 3 study in SPMS	1105	546
Study A2304 (Extension) Open label extension trial in SPMS	1220	-
All MS Patients Total Exposed	1737	608
Study A2202 A multi-center, double-blind, placebo controlled, proof of concept study to evaluate the efficacy and tolerability in patients with polymyositis and dermatomyositis.	18*	9*
Study X2205 A multi-center, double-blind, placebo controlled, proof of concept study to evaluate the efficacy and tolerability in patients with polymyositis.	14*	7*
Study X2206 A double-blind, randomized, placebo-controlled study to evaluate safety, tolerability, efficacy and preliminary dose response in patients with active dermatomyositis	12	5

Source: Tabular listing of all clinical studies, NDA 209884

*Patients in these trials would crossover from placebo to siponimod treatment; thus, the same patients are included in both the siponimod and placebo treatment population n.

Clinical Pharmacology Studies

The applicant reported twenty clinical pharmacology studies. (b) (4)

Study A2126 was added to assess single dose bioavailability of siponimod. In these twenty studies, a total of 1281 subjects were enrolled. There were 880 healthy subjects, 24 hepatic impaired subjects and 8 renal impaired subjects who received siponimod and 434 healthy subjects who received placebo or placebo followed by siponimod. Some subjects sequentially received placebo and siponimod. In addition, 363 healthy subjects were exposed to other study drugs either alone or in combination with siponimod. The clinical pharmacology studies included in this application are presented in the following table.

Table 4: Listing of Clinical Pharmacology Studies in Application

Study	Description	Population

Study	Description	Population
A2101	Two-part, single center randomized, double-blind, placebo-controlled, single ascending dose Phase 1 study to explore safety, tolerability, PK and PD	Healthy subjects
A2102	Randomized, parallel, double-blind, placebo-controlled, time-lagged, multiple ascending dose Phase 1 study to evaluate safety, tolerability, PK and PD	Healthy subjects
A2105	Randomized, parallel, double-blind, placebo-controlled, time-lagged, multiple ascending dose Phase 1 study to evaluate safety, tolerability, PK and PD	Healthy subjects
A2107	Double-blind, placebo-controlled, parallel-group dose titration Phase 1 study to investigate the negative chronotropic effect of siponimod	Healthy subjects
A2110	Randomized, partially double-blind, placebo-controlled Phase 1 study with 3 periods (10 days of single dose drug treatment, drug discontinuation, 1 day of single dose drug re-initiation) to investigate the effect of siponimod treatment re-initiation on the initial negative chronotropic effect	Healthy subjects
A2104	Open-label, single oral dose Phase 1 study in healthy subjects with the CYP2C9*1*1 genotype	Healthy CYP2C9*1*1 subjects
A2111	Randomized, open-label, 3- period, 3-treatment, 6-sequence, single dose, crossover Phase 1 study to assess both the bioequivalence of the siponimod final market image tablet formulation as compared to the siponimod market formula and the effect of food on the PK of the final market image	Healthy CYP2C9*1*1 subjects
A2119	Randomized, double-blind, placebo-controlled, parallel group, single dose Phase 1 study to assess the tolerability, PD and PK of 2 modified-release siponimod tablets compared to the immediate release tablet and placebo	Healthy subjects
A2125	Open-label, 2-period, drug interaction Phase 1 study to evaluate the effect of the CYP2C9/3A4 inducer rifampin on siponimod PK	Healthy CYP2C9*1*1 subjects
A2108	Open-label, single dose, 2- period, drug interaction Phase 2 study to evaluate the safety, tolerability and PK of siponimod when given alone and in combination with the CYP2C9/3A4 inhibitor fluconazole	Healthy CYP2C9*1*1 subjects
A2124	Open-label, 3-period, single-sequence, crossover, drug interaction Phase 1 study to evaluate the effect of the CYP3A4 inhibitor itraconazole on siponimod PK, safety, and tolerability	30 healthy CYP2C9*1*2 and *1*3 subjects

Study	Description	Population
A2130	Randomized, double-blind, placebo-controlled, parallel-group, multiple dose Phase 1 study to evaluate the modulation of immune response to T-cell dependent and T-cell independent antigen stimuli by preceding, concomitant and interrupted administration of multiple therapeutic doses of siponimod	Healthy subjects (CYP2C9*3*3 genotype subjects excluded)
A2121	Open-label, multiple dose, 2-period Phase 1 study to evaluate the effect of oral siponimod on the PK and PD of monophasic oral contraceptive	Healthy female CYP2C9*1*1 subjects
A2116	Randomized, double-blind, placebo-controlled, multiple dose Phase 1 study to evaluate PD and/or PK interaction of siponimod and propranolol co-administration	Healthy subjects (CYP2C9*3*3 genotype subjects excluded)
A2126	Open-label, single dose, 2-part Phase 1 study to measure the absolute bioavailability, safety, tolerability, and PD of oral and iv siponimod	Healthy CYP2C9*1*1 subjects
A2118	Randomized, double-blind, parallel-group, placebo- and moxifloxacin-controlled Phase 1 study to assess the effects on QT interval (cardiac repolarization) at oral therapeutic and supratherapeutic doses of siponimod	healthy subjects (CYP2C9*3*3 genotype subjects excluded)
A2122	Single dose, open-label, parallel-group Phase 1 study in subjects with the CYP2C9*1*1 to compare the PK, safety and tolerability of siponimod in subjects with mild, moderate and severe hepatic impairment and healthy control subjects	Healthy and hepatic impaired CYP2C9*1*1 subjects
A2129	Single dose, open-label, parallel-group Phase 1 study in CYP2C9*1*1 subjects (wild type genotype) to compare the PK, safety and tolerability of siponimod in subjects with renal impairment and normal renal function	Healthy and renal impaired CYP2C9*1*1 subjects
A1101	Randomized, double-blind, placebo-controlled, ascending single dose Phase 1 study to evaluate safety, tolerability, PK and PD in Japanese subjects	Healthy male Japanese subjects
A2128	Open-label, 2-part, single and multiple dose Phase 1 study to assess the safety, tolerability, and PK of siponimod in subjects with CYP2C9 extensive metabolizers (CYP2C9*1*1 genotype) and poor metabolizers (CYP2C9*2*3 or *3*3 genotype)	Healthy CYP2C9*1*1 and CYP2C9*2*3/*3*3 subjects

Source: Summary of Clinical Pharmacology Studies

In the clinical pharmacology programs, healthy subjects have received siponimod as single doses (0.1 to 75 mg) or multiple doses (0.25 to 20 mg) daily up to 38 days. Based on the findings from the clinical pharmacology studies, the maximum tolerated dose for a single dose of

siponimod was determined to be 25 mg based upon the occurrence of symptomatic bradycardia after a single dose of 75 mg.

> *Reviewer Comment: Single dose and multiple dose trials in healthy volunteers are of limited clinical utility for generalization to an indicated population. There were no deaths and few SAEs reported in any of these trials. Review of the safety findings in these clinical pharmacology programs failed to reveal significant or new safety findings that were not identified in controlled or open label trials in patients with MS or other autoimmune diseases. Studies in other autoimmune diseases are reviewed in Sections 8.4.4. and 8.4.5.*

Safety Population Definition

The applicant defined the safety set population as follows:

"... all patients [with MS] who received at least one dose of study medication. Patients were analyzed according to the actual treatment received, using all available data up to and including thirty days after last dose of study drug or the day before start of open-label siponimod, whatever came first."

Siponimod was administered at several doses (0.25, 0.5, 1.25, 2, and 10 mg) in the studies included in this safety review. The proposed regimen, utilized in the Applicant's pivotal trial in SPMS (Study A2304), begins with a 6-day dose titration as follows:

Day 1: 0.25 mg one time by mouth
Day 2: 0.25 mg one time by mouth
Day 3: 0.5 mg (2 x 0.25 mg) one time by mouth
Day 4: 0.75 mg (3 x 0.25 mg) one time by mouth
Day 5: 1.25 mg (5 x 0.25 mg) one time by mouth
Day 6: 2 mg (maintenance dose)

The maintenance dose, 2 mg by mouth daily, begins on Day 6 following successful titration. For patients with the CYP2C9 *1*3 or *2*3 genotypes, the maintenance dose was 1 mg by mouth once daily.

The applicant submitted four safety pools, as had been agreed upon in a pre-NDA meeting, as follows:

Safety Database 1 (N=1941 total, n=1134 siponimod treatment, n=607 placebo treatment), the Controlled Pool, includes patients in the placebo-controlled, double-blind phases of studies A2304 and A2201 and assesses safety in controlled conditions as compared to placebo. Data

collected during the double-blinded treatment period including a 30-day follow-up period are included. Data collected under A2304 core part open-label siponimod treatment (i.e. after permanent discontinuation of double-blind study drug) are not included. Since the placebo-controlled, double-blind part of the studies ended prior to the original SCS cut-off date, there were no updates to this pool contained in the 120-Day Safety Update.

Safety Database 2 (N=1737 total), Long-term Safety Pool, includes data for patient exposure only while receiving siponimod 2 mg or higher. The following data are included in Safety Database 2:

- Data collected during the treatment period when patient was treated with siponimod 2 mg or 10 mg in the core (controlled and open-label) and/or extension phases of Studies A2201 and A2304, including A2304 CP open-label siponimod treatment, if any.
- Data collected during the dose titration up to the target dose prior to period (a) above.
- Data collected after a dose reduction from siponimod 2 mg to 1 mg (permitted per protocol due to low lymphocyte counts or tolerability). Similarly, for patients who received the 10 mg dose and then switched to 2 mg (and subsequently from 2 mg to 1 mg dose), data collected while receiving reduced dose.
- Data collected during a 30-day follow-up period after last dose of study drug are included.

Safety Database 3 (N=1545), Titration Pool, includes data from the initiation of siponimod and up-titration period. The titration pool includes patient data in the titration periods (up to 15 days) when patients underwent dose titration to siponimod 2 mg at dose initiation or at a later point in the core and/or extension portion of studies A2201 and A2304. Safety database 3 includes patients who underwent dose titration from no-treatment or placebo to siponimod 2 mg either at dose initiation in the core and/or extension phases of studies A2201 and A2304 or during dose restart after an interruption of 4 days or more. Patients from Study A2201 receiving siponimod 2 mg in core phase without titration and titrated up to siponimod 2 mg in the extension phase are included for the periods when they had dose titration only. That is, there are 29 patients from Study A2201 included in the titration pool, 7 of these patients at the time of dose initiation data and 23 at the time of dose restart data.

In Safety Database 3, the applicant defined dose initiation and dose restart to siponimod 2 mg as follows:

> "Dose initiation to siponimod 2 mg: the first titration for a patient receiving the siponimod 2 mg dose, regardless if the first titration to siponimod 2 mg for that patient occurred during double-blind, dose-blinded, or open-label treatment and regardless of previous treatment with (or titration to) siponimod doses other than 2 mg (or placebo). This pool does not include patients who received the first siponimod 2 mg dose without

titration."

"Dose restart to siponimod 2 mg: patients who missed treatment for ≥ 4 consecutive days were to have dose titration upon restarting treatment. If a patient took the first siponimod 2 mg dose without titration, any subsequent titration periods up to siponimod 2 mg are considered dose restart and are therefore included in this pool regardless of whether the titration occurred during double-blind, dose-blinded, or open-label treatment and regardless of previous treatment with (or titration to) siponimod doses other than 2 mg or placebo). Dose restarts after interruption of 4 days or more include: restarting siponimod after stopping/completing the Core Part of A2304 and then receiving siponimod in the extension of A2304 (majority of dose restarts), and restarting siponimod after interruption, related to e.g. safety event or per protocol."

Safety Database 4 (N=1737), Long-term Safety Pool, includes data exposure while on any lower doses of siponimod in addition to exposure while on siponimod 2 mg or higher (up to 10 mg). This safety database includes data collected during the siponimod treatment period with any dose, provided the patient received at least one dose of siponimod 2 mg or 10 mg. This includes the period when patients from Study A2201 were receiving siponimod 0.25 mg, 0.5 mg, 1.25 mg or 10 mg prior to switching to siponimod 2 mg. Controlled double-blinded, open-label, and open-label extension data are included in this pool. This database is based on Safety Databases 1, 2, and 3.

Note: Safety Databases 2 and 4 include the same patients (all patients receiving at least one dose of siponimod 2 mg or higher) but for different exposure periods. Safety Database 2 encompasses the longest duration of siponimod exposure. In tables, data originating from Safety database 2 are indicated with *, and data originating from Safety Database 4 with **.

Reviewer Comment: The pooling strategy was discussed in advanced of the submission and agreed to by the Agency. Given the differences in durations and doses between the controlled trials, the existence of several pools of subjects was appropriate. While all four pools are relevant, this reviewer found Safety Databases 1 and 2 to be the most informative because these databases contained all controlled and open label data for exposures across the whole range of doses in the MS trial program for the longest time interval available for review. Tables in this document will refer to the safety database used to generate the findings.

The table below summarizes exposure by duration in trials enrolling patients with MS and supports the assertion that exposure within the development programs for MS exceeded ICH guidelines (100 patients on treatment for at least 1 year). These data include safety data provided in the 120-day safety update.

Table 5: Applicant Table, Duration of Exposure to Siponimod by Dose for Patients with MS, Long-Term Safety Pool* (Safety Database 2)

		Number of patients with MS exposed to siponimod				
Dosage	**≥ 1 dose**	**≥ 1 month**	**≥ 3 months**	**≥ 12 months**	**≥ 24 months**	**≥ 36 months**
0.25 mg	N=51	N=50	N=0	N=0	N=0	N=0
0.5 mg	N=43	N=42	N=39	N=0	N=0	N=0
1.25 mg	N=42	N=42	N=32	N=0	N=0	N=0
2 mg	N=1148	N=1117	N=1083	N=865	N=277	N=81
10 mg	N=50	N=42	N=38	N=0	N=0	N=0
2-10 mg*	N=1737	N=1692	N=1648	N=1449	N=1024	N=776

*includes all exposures of 1 dose or more in long-term extension trials
Sources: Summary of Clinical Safety in Multiple Sclerosis, Table 1-4, SCS Appendix 1, Table 1.2-1.2, and Table 1-3 of 120-day safety update

The following table summarizes the durations of exposures at the doses used in MS development program. These data incorporate the safety data provided in the 120-day safety update:

Table 6: Applicant Table, Duration of Exposure to Study Drug by Dosage for Patients with MS, Long-Term Safety Pool* (Safety Database 2)

Dosage	Mean Exposure (months)	SD	Median	Min	Max	Patient-Years
0.25 mg	3.05	0.51	3.15	0.03	3.78	12.94
0.5 mg	5.52	1.39	5.95	0.39	6.60	19.78
1.25 mg	3.06	0.40	3.15	1.22	3.58	10.70
2 mg	17.73	8.50	17.36	0.03	36.24	1696.11
10 mg	4.63	2.33	5.91	0.03	6.87	19.29
2-10 mg*	31.92	18.35	32.39	0.03	75.01	4619.84

*includes all exposures of at least 1 dose in all trials of siponimod
Source: SCS Appendix 1 Tables 1.2-1.1 & 1.2-1.2, Table 1-3 of 120-day safety update

8.2.2. Relevant characteristics of the safety population:

MS predominantly affects white, non-Hispanic women, and therefore MS incidence and prevalence are highest in temperate climates in Canada, Europe, New Zealand, southern Australia, and the United States.[5] The demographic characteristics of the patients with MS in the siponimod clinical trial populations appeared to represent the intended treatment population. The demographic representations of all non-white and male study patients were manifestly limited because of the predominance of MS diagnosis in white women, and there were fewer patient exposures in individuals below age 30 because SPMS is more often diagnosed in patients > 30 years old.[6]

Considering all exposed patients with MS in the Safety Set, the mean age was 38.5 years (range 19 - 61 years), 62.3% of the patients were women and 95.5% of the patients were white. These findings are consistent with the reported worldwide demographics of MS.[5]

The following table summarizes the demographic baseline characteristics for all patients (including all patients with MS exposed) included in the updated siponimod safety database.

Table 7: Reviewer Table, Summary of Exposure by Dose Demographic Data – All Patients as of 120-day Update

	Siponimod 0.25 mg	**Siponimod 0.5 mg**	**Siponimod 1.25 mg**	**Siponimod 2 mg**	**Siponimod 10 mg**	**Siponimod 2-10 mg**
All Patients	N=51 (100%)	N=43 (100%)	N=42 (100%)	N=1148 (100%)	N=50 (100%)	N=1737 (100%)
Gender						
Male	9 (17.6%)	13 (30.2%)	11 (26.2%)	450 (39.2%)	20 (40.0%)	677 (39.0%)
Female	42 (82.4%)	30 (69.8%)	31 (73.8%)	698 (60.8%)	30 (60.0%)	1060 (61%)
Age (years)						
18-30	10 (19.6%)	10 (23.3%)	12 (28.6%)	38 (3.3%)	13 (26.0%)	91 (5.2%)
31-45	33 (64.7%)	26 (60.5%)	26 (61.9%)	391 (34.1%)	31 (62.0%)	634 (36.5%)
46-55	8 (15.7%)	7 (16.3%)	4 (9.5%)	519 (45.2%)	6 (12.0%)	719 (41.4%)
>55	0	0	0	200 (17.4%)	0	293 (16.9%)
Race						
White	50 (98.0%)	42 (97.7%)	41 (97.6%)	1093 (95.2%)	48 (96.0%)	1653 (95.2%)
Black	1 (2.0%)	0	1 (2.4%)	8 (0.7%)	0	11 (0.6%)
Asian	0	0	0	30 (2.6%)	0	43 (2.5%)
Other	0	1 (2.3%)	0	12 (1.0%)	2 (4.0%)	20 (1.2%)
Unknown	0	0	0	5 (0.4%)	0	10 (0.6%)
CYP2C9 Genotype						
***1/*1, *1/*2,**	47 (92.2%)	35 (81.4%)	36 (85.7%)	968	41 (82.0%)	523

	Siponimod 0.25 mg	Siponimod 0.5 mg	Siponimod 1.25 mg	Siponimod 2 mg	Siponimod 10 mg	Siponimod 2-10 mg
***2/*2**				(84.3%)		(86.2%)
***1/*3, *2/*3**	4 (7.8%)	7 (16.3%)	6 (14.3%)	176 (15.3%)	9 (18.0%)	83 (13.7%)
Missing	0	1 (2.3%)	0	4 (0.3%)	0	1 (0.2%)
Ethnicity						
Hispanic/Latino	1 (2.0%)	1 (2.3%)	1 (2.4%)	75 (6.5%)	1 (2.0%)	33 (5.4%)
Not Hispanic/Latino	50 (98.0%)	42 (97.7%)	41 (97.6%)	871 (75.9%)	49 (98.0%)	470 (77.4%)
Not Reported	0	0	0	95 (8.3%)	0	58 (9.6%)
Unknown	0	0	0	107 (9.3%)	0	46 (7.6%)
Region						
United States	7 (13.7%)	5 (11.6%)	6 (14.3%)	109 (9.5%)	6 (12.0%)	165 (9.5%)
Outside U.S.	44 (86.3%)	38 (88.4%)	36 (85.7%)	1039 (90.5%)	44 (88.0%)	1572 (90.5%)

Sources: SCS Appendix 1 Tables 1.2-1.2a, 1.2-2.1, 1-2.2.1a, 1-2.2.2, 1.3-1.1, 1.3-1.2, dm.xpt

8.2.3. Adequacy of the safety database:

In the 120-day safety update, the applicant identified a total of 888 patients exposed to any dose of siponimod for ≥ 365 days. The submitted patient exposure data therefore demonstrate that siponimod exposure exceeded the ICH Guidelines for chronically administered medications (*i.e.,* n=100 for one year). The siponimod safety database is of adequate size with a sufficient number of patients treated for an appropriate duration to generate meaningful conclusions regarding safety risks.

The applicant intends to recommend a titration schedule followed by a single daily dose (1 or 2 mg) based on genotype in their proposed labeling. Most of the subjects in the MS trials received doses of 2 mg.

There are practical limitations to the database due to disease predilections resulting in small numbers of exposed men and very few patients from racial groups other than white. Due to study design enrollment criteria and disease characteristics, less than half of the enrolled patients are < 31 or > 45 years old. Nevertheless, the demographic characteristics of the applicant's safety database patient population are similar to the intended treatment population, patients with MS. Therefore, the safety database is adequate and sufficient for the

purposes of a review for the desired indication.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The safety data provided by the applicant are of sufficient quality to permit a review. A data fitness assessment by the Agency's Office of Computational Science concluded that the datasets submitted for review were substantially complete and found few examples of duplicated, inconsistent, or missing data. The applicant responded appropriately to all queried issues with the submitted data sets in their responses to several of the Agency's Information Requests and apprised the Agency promptly of all database issues that arose during the review period.

During the review, I was able to replicate the key findings of the summaries provided by the applicant as presented in the Safety Set. For individual patients, I compared data across several sources and did not find gross discrepancies between datasets, narratives, supplied CRFs, listing, or summary tables. The applicant provided timely responses to requests for information and clarifications.

A database integrity issue became apparent during review. The applicant reported an issue with database access at multiple sites. An investigation by the Office of Scientific Integrity found that there were 62 clinical sites (out of 294 total clinical sites) in which site personnel were granted and had inappropriate access to the first dose or main databases affecting 247 out of 1651 total study subjects. This access involved:

- 34 users of the main database who had inappropriate access to the first dose database potentially affecting 101 subjects; These users were part of the main study team which included the clinical investigators who assess the time 25-foot walk test.
- 12 EDSS raters who were granted and had inappropriate access to the first dose or main databases
- 3 EDSS raters had inappropriate access to the first dose database for 13 subjects
- 9 EDSS raters had inappropriate access to the main database for 57 subjects

The details of this inappropriate access are described further in the Clinical Review of Efficacy by Dr. David Jones and in the OSI review.

> *Reviewer Comment: The implications of the inappropriate database access with regards to the safety database appear less concerning than they are for the efficacy review. While it is theoretically possible that providing study investigators with a means of violating the blinding to treatment status and knowing patient assignments might lead to underreporting of AEs for siponimod, there is no evidence of systematic deficiencies in*

the safety reporting for siponimod-treated patients in Study A2304. Also, the pooling of safety data from multiple controlled studies should provide a broad sampling of data from studies not impacted by this database access issue and would supply evidence of safety issues missed, for whatever cause, in a compromised study. It is this reviewer's opinion that there are no obvious quantitative nor qualitative differences between the safety findings in Study A2304 and the safety findings from the other studies included in the safety database to suggest any evidence of malfeasance or suppression of safety data.

8.3.2. Categorization of Adverse Events

The applicant used common definitions of AEs and SAEs. The applicant's coding process for verbatim AE terms using MedDRA coded terms was adequate and allowed for accurate estimates of event risks. The applicant's assessment of AEs, and AEs of special interest were also adequate and appropriate.

The protocol definition of an "adverse event" was "any untoward medical occurrence (*i.e.,* any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product."

Investigators solicited AEs by questioning of the patients at each visit during the studies. Patients could also volunteer AEs during or between visits.

Laboratory test results physical examinations, and other study assessments could be sources for AEs as well. Abnormal laboratory values or test results constituted AEs only if they fulfilled at least one of the following criteria:

- they induced clinical signs or symptoms
- they were considered clinically significant
- they required therapy

The study protocols defined clinically notable laboratory findings according to the Common Terminology Criteria for Adverse Events (CTCAE). Investigators recorded AEs in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them accompanied by the following information:

- CTCAE grade (If CTCAE grading does not exist for an adverse event, use 1=mild, 2=moderate, 3=severe, and 4=life-threatening. CTCAE Grade 5 (death) is not used, but is

collected in other CRFs (Study Completion, Death/Survival).
- Relationship to the study treatment (no/yes)
- Duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- Whether it constitutes a serious adverse event (SAE)
- Action taken regarding study treatment
- Whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

The study protocols defined an SAE as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
    - is medically significant, i.e. defined as an event that jeopardizes the patient or may require
- medical or surgical intervention to prevent one of the outcomes listed above.

The protocols stipulated that investigators denote all malignant neoplasms as "serious" under "medically significant" if other seriousness criteria were not met.

The protocols instructed all investigators to treat all adverse events appropriately. Treatment could include one or more of the following: no action taken (*i.e.,* further observation only); study treatment dosage interrupted; study drug permanently discontinued; concomitant medication given; non-drug therapy given. Investigators recorded the action taken to treat the adverse event on the Adverse Event CRF.

Once an adverse event was detected, investigators were to follow the AE until it was resolved or until it was judged to be permanent. Investigators were instructed to assess AE progress should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug were found in the Investigator Brochure (IB) or were communicated between IB updates in the form of Investigator Notifications. This information was included in the patient informed consent, and investigators discussed these side effects with the patients during the study as needed.

The investigators instructed each patient to report any new AE (beyond the protocol observation period) that the patient, or the patient's personal physician, believed might be related to study treatment. This information was recorded in the investigator's source documents; however, if the AE met the criteria of a serious adverse event, it had to be reported to the applicant.

Serious Adverse Events

To ensure patient safety, the protocols for the MS trials in this application stated that every serious adverse event (SAE), regardless of causality, occurring after the patient had provided informed consent and until 30 days after the last study visit must be reported to the applicant within 24 hours of learning of its occurrence. Investigators reported any SAEs experienced after the 30 day-period to the applicant only if the investigator suspected a causal relationship to study treatment.

Investigators had to report recurrent episodes, complications, or progression of the initial SAE as follow-ups to the original episode, regardless of when the event occurred. Investigators had 24 hours to submit follow-up reports after receiving the follow-up information. Any SAE that an investigator considered completely unrelated to a previously reported SAE were reported separately as new events.

Investigators collected information about all SAEs and recorded the data on the Serious Adverse Event Report Form. The reporting investigators had to complete all applicable sections of the form to provide a clinically thorough report. The reporting investigator assessed the relationship of each SAE to each specific component of the study treatment and submitted the completed form within 24 hours to the applicant. Detailed instructions regarding the submission process and requirements for signature were in the investigator folders provided to each site.

Investigators submitted follow-up information as instructed in the investigator folder. They

reported each reoccurrence, complication, or progression of the original event as a follow-up to that event regardless of when the event had occurred. The follow-up information described whether the event had resolved or continued, if and how it had been treated, whether the blind had been broken, and whether the patient continued or withdrew from study participation.

If there was no prior documentation of the SAE in the Investigator's Brochure or Package Insert (new occurrence) and was thought to be related to the investigational treatment, a Drug Safety and Epidemiology Department associate urgently required further information from the investigator for Health Authority reporting. Suspected Unexpected Serious Adverse Reactions (SUSARs) were collected and reported to the competent authorities and relevant ethics committees in accordance with directives or as per national regulatory requirements in participating countries.

MS Relapses

MS relapses were one of the efficacy endpoints in the A2201 and A2304 studies; hence MS relapses were exempt from SAE reporting although they may have met the SAE definition on the basis that they are considered medically significant and are frequently associated with hospitalization. Investigators reported these events on the MS relapse electronic Case Report Form instead of the SAE form. However, if, in the judgment of the investigator, a MS relapse was unusually severe or medically unexpected and warranted specific notification, then an SAE form was completed and submitted.

> *Reviewer Comment: The inclusion of MS relapses as a SAE creates potential difficulties in interpreting findings in the safety analysis because patients with MS will experience relapses of varying severity regardless of treatment. The compromise of allowing the investigators to include them base on clinical judgment if the relapse represented an unusual event appears appropriate. One specific concern for a safety database of a S1P modulator is that patients withdrawing from the S1P modulator fingolimod can experience severe exacerbations of disability and lesion number and therefore capturing these events for this S1P modulator is potentially meaningful.*

Disability Progression

Disability progression was one of the efficacy endpoints in the A2304 study; hence it was exempt from SAE reporting although it could meet the SAE definition "results in persistent or significant disability/incapacity." However, if, in the judgment of the investigator the disability progression was unusually severe or medically unexpected and warranted specific notification, then investigators completed and submitted an SAE form.

8.3.3. Routine Clinical Tests

Hematology

In the key trials included in this application, blood samples were collected at scheduled visits and the parameters assessed included: red blood cell count, total and differential white blood cell count (basophils, eosinophils, lymphocytes, monocytes, neutrophils, CD4 and CD8 subtype), platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red blood cell morphology.

Assessment of clinical laboratory parameters in Study A2304 took place at screening, baseline, Day 28 and Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and Month 36 post-baseline, end of treatment, end of study, and follow-up.

The reference ranges defining normal values for these laboratory studies varied to a small degree from site-to-site. The applicant would accept a value's designation as "abnormal" based on local laboratory standards and did not appear to realign all obtained values against a single reference standard.

For Study A2201 clinical laboratory parameters were assessed at screening, baseline, Day 7 and Months 1, 2, 3, 4 and 5 post-baselines, end of treatment, and follow-up. In Study A2201E1 clinical laboratory parameters were assessed at screening, baseline, Day 7 and Months 1, 3, 6, 9, 12, 15, 18, 21, 24 post-baseline and every 6 months until Month 57, end of study, and follow-up.

Siponimod reduces serum lymphocyte counts. To maintain blinding of investigators and patients, after the baseline visit, only the absolute counts for eosinophils, basophils and monocytes were communicated to sites by the central laboratory. The absolute total white blood cell count (WBC), neutrophil and lymphocyte counts were measured at each visit by the central laboratory and were blinded from the applicant and the investigator and were communicated to the site only in case of a notable abnormality which could necessitate a dose change. In the extension phase, these values were reported back to the center only after the patient's first visit to ensure final assessments of the blinded core phase were obtained while patient and investigators were blind to the lymphocyte counts.

Chemistry

Blood samples were collected at scheduled visits and the parameters assessed included: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, P), random glucose, albumin, alkaline phosphatase, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), amylase, total bilirubin, conjugated bilirubin, total cholesterol, C-reactive protein, triglycerides, high density lipoprotein (HDL) and low-density lipoprotein (LDL).

In study A2304, twelve-hour fasted blood samples were obtained for lipid profiling at several core phase visits. No fasted samples are required during the extension phase.

Urinalysis
Urine was collected at scheduled visits and the parameters assessed included: leukocytes, bilirubin, blood, glucose, ketones, pH, protein and urobilinogen.

Submission Specific Tests
Siponimod is sufficiently like fingolimod that it was expected that safety issues such as cardiac rhythm disturbances, altered pulmonary function testing, increased risk of infections, macular edema, and skin malignancies noted in the fingolimod development program could be evident with siponimod administration. Therefore, the protocols for the siponimod trials stipulated required testing for infections, skin cancer, cardiac monitoring, ophthalmology, and pulmonary function.

Vital Signs and Cardiac Monitoring
In the A2304 and A2201 core and extension studies, investigators obtained vital signs that included sitting pulse rate, sitting systolic and diastolic blood pressure, and oral temperature. Height and weight were recorded at the screening visit.

Electrocardiograms were performed at the following visits per protocol for the trials in the MS development program:

Study A2304 and A2304EP: Screening and pre-dose on Day 1, Day 7, Month 3, Month 12, and every 12 months thereafter during the Core Part and the Extension Part, and as needed if study drug was interrupted.

Study A2201: Screening, pre-dose and post-dose on Day 1 and at Month 3 for Period 1 patients; pre-dose and post-dose on Day 1, Day 2, and Day 7 for Period 2 patients, and as needed if study drug was interrupted.

Study A2201E1: Screening, pre-dose and post-dose on Day 1, Day 2, Day 7, Month 24, and every 12 months thereafter, and as needed if study drug was interrupted.

Normal Vital Sign Ranges
The following were notable vital sign ranges used to identify abnormal values in the controlled trials in MS.

Heart Rate:
- Pulse (beats/min) >120 BPM or < 50 BPM

Blood Pressure:
- Systolic BP (mmHg) ≥ 160 mmHg or ≤ 90 mmHg

- Diastolic BP (mmHg) ≥ 100 mmHg or ≤ 50 mmHg

Body Temperature:

- Temperature (°C) >38.3 °C/ 101°F

Body weight (kg)

- ± 7% from baseline weight

A2304 Cardiac Monitoring

Given concerns about safety issues regarding bradycardia and cardiac conduction block associated with fingolimod that were noted in previous trials with siponimod, the Study A2304 protocol allowed the first half of the overall patient population to undergo extensive cardiac monitoring in order to collect comprehensive treatment initiation data in patients with previously normal cardiovascular status. In the second half of the study, patients with normal cardiovascular status had a less rigorous assessment.

Patients who had any of the following abnormalities had to undergo expanded cardiovascular monitoring to enter Study A2304.

1. Heart rate < 55 BPM at screening

2. Cardiac conduction disorders such as incomplete left bundle branch block or second-degree AV block Mobitz type I (Mobitz I) (either history or observed at screening)

3. Minor ECG findings at screening PR interval: >200 msec and ≤230 msec; QRS duration ≥120 msec; QTcF >430 msec ≤450 msec (males); QTcF >450 msec ≤470 msec (females)

4. History of or current cardiac disease such as heart failure NYHA class I, history of myocardial infarction prior to enrollment.

5. Patients receiving treatment with beta-blockers

6. Any other condition which, in the opinion of the investigator, has a potential for AV conduction suppression and/or other risk factors that may require expanded cardiac monitoring

7. Patients diagnosed with right bundle branch block, either at the Screening visit for entry in the CP of the study or during the conduct of the study, should enter the EP under the expanded cardiac monitoring subpopulation with all required cardiac monitoring.

The "expanded cardiac monitoring" process was as follows:

On Days 1 and 7 of the initiation of therapy, after the patient has been sitting for five minutes, with their back supported and both feet placed on the floor, systolic and diastolic blood pressure were measured three times using an automated validated device (manual sphygmomanometer was used if automated device is not available at the study site). The repeat sitting measurements of blood pressure and pulse were made at one or two-minute intervals.

Patients had pre-dose electrocardiogram assessments on Days 1 and 7. Additionally, patients received mobile heart rate monitoring with telemetry, or a device with similar (or better) registration capability, for continuous registration of heart rate and cardiac events, minimally 6 hours post-dose, for expanded cardiac monitoring patients during their outpatient phase of the siponimod titration period. If mobile cardiac telemetry was not possible, patients were required to wear a Holter on the day of screening, Day 1 and Day 4 for 24 hours and for 6 hours on Day 7. The patients who wore a Holter had monitoring start 30 minutes prior to siponimod intake on each day of monitoring.

The Data Monitoring Committee subsequently confirmed that, based on the available treatment initiation cardiac monitoring results from the expanded cardiac monitoring patients, the 6-hour first dose cardiac monitoring (on Days 1 and 7) in subjects with normal cardiovascular status could be discontinued. The DMC supported continued data capture with mobile cardiac telemetry and Holter monitoring in all patients to facilitate the assessment of any relevant events occurring during treatment initiation.

> *Reviewer Comment: The Division agreed to waiving the 6-hour cardiac monitoring on Days 1 and 7 in subjects with normal cardiovascular status based on the DMC recommendation and data submitted by the applicant as part of a protocol amendment to Study A2304. The applicant's proposed labeling reflects the absence of a need for monitoring normal cardiovascular status patients.*

Pulmonary Monitoring

All patients underwent Pulmonary Function Tests (PFTs) according to the schedule of core study assessments in Study A2304.

Patients with mild or moderate asthma, and patients with other mild or moderate pulmonary disease (such as Chronic Obstructive Pulmonary Disease, COPD) were included in Study A2304 but had to conduct additional pulmonary assessments at certain visits throughout the study.

Ophthalmology Monitoring

All patients had ophthalmology examinations and optical coherence tomography evaluations

according to the schedule of core study assessments in Study A2304.

Patients with a history of uveitis, active uveitis, a history of macular edema or diabetes mellitus (well controlled and without known organ complications) were included in Study A2304 but had to undergo additional ophthalmology and OCT assessments at certain visits throughout the study.

Dermatology
Dermatologists completed dermatological examinations throughout Study A2304 and A2201 to monitor for the potential development of new skin cancers during the study.

Serology
Serology testing was conducted at screening only to determine the patient's immune status and eligibility for inclusion in the study with respect to several viruses.

A positive result for HIV antibodies or for any of the following serological markers for hepatitis A, B, C, and E indicating acute or chronic infection was an exclusion criterion:

- anti-hepatitis A virus IgM
- hepatitis B surface antigen and anti-hepatitis B core antigen IgM
- anti-hepatitis C virus IgG or IgM
- anti-hepatitis E virus IgM (positive IgG and/or IgM: do HEV-RNA PCR: if negative, patient can be included).

Anti-VZV IgG was measured. Patients who are negative for varicella-zoster virus IgG antibodies at screening were excluded from the study but were eligible to be re-screened after successful vaccination.

CYP2C9 Testing
CYP2C9 is the major metabolizing enzyme for siponimod. CYP2C9 haplotype testing was conducted once at the screening visits for Studies A2304 and 2201 to determine the patient's eligibility for inclusion into the study. The A2304 study excluded patients with the *3/*3 genotype because of their poor metabolism of siponimod.

8.4. Safety Results

8.4.1. Deaths

The applicant reported 20 deaths in patients exposed to either placebo or siponimod, and these deaths occurred exclusively in the patients with MS treated in Studies A2201, A2201E1, A2304, and 2304 Extension Phase.

Of these 20 deaths, 16 (0.6%, 16/2760 exposed to at least one dose) occurred in patients exposed to siponimod, and 6 deaths occurred in patients who were considered "on treatment" with siponimod at the time of their deaths.

During the controlled phase of Study A2304, the mortality rates were approximately balanced in number but not frequency with 5 deaths (5/1099, 0.5%) in the siponimod arm and 4 deaths (4/546, 0.7%) in the placebo treatment arm in the controlled portion of the trial conducted in patients with SPMS.

> *Reviewer Comment: A screened patient in Study A2304* (b) (6) *died from unknown causes during the screening period. The patent was not exposed to study drug and details regarding the cause and circumstances of the death were not available. This patient is not included in calculation of mortality nor the summary table because they never received any study treatment, and therefore the cause of death is not related to either siponimod or placebo. The case is included for completeness at the end of this section.*

The 120-day safety update for Study A2304 added 9 additional deaths in siponimod-treated patients to the prior reported deaths, bringing the combined total number of deaths in siponimod-exposed patients from Study A2304 and its Extension Phase to 14 patients.

There were two deaths reported in studies of patients with relapsing multiple sclerosis. There was one death reported in a patient exposed to siponimod during the core phase of Study A2201, and there was one death reported in Study A2201E.

Thus, there were sixteen deaths total among patients with MS exposed to siponimod in the siponimod clinical development program up to the 120-day update cut-off date (December 31, 2017). Thus, for all trials conducted in patients with MS who received at least one siponimod dose, 0.92% (16/1737) of siponimod-exposed patients died. The overall mortality rate in the MS patient population was 0.346/100 patient-years (16/4619.84 PY).

There were no reported deaths in the healthy volunteer, dermatomyositis, or polymyositis studies.

Table 8: Causes of Death in Patients Exposed to Siponimod, All Studies

Study	Patient ID	Preferred Term Cause of Death	Study Day Relative to Start Date of Study Medication	Study Date Relative to Last Date on Study Medication	Causality of Siponimod to Cause of Death per Investigator
A2201	(b) (6)	Cardiac arrest/Myocardial Infarction	79	27	Yes
A2201E1		Craniocerebral Injury	1859	17*	No
A2304		Completed Suicide	257	2*	No
A2304		Urosepsis	347	72	No
A2304		Septic Shock	716	5*	Yes
A2304		Malignant Melanoma	278	31	Yes
A2304		Lung Adenocarcinoma	482	153	Yes
A2304 (placebo)		Hemorrhagic Stroke	151	15	No
A2304 (placebo)		Lung Adenocarcinoma	785	50	No
A2304 (placebo)		Unknown	825	232	No
A2304 (placebo)		Gastric Cancer	672	204	No
A2304 Extension		Amyotrophic Lateral Sclerosis	1155	105	No
A2304 Extension		Respiratory Paralysis	865	267	No
A2304 Extension		Testicular Cancer ("Unknown")	747	93	No
A2304 Extension		Sudden Cardiac Death ("Unknown")	1035	0*	No
A2304 Extension		Pneumonia	1352	12*	Yes

Study	Patient ID	Preferred Term Cause of Death	Study Day Relative to Start Date of Study Medication	Study Date Relative to Last Date on Study Medication	Causality of Siponimod to Cause of Death per Investigator
A2304 Extension	(b) (6)	Pulmonary Embolism	1405	173	No
A2304 Extension		Pulmonary Embolism	1197	100	No
A2304 Extension		Myocardial Infarction	1768	1*	No
A2304 Extension		Cardiorespiratory Arrest	1563	58	No

Sources: SCS Section 2.1.2, 120-day Update SCS Listing 2.1-8.3, Information Request dated December 20, 2018

*Indicates patient on siponimod treatment, defined as enrolled in trial and receiving active treatment as of last visit in study

With so few events, it is difficult to support definitive conclusions regarding mortality risk associated with siponimod treatment. However, while the causes of death in the entire MS development program were largely heterogeneous, there were some deaths with broadly similar origins such infectious, neoplastic, and cardiac causes. Cases with broad overlap are discussed as follows:

Infections/Sepsis

There were more deaths due to infection (pneumonia) or overwhelming infection/sepsis (urosepsis, septic shock) associated with siponimod treatment (n=3) in comparison to placebo treatment (n=0) in Study 2304. Sepsis/overwhelming infection is a potential risk of S1P modulators because S1P modulator therapies reduce the number of circulating lymphocytes. The reported cases of sepsis have relevant contributory factors discussed with the narratives that preclude rendering any confirmation of a definitive higher risk of sepsis associated with siponimod.

Acinetobacter Pneumonia

Patient (b) (6) a 48-year-old man who had first multiple sclerosis (MS) symptoms in (b) (6), was diagnosed with MS in (b) (6). he was diagnosed with secondary progressive multiple sclerosis in (b) (6) The patient did not experience any relapse in the 12 to 24 months prior to enrolling in the study; his most recent MS relapse occurred in (b) (6). His prior disease-modifying treatments for MS included glatiramer acetate (discontinued in (b) (6)) and azathioprine (discontinued in (b) (6)); both therapies were discontinued due to adverse events.

The patient's baseline EDSS score on (b) (6) was 6.5.

The patient's medical history included depression, nephrolithiasis, melanocytic nevus, onychomycosis, and skin hyperpigmentation. Concomitant medications included mirtazapine for depression, Ganoderma lucidum for multiple sclerosis, methylprednisolone for multiple sclerosis relapse, ciclopirox olamine and urea for onychomycosis, lactulose for constipation, pantoprazole sodium sesquihydrate and lansoprazole for gastric protection, fampridine for walking difficulties due to MS, fosfomycin trometamol, ciprofloxacin and nitrofurantoin for urinary tract infection, a calcium supplement, baclofen and amantadine for spasticity related to MS, and pregabalin for neuropathic pain.

The patient received the first dose of Core study medication (siponimod) on Day 1 (b) (6) and received the last dose of Core study medication on Day 757 (b) (6).

The patient entered the Extension part of the study and received the first dose of study medication on Extension Day 1 (b) (6).

On Extension Day 405 (b) (6), the patient was diagnosed with an initial episode of pneumonia which resulted in hospitalization. Treatment included moxifloxacin, piperacillin-tazobactam, ipratropium bromide-salbutamol sulfate, and budesonide. The study medication was temporarily interrupted due to the hospitalization for pneumonia from Extension Day 405 (b) (6) and was restarted on Extension Day 407 (b) (6). The patient received physical/physiotherapy (from (b) (6)) for pneumonia. The initial pneumonia episode was considered resolved on Extension Day 412 (b) (6), and the patient was discharged from the hospital on an unspecified date.

On Extension Day 526 (b) (6), the patient was again hospitalized with fever, cough and sputum and his chest examination showed bilateral rhonchi. The patient's CT scan of thorax showed pneumonic infiltration in left lung and was diagnosed with a recurrence of pneumonia. The patient's sputum culture revealed Acinetobacter species (100 CFU/mL) resistant to antibiotics (imipenem, meropenem, amikacin, gentamycin, ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole). Treatment included metamizole sodium, cefazolin sodium, ranitidine, salbutamol, furosemide, and theophylline.

Treatment with the study medication was permanently discontinued due to the recurrence of pneumonia, and the patient received the last dose on Extension Day 528 (b) (6). On (b) (6), 12 days after the last dose of the study medication, the patient's condition worsened, and the patient died due to pneumonia. An autopsy was not performed.

Of note, the other non-serious AEs included urinary tract infection-first episode (b) (6)

(b) (6), heart rate decreased (b) (6), upper respiratory tract infection (b) (6), urinary tract infection-second episode (b) (6) constipation-first episode (related to MS) and dysuria (both started on (b) (6), influenza (b) (6) onychomycosis, skin hyperpigmentation (back and face), melanocytic nevus, (on all the body, all started on (b) (6)), constipation-second episode (related to MS, (b) (6)), and cataract sub capsular (right eye) and decubitus ulcer (both started on (b) (6) all the events were ongoing at time of patient's death.

The Investigator suspected a relationship between the initial and recurrence of pneumonia and the study medication. The Investigator's reported that lack of care by the family was other possible contributory factor for the death of the patient due to pneumonia (second-episode).

> *Reviewer Comment: Infections occur at a higher rate in patients treated with siponimod presumably because of reduced circulating lymphocytes. Death due to pneumonia is plausibly associated with siponimod therapy. Increased risk of infection and related complications will be noted on siponimod labeling. Infections associated with siponimod are discussed in Sections 8.4.5 and 8.5.*

Urosepsis

Patient (b) (6) was a 45-year-old woman with multiple sclerosis (MS) symptoms in 1991, was diagnosed with MS in (b) (6). She was diagnosed with secondary progressive multiple sclerosis in (b) (6). The patient experienced more than one relapse; the most recent was in (b) (6) Prior disease-modifying treatment for MS included interferon beta-1a (discontinued in (b) (6)), interferon beta-1b (discontinued in (b) (6)), glatiramer acetate (discontinued in (b) (6)), dimethyl fumarate (discontinued in (b) (6)), and natalizumab (discontinued in (b) (6)). All these therapies had been discontinued due to lack of efficacy except natalizumab, which was discontinued in (b) (6) due to unspecified reasons. The patient's medical history included hypothyroidism, fatigue, optic neuritis (b) (6), cholecystectomy (b) (6), skin cancer (b) (6), gait disturbance, depression, anxiety, bladder catheterization, cognitive disorder, muscle spasticity, urinary tract infection, and dry eye. He had a smoking history (5 pack-years). Concomitant medications included alprazolam and buspirone for anxiety, venlafaxine for depression secondary to MS, povidone-benzalconium chloride for dry eyes, imiquimod for superficial basal cell carcinoma, amantadine for fatigue secondary to MS, colecalciferol as nutritional supplement, fampridine for gait issues secondary to MS, diazepam and lorazepam for anxiety prophylaxis, atropine as excessive secretions prophylaxis, nicotine patch for smoking cessation, melatonin, and trazodone for insomnia, calcium compounds, paracetamol, morphine sulfate, and ketorolac tromethamine for pain prophylaxis, bisacodyl and polyethylene glycol for constipation, enoxaparin sodium for deep vein thrombosis prophylaxis and restrictive mobility, influenza vaccine for flu prophylaxis, baclofen for spasticity secondary to MS, donepezil for cognitive decline secondary to MS, and levothyroxine for hypothyroidism. The patient also

underwent oxygen supplementation for hypoxia.

During the screening period, the patient underwent a skin biopsy (shave biopsy), which revealed superficial basal cell carcinoma. No treatment was reported, and no action was taken with the study medication due to the event (basal cell carcinoma). The event (basal cell carcinoma) was considered resolved on the same day.

The patient's baseline EDSS score on (b) (6) was 6.5. The patient received the first dose of the study medication on Day 1 (b) (6) On Day 108, the patient presented with generalized weakness (asthenia) and was diagnosed with a urinary tract infection (confirmed by urine culture which showed mixed flora >100000 colonies/mL on (b) (6)), which resulted in hospitalization. The patient was treated with Vaccinium macrocarpon, ciprofloxacin and cranberry extract-vitamin C. No action was taken with the study medication due to the events (asthenia, urinary tract infection- first episode). The event (urinary tract infection-first episode) was considered resolved with sequelae on Day 113 (b) (6) and the patient was discharged from the hospital. The patient was treated with physical therapy for asthenia.

On Day 251, the patient had another episode of urinary tract infection (non-serious; second episode) and was treated with ciprofloxacin. The event (urinary tract infection – second episode) was considered resolved on Day 257. On Day 273, the patient was diagnosed with another episode of urinary tract infection (non-serious; third episode) for which she was again treated with ciprofloxacin. The patient received the last dose of the study medication on Day 275 and discontinued therapy due to disease progression and perceived lack of efficacy. The event (urinary tract infection – third episode) was considered resolved on Day 279. The patient received intravenous rituximab (after discontinuation of study medication) for MS disease progression.

On (b) (6), 50 days after the last dose of the study medication, the patient was diagnosed with fourth episode (second serious episode) of urinary tract infection, which resulted in hospitalization. On the same day (b) (6), WBC count was 15.8, RBC was 8/high power field, urine WBC was 146 (units and reference range not reported) and urine culture showed greater than 100000 colonies/mL of pseudomonas. Treatment included ciprofloxacin. The event (urinary tract infection-second episode) was improving and she was discharged from the hospital on (b) (6) with a WBC of 10.4 (units and reference range not reported).

On (b) (6), 56 days after the last dose of the study medication, the patient was diagnosed with urosepsis. No treatment was reported for the event (urosepsis). On (b) (6), 72 days after the last dose of the study medication, the patient died due to urosepsis. An autopsy was not performed.

Of note, the other non-serious AEs during the study included worsening of cognitive function

(b) (6), excessive premenopausal bleeding (b) (6) confusion, mental status change (both from (b) (6)), constipation (b) (6) and edema of ankles, dysphagia, hair loss, dyspnea, left sided visual field cut, hypoxia (from (b) (6)). All these events were ongoing at the time of death.

The Investigator did not suspect a relationship between the events (basal cell carcinoma, asthenia, urinary tract infection-two episodes, and urosepsis) and the study medication. The possible contributory factors for both serious episodes of urinary tract infection-included supra pubic catheter and disease progression; and for general weakness a possible contributory factor was MS disease progression.

Septic Shock (Metastatic Adenocarcinoma of the Colon)
Patient (b) (6) was a 44-year-old woman who had initial MS symptoms in (b) (6), was and was diagnosed with MS in (b) (6); She received a diagnosis of secondary progressive multiple sclerosis in (b) (6). The patient experienced more than one relapse; the most recent was in (b) (6). Her prior disease-modifying treatments for MS included interferon beta-1a (which was discontinued in (b) (6) due to lack of efficacy). The patient's baseline EDSS score was 5.5. The patient's medical history included asthma, psoriasis, irritable bowel syndrome with spastic colon, and a history of fecal occult blood positive. The patient had family history of colon cancer in 2 paternal uncles (40 years and 75 years old). Concomitant medication included amantadine for fatigue due to MS.

The patient received the first dose of study medication on Day 1. The patient received her last dose of double-blind study medication (siponimod) on Day 493 and switched to open label treatment on Day 500. The patient reported no non-serious AEs during the study.

On Day 709, the patient presented with severe persistent constipation and was hospitalized. The patient was given Macrogol, however it was unsuccessful. On Day 713, the patient underwent an abdominal CT, which showed a mass in the colon and several hepatic lesions suggestive of malignant tumor. The results of CT scan were compatible with the intestinal obstruction secondary to thickening of the sigmoid colon. In addition, focal liver lesions compatible with metastases were found. On Day 714, the patient underwent a colonoscopy confirming sigma stenosis suggestive of malignant tumor. The patient thusly was diagnosed with stage 4 colon cancer. Tissue samples were taken, and stenting was performed. On the same day, the patient's biopsy showed fragments of large intestine mucosa with infiltration by a low-grade enteroid adenocarcinoma. During admission, the patient developed respiratory symptoms. On the same day (Day 714), the patient's thoracic X-ray showed bilateral aspiration pneumonia, and the patient was diagnosed with septic shock in context of bilateral aspiration pneumonia and confirmed stenosing colon cancer stage IV. Treatment included norepinephrine, digoxin, linezolid, piperacillin-tazobactam, and neostigmine. Treatment with the study medication was permanently discontinued due these events (colon cancer stage IV,

pneumonia aspiration, septic shock), and the patient received the last dose of open label study medication on Day 711.

On Day 716, the patient died due to the events (colon cancer stage IV, pneumonia aspiration, septic shock). An autopsy was not performed.

The Investigator suspected a relationship between the events (colon cancer stage 4, pneumonia aspiration, septic shock) and the study medication.

> *Reviewer Comment: Siponimod, like the S1P modulator fingolimod, reduces serum white blood cell counts and reduces immune competence. Therefore, siponimod therapy will be consequentially associated with a higher risk of infection. A case of urosepsis in a patient with recent recurrence of a urinary tract infections associated with self-catheterization suggests possible antibiotic resistant bacteria which would complicate treatment. A more significant concern is the use of rituximab on the same day as the discontinuation of siponimod therapy. It is likely that rituximab had achieved its maximum effects on immune suppression at 72 days, but it highly unlikely that siponimod's effects would be present at 72 days after discontinuation. The administration of rituximab on the day siponimod therapy ended raises the possibility that the lymphocyte recovery expected in this patient did not occur or was blunted by rituximab and fostered conditions favorable for urosepsis due to a partially treated infection acquired on Day 50. The second case, septic shock in the setting of metastatic colon cancer is equally difficult to assign an association with study therapy. The patient in the second case discontinued siponimod 5 days before death, an inadequate duration in which to expect significant lymphocyte count recovery. The advanced nature of the colon cancer would compromise all aspects of care and foster conditions favorable to sepsis. It is possible siponimod reduced immune surveillance and had a role in cancer progression, but there is a positive family history and history of irritable bowel which are independent risk factors for colon cancer. Therefore, while an association with siponimod cannot be ruled out in either case, there are significant historical and medical factors in both cases that could predispose to sepsis and would provide risk of mortality independent of siponimod therapy.*

Pulmonary Embolism

There were two deaths due to pulmonary embolism with few available details.

A 58-year-old woman with pulmonary embolism as cause of death (b) (6) had a listed contributing cause of death of "squamous cell carcinoma of the vagina." Her last dose of siponimod had been 173 days prior to the date of her death.

Patient (b) (6), a 57-year-old female, discontinued from the study (last dose of siponimod was on (b) (6)) and later died on (b) (6), due to a pulmonary embolism,

100 days after last dose of siponimod.

> *Reviewer Comment: These two cases had discontinued siponimod therapy 173 and 100 days, respectively, before their deaths and have few reported details (one case was noted in the applicant's internal safety database without any study report on file) making it difficult to establish a clear primary relationship between siponimod and pulmonary embolism. The presence of a diagnosed malignancy is itself a risk factor for hypercoagulable events such as pulmonary emboli and cannot be dismissed as a possible cause. Pulmonary embolism is discussed along with other serious thromboembolic adverse events in Sections 8.5.*

Myocardial Infarction and Sudden Cardiac Death

There were two fatal cases of myocardial infarction, and one case of a reported abrupt fatal cardiac event.

Patient (b) (6) was a 43-year-old Caucasian male patient with relapsing remitting multiple sclerosis was enrolled in study CBAF312A2201. At the time of screening, the patient was an active smoker and had been smoking an average of 22 cigarettes per day for 30 years. There was a family history of coronary artery disease. On Day 29 of 1.25 mg siponimod treatment, the patient experienced severe retrosternal chest pain. The event (chest pain) persisted leading to permanent discontinuation of the study medication on Day 52. The patient was found dead in his apartment on Day 79, 27 days after the study medication was discontinued. The investigator mentioned that the patient was last seen by study personnel on Day 57; however, he did not wait for the treating physician to evaluate him. The investigator indicated that cardiac arrest could be a possible cause of death. The coroner's report concluded the reason for death as acute myocardial insufficiency. The patient's coronary arteries had stenosis of 75% and 85% in the circumflex and anterior descending artery respectively. The patient's brain imaging showed anoxic ischemic encephalopathy and MS plaques. The toxicology screen was negative. The investigator's conclusion was "probably exacerbation by study drug of underlying premature coronary artery disease leading to angina and subsequent death by myocardial infraction and arrest as the angina symptoms began while the patient was on study medication and is known to cause potential arteriolar vasoconstriction." The applicant's overall medical conclusion was that the events may be explained by the patient's coronary artery disease. Smoking and family history were identified risk factors for myocardial infarction. A causal relationship with study drug cannot be excluded for the event retrosternal chest pain that occurred when the patient was on study drug. However, study drug as an acute cause of death was deemed not plausible as siponimod's elimination half-life is about 36 hours and the patient had discontinued treatment 27 days prior to death.

Myocardial Infarction with Ventricular Rupture and Tamponade

Patient (b) (6) a 61-year-old female, died while in the study due to myocardial

infarction on (b) (6) (autopsy findings included myocardial infarction with ventricle rupture and heart tamponade)

Patient (b) (6), a 51-year-old man, died of "sudden cardiac death" on Day 1035 of siponimod treatment. An autopsy was not performed.

> *Reviewer Comment: Siponimod was not an acute cause of myocardial infarction for Patient (b) (6) because the patient's death occurred weeks after discontinuing siponimod therapy. The patient's history of tobacco use, and the patient's family history of coronary artery disease, are significant risk factors for myocardial infarction independent of treatment. A potential contribution of siponimod to the patient's cardiovascular disease cannot be ruled out, however. There is too little reported data available regarding the other two cases to generate a plausible causal attribution.*

Malignancies

There were four patients noted to have deaths attributable to malignancies. Two have been discussed above, with diagnoses of metastatic colon cancer and squamous cell carcinoma of the vagina.

Gastrointestinal Melanoma

Patient (b) (6) was a 51-year-old woman who had her first MS symptoms in (b) (6), was diagnosed with MS in (b) (6), and converted to secondary progressive multiple sclerosis in (b) (6). The patient experienced more than one relapse; the most recent relapse occurred in (b) (6) Prior disease-modifying treatments for MS included interferon beta-1a, which was discontinued in (b) (6) due to unspecified reasons.

At screening (b) (6), the patient's dermatological examinations revealed benign lesions, which specified melanocytic nevus, seborrheic keratosis, and solar lentigines. The patient's baseline EDSS score on (b) (6) was 5.0.

The patient's medical history included history of caesarean section (b) (6), appendectomy (b) (6), trigeminal neuralgia, solar lentigo, fibrous histiocytoma, and melanocytic nevus (excised in (b) (6). Concomitant medications included paracetamol for headache, clonixinlysinate and pregabalin for trigeminal neuralgia.

The patient received the first dose of study medication on Day 1.

On an unspecified date in (b) (6) the patient had an itching in the anus and her general practitioner identified an excrescent mass, which was initially attributed to be an external hemorrhoid. On Day 120, the patient was diagnosed with malignant melanoma of the anus (later confirmed as metastatic from a gastrointestinal melanoma). On Day 217 (b) (6), an

excisional biopsy of the rectal mass confirmed a malignant melanoma (non-vascular and non-lymphatic), affecting the resection margins. Staging of cancer was reported as Stage IV. A total body CT-scan revealed the presence of multiple metastases in lungs and liver. Immunochemistry markers showed positive HnB-45, melan-A, negative CK7, CK 20, CK5/6 and CD45 with proliferative index Ki > 60%. The results from B-RAF mutation were wild type. Treatment with the study medication was permanently discontinued due to this event (gastrointestinal melanoma) and received the last dose of study medication on Day 248 (b) (6) and on the same day she attended the End of study visit. On Day 259, first line chemotherapy with decarbazine was initiated. The patient underwent bladder catheterization on Day 261 due to malignant melanoma. On Day 277, the patient was hospitalized to emergency department due to general progressive systemic deterioration; her blood pressure was 89/36 mmHg; ECG showed sinus rhythm, 106 BPM; normal atrioventricular and intraventricular conduction; chest X-ray showed multiple nodullary lesions in both lungs; non-specific abdominal X-ray. The patient's condition deteriorated, and she died on Day 278. An autopsy was not performed.

Of note, the other non-serious AEs during the study included trigeminal neuralgia (b) (6), trigeminal neuralgia-second episode (b) (6) and a hematoma (b) (6)

The Investigator suspected a relationship between the event (gastrointestinal melanoma) and study medication. The Investigator provided a rationale for causality assessment as skin cancer and melanoma was previously described in S1P1 antagonist therapy.

Metastatic Lung Adenocarcinoma
Patient (b) (6) was a 60-year-old woman. Her initial MS symptoms occurred in (b) (6) She was diagnosed with MS in (b) (6) and converted to a secondary progressive multiple sclerosis diagnosis in (b) (6) The patient experienced more than one relapse, and her most recent relapse was on in (b) (6). Prior disease modifying treatments for MS included interferon beta-1a, which was discontinued in (b) (6) methotrexate which was discontinued in (b) (6), and interferon beta-1b which was discontinued in (b) (6). The patient's baseline EDSS score on (b) (6) was 6.0.

The patient's medical history included peripheral edema, skin lesion (benign), hypertension, hypothyroidism, muscle spasticity (all ongoing), and smoking (25 pack-years, stopped in (b) (6)). Concomitant medications included paracetamol, fentanyl, valdecoxib, methylprednisolone for pain, calcium, and vitamin D for protection of bones, pantoprazole sodium sesquihydrate for gastric prophylaxis, calcium carbonate-colecalciferol for dietary supplementation, enalapril maleate-lercanidipine for arterial hypertension, furosemide for leg edema, enoxaparin sodium for deep vein thrombosis (DVT) prophylaxis, levothyroxine for thyroid disorder, fortex for constipation, ciprofloxacin for urinary infection, and baclofen for spasticity.

The patient received her first dose of the study medication on Day 1. On an unspecified date in (b) (6), the patient presented with bone pain in lumbar and pelvic region causing insomnia. She also complained of slight irritating cough without expectoration. She had weight loss of 2 kg over the previous 3 weeks with normal appetite. There was no fever or any other symptoms. Clinical examination showed hypoventilation of the base of right lung. On an unspecified date, the patient's laboratory details showed normocytic normochromic anemia with hemoglobin at 9.9 (units and reference range not reported), lymphocytopenia at 648/mm3 with C-reactive protein at 30.5 mg/deciliter (RR not reported), and platelets at 443000 (units and reference range not reported). On Day 250, the patient was diagnosed with lung adenocarcinoma. On Day 318 (b) (6), the patient's scintigraphy showed multiple bones metastasis. The diagnosis of metastatic lung adenocarcinoma was suspected. On Day 325, a CT scan showed pulmonary lesions. Bronchial adenocarcinoma with plurifocal metastatic invasion of the bones was diagnosed. Treatment with the study medication was permanently discontinued due to this event and the patient received the last dose on Day 330. On Day 344, the patient was hospitalized (elective) for study of metastasis with a view for pain management and treatment of pulmonary neoplasia. On Day 246, a CT scan of the pelvis revealed multiple osteolytic lesions associated with pathological fracture at the uppermost part of the right iliac crest. On (b) (6), a CT scan of lumbar and thoracic spine showed presence of multiple osteolytic and bone-condensing lesions on almost all the vertebrae. On Day 251, the patient's pain decreased with analgesic treatment and radiotherapy. It was reported that the bone pain was due to secondary bone-condensing and osteolytic lesions of the spine and pelvis, complicated by a pathological fracture of the right iliac wing. On Day 259, the patient was discharged from the hospital. Discharge medications included furosemide, enalapril maleate-lercanidipine, L-thyroxin, baclofen, enoxaparin, paracetamol tilidine, calcium carbonate-vitamin D, methylprednisolone after radiotherapy courses, pantoprazole and Macrogol.

The patient withdrew consent and attended the End of Study visit. On Day 374, the patient died due to adenocarcinoma of the lung with bone metastases. An autopsy was not performed.

Of note, the other non-serious AEs during the study included urinary tract infection (b) (6) depression (b) (6) ongoing at the time of death) and constipation (b) (6)).

The Investigator suspected a relationship between the event (lung adenocarcinoma metastatic) and the study medication. The Investigator provided a rationale for causality assessment: immuno-modulatory effects of study medication which impacted the immune-surveillance.

Unknown (Testicular Cancer)

Patient (b) (6) was a 52-year-old man who had his first multiple sclerosis symptoms in (b) (6) He was diagnosed with MS in (b) (6); he converted to secondary progressive multiple sclerosis on (b) (6) The patient experienced one relapse;

the most recent was on (b) (6). No prior disease-modifying treatment for MS was reported for this patient. The patient's baseline EDSS score on (b) (6) was 2.5. The patient received study drug (placebo) and later switched to open label BAF 2 mg during the core study.

The patient's medical history included nephroptosis, pyelonephritis chronic, varicose veins. The patient received the first dose of study medication on (b) (6)

On Extension Day 260 (b) (6), the patient experienced pain with increase in size of left testicle and was diagnosed with cancer of the left testicle T3N0M0, which resulted in hospitalization. On Extension Day 262 (b) (6), the patient underwent the procedure of orchidectomy. On the next day (b) (6) the patient's histological examination showed dysgerminoma with presence of cytotrophoblast cells, invasion of tunica albuginea and presence of tumor emboli in the lumen of vessels of small caliber. It was reported that, the appendage had no elements of tumor. Treatment included diclofenac sodium. Treatment with the study medication was permanently discontinued due the event (testis cancer), and the patient received the last dose on Extension Day 276 (b) (6). On the same day (b) (6)), the patient was discharged from the hospital.

The patient was discontinued from the study due to testis cancer and attended the End of Study visit on (b) (6).

On (b) (6), 105 days after end of study visit, the patient died due to an unknown reason. The Investigator suspected a relationship between the event (testis cancer) and the study medication.

> *Reviewer Comment: There is mechanistically plausible rationale for an association between S1P modulators and increased risk of any malignancy due to reduced numbers of circulating lymphocytes providing immune surveillance for malignant potential cells. Death due to lung cancer in a patient with a chronic smoking history is unlikely to be primarily due to study treatment, but one cannot exclude the possibility of a reduction in the circulating lymphocyte pool yielding an increased risk of skin malignancy due to diminished immune surveillance. The mechanism for this increased skin lesion frequency is conjectured to be related to reduced lymphocyte counts leading to lower rates of surveillance for malignant cells, and siponimod's labeling will address this known increased risk of skin malignancy. While the cause of death is officially unknown for the third case, the patient was diagnosed with a potentially fatal condition, testicular cancer, four months prior to his death, and thus it is plausible that the cause of death may have been related to the cancer. Increased rates of cancer would be expected with reduced serum lymphocyte counts because of reduced immune surveillance for cancerous cells.*

MS Progression

Two patients died from causes attributed to MS progression.

Patient (b) (6), a 45-year-old woman, died of respiratory depression in the setting of suspected aspiration pneumonia due to progression of her MS to involve nerves supplying the respiratory muscles.

Patient (b) (6) a 54-year-old male, discontinued from the study on (b) (6) and died on (b) (6) due to MS progression causing bradypnea, depressed level of consciousness due to poor respiratory effort, and eventually cardiorespiratory arrest.

> *Reviewer Comment: Patients with progressive forms of MS can have life-threatening damage to nerves and brainstem nuclei that serve respiratory muscles. It is not unexpected that a trial of this size and duration in a SPMS patient population would note several deaths due to complications of MS progression. These patients had baseline EDSS >6.5, indicating an advanced disability at start of the study.*

Other Causes of Death

There were several individual cases with features meriting discussion.

Traumatic Brain Injury

Patient (b) (6) was a 35-year-old man diagnosed with MS in (b) (6). The patient's general medical history at Core Study Screening included phenylketonuria, optic nerve atrophy, history of stroke, and epilepsy. Concomitant medications included levetiracetam for seizure prophylaxis. The patient had experienced two MS relapses prior to entering Core Study. The patient received interferon beta 1a and glatiramer as treatments for MS prior to the Core Study entry. When entering the study, the patient had an EDSS score of 4.5. He entered the Core Study CBAF312A2201 and was randomized to placebo. He completed the Core Study and subsequently entered the dose-blinded phase of the Extension Study (CBAF312A2201E1). On Extension Day 738, the patient entered the open-label phase of the extension and received siponimod 2 mg daily. During the Core Study, the patient had no relapses. When entering the Extension Study, the patient's EDSS score was 4.5. The last known EDSS score before death was 4.5.

On Extension Day 1841, while receiving siponimod 2 mg/day during the open-label treatment phase of the Extension Study, the patient experienced confused state and altered mental status (mental status changes). He experienced a seizure resulting in a fall with head trauma and was hospitalized. The patient's CT of the head without contrast showed no obvious abnormalities. The patient showed post ictal symptoms including somnolence. During hospitalization, siponimod therapy was discontinued temporarily due to the patient being unable to take medications by mouth. On Extension Day 1844, the patient underwent MRI of head (with and

without contrast), which showed bilateral anterior frontal parenchyma hemorrhages and contusion, suggesting post-traumatic etiology. On Extension Day 1846, a repeat CT without contrast was overall similar to prior exams, showing bi-frontal edema and scattered small areas of hemorrhage. No new hemorrhages or acute findings were identified. Treatment included levetiracetam and phenytoin. On Extension Day 1848, the patient had returned to baseline and was discharged back to his nursing home.

On Extension Day 1850, the patient experienced an episode of altered mental status, a second seizure, and experienced a fall. Emergency services transported the patient to an emergency department where a repeat CT of the brain showed improvement in edema and scattered areas of small hemorrhages. The patient hospitalized. On Extension Day 1852, the patient's MRI of the brain showed evolution of hemorrhagic contusions of both frontal lobes, enlargement of CSF signal intensity hygroma along the left side subdural space without midline shift or herniation and was negative for acute infarction. On Extension Day 1854, the patient's head CT showed stable frontal edema and stable left hygroma. On Extension Day 1858, the patient had returned to baseline status and was discharged from the hospital to his nursing home.

On Extension Day 1859, the patient experienced a seizure with cardiac arrest. He had a fall resulting in traumatic brain injury. Neuroimaging revealed that the patient had significant contusions to the frontal regions with bilateral frontal and subdural hemorrhagic components. The patient died on Day 1859 due to traumatic injury suffered during repeated post-ictal falls. It was never determined whether autopsy was performed.

The Investigator did not suspect a causal relationship between events (multiple seizures, craniocerebral injury, cardiac arrest) and the study medication. The Investigator stated that fall led to the head injury that was the patient's ultimate cause of death.

> *Reviewer Comment: The cause of death, traumatic brain injury because of a traumatic fall, was precipitated by a relevant prior event, seizure. The patient had a diagnosis of epilepsy and was treated concurrently during the trial with levetiracetam, an anticonvulsant. Epilepsy is more common in patients with MS than the general population. However, the incidence of seizures is higher in the siponimod-exposed patients with MS than in placebo-treated patients with MS. Therefore, siponimod could have contributed to the risk of seizure (that preceded the fall) and therefore had a contributory role in the patient's death.*

Completed Suicide

Patient (b) (6) was a 54-year-old man who had first multiple sclerosis symptoms and was diagnosed with MS in (b) (6). He was diagnosed with secondary progressive multiple sclerosis in (b) (6). The patient experienced more than one relapse; the most recent was in (b) (6). Prior disease-modifying treatment for MS included interferon Beta-1b, which was discontinued

in (b) (6) due to lack of efficacy. The patient's baseline EDSS score in (b) (6) was 4.0. The patient's medical history included muscle spasticity and fatigue (both in (b) (6), ongoing), intervertebral disc protrusion and neck pain (both in (b) (6), ongoing), bladder disorder, and depression (both in (b) (6), ongoing); smoking (2 pack years); and recurrent fungal skin infection. Concomitant medications included fampridine for improving walking, baclofen for spasticity, tilidine for MS related pain, tamsulosin and solifenacin succinate for bladder problems, rivastigmine and amantadine for fatigue and cognition, diclofenac and methylprednisolone for cervicocephal pain, methylprednisolone for MS relapse, citalopram for minor depression, omeprazole for stomach protection and amitriptyline for insomnia. All these conditions were secondary to multiple sclerosis. The patient received the first dose of study medication on Day 1.

On Day 242, the patient was noted with worsening of depression. Treatment included citalopram. On Day 257, the patient committed suicide by hanging himself. The patient received the last dose of study medication on Day 255. The Investigator also reported that Columbia Suicide Severity Rating Scale assessment at baseline and at all visits were negative for any lifetime or recent suicidal ideation or behavior. An autopsy was not performed. The Investigator did not suspect a relationship between the events (depression, completed suicide) and the study medication. The Investigator considered the cause of death was suicide, and there was a report of recent stress and high pressure experienced by the patient in his professional career in a legal firm.

> *Reviewer Comment: Patients with MS are at as high as a two-fold higher risk of depression and suicide than the general population.[7] The observation that all the patient's Columbia Suicide Severity Rating Scale assessments were negative for suicidal ideation is troubling given the outcome. As demonstrated in Section 8.4.5., there was not an obvious mismatch in frequency of suicidal ideation and behavior in patients in the siponimod (8.2%) versus placebo treatment (8.7%) groups. Depression frequency in the siponimod treatment group was similar at randomization and reported depressive symptom frequency was slightly lower during the trial as compared to the placebo treatment group frequencies. The patient's reported worsening depression and recent initiation of citalopram to treat this exacerbation of depression are significant risk factors for suicide. Citalopram has a Boxed Warning regarding increased suicidality risk during initiation of treatment. A relationship to siponimod cannot be ruled out but other known suicide risk factors are present.*

Amyotrophic Lateral Sclerosis

Patient (b) (6), a 61-year-old woman, died of complications of amyotrophic lateral sclerosis 105 days after her last dose of siponimod. The patient experienced worsening dysphagia and refused further nutritional support given her fatal diagnosis.

> *Reviewer Comment: The etiology of amyotrophic lateral sclerosis is unknown. A role for*

siponimod cannot be ruled out.

Unknown Cause
Patient (b) (6) was a 57-year-old Caucasian man who died during the screening epoch. The patient's medical history was notable for spasticity and trigeminal pain, and medications included tolperisone and pregabalin. A cause of death was unknown, no autopsy was performed on the patient, and no further details of the death were provided to the screening site.

Reviewer comment: The death of a patient during screening, prior to initiating trial-related therapy, cannot be attributed to study treatment. This patient is not included in the deaths attributed to study treatment, appropriately.

8.4.2. Serious Adverse Events

Controlled Pool
Serious adverse events (SAEs), and deaths, occurred less frequently than treatment-related adverse events in patients exposed to siponimod. There was a trend toward dose dependency observed in frequencies of SAEs. The following table summarizes all types of adverse events and deaths during the controlled phases of trials using siponimod:

Table 9: Summary of Adverse Events, Serious Adverse Events, and Deaths, Controlled Pool, Safety Set (Safety Database 1)

	Siponimod 0.25mg N=51 n (%)	Siponimod 0.5mg N=43 n (%)	Siponimod 1.25mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
All deaths	0	0	1 (2.4%)	3 (0.3%)	0	4 (0.3%)	4 (0.7%)
On-treatment deaths	0	0	1 (2.4%)	1 (0.1%)	0	2 (0.2%)	1 (0.2%)
Serious Adverse Events	0	8 (18.6%)	2 (4.8%)	198 (17.2%)	3 (6.0%)	211 (15.8%)	78 (12.8%)
Adverse events	41 (80.4%)	37 (86.0%)	30 (71.4%)	1027 (89.5%)	48 (96.0%)	1183 (88.7%)	494 (81.4%)

Source: adae.xpt

Non-fatal Serious Adverse Events (SAEs) in Safety Database 1, the safety set containing all data from controlled phases of trials using siponimod, occurred in 0%, 18.6%, 4.8%, 17.2%, 6.0%, and 12.8% of patients in the siponimod 0.25 mg, 0.5mg, 1.25 mg, 2 mg, 10 mg, and placebo groups, respectively Combining all exposed to siponimod the frequency of SAEs for siponimod-treated patients was 16.5% vs. 12.9% of placebo-treated patients.

The most common SAEs during controlled trials were in the Nervous System Disorders and in the Infections and Infestations SOCs with some evidence of a dose response among siponimod doses for events.

To assess AEs, I examined the applicant's presentations and tables. I read the CRFs and narrative summaries for common SAEs and for select events of interest/ This review starts by identifying SAEs occurring in at least 2 patients from the overall controlled study population in MS trials. I review narratives for select SAEs that were common and appeared more frequently with siponimod or for infrequent, unexpected SAEs that may be of concern.

> *Reviewer Comment: The applicant provided two databases for SAEs. One database included only SAEs that occurred within a 30-day cut-off date of the double-blind phase and another that included any SAEs during the core phase of the study, irrespective of a cut-off date, until a patient entered open label therapy or discontinued therapy. There were seven additional SAEs in siponimod-treated patients and four additional SAEs in placebo-treated patients in the database that included all events until patients entered open label therapy or discontinued. The analysis in this review is derived from this larger, more inclusive database. The overall findings and conclusions from the 30-day cutoff*

database were consistent with those that were recorded until the end of follow-up or start of open label therapy, and the larger database did not reveal a safety finding not present in the smaller database pool. The half-life of siponimod is approximately 36 hours. It is therefore expected that after 5 half-lives, or approximately 7.5 days, that adverse events directly attributable to siponimod therapy would be diminished markedly. Therefore, the difference in event rates between a database with a strict 30-day cut-off and a database including would not be expected to be markedly different. It is worth noting, however, that some effects of siponimod, e.g., reduced serum white cell count, may still be resolving at 30 days which obligates that a review of safety data be based on the database with the longest possible duration of observation to account for any SAEs that occurred in patients discontinuing therapy that would be missed by a strict 30-day cutoff.

The number SAEs in at least 2 patients in any treatment group in the controlled studies are presented in the following table. In siponimod treatment groups, the SOC with the most frequently reported SAEs was the Nervous System Disorders SOC (40 patients, 3.5%), and the most frequently reported SAEs within this SOC were seizures and related terms (10 patients, 0.9%). In placebo treatment groups, the Nervous System Disorders SOC was also the most frequently reported SOC (18 patients, 3.0%), but the most common SAEs reported for placebo-treated patients in this SOC were multiple sclerosis relapse and related terms (7 patients, 1.2%).

There were no SAEs for the 0.25 mg dose; the 0.25 mg dose therefore is not represented in the following table.

Table 10: Reviewer Table, All Serious Adverse Events in At Least 2 Patients in Any Treatment Group by System Organ Class and Preferred Term, Controlled Pool, Safety Set (All Data), Safety Database 1.

Primary Organ System Organ Class Preferred Term	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Any Patient w/SAE	8 (18.6%)	2 (4.8%)	198 (17.2%)	3 (6.0%)	211 (15.8%)	78 (12.9%)
Nervous System Disorders	3 (7.0%)	0	40 (3.5%)	1 (2.0%)	44 (3.3%)	18 (3.0%)
Epilepsy and Seizures[1]	0	0	10 (0.9%)	0	10 (0.8%)	0
Syncope	0	0	4 (0.3%)	0	4 (0.3%)	1 (0.2%)

Primary Organ System Organ Class Preferred Term	**Siponimod 0.5 mg N=43** **n (%)**	**Siponimod 1.25 mg N=42** **n (%)**	**Siponimod 2 mg N=1148** **n (%)**	**Siponimod 10 mg N=50** **n (%)**	**Siponimod All Doses N=1334** **n (%)**	**Placebo N=607** **n (%)**
Hemiparesis	0	0	3 (0.3%)	0	3 (0.2%)	0
Trigeminal neuralgia	0	0	3 (0.3%)	0	3 (0.2%)	0
Stroke	0	0	2 (0.2%)	0	2 (0.1%)	0
Multiple Sclerosis and MS Relapse	1 (2.3%)	0	2 (0.2%)	0	3 (0.2%)	7 (1.2%)
Paraparesis	0	0	0	0	0	3 (0.5%)
Infections and Infestations	1 (2.3%)	1 (2.4%)	36 (3.1%)	0	38 (2.8%)	16 (2.6%)
Urinary tract infection	0	0	15 (1.3%)	0	15 (1.1%)	7 (1.2%)
Urosepsis and Sepsis	0	0	4 (0.3%)	0	4 (0.3%)	1 (0.2%)
Appendicitis	0	0	3 (0.3%)	0	3 (0.2%)	0
Upper respiratory tract infection	0	0	3 (0.3%)	0	3 (0.2%)	0
Gastroenteritis	0	0	2 (0.2%)	0	2 (0.1%)	1 (0.2%)
Pneumonia	0	0	1 (0.1%)	0	1 (<0.1%)	2 (0.3%)
Neoplasms Benign, Malignant and Unspecified	2 (4.7%)	0	27 (2.4%)	0	29 (2.2%)	16 (2.6%)
Basal cell carcinoma	1 (2.3%)	0	12 (1.0%)	0	13 (1.0%)	6 (1.0%)
Malignant melanoma *in situ*	0	0	2 (0.2%)	0	2 (0.1%)	0
Seminoma	0	0	2 (0.2%)	0	2 (0.1%)	0
Prostate cancer	0	0	0	0	0	2 (0.3%)
Blood and	0	0	2 (0.2%)	0	2 (0.1%)	2

Primary Organ System Organ Class Preferred Term	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Lymphatic System Disorders						(0.3%)
Anemia	0	0	0	0	0	2 (0.3%)
Cardiac Disorders	1 (2.3%)	0	13 (1.1%)	2 (4.0%)	16 (1.2%)	3 (0.5%)
AV block 2nd degree	0	0	5 (0.4%)	1 (2.0%)	6 (0.5%)	0
Bradycardia	1 (2.3%)	0	3 (0.3%)	0	4 (0.3%)	0
Eye Disorders	0	0	4 (0.3%)	0	4 (0.3%)	2 (0.3%)
Macular Edema	0	0	3 (0.3%)	0	3 (0.2%)	0
Gastrointestinal Disorders	0	0	9 (0.8%)	0	9 (0.7%)	9 (0.5%)
Constipation	0	0	2 (0.2%)	0	2 (0.1%)	1 (0.2%)
General Disorders and Administrative Conditions	0	1 (2.4%)	5 (0.4%)	0	6 (0.5%)	3 (0.5%)
Asthenia	0	0	2 (0.2%)	0	2 (0.1%)	0
Pyrexia	0	0	2 (0.2%)	0	2 (0.1%)	0
Gait disturbance	0	0	1 (0.1%)	0	1 (<0.1%)	3 (0.5%)
Hepatobiliary Disorders	0	0	6 (0.5%)	0	6 (0.5%)	1 (0.2%)
Cholelithiasis	0	0	2 (0.2%)	0	2 (0.1%)	0
Injury, Poisoning and Procedural Complications	0	0	22 (1.9%)	0	22 (1.7%)	6 (1.0%)
Concussion	0	0	5 (0.4%)	0	5 (0.4%)	0
Laceration	0	0	4 (0.3%)	0	4 (0.3%)	0
Femoral neck fracture	0	0	3 (0.3%)	0	3 (0.2%)	1 (0.2%)

Primary Organ System Organ Class Preferred Term	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Ankle fracture	0	0	2 (0.2%)	0	2 (0.1%)	0
Fall	0	0	2 (0.2%)	0	2 (0.1%)	0
Hip fracture	0	0	0	0	0	2 (0.3%)
Psychiatric Disorders	1 (2.3%)	0	22 (1.9%)	0	23 (1.8%)	7 (1.2%)
Depression	0	0	5 (0.4%)	0	5 (0.4%)	2 (0.3%)
Suicide attempt	0	0	4 (0.3%)	0	4 (0.3%)	3 (0.5%)
Suicidal ideation	0	0	3 (0.3%)	0	3 (0.2%)	1 (0.2%)
Investigations	0	0	21 (1.8%)	0	21 (1.6%)	3 (0.5%)
AST/ALT/hepatic enzyme increased	0	0	16 (1.4%)	0	16 (1.3%)	3 (0.3%)
Columbia suicide severity rating scale abnormal	0	0	2 (0.2%)	0	2 (0.1%)	0
Metabolism and Nutrition Disorders	0	0	3 (0.3%)	0	3 (0.2%)	1 (0.2%)
Dehydration	0	0	2 (0.2%)	0	2 (0.1%)	0
Musculoskeletal and Connective Tissue Disorders	1 (2.3%)	0	13 (1.1%)	0	14 (1.1%)	3 (0.5)
Muscle weakness	0	0	3 (0.3%)	0	3 (0.2%)	0
Renal and Urinary Disorders	0	0	15 (1.3%)	0	15 (1.2%)	3 (0.5%)
Urinary retention	0	0	3 (0.3%)	0	3 (0.2%)	2 (0.3%)
Bladder dysfunction	0	0	2 (0.2%)	0	2 (0.1%)	0

Primary Organ System Organ Class Preferred Term	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Hydronephrosis	0	0	2 (0.2%)	0	2 (0.1%)	1 (0.2%)
Urinary incontinence	0	0	2 (0.2%)	0	2 (0.1%)	0
Reproductive System and Breast Disorders	0	0	4 (0.3%)	0	4 (0.3%)	3 (0.5%)
Menorrhagia	0	0	2 (0.2%)	0	2 (0.1%)	0
Respiratory, Thoracic and Mediastinal Disorders	0	0	5 (0.4%)	0	5 (0.4%)	1 (0.2%)
Skin and Subcutaneous Tissue Disorders	0	0	3 (0.3%)	0	3 (0.2%)	1 (0.2%)
Vascular Disorders	0	0	5 (0.4%)	0	5 (0.4%)	1 (0.2%)

Source: adae.xpt, Table 2.1-8.1.2 of SCS.

[1]Includes events coded as partial seizure, seizure, generalized tonic-clonic seizure, and epilepsy

Notes: A patient with multiple SAEs within primary SOC is counted only once in the total row. A patient with multiple occurrences of a SAE under each treatment is counted only once in this SAE category for that treatment.

> *Reviewer Comment: Seizures are discussed in Section 8.5.8. The presence of serious MS relapses in the placebo treatment group is not surprising. There were more arrhythmia-related SAEs in siponimod treatment, an anticipated outcome based on S1P modulator's known cardiac effects. Trigeminal neuralgia is a known, common symptom of MS occurring in approximately 5% of patients with MS and its overrepresentation in the treatment group is puzzling but given the lifetime prevalence of this symptom in MS, a 0.3% rate is within the expected frequency independent of treatment effects. Cerebrovascular events, e.g., strokes and transient ischemic attacks, are present at higher frequencies in siponimod-treated patients and are discussed below. Other findings appeared balanced in frequency between siponimod and placebo treatment.*

Long-term Safety Pool

In the long-term safety pool, reported frequencies of deaths and SAEs increased from rates reported in controlled trials of MS. Approximately 21% of patients exposed to at least one dose of siponimod 2 mg or 10 mg experienced a SAE as compared to approximately 16% in controlled trials. Overall, the rate of death in exposed patients rose from 0.3% in controlled trials to 0.5%, but on treatment death rate remained the same at 0.2%. The following table summarizes deaths and

Table 11: Summary of Adverse Events, Serious Adverse Events, and Deaths, Long-term Safety Pool, Safety Set (Safety Databases 2 and 4)

	Siponimod 2-10 mg* N=1737 n (%)	**Siponimod 2-10 mg** N=1737 n (%)**
Adverse Events	1563 (90.0%)	1556 (89.6%)
Deaths	9 (0.5%)	9 (0.5%)
On-treatment Deaths	4 (0.2%)	4 (0.2%)
Serious Adverse Events	360 (20.7%)	358 (20.6%)

Source: adae.xpt

The most frequently reported SAEs in the Long-term Safety Databases were urinary tract infections (1.6%), basal cell carcinoma (1.3%), and increased liver transaminases (1%, pooled).

Table 12: Serious Adverse Events Reported by At Least 3 Patients, Long-term Safety Pool, Safety Databases 2 and 4

Preferred Term	**Siponimod 2-10 mg* N=1737**	**Siponimod 2-10 mg** N=1737**
Patients with ≥1 SAE	360 (20.7%)	358 (20.6%)
Urinary tract infection	28 (1.6%)	28 (1.6%)
Basal cell carcinoma	22 (1.3%)	22 (1.3%)
ALT/AST/GGT increased[1]	18 (1.0%)	18 (1.0%)
Sepsis[2]	8 (0.5%)	5 (0.5%)
Concussion	7 (0.4%)	7 (0.4%)
Depression	7 (0.4%)	7 (0.4%)
Multiple Sclerosis and Multiple Sclerosis Relapse[3]	7 (0.4%)	7 (0.4%)
Epilepsy and Seizures[4]	7 (0.4%)	7 (0.4%)
AV block 2nd degree	6 (0.3%)	6 (0.3%)
Bradycardia	6 (0.3%)	6 (0.3%)

Preferred Term	Siponimod 2-10 mg* N=1737	Siponimod 2-10 mg** N=1737
Femoral neck fracture	6 (0.3%)	6 (0.3%)
Laceration	6 (0.3%)	6 (0.3%)
Suicide attempt[5]	6 (0.3%)	6 (0.3%)
Fall	5 (0.3%)	5 (0.3%)
Inguinal hernia	5 (0.3%)	5 (0.3%)
Muscle spasticity	5 (0.3%)	5 (0.3%)
Suicidal ideation[6]	5 (0.3%)	5 (0.3%)
Syncope	5 (0.3%)	5 (0.3%)
Trigeminal neuralgia	5 (0.3%)	5 (0.3%)
Ankle fracture	4 (0.2%)	4 (0.2%)
Appendicitis	4 (0.2%)	4 (0.2%)
Breast cancer	4 (0.2%)	4 (0.2%)
Headache[7]	4 (0.2%)	4 (0.2%)
Muscular weakness	4 (0.2%)	4 (0.2%)
Pyrexia	4 (0.2%)	4 (0.2%)
Upper respiratory infection	4 (0.2%)	4 (0.2%)
Urinary retention	4 (0.2%)	4 (0.2%)
Asthenia	3 (0.2%)	3 (0.2%)
Back pain	3 (0.2%)	3 (0.2%)
Stroke	3 (0.2%)	3 (0.2%)
Cholecystitis	3 (0.2%)	3 (0.2%)
Confusional state	3 (0.2%)	3 (0.2%)
Cystitis	3 (0.2%)	3 (0.2%)
Gastroenteritis	3 (0.2%)	3 (0.2%)
Hemiparesis	3 (0.2%)	3 (0.2%)
Herpes zoster	3 (0.2%)	3 (0.2%)
Macular edema	3 (0.2%)	3 (0.2%)
Metrorrhagia	3 (0.2%)	3 (0.2%)
Osteoarthritis	3 (0.2%)	3 (0.2%)
Spondylolisthesis	3 (0.2%)	3 (0.2%)
Transient ischemic attack	3 (0.2%)	3 (0.2%)
Urinary incontinence	3 (0.2%)	3 (0.2%)
Uterine leiomyoma	3 (0.2%)	3 (0.2%)

Sources: adae.xpt, SCS Appendix 1-Table 2.1-9.2

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

[1]includes events coded as ALT increased, AST increased, GGT increased, bilirubin increased, and hepatic enzyme increased
[2]includes events coded as sepsis and urosepsis
[3]includes events coded as multiple sclerosis, multiple sclerosis relapse
[4]includes events coded as seizure, epilepsy, partial seizure, generalized tonic clonic seizure
[5]includes events coded as suicide attempt, suicidal behavior, intentional overdose
[6]includes events coded as suicidal ideation and Columbia suicide rating scale abnormal
[7]includes events coded as headache, status migrainosus

> *Reviewer Comment: SAEs occurring at > 1% frequency in this pool are urinary tract infections, basal cell carcinoma, and liver transaminases increased. Urinary tract infections are a common pathological consequence in patients with MS[8] and is unrelated to treatment. Basal cell carcinoma was captured because of dermatological screening required by the study and was present in placebo treatment patients at a similar frequency. Liver transaminase elevations are a known consequence of siponimod and similar therapies and can be addressed by labeling for risk and recommending monitoring.*

120-day Safety Update

In the 120-day update to the long-term safety pool, the addition of more SAEs raised the overall frequency of SAEs for exposed patients from 20.7% to 23.3%.

	Siponimod 2-10 mg* N=1737 n (%)	**Siponimod 2-10 mg** N=1737 n (%)**
Adverse Events	1592 (91.7%)	1585 (91.2%)
Deaths	10 (0.6%)	10 (0.6%)
On-treatment Deaths	5 (0.3%)	5 (0.3%)
Serious Adverse Events	405 (23.3%)	403 (23.2%)

A summary by single preferred terms revealed that urinary tract infection and basal cell carcinoma remained the most frequent SAEs. Seizures more than doubled in frequency (0.4% to 0.9%) from the original long-term safety database. Sepsis and other infectious SAEs remained at approximately the same frequencies as in the previous database.

Table 13: Serious Adverse Events Reported by At Least 3 Patients, 120-day update, Long-term Safety Pool, Safety Databases 2 and 4

Preferred Term	Siponimod 2-10 mg* N=1737	Siponimod 2-10 mg** N=1737
Patients with ≥1 SAE	405 (23.3%)	403 (23.2%)
Urinary tract infection	31 (1.8%)	32 (1.8%)
Basal cell carcinoma	26 (1.5%)	26 (1.5%)
ALT/AST/GGT increased[1]	18 (1.0%)	18 (1.0%)
Epilepsy and Seizures[2]	15 (0.9%)	15 (0.9%)
Multiple Sclerosis and Multiple Sclerosis Relapse[3]	9 (0.5%)	9 (0.5%)
Sepsis[4]	8 (0.5%)	8 (0.5%)
Concussion	7 (0.4%)	7 (0.4%)
Depression	7 (0.4%)	7 (0.4%)
Femoral neck fracture	7 (0.4%)	7 (0.4%)
Laceration	7 (0.4%)	7 (0.4%)
Suicidal ideation[5]	7 (0.4%)	7 (0.4%)
Suicide attempt[6]	7 (0.4%)	7 (0.4%)
AV block 2nd degree	6 (0.3%)	6 (0.3%)
Bradycardia	6 (0.3%)	6 (0.3%)
Breast cancer	6 (0.3%)	6 (0.3%)
Fall	6 (0.3%)	6 (0.3%)
Inguinal hernia	6 (0.3%)	6 (0.3%)
Syncope	6 (0.3%)	6 (0.3%)
Urinary retention	6 (0.3%)	6 (0.3%)
Ankle fracture	5 (0.3%)	5 (0.3%)
Muscle spasticity	5 (0.3%)	5 (0.3%)
Muscular weakness	5 (0.3%)	5 (0.3%)
Osteoarthritis	5 (0.3%)	5 (0.3%)
Trigeminal neuralgia	5 (0.3%)	5 (0.3%)
Appendicitis	4 (0.2%)	4 (0.2%)
Asthenia	4 (0.2%)	4 (0.2%)
Dehydration	4 (0.2%)	4 (0.2%)
Pyrexia	4 (0.2%)	4 (0.2%)
Rib fracture	4 (0.2%)	4 (0.2%)
Stroke	4 (0.2%)	4 (0.2%)
Headache	4 (0.2%)	4 (0.2%)
Upper respiratory infection	4 (0.2%)	4 (0.2%)
Acute kidney injury	3 (0.2%)	3 (0.2%)

Preferred Term	Siponimod 2-10 mg* N=1737	Siponimod 2-10 mg** N=1737
Cholecystitis	3 (0.2%)	3 (0.2%)
Confusional state	3 (0.2%)	3 (0.2%)
Constipation	3 (0.2%)	3 (0.2%)
Cystitis	3 (0.2%)	3 (0.2%)
Decubitus ulcer	3 (0.2%)	3 (0.2%)
Deep vein thrombosis	3 (0.2%)	3 (0.2%)
Gastroenteritis	3 (0.2%)	3 (0.2%)
Hemiparesis	3 (0.2%)	3 (0.2%)
Herpes zoster	3 (0.2%)	3 (0.2%)
Influenza	3 (0.2%)	3 (0.2%)
Macular edema	3 (0.2%)	3 (0.2%)
Metrorrhagia	3 (0.2%)	3 (0.2%)
Spondylolisthesis	3 (0.2%)	3 (0.2%)
Osteoarthritis	3 (0.2%)	3 (0.2%)
Subdural hematoma	3 (0.2%)	3 (0.2%)
Transient ischemic attack	3 (0.2%)	3 (0.2%)
Urinary incontinence	3 (0.2%)	3 (0.2%)
Uterine leiomyoma	3 (0.2%)	3 (0.2%)

Sources: adae.xpt, 120-day Update SCS Appendix 1-Table 2.1-8.2.

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

[1]includes events coded as ALT increased, AST increased, GGT increased, bilirubin increased, and hepatic enzyme increased
[2]includes events coded as seizure, epilepsy, partial seizure, generalized tonic clonic seizure
[3]includes events coded as multiple sclerosis, multiple sclerosis relapse
[4]includes events coded as sepsis and urosepsis
[5]includes events coded as suicidal ideation and Columbia suicide rating scale abnormal
[6]includes events coded as suicide attempt, suicidal behavior, intentional overdose

Reviewer Comment: The 120-day safety update does not dramatically change the previously observed frequencies of many expected events. The emergence of seizures and epilepsy is of interest and will be discussed in Section 8.5.8 as will injuries in the

setting of increased fall risk.

Titration Pool

During Studies A2201 and A2304, the applicant instituted a titration schedule for initiation of siponimod treatment that was implemented to reduce cardiovascular-related adverse events. Analysis of Safety Database 3, which include SAEs captured during titration to a goal dose of siponimod, revealed few SAEs. There were few SAEs recorded during the 5-day titration periods. The most common SAEs were confined to the Cardiac Disorders SOC (11 patients, 0.7%), and the most common SAE was bradycardia (0.4%).

Table 14: All Serious Adverse Events During Titration, Titration Pool, Safety Set (Safety Database 3)

Primary System Organ Class	Siponimod 0.25-2 mg N=1544 n (%)	Placebo N=546 n (%)
Any SAE	29 (1.9%)	2 (0.4%)
Cardiac Disorders	11 (0.7%)	0
Bradycardia	6 (0.4%)	0
AV block 2nd degree	2 (0.1%)	0
Angina pectoris	1 (0.1%)	0
Arrhythmia	1 (0.1%)	0
Atrial fibrillation	1 (0.1%)	0
Palpitations	1 (0.1%)	0
Supraventricular extra-systoles	1 (0.1%)	0
Ventricular tachycardia	1 (0.1%)	0
Gastrointestinal Disorders	0	1 (0.2%)
Constipation	0	1 (0.2%)
Diarrhea	0	1 (0.2%)
Nervous System Disorders	7 (0.5%)	0
Dizziness	2 (0.1%)	0
Epilepsy and Seizures	2 (0.1%)	0
Aphasia	1 (0.1%)	0
Intention tremor	1 (0.1%)	0
Ischemic stroke	1 (0.1%)	0
Syncope	1 (0.1%)	0
Infections and Infestations	5 (0.3%)	0
Urinary tract infection	3 (0.2%)	0
Cystitis	1 (0.1%)	0
Pyelonephritis	1 (0.1%)	0

Psychiatric Disorders	3 (0.2%)	0
Panic attack	1 (0.1%)	1 (0.2%)
Suicidal behavior	1 (0.1%)	1 (0.2%)
Suicidal ideation	1 (0.1%)	0
Eye Disorders	1 (0.1%)	0
General Disorders and Administration Site Conditions	2 (0.1%)	0
Fatigue	1 (0.1%)	0
Gait disturbance	1 (0.1%)	0
Photophobia	1 (0.1%)	0
Immune System Disorders	1 (0.1%)	0
Vascular Disorders	2 (0.1%)	0
Hypertensive emergency	1 (0.1%)	0
Orthostatic hypotension	1 (0.1%)	0
Hypersensitivity	1 (0.1%)	0
Injury, Poisoning and Procedural Complications	1 (0.1%)	0
Concussion	1 (0.1%)	0
Investigations	1 (0.1%)	0
Heart rate decreased	1 (0.1%)	0
Neoplasms Benign, Malignant and Unspecified	1 (0.1%)	0
Renal cell carcinoma	1 (0.1%)	0
Renal and Urinary Disorders	1 (0.1%)	0
Acute kidney injury	1 (0.1%)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.1%)	0
Dyspnea	1 (0.1%)	0

Source: SCS Appendix 1 Table 2.1-8.3 of 120-Day Safety Update

Notes: Treatment-emergent serious adverse events occurred during titration period (up to 15 days) of dose initiation or dose restart are reported. A patient with multiple serious adverse events within a primary system organ class is counted only once in the total row. A patient with multiple occurrences of an SAE under one treatment is counted only once in this SAE category for that treatment. System organ classes are presented in alphabetical order; preferred terms are sorted within system organ class in descending frequency of SAEs based on siponimod 2mg.

Reviewer Comment: SAEs during titration of siponimod occurred for <2% of all patients. The most common SAEs were cardiovascular in origin, but I would include the case of syncope as being related to cardiovascular effects in this sampling. The observed SAE

frequencies confirm that immediate cardiovascular effects of siponimod acting at cardiac S1P receptors predominate during initial administration despite the therapy's targeted selectivity for non-cardiac S1P receptors. The overall rate of serious adverse events is significantly reduced compared to prior trials without titration. However, the presence of Cardiac Disorder SAEs during titration indicates that titration is not entirely successful at mitigating risk of Cardiac Disorders SAEs including, but not limited to, atrioventricular block. It is worth noting that one case of symptomatic first-degree AV block led to siponimod discontinuation, but other cases of first-degree blockade rectified spontaneously without permanent discontinuation of siponimod. The two cases of AV second degree AV block noted in the titration period occurred in patients who were in the higher risk cardiac monitoring group and following guidelines in proposed labeling would capture these cases in general use. There were no cases of second-degree block in patients without cardiac risk factors, and thus the titration scheme does appear to mitigate risks of serious conduction blockade in the routine cardiac risk patients. The applicant's proposed labeling for first dose monitoring, which (b) (4) *recommends more monitoring for patients with histories of cardiac disease, appears to mitigate the cardiac risks associated with initiation of siponimod.*

Study A2304

The overall frequencies of SAEs in Study A2304 (excluding SAEs occurring during titration and prior to the 120-day Safety Update cut-off) were 16.9% in siponimod-treated patients and 13.6% in placebo-treated patients. The most common SAE associated with siponimod therapy by SOC was in the Nervous System Disorders SOC for 40 patients (3.6%), and, by Preferred Term was urinary tract infection reported in 13 patients (1.2%).

Table 15: Serious Adverse Events by System Organ Class and Preferred Term, in At Least 2 Patients, Study A2304, Safety Set

	Siponimod N=1099 n (%)	Placebo N=546 n (%)
Patients with at least 1 SAE	186 (16.9%)	74 (13.6%)
Nervous System Disorders	40 (3.6%)	17 (3.1%)
Epilepsy and Seizures[1]	6 (0.6%)	0
Syncope	4 (0.4%)	1 (0.2%)
Hemiparesis	3 (0.3%)	0
Trigeminal neuralgia	3 (0.3%)	0
Stroke	2 (0.2%)	0
Multiple sclerosis and multiple sclerosis relapse[2]	4 (0.4%)	7 (1.3%)
Muscle spasticity	2 (0.2%)	0
Infections & Infestations	33 (3.0%)	15 (2.7%)

	Siponimod N=1099 n (%)	**Placebo N=546 n (%)**
UTI	13 (1.2%)	6 (1.1%)
Appendicitis	3 (0.3%)	0
URI	3 (0.3%)	0
Gastroenteritis	2 (0.2%)	1 (0.2%)
Urosepsis	2 (0.2%)	1 (0.2%)
Neoplasms	23 (2.1%)	15 (2.7%)
Basal cell carcinoma	11 (1.0%)	6 (1.1%)
Malignant melanoma *in situ*	2 (0.2%)	0
Seminoma	2 (0.2%)	0
Psychiatric Disorders	22 (2.0%)	7 (1.3%)
Depression	5 (0.5%)	2 (0.4%)
Suicide Attempt[3]	4 (0.4%)	3 (0.5%)
Suicide Ideation[4]	3 (0.3%)	1 (0.2%)
Investigations	21 (1.9%)	3 (0.5%)
ALT or AST increased	15 (1.4%)	3 (0.5%)
Injury, Poisoning, & Procedural Complications	20 (1.8%)	5 (0.9%)
Concussion	5 (0.5%)	0
Laceration	4 (0.4%)	0
Femoral neck fracture	3 (0.3%)	1 (0.2%)
Fall	2 (0.2%)	0
Renal & Urinary Disorders	14 (1.3%)	3 (0.5%)
Urinary retention	3 (0.3%)	2 (0.4%)
Bladder dysfunction	2 (0.2%)	0
Hydronephrosis	2 (0.2%)	1 (0.2%)
Urinary incontinence	2 (0.2%)	0
Musculoskeletal & Connective Tissue Disorders	12 (1.1%)	3 (0.5%)
Muscle weakness	2 (0.2%)	0
Gastrointestinal Disorders	9 (0.8%)	9 (1.6%)
Constipation	2 (0.2%)	1 (0.2%)
Cardiac Disorders	7 (0.6%)	3 (0.5%)
Bradycardia	3 (0.3%)	0
AV block 2nd degree	2 (0.2%)	0
General Disorders	5 (0.5%)	3 (0.5%)
Asthenia	2 (0.2%)	0
Pyrexia	2 (0.2%)	0
Eye Disorders	4 (0.4%)	2 (0.4%)
Macular edema	3 (0.3%)	0

	Siponimod N=1099 n (%)	Placebo N=546 n (%)
Reproductive System & Breast Disorders	4 (0.4%)	3 (0.5%)
Menorrhagia	2 (0.2%)	0
Metabolism & Nutrition Disorders	3 (0.3%)	1 (0.2%)
Dehydration	2 (0.2%)	0

Source: CSR Study A2304 Table 14.3.1-1.7

[1]includes events coded as epilepsy, seizure, partial seizure
[2]includes events coded as multiple sclerosis, multiple sclerosis relapse
[3]includes events codded as suicide attempt, suicide behavior
[4]includes events coded as suicidal ideation and Columbia Suicide Severity Rating Scale Abnormal

Reviewer Comment: There is a mismatch between SAEs in the Injury, Poisoning, and Procedural Complications SOC between the siponimod and placebo treatment groups because of more falls and injuries related to falls. There is a mismatch in the Malignancy SOC because there are two cases of seminoma and malignant melanoma in situ *in siponimod-treated patients. Fall and malignancy risks are discussed in Section 8.5.*

Study A2201

In Study A2201, a controlled trial in patients with RMS, the overall risk for SAEs was 9.2% for all doses of siponimod as compared to no SAEs in placebo-treated patients. The most frequently reported SAE associated with siponimod therapy were Cardiac Disorders (3.3%), specifically, second degree AV block reported in four patients (2.2%).

The following table describes all SAEs experienced by patients with RMS in the A2201 controlled trial portion (Periods 1 and 2). There were no SAEs associated with the 0.25 mg dose of siponimod, and thus this dose is not reported in the table.

Table 16: All Serious Adverse Events by System Organ Class, Preferred Term, and Treatment, Study A2201, All Periods, Safety Set

	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=49 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=184 n (%)	Placebo N=61
Any SAE	8 (18.6%)	2 (4.8%)	4 (8.2%)	3 (6.0%)	17 (9.2%)	0
Cardiac disorders	1 (2.3%)	0	3 (6.1%)	2 (4.0%)	6 (3.3%)	0
AV block 2nd degree	0	0	3 (6.1%)	1 (2.0%)	4 (2.2%)	0

	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=49 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=184 n (%)	Placebo N=61
Myocardial infarction	0	0	0	1 (2.0%)	1 (0.5%)	0
Bradycardia	1 (2.3%)	0	0	0	1 (0.5%)	0
General Disorders	0	1 (2.4%)	0	0	1 (0.5%)	0
Death	0	1 (2.4%)	0	0	1 (0.5%)	0
Infections & Infestations	1 (2.3%)	1 (2.4%)	0	0	1 (0.5%)	0
Perineal abscess	0	1 (2.4%)	0	0	1 (0.5%)	0
Pyelonephritis	1 (2.3%)	0	0	0	1 (0.5%)	0
Injury, Poisoning and Procedural Complications	0	0	1 (2.0%)	0	1 (0.5%)	0
Intentional overdose	0	0	1 (2.0%)	0	1 (0.5%)	0
Musculoskeletal & Connective tissue Disorders	1 (2.3%)	0	0	0	1 (0.5%)	0
Myopathy	1 (2.3%)	0	0	0	1 (0.5%)	0
Neoplasms Benign, Malignant & Unspecified (incl. cysts and polyps)	2 (4.7%)	0	0	0	2 (1.1%)	0
Basal cell carcinoma	1 (2.3%)	0	0	0	1 (0.5%)	0
Uterine leiomyoma	1 (2.3%)	0	0	0	1 (0.5%)	0
Nervous System Disorders	3 (7.0%)	0	0	1 (2.0%)	4 (2.2%)	0
Benign intracranial hypertension	0	0	0	1 (2.0%)	1 (0.5%)	0
Headache	1 (2.3%)	0	0	0	1 (0.5%)	0
Multiple sclerosis relapse	1 (2.3%)	0	0	0	1 (0.5%)	0
Optic neuritis	1 (2.3%)	0	0	0	1 (0.5%)	0
Psychiatric Disorders	1 (2.3%)	0	0	0	1 (0.5%)	0
Schizophreniform disorder	1 (2.3%)	0	0	0	1 (0.5%)	0

Source: CSR Study A2201 PT-Table 14.3.1-1.11

Reviewer Comment: Period 1 of Study A2201 did not employ a titration schedule used in Period 2 of this trial. The overall higher frequency of cardiac events reflects this lack of titration. Otherwise, the SAE database for this trial in patients with RMS is largely consistent with the SAE findings in the larger trial in patients with SPMS, Study A2304. There are fewer urinary tract infections in this database possibly indicative of there being fewer patients with urinary outflow compromise because relapsing MS does not feature this symptom as frequently. It is reassuring that the SAE frequency and type in this study population with RMS have similar characteristics to SAE findings from a trial population with SPMS because of the clinical overlap between these diseases and the high likelihood

that patients with RMS will receive siponimod.

Study A2202

In a controlled trial of siponimod for polymyositis and dermatomyositis, there were no deaths, and there were four SAEs reported in three patients. All SAEs were reported while patients were in the placebo treatment arm or before initiation of siponimod during a cross-over phase in the trial. The four SAEs were cholelithiasis, back pain, compression fracture, and peritonitis.

Reviewer Comment: SAEs in this study were confined to placebo treatment and therefore do not provide information relevant to understanding siponimod's safety.

Study X2205

In a controlled trial of siponimod for polymyositis, there were no deaths. One patient experienced three SAEs (acute kidney injury, hemolytic anemia, and hemolytic uremic syndrome) while in the siponimod 2 mg treatment arm. The narrative associated with the three SAEs is included in the narratives section below. There were no other SAEs.

Study X2206

In a controlled trial of siponimod for active dermatomyositis, there were no deaths. Four patients reported a total of seven SAEs as indicated in the following table:

Table 17: Reviewer Table, Incidence of Serious Adverse Events by Preferred Term, All Periods, Study X2206, Safety Set

	Siponimod 0.5 mg N=4	Siponimod 2 mg N=4	Siponimod 10 mg N=4	Siponimod Any Dose N=12	Placebo N=5
Patients with at least one SAE	0	1 (25.0%)	2 (50.0%)	3 (0.25%)	1 (20.0%)
Preferred Term					
Dermatomyositis	0	0	0	0	1 (20.0%)
Pneumonia	0	0	0	0	1 (20.0%)
Procedural pain	0	0	1 (25.0%)	1 (8.3%)	0
Pulmonary embolism	0	0	1 (25.0%)	1 (8.3%)	0
Laceration	0	0	1 (25.0%)	1 (8.3%)	0
Subarachnoid hemorrhage	0	1 (25.0%)	0	1 (8.3%)	0
Syncope	0	0	1 (25.0%)	1 (8.3%)	0

Source: CSR Study X2206, Tables 12-8 and 12-9

Clinical Pharmacology Studies

In single dose studies, there was one patient who experienced two SAEs (presyncope and bradycardia) for siponimod 4 mg. In multiple dose studies, there were three SAEs reported in siponimod-treated subjects. The SAEs were heterogeneous (fibrillation, dengue fever,

exertional rhabdomyolysis) and only fibrillation was deemed directly related to study drug exposed.

Reviewer Comment: Three out of the five SAEs reported in Clinical Pharmacology studies are Cardiac SOC events as would be anticipated in short duration trials largely performed without titration schedules. A role for siponimod in the other two SAEs, dengue fever and exertional rhabdomyolysis, cannot be ruled out.

Summary of SAEs including Pertinent Narratives

The following section discusses SAEs of specific interest. These SAEs were either reported more frequently in any siponimod treatment group compared to placebo or were SAEs of special interest based on clinical significance (*e.g.,* pancreatitis). Narratives are included to illustrate circumstances regarding association with study treatment.

Epilepsy and Seizures

In the controlled poor, there is a clear mismatch between the frequency of any type of SAE related to seizures occurring in siponimod-treated patients (10/1148 patients, 0.9%) versus placebo-treated patients (0/607). Nine of the ten SAE narratives for seizures and epileptic events are included here, and the tenth case, a SAE of seizure associated with a patient death, is discussed in Section 8.4.1. A full discussion of seizures and relationship to treatment can be found in Section 8.5.8.

1. Patient (b) (6), a 47-year-old man with relapsing MS, received his first dose of siponimod on (b) (6). The patient's prior medical history did not include epilepsy or seizures. On an unspecified date, the patient presented with memory loss, unconsciousness, convulsions and muscle rigidity. On Extension Day 795 (b) (6), while receiving siponimod 2 mg/day during the open-label treatment phase of the extension phase of Study A2201, the patient had generalized tonic-clonic seizure which resulted in hospitalization. During hospitalization, the patient's blood pressure was 140/90 mmHg, his pulse rate was 80/minute and the Investigator reported that seizures were witnessed. On the same day (b) (6), the patient's cranial CT scan showed sub-acute vascular lesions on the left ventricle and cerebral atrophy; the Investigator noted a few additional old lesions which may have been vascular, but were more likely due to MS. On Extension Day 1532 (b) (6), the patient received the last dose of study medication. On Extension Day 1544 (b) (6), the patient withdrew consent and did not enter the follow-up phase of study.

2. Patient (b) (6) was a 48-year-old woman with MS diagnosed in (b) (6) with conversion to SPMS in (b) (6). Prior disease-modifying treatment for MS included azathioprine, which was discontinued in (b) (6) due to an unspecified reason and glatiramer acetate, which was discontinued on (b) (6) due to lack of efficacy. The

patient's baseline EDSS score on (b) (6) was 6.5. The patient's medical history included optic neuritis (b) (6) vitamin D deficiency ((b) (6), ongoing) and vertigo ((b) (6), ongoing). Concomitant medications included vitamin D for vitamin D deficiency, expanthenol for inflammation of skin, methylprednisolone for MS relapse and reviparin sodium as prophylaxis. The patient received the first dose of study medication on Day 1 (b) (6). On Day 244 (b) (6), the patient experienced an epileptic seizure (epilepsy) and was hospitalized on an unspecified date. Later, on the same day (b) (6), the event (epilepsy) improved to non-serious and the patient was treated with levetiracetam. No action was taken with siponimod due to the event (epilepsy). The patient's hospital discharge details were not reported. The patient received the last dose of study medication on Day 728 (b) (6) and completed the study. The epilepsy had not resolved at the time of last reporting.

Reviewer Comment: These cases are concerning because they represent first seizures in patients without prior history of epilepsy.

3. Patient (b) (6) was a 44-year-old man with MS diagnosed in (b) (6) and SPMS diagnosed in (b) (6) Prior disease-modifying treatment for MS included interferon beta-1a, which was discontinued due to conversion to SPMS on (b) (6). The patient's baseline EDSS score on (b) (6) was 6.5. The patient's medical history included rib fracture and folate deficiency (both in (b) (6)), fatigue ((b) (6), ongoing), muscle spasticity ((b) (6), ongoing), and depression, hemangioma, melanocytic nevus, and onychomycosis (all in (b) (6), ongoing). Concomitant medications included baclofen for spasticity; amantadine for fatigue; Tamsulosin for urinary retention; sulfamethoxazole/trimethoprim for urinary tract infection; cholecalciferol, thiamine, methylprednisolone, and tocopherol for prophylaxis of MS progression; potassium chloride for loss of potassium because of steroid treatment; and pantoprazole sodium sesquihydrate for prevention of gastric ulcer. The patient received the first dose of study medication on Day 1 ((b) (6). On Day 267 ((b) (6)), the patient was hospitalized with a diagnosis of epilepsy. Treatment for epilepsy included carbamazepine. No action was taken with the study medication due to this event. Epilepsy was considered resolved on the same day (b) (6). On Day 278 (b) (6), treatment with carbamazepine was stopped and levetiracetam was started. The patient's hospital discharge details were not reported. The patient received the last dose of study medication on Day 1008 (b) (6) and completed the study.

Reviewer Comment: The diagnosis of epilepsy requires two seizures without obvious inciting cause. This patient's events are not described with sufficient detail to justify the diagnosis given, and the rapid treatment switch from carbamazepine to levetiracetam raises questions about whether a focal finding on EEG prompted the initial therapy choice. Of note, the patient's chronic medications include amantadine, which lowers

seizure threshold.

4. Patient (b) (6) was a 52-year-old woman with MS diagnosed in (b) (6) and SPMS diagnosed in (b) (6). Prior MS therapies included interferon-beta 1a discontinued on (b) (6) due to an adverse event and glatiramer acetate discontinued on (b) (6) due to lack of efficacy. The patient's baseline EDSS score on (b) (6) was 6.5. The patient's medical history included depression ((b) (6), ongoing), hypothyroidism ((b) (6), ongoing), urine incontinence ((b) (6), ongoing), iron deficiency ((b) (6), ongoing), eye nevus, mitral valve incompetence (both in (b) (6), ongoing), and gait disturbance (diagnosis year not reported). Concomitant medications included tamsulosin for urinary incontinence, fluoxetine for depression and fatigue, amantadine sulfate for MS related fatigue, fampridine as prophylaxis for improvement of walking ability, ramipril and hydrochlorothiazide for hypertension, levothyroxine sodium for hypothyroidism, influenza vaccine as prophylaxis, acetylsalicylic acid for headache, and simvastatin for hypercholesterinemia. The patient underwent skin biopsy for atypical nevus on the nose, mole excision of left lower leg for atypical nevus, and rehabilitation therapy for stabilization of MS. The patient received the first dose of the study medication on Day 1 ((b) (6)). On Day 899 ((b) (6)), the patient was hospitalized with acute left sided hemiparesis. On the same day, the patient was also diagnosed with epileptic seizure and cerebral ischemia. Differential diagnosis was ischemic stroke and Todd's paresis after seizure. Treatment included acetylsalicylic acid, alteplase, levetiracetam, and midazolam. The patient also underwent lysis therapy with tissue plasminogen activator. No action was taken with siponimod due to these events. The events (hemiparesis, epilepsy, cerebral ischemia) were considered resolved on the same day ((b) (6)). On Day 900 ((b) (6)), the patient's electroencephalogram and ultrasound scan were normal, and angiogram was abnormal which showed a lesion due to multiple sclerosis with suspected cerebral anterior aneurysms. The patient started rehabilitation therapy and was discharged from the hospital on Day 905 ((b) (6)) after complete recovery. On Day 963 ((b) (6)), the patient was hospitalized with partial seizures. The patient's CT scan and angiography showed known lesions due to MS and creatine kinase elevated (181 U/L). The patient was treated with levetiracetam. No action was taken with siponimod due to this event. The event was considered resolved on the next day ((b) (6)) and the patient was discharged from the hospital. The patient received the last dose of the study medication on Day 1072 ((b) (6)) and completed the study. Of note, the other non-serious AEs during the study included fall-four episode ((b) (6))

Reviewer Comment: The patient received alteplase for suspected stroke which was retrospectively changed to a Todd's paralysis diagnosis. The patient's chronic medications include several (i.e., fluoxetine, fampridine) associated with increased risks

of seizure. The repeated falls raise concern for occult epileptic events preceding the event prompting the epilepsy diagnosis.

5. Patient (b) (6) was a 59-year-old woman with MS diagnosed in (b) (6) and SPMS diagnosed in (b) (6) Prior disease-modifying treatment for MS included mitoxantrone, which was discontinued in (b) (6) due to unspecified reasons and azathioprine, discontinued in (b) (6) due to lack of efficacy. The patient's medical history included urinary incontinence, ((b) (6), ongoing), epilepsy ((b) (6), ongoing), depression ((b) (6), ongoing), subdural hematoma ((b) (6)), upper limb fracture ((b) (6)), varicose vein ((b) (6), ongoing), and osteopenia ((b) (6), ongoing). Concomitant medications included sertraline for depression, tolterodine tartrate for urinary incontinence, baclofen for spasticity, oxcarbazepine for epilepsy, and calcium-vitamin D for dietary supplement therapy. At screening (b) (6), the patient's blood pressure was 140/80 mmHg, heart rate was 66 BPM, and ECG was normal. The patient's baseline EDSS score on (b) (6) was 6.5. The patient received the first dose of the study medication on Day 1 ((b) (6)). On Day 46 ((b) (6)), the patient presented with headache lasting 2 days and was diagnosed with hypertension. On Day 48 ((b) (6), the patient went to the emergency room due to an epileptic seizure first episode. She was treated with valsartan and isotonic serum injection. No action was taken with the study medication due to these events. On Day 49 ((b) (6)), the first seizure was considered resolved and the patient was discharged from the emergency room. On Day 394 ((b) (6)), the patient had a second epileptic seizure which resulted in hospitalization. The patient's MRI showed no hemorrhage or acute infarction. Treatment included levetiracetam, acetylsalicylic acid, and physiological saline solution. No action was taken with the study medication due to this event. On Day 398 ((b) (6)), the second seizure was considered resolved and the patient was discharged from the hospital. An electroencephalogram on Day 403 ((b) (6)) did not demonstrate epileptic discharge. On Day 452 ((b) (6)), the patient had a third epileptic seizure and was hospitalized. The patient was treated with diazepam, phenytoin, and midazolam. No action was taken with the study medication due to this event. On Day 456 ((b) (6)), the third seizure was considered resolved and the patient was discharged from the hospital. On Day 541 ((b) (6)), the patient had a fourth epileptic seizure and was hospitalized. No treatment was reported for this event. No action was taken with the study medication due to this event. On Day 543 ((b) (6)), the patient had recovered from the fourth seizure and was discharged from the hospital on next day ((b) (6)). The patient received the last dose of study medication on Day 568 ((b) (6)) and completed the study.

Reviewer Comment: This case has several notable confounding factors. She has epilepsy treated with an anticonvulsant approved for partial seizures, but several EEGs failed to

reveal an epileptic focus suggesting a possibility of a generalized epilepsy. There is a history of head trauma (subdural hematoma), an independent risk factor for epilepsy. Sertraline, which can lower seizure threshold, was listed as a chronic medication.

6. Patient (b) (6) was a 55-year-old woman with MS diagnosed in (b) (6) and SPMS diagnosed in (b) (6) Prior disease-modifying treatment for MS included mitoxantrone which was discontinued on (b) (6) due to lack of efficacy. The patient's baseline EDSS score on (b) (6) was 6.5. The patient's medical history included epilepsy ((b) (6)). Concomitant medications included baclofen, oxybutynin, and tizanidine for MS symptoms, potassium chloride and methylprednisolone sodium succinate for MS relapse, Augmentin, nystatin, akritoin for urinary tract infection, and nadroparin calcium as prophylaxis. The patient received the first dose of study medication on Day 1 ((b) (6)). On Day 920 ((b) (6)), the patient presented with post-ictal confusion, weakness and somnolence and was hospitalized with a diagnosis of tonic clonic seizures. Treatment included levetiracetam. No action was taken with the study medication due to this event. The seizure was considered resolved on same day ((b) (6)). On Day 924 ((b) (6)), EEG showed generalized paroxysmal abnormalities. On Day 930 ((b) (6)) the patient was discharged from the hospital. The patient received the last dose of study medication on Day 987 ((b) (6)) and completed the study.

7. Patient (b) (6) was a 55-year-old woman with MS diagnosed in (b) (6) and SPMS diagnosed in (b) (6) Prior disease-modifying treatment for MS included interferon beta-1a, which was discontinued on (b) (6), due to lack of efficacy. The patient's baseline EDSS score on (b) (6) was 4.5. The patient's medical history included appendicitis ((b) (6)), tonsillectomy ((b) (6)), aortic valve disease ((b) (6), ongoing), and hysterectomy ((b) (6)). Concomitant medication included fampridine for stabilization of ambulatory ability. The patient received the first dose of study medication on Day 1 ((b) (6)). On Day 614 ((b) (6)), the patient experienced loss of consciousness, convulsions, muscle rigidity and had postictal memory loss. She was diagnosed with epilepsy and was hospitalized. Treatment included clobazam. Treatment with the study medication was temporarily interrupted from Day 615 ((b) (6)) due to the seizure. On the same day ((b) (6)), fampridine was discontinued and the epilepsy was considered resolved. Treatment with the study medication was restarted on Day 616 ((b) (6)). The patient was discharged from the hospital the next day ((b) (6)). The patient received the last dose of study medication on Day 820 ((b) (6)) and completed the study.

Reviewer Comment: This patient, and others within this group of narratives, was being treated with fampridine, a therapy with a known, labeled risk of seizures. The

discontinuation of fampridine noted in the history demonstrates someone's concern that fampridine had a role in this event. A role for siponimod cannot be excluded, however.

8. Patient (b) (6) was a 45-year-old woman diagnosed with MS in (b) (6) and SPMS in (b) (6) Prior disease-modifying treatment for MS included betaferon and azathioprine, both discontinued due to lack of efficacy in (b) (6) and (b) (6), respectively. The patient's baseline EDSS score on (b) (6) was 6.0. The patient's medical history included brain biopsy (result unknown, (b) (6)) and epilepsy ((b) (6), ongoing). Concomitant medications included valproic acid for epilepsy, baclofen, amitriptyline and oxybutynin for MS, ranitidine for prophylaxis, lamotrigine for epilepsy, emollients and protectives, bilastine, clemastine fumarate for atopic dermatitis, omeprazole for erosive gastropathy, methylprednisolone for MS relapse, diazepam for epileptic seizures and nitrofurantoin for acute cystitis. On (b) (6), during the screening epoch, the patient was hospitalized in intensive care due to recurrent epileptic seizures. She was treated with thiopental, bemiparin, and treatment with valproic acid was ongoing. The patient did not experience attacks post-treatment. Epilepsy was considered resolved on (b) (6), and the patient was discharged from the hospital. The patient received the first dose of study medication on Day 1 ((b) (6)). There were no further events.

   Reviewer Comment: Seizures occurred prior to initiation of siponimod therapy in a patient with a history of epilepsy.

9. Patient (b) (6) was a 48-year-old woman with MS diagnosed in (b) (6) and SPMS diagnosed in (b) (6) Prior disease-modifying treatment for MS included interferon beta 1a, discontinued in (b) (6) due to an unspecified (other) reason. The patient's baseline EDSS score on (b) (6) was 4.5. The patient's medical history included subdural hygroma and CSF shunt operation ((b) (6), ongoing), CSF shunt operation ((b) (6), ongoing), epilepsy ((b) (6), ongoing), presbyopia ((b) (6), ongoing), humerus fracture ((b) (6)), onychomycosis, ulna fracture, subarachnoid hemorrhage, skull fracture, and spinal compression fracture ((b) (6)), and osteoporosis ((b) (6) ongoing). Concomitant medications included ergenyl chrono and levetiracetam for epilepsy, calcium carbonate, colecalciferol, and alendronate sodium for osteoporosis, itraconazole for onychomycosis, azithromycin for pharyngitis, potassium chloride for prevention of hypokalemia, valproate sodium, and pantoprazole sodium sesquihydrate for prophylaxis during steroid treatment, atorvastatin calcium for hypercholesterolemia, ketoprofen, ascorbic acid-rutoside for laryngitis, pseudoephedrine cetirizine for runny nose, acyclovir for labial herpes. The patient received the first dose of study medication on Day 1 ((b) (6). On Day 14 ((b) (6)), the patient experienced speech disability,

motor aphasia along with weakness of right upper limb and was hospitalized with the diagnosis of Tod's aphasia and seizure. On the same day ([(b) (6)], the laboratory tests showed hyponatremia (sodium at 129.3215 mmol). At the time of the events, the patient was on valproic acid and levetiracetam for epilepsy. On the same day [(b) (6)], the event (seizure) was considered resolved. On Day 16 [(b) (6)], the treatment with study medication was temporarily interrupted due to the events of aphasia and seizure, with the last dose reported on Day 15 [(b) (6)]. On an unspecified date, the patient's CT scan of the head showed subdural hygroma in the left frontal parietal region, MRI of the head showed inactive demyelination plaques in the brain stem and cerebellum, two active demyelination foci on the left and right sides of the semioval centre, drain of the shunt outside the ventricular system. On Day 16 [(b) (6)], the patient continued to have problems with speech. MRI of the head showed subdural bilateral hygroma, signs of the shunt drain sliding out of the ventricular system, demyelination lesions and atrophic dilation of the supratentorial ventricular system; however, two active demyelination foci previously observed, in the semiovale centres on the left and right sides were not visible. The patient was treated with methylprednisolone sodium succinate, ketoprofen, mannitol, metamizole sodium and omeprazole. On Day 23 [(b) (6)], the patient was discharged from the hospital and the event (aphasia) was considered resolved on the following day [(b) (6)]. The treatment with study medication was restarted on Day 28 [(b) (6)]. On Day 146 [(b) (6)], the patient again experienced a speech abnormality, motor aphasia. She was hospitalized and was diagnosed with a second seizure. The duration of each seizure episode was about 20 to 30 minutes. The patient was treated with an increased dose of levetiracetam with gradual withdrawal of valproic acid. No action was taken with the study medication due to this event. On Day 153 [(b) (6)], the seizure was considered resolved and the patient was discharged from the hospital. The patient received the last dose of study medication on Day 581 [(b) (6)] and completed the study.

Reviewer Comment: This patient had an intracerebral shunt showing signs of displacement with an enhancing juxtacortical lesion near the shunt itself. A patient with longstanding history of epilepsy with these two independent risk factors for provoked seizures would be at higher risk of seizing compared to other patients with MS.[9]

10. Patient [(b) (6)] was a 43-year-old man with MS diagnosed in [(b) (6)] with SPMS diagnosed in [(b) (6)] Prior disease-modifying treatment for MS included interferon beta-1b which was discontinued on [(b) (6)] due to an unspecified reason. The patient's baseline EDSS score on [(b) (6)] was 6.0. The patient's medical history included anxiety, hypoacusis, hypertension (ongoing), epilepsy, micturition urgency, and incontinence ([(b) (6)], ongoing). Concomitant medications included venlafaxine and

alprazolam, sertraline for anxiety, oxybutynin, alfuzosin, and fosfomycin trometamol for urinary urgency, bisoprolol fumarate for tachycardia, methylprednisolone and baclofen for multiple sclerosis, levetiracetam, phenytoin sodium, valproic acid for epilepsy, and desloratadine, betamethasone, and prednisolone for cutaneous rash. The patient received the first dose of study medication on Day 1 ((b) (6)). The treatment with study medication was permanently discontinued on Day 86 ((b) (6)) due to a protocol deviation (patient had been taking prohibited drug, hidantine). The patient started following the abbreviated visit schedule. The patient received the last dose of study medication on Day 85 ((b) (6). On 1(b) (6), 589 days after the last dose of study medication, the patient had a generalized tonic colonic seizure. The patient was hospitalized and experienced another episode of tonic colonic seizure. The patient's scheduled MRI scans performed on Month 12 visit ((b) (6)) showed appearance of a new T2 lesion. An MRI scan at the Month 24 visit ((b) (6)) showed two new T2 lesions with one Gadolinium enhancing lesion. Based on these MRI reports, new enhancing cortical lesions, the consequence of MS relapse, were considered to be the reason for the seizure. On (b) (6), his ECG showed sinus rhythm and he was diagnosed with epilepsy, and respiratory depression. On an unspecified date, the patient underwent Bilevel Positive Airway Pressure treatment (18/6) until he recovered his regular respiratory function. The patient had a partial motor seizure (lower right limb) and another partial seizure on his right face. Treatment included levetiracetam, valproic acid, methylprednisolone and baclofen. The seizure stopped after receiving the medication. The event (respiratory depression) was considered resolved on the same day ((b) (6)). The patient completed the study and attended the End of Study visit.

Reviewer Comment: The patient was discharged from the study for taking hidantine, a phenytoin derivative used for epilepsy with simultaneous treatment with levetiracetam and valproate. A patient requiring three anticonvulsants has refractory epilepsy by definition and therefore it is not surprising that they had a seizure, and the event occurring 589 days after last dose of siponimod in setting of new enhancing lesions strongly suggests etiologies other than siponimod.

Strokes, Transient Ischemic Attacks, Subarachnoid Hemorrhage, Aneurysm

There were nine neurovascular SAEs reported in patients in the long-term safety pools. There were four strokes and three transient ischemic attacks in siponimod-treated patients. There was a single case of subarachnoid hemorrhage reported in Study X2206. Finally, there was an intracranial aneurysm reported for a patient in Study A2304.

One stroke was identified during the titration period and three occurred during maintenance therapy. All transient ischemic attacks (TIAs) and the subarachnoid hemorrhage were reported during maintenance therapy. The SAE of aneurysm was noted two days after discontinuation of

siponimod.

The lone case of aneurysm was noted in a patient with a history of a carotid aneurysm predating siponimod therapy, with evolution of aneurysms over 200 days after discontinuation of siponimod. The relationship between the aneurysms and siponimod is not clear but patient's history suggests smoking, a previous history of vasculopathy as indicated by aneurysms, angioedema, and nosebleeds did play a role.

There was a single fatal stroke in a placebo-treated patient in Study A2304.

Ischemic Stroke

Patient (b) (6) was a 58-year-old man with SPMS who received his first dose of siponimod on (b) (6) On Day 5 (b) (6), the patient felt sick and experienced symptoms including motor deficit and difficulty in speaking/expressive aphasia. On the same day, the patient was diagnosed with an ischemic stroke which led to hospitalization. The patient was treated with acetylsalicylic acid, betahistine, and pramiracet. Treatment with study medication was permanently discontinued due this SAE, and the patient received the last dose on Day 05 (b) (6). The patient was discharged from the hospital on Day 8 (b) (6). The ischemic stroke was considered resolved on Day 382 (b) (6) with patient returning to reported baseline neurological examination status. The patient discontinued the study due to this SAE and attended the End of Study visit.

Subarachnoid Hemorrhage

Patient (b) (6) was a 46-year-old woman with dermatomyositis who received her first dose of siponimod on (b) (6). The patient was hospitalized on Day 302 (b) (6) for the event of subarachnoid hemorrhage after presenting to an emergency room. A chest X ray was performed on the same day and was interpreted as normal. The patient was admitted to the emergency room, stating exertional headaches since Day 292 (b) (6) that were not resolving. A CT of the head and an MRI of the head showed diffuse subarachnoid hemorrhage (CTCAE grade 4) in the right frontal temporal lobes. Study medication was temporary interrupted. A neurosurgical consult recommended an angiogram which was performed the next day. The angiogram found no aneurisms and was interpreted as a normal cervical and cerebral angiogram. There was no explanation for the subarachnoid hemorrhage. The patient remained in the hospital for monitoring. On Day 304 (b) (6) the patient received a lumbar puncture that demonstrated the presence of red blood cells but no findings consistent with infection. An angiogram performed on Day 309 (b) (6) confirmed normal cervical and cerebral angiogram, with no evidence of aneurysms or vasculitis. The patient had no weakness and no syncopal symptoms. Her headaches improved over her hospitalization. On Day 309 (b) (6), the patient was reported to be completely recovered from the event and was discharged from hospital on same day. Siponimod remained discontinued.

Aneurysm

Patient (b) (6) was a 50-year-old woman with secondary progressive MS who received her first dose of siponimod on (b) (6). The patient's medical history included knee arthroplasty (b) (6), laparoscopy (b) (6) gestational diabetes (b) (6), premature menopause (b) (6), bradycardia ((b) (6), ongoing), depression (b) (6), pneumonia (b) (6) aortic valve incompetence, left ventricular hypertrophy, headache, chronic pain, nosebleeds, migraine, tinnitus, angioedema (all in (b) (6) ongoing), Gilbert's syndrome, gallbladder disorder (both in (b) (6)), and carotid artery aneurysm ((b) (6), ongoing). The patient was attempting to quit smoking with a lengthy history of tobacco use. The patient received the last dose of study medication on Day 268 (b) (6) and completed the study. On (b) (6), two days after the last dose of study medication, the patient's MRI showed alteration in the brain volume with T2 lesions, new T1 hypointense lesions, new enlarged T2 lesions, and gadolinium-enhanced T1 lesions and was diagnosed with intracranial aneurysm (left-sided intracranial artery aneurysm). On (b) (6), 93 days after the last dose of study medication, the patient further developed left A1/2 junction and intracranial aneurysm (left-sided anterior communicating artery aneurysm). On (b) (6), 212 days after the last dose of study medication, the patient was hospitalized due to the event (intracranial aneurysm) and underwent stent and coil procedure on the same day. The event (intracranial aneurysm) was considered resolved on the same day (b) (6) and the patient was discharged from the hospital on the next day (b) (6).

Falls, Tendon Rupture, and Fractures

There appears to be an imbalance of SAEs related to patients falling and suffering significant orthopedic injuries. I identified five patients in the siponimod treatment reporting SAEs of fall, but many SAEs such as concussions, laceration, and fractures of the ankle, tibia with fibula, and femur that occurred with preceding falls were not coded with the SAEs of fall but simply noted by the injuries themselves. There were seven patients with SAEs of femoral neck fracture and six of these fractures occurred with a preceding documented fall in siponimod-treated patients; there was single fall with hip/femoral neck fracture in a placebo-treated patient. There was a SAE report of traumatic fractures caused by a cow kick with possible fall preceding the cow-induced injury. Additionally, there was a traumatic subdural hematoma identified in that was to a fall, and a fatal fall associated with possible seizure was discussed in Section 8.4.1. Finally, there was a single patient with SAE of tendon rupture with an unclear precipitating event.

While falls are not an unexpected event in patients with SPMS because of the progressive disability associated with the disease, the individuals who were falling and experiencing significant injuries did not, on average, have the most advanced disability. The mean EDSS of patients with these fall-related events was 4.8, a score below the reported median EDSS (6.0) for enrollment in Study A2304, and a score that is not associated with disability requiring a walking aid.

There was no clear relationship to duration of treatment and these traumatic falls with events

occurring between Study Days 10 and 1583. It is notable that none of these SAEs occurred during the titration period when cardiovascular changes that might promote bradycardia and syncope are most likely to occur, and only one event coincided with a reported syncopal event. Without a clear pattern of onset and plausible etiology to explain the higher frequency in siponimod-treated patients, establishing a clear relationship to siponimod is difficult.

Traumatic Fracture

Patient (b) (6), a 58-year-old woman with SPMS, received her first dose of study medication on (b) (6) Her EDSS was 4.0 prior to this event. There was a remote history of sciatica. On Day 644 (b) (6), the patient received multiple kicks from a cow resulting in bilateral rib fractures with flail chest, C7 facet joint fracture, splenic laceration, traumatic liver injury, left lateral clavicle fracture, and traumatic right hemothorax. The patient's history noted living on a farm and the injury is presumed to have occurred during routine daily activities of living. She was hospitalized due to her injuries. The hemothorax was managed by thoracostomy and placement of a chest tube. Most of the fractures were managed non-operatively with splints. The C7 fracture was stabilized surgically. No action was taken with the study medication during hospitalization. The events (traumatic liver injury, splenic rupture, traumatic hemothorax, traumatic fracture) were considered resolved on Day 658 (b) (6) and the patient was discharged from hospital and transferred to a rehabilitation center. On Day 672 (b) (6), the patient was hospitalized due to mechanical fall and right buttock pain due to the fall. Imaging of the pelvis and right hip showed no fracture. Pain was managed with oxycodone. No action was taken with the study medication due to these events. The event (musculoskeletal pain) was considered resolved on Day 679 (b) (6) and the patient was discharged from the hospital. The patient experienced SAEs of Bowen's disease and basal cell carcinoma on Day 717 (b) (6) diagnosed during a study-related visit. The patient received the last dose of study medication on Day 723 (b) (6) and completed the study.

Displaced Tibia and Fibula Fractures

Patient (b) (6) was a 54-year-old woman with SPMS who received her first dose of siponimod on (b) (6) She had a past medical history notable for ankle fracture (b) (6) upper limb fracture (b) (6) and concurrent medical conditions included muscle spasticity, osteoporosis, and vitamin D deficiency. She was taking fampridine for symptomatic gait improvement. Her EDSS was 6.0. On Day 667 (b) (6) the patient fell at home and was hospitalized with fractures of both tibial bones and left fibular bone. A CT scan of lower limbs showed displaced communitive mid-diaphyseal fracture of the left tibia and proximal fracture of the left fibula and non-displaced burst fracture of the proximal part of the right tibia. On Day 668 (b) (6) a CT of the right knee showed right intra-articular proximal tibia and fibula fracture with swelling supra patellar and soft tissue and there was no significant displacement. On the next day (b) (6), the patient underwent orthopedic surgery with external fixation of the right leg under general anesthesia and during the procedure, the patient was noted to have osteoporosis. On Day 671 (b) (6), the patient underwent physical therapy. No

action was taken with the study medication due to these events. The investigator stated that the patient had trouble with walking and there was more pronounced weakness in both legs. The patient was discharged from the hospital on Day 681 (b) (6). On Day 776 (b) (6), the patient's external fixators were removed. The events (fracture displacement - fibula and tibia) were considered resolved with sequelae on Day 784 (b) (6). The patient received last dose of study medication on Day 1012 (b) (6) and completed the study without additional SAEs.

Femoral Neck Fracture

1. Patient (b) (6) was a 55-year-old woman with SPMS who received her first dose of siponimod on (b) (6). The patient's baseline EDSS was 6.0. One Day 64 (b) (6) the patient had a fall which resulted in hospitalization with the diagnosis of femoral neck fracture. Treatment included paracetamol and enoxaparin. No action taken with the study medication due to this event. The patient underwent prosthesis implantation under general anesthesia on Day 67 (b) (6) and the event (femoral neck fracture) was considered resolved. The patient also underwent rehabilitation therapy on Day 105 (b) (6). The patient received the last dose of double-blind study medication (siponimod) on Day 740 (b) (6) and switched to open label study medication on Day 741 (b) (6). The patient received the last dose of open label study medication on Day 1076 (b) (6) and completed the study.

2. Patient (b) (6) was a 46-year-old woman with SPMS who received her first dose of siponimod on (b) (6). Her past medical history was notable for epilepsy, but no anticonvulsants were listed among her concurrent medications. The patient had an EDSS of 3.5. She experienced a SAE of erosive gastritis on Day 60 (b) (6). On Day 150 (b) (6), the patient lost consciousness and fell. On the same day, the patient was hospitalized. A radioisotope thermoelectric generator study confirmed a left femoral neck fracture. The patient underwent surgical reposition of the fractured bone. No action was taken with the study medication due to the femoral neck fracture. The femoral neck fracture was considered resolved on Day 155 (b) (6) and the patient was discharged from the hospital. The patient received the last dose of study medication on Day 460 (b) (6) and completed the study.

3. Patient (b) (6) was a 43-year-old woman with SPMS who received her first dose of siponimod on (b) (6). Her baseline EDSS was 6.0. Her prior medical history was notable for muscle spasticity and gait disturbance, for which she received fampridine. On Day 515 (b) (6), she experienced a fall which resulted in femoral neck fracture and hospitalization. On the following day (b) (6), radiography confirmed a femoral fracture for which he underwent open reduction internal fixation. Treatment with study medication was interrupted on Day 516 (b) (6) due to the fracture and need for avoidance of oral medication prior to surgery. Study medication

was restarted the next day (b) (6). The patient was discharged from the hospital on Day 559 (b) (6). She experienced no other SAEs during the study. She received her last dose of study medication on Day 620 (b) (6) and completed the study.

Ankle Fracture

Patient (b) (6) a 31-year-old woman with relapsing MS who received her first dose of siponimod 0.5 mg on (b) (6). On Day 29 (b) (6), while receiving siponimod 0.5 mg/day during the during dose-blinded phase of the extension phase of Study A2201, the patient had a fall resulting in dislocation and fracture of the left ankle joint; there was radiographic evidence of a multifragment fracture on the fibular side. The patient was hospitalized on the same day (b) (6). The final diagnosis was closed highly dislocated bimalleolar Weber C-type ankle joint dislocation fracture and closed soft tissue lesion. On the same day (b) (6), the patient underwent an osteosynthesis operation. Of note, the patient's last recorded EDSS prior to the fall was 2.0. She underwent a surgical revision of this ankle procedure (screw removal) on (b) (6). The patient completed the dose-blinded and open-label phases of the extension study without further SAEs.

Femur Fracture

Patient (b) (6), a 42-year-old woman with relapsing MS, received the first dose of Core Study medication on (b) (6). The last known EDSS score before the event was 4.0 on Extension Day 51 (b) (6). The patient received the last dose of study medication on Extension Day 32 (b) (6) On (b) (6), 30 days after the last dose of study medication, during the dose-blinded phase of the Extension Study, the patient fell on the stairs and was taken to the emergency room of a hospital. The patient was diagnosed with right femur fracture. The patient was operated on the same day. Treatment included enoxaparin, paracetamol and morphine. The event (femur fracture) was ongoing at the time of last reporting. The patient withdrew consent on (b) (6) and was lost to follow-up.

Radius Fracture

Patient (b) (6) is a 59-year-old woman with SPMS who received her first dose of siponimod on (b) (6) She had a history of a bunionectomy in (b) (6) and concurrent medical problems included osteoarthritis of the spine and hypothyroidism (treated with levothyroxine). Her baseline EDSS was 4.5. On Day 561 (b) (6), the patient had a fall which resulted in a fracture of the left distal radius. The patient came to the emergency department where a fracture in the distal epiphysis of the left radius bone was confirmed. The articular surface was also involved; multiple fracture lines and a small bone fragment separation were also noted. On Day 567 (b) (6), the patient was hospitalized and underwent fracture reduction and osteosynthesis. No action was taken with siponimod due to this event. On Day 584 (b) (6), the plaster cast was removed. On an unspecified date, X-ray showed good evolution of the surgically repaired injury. The patient condition was improving from the event (radius fracture) at the time of last reporting. There were no other

SAEs reported for this patient. The patient received the last dose of study medication on Day 639 (b) (6) and completed the study.

Laceration

1. Patient (b) (6) was a 41-year-old woman with SPSM. Her first dose of siponimod was on (b) (6). There was distant history of seizure noted in (b) (6) She had a concurrent diagnosis of gait disturbance and was taking dantrolene and baclofen for spasticity. On Day 206 (b) (6), the patient was hospitalized after falling backwards and sustaining a laceration on the back of her head (grade 3) at the site of a previous injury sustained from a fall that had occurred 11 days prior. Her CT scan showed no cranial vault fracture or intracranial pathology. The patient underwent cleaning and closure of the laceration. No action was taken with siponimod. The patient experienced more falls on Day 448 (b) (6), Day 450 (b) (6), and Day 454 (b) (6) and reported from left knee pain and swelling on Day 456 (b) (6). An X-ray of the knee showed no fracture. Further examination showed mild swelling but no focal tenderness. The head laceration was considered resolved on Day 456 (b) (6), and the patient was discharged from the hospital. On Day 468 (b) (6) the patient had knee stiffness with pain. On Day 483 (b) (6), the patient reported immobility. On the following day (b) (6), the patient complained of an increase in stiffness and pain in her knee and was unable to bear weight or transfer from wheelchair. On Day 485 (b) (6), the patient was diagnosed with immobility, and was hospitalized for surgical repair of the flexor in her left knee. On Day 491 (b) (6) an MRI scan showed a small longitudinal vertical tear of lateral meniscus reaching both articular surfaces. Siponimod therapy continued. The event (immobility) was considered resolved with sequelae on Day 573 (b) (6) and the patient was discharged. The patient received the last dose of study medication on Day 587 (b) (6) and completed the study without further SAEs.

2. Patient (b) (6) was a 51-year-old man with MS diagnosed in (b) (6) and SPMS diagnosed in (b) (6) On Day 318 (b) (6), the patient had a fall and was hospitalized with the diagnosis of cut wound of the scalp (laceration), concussion, and 9th rib fracture on the left side (rib fracture). The patient was treated with metamizole sodium, papaver somiferum tincture and did not require any operative treatment. No action was taken with the study medication due to these events. The event (laceration) was considered resolved on the same day (b) (6). The event (concussion) was considered resolved on Day 320 (b) (6) and the patient was discharged from the hospital. The event (rib fracture) was considered resolved on Day 372 (b) (6).

Subdural Hematoma

Patient (b) (6) was a 55-year-old woman with SPMS who received her first dose of siponimod on (b) (6) Her past medical history was notable for a subdural hematoma in

(b) (6). Her EDSS prior to this SAE was 6.0. On Day 418 (b) (6), the patient experienced a fall. On the next day (b) (6), the patient was hospitalized. She reported increased pain in her head and a problem with memory; the patient was diagnosed with traumatic intracranial hemorrhage, spinal deformity (end plate deformity of 5th lumbar vertebra), subarachnoid hematoma, cerebral contusion, and subdural hematoma. On Day 431 (b) (6), the patient's CT scan of the skull showed abnormal results (bleeding in right temporal area due to contusion). On Day 438 (b) (6), the patient's abdominal CT scan showed abnormal results (end plate deformity 5th lumbar vertebra). No action was taken with the study medication due to these events. On Day 442 (b) (6), the events (subdural hematoma, traumatic intracranial hemorrhage, subarachnoid hematoma, contusion) were considered resolved and the patient was discharged from the hospital. The patient received the last dose of study medication on Day 601 (b) (6) and completed the study without further SAEs.

Concussion

Patient (b) (6) was a 58-year-old woman with SPMS who received her first dose of siponimod on (b) (6) She had a past medical history notable for a prior osteoporotic fracture and was on several treatments for osteoporosis. Her EDSS was 4.5. On Study Day 10 (b) (6), the patient fell down stairs due to her disability. On the same day, the patient was presented with a skull fracture (temporal bone) and concussion which resulted in hospitalization. The CT scan further confirmed concussion and no fracture. Treatment included an unspecified antibiotic. No action was taken with siponimod due to the event. On Day 15 (b) (6), the concussion was considered resolved and the patient was discharged from the hospital. There were no more SAEs reported for this patient. The patient received the last dose of study medication on Day 844 (b) (6) and completed the study.

Patient (b) (6) was a 57-year-old man with SPMS who received his first dose of siponimod on (b) (6) He had a history of optic neuritis and diplopia. His concurrent medical conditions included muscle spasticity. His baseline EDSS was 6.5. He experienced a SAE during the screening period (pyelonephritis) that was resolved with hospitalization and intravenous antibiotics. He experienced dyspnea and was diagnosed with pulmonary hypertension (a SAE) on Study Day 120. On Study Day 269 (b) (6), the patient experienced a fall. On the same day, the patient underwent CT scan of head and cervical spine and was diagnosed with a concussion. The patient was also noted to have a hematoma on his occipital scalp. Siponimod therapy continued and the concussion was treated conservatively. On Day 272 (b) (6), the patient was discharged from the hospital. The concussion was considered resolved on Study Day 276 (b) (6) The patient received his last dose of siponimod on Day 435 (b) (6) and completed the study.

Tendon Rupture

Patient (b) (6), a 51-year-old woman with relapsing MS received her first dose of siponimod 0.25 mg on (b) (6). The last EDSS recorded nearest to the SAE was 3.0. On Day

1549 (b) (6) of the extension phase of Study A2201, while receiving siponimod 2 mg/day during the open-label treatment phase of the Extension Study, the patient had a tendon rupture (biceps sinew tear) of the left arm. There was no reported preceding event. On Extension Day 1583 (b) (6), the patient was hospitalized, and her supraspinatus and biceps tendon were repaired. No action was taken on the study medication due to this event. The event (tendon rupture) was considered resolved on Extension Day 1583 (b) (6). On Extension Day 1586 (b) (6), the patient was discharged from the hospital. The patient completed the dose-blinded and open-label phases of the Extension Study (last study medication taken on Extension Day 2028 (b) (6) without further SAEs and entered the follow-up phase of the study.

> *Reviewer Comment: Falls and trauma are extremely common in patients with MS. Estimates of annual falling rates are greater than 50%.[10] While there is a small numerical imbalance in cases of serious injury following falls, there is no clear pattern in fall timing relative to initiation of drug, nor a clear unique and plausibly treatment-emergent symptom preceding the falls such as pronounced dizziness or syncope. There are no data on patient's bone status and the role of steroid-induced osteoporosis cannot be understated. A role for siponimod cannot be ruled out but considering the high frequency of falls in this population, and the myriad of risk factors that may exacerbate falls and fall-related trauma in patients with MS, ascertaining what would be at most a very small treatment-emergent effect is difficult.*

Pancreatitis

Pancreatitis is a concern in any drug development program. I identified a single SAE of pancreatitis in any of the clinical trials. The role of siponimod is not clear. Postmarketing reports should be monitored for more cases.

Patient (b) (6), a 51-year-old man with relapsing MS received his first dose of study medication on (b) (6) The patient's general medical history at Core Study Screening included inguinal hernia repair (b) (6), cholecystectomy (diagnosis year not reported), and nephrolithiasis (b) (6). His chronic medical conditions at Core Study Screening included erectile dysfunction (b) (6) hypercholesterolemia (b) (6), diarrhea (b) (6), and depression (b) (6). Concomitant medications during the Extension Study included simvastatin for hypercholesterolemia, citalopram for depression, sildenafil for sexual deficit, loperamide for diarrhea, amlodipineperindopril, amlodipine-olmesartan medoxomil, and hydrochlorothiazide for hypertension, and tizanidine for spasticity. On Extension Day 882 (b) (6), while receiving siponimod 2 mg/day during the open-label treatment phase of the Extension phase of Study A2201, the patient experienced an abdominal pain which resulted in hospitalization. The pain was non-radiating and diffused throughout the abdomen. The patient was afebrile with normal bowel movement without nausea. On the same day (b) (6), the patient's laboratory reports revealed lactate at 3.3 mmol/L (RR: 0.5 to 2.2 mmol/L), C-reactive protein

(CRP) at 30 mg/L (RR: <5 mg/L), AST at 28 U/L (RR: <41 U/L), ALT at 52 U/L (RR: <41 U/L), pancreatic amylase at 1470 U/L (RR: <46 U/L), lipase at 1800 U/L (RR: <60 U/L), leukocytes at 12.7×109/L. On the same day (b) (6), the patient was diagnosed with acute pancreatitis. The study medication was permanently discontinued due to the event (pancreatitis acute) and the patient received the last dose of the study medication on extension Day 882 (b) (6). The patient's abdominal ultrasound showed a slightly enlarged pancreas but no stones. On the next day (b) (6), the patient's abdominal CT scan confirmed the diagnosis of acute pancreatitis with probable calculosis of the distal portion of the main pancreatic duct, which was moderately ectatic upstream with calcifications of the head of pancreas due to chronic inflammation; a hepatic bile cyst was also observed. On Extension Day 889 (b) (6), the event (pancreatitis acute) was considered resolved and the patient was discharged from the hospital with plan of light diet and was recommended to avoid alcohol. He was also advised to take therapy for reconditioning with exercises. The patient discontinued the study due to adverse event (pancreatitis acute) and attended the last visit on (b) (6).

> *Reviewer Comment: This case appears to be confounded by concomitant alcohol use. A possible role of siponimod cannot be excluded. No other cases of pancreatitis were reported in the development program, however.*

Myocardial Infarction

There were two reported SAEs of myocardial infarctions in patients exposed to siponimod. Additionally, there were two deaths attributed to myocardial infarction in siponimod-exposed patients as discussed in 8.4.1. There were no placebo-treated patients who experienced myocardial infarction. There were multiple significant risk factors for myocardial infarction such as smoking history, hypertension, and hypercholesterolemia present in all cases of myocardial infarction that make the relationship of these events to siponimod uncertain.

Patient (b) (6) was a 42-year-old man with RMS. He received his first dose of siponimod 10 mg on (b) (6) At the time of screening, the patient was an active smoker and had been smoking 15 cigarettes per day for 10 years. The patient was hypertensive at screening and during titration with numerous documented systolic blood pressures > 145 mmHg and diastolic blood pressures > 80. Elevated total and LDL cholesterol values were noted on Study Day 7. The patient completed the study and received the last dose of study medication on Day 189 (b) (6). There was a follow-up on Study Day 475, and the patient informed the site that he had been experienced initial symptoms of a myocardial infarction in (b) (6), on Study Day 233, or 45 days after last dose of siponimod. He was hospitalized on Study Day 235; on the same day his creatine kinase was 96.55 µmol/l with a tropinin T of 14.28 µg/l. He had a cardiac catheterization and percutaneous transluminal coronary angioplasty with implantation of a bare metal stent. He was discharged from hospital on Study Day 242. On Study Day 433, he received reassessment for control of the stent.

Reviewer Comment: Myocardial infarction and a possible relationship to siponimod is discussed in 8.5.7.

Hemolytic Uremic Syndrome, Acute Kidney Injury

Patient [(b) (6)]7 was a 47-year-old woman with polymyositis who received her first dose of siponimod on [(b) (6)]. Baseline screening indicated the presence of a normocytic anemia, elevated neutrophil count, elevated C-reactive protein, creatine kinase, aldolase, LDH, ALT, and ANA titer. On Study Day 10, these elevated values remained unchanged and a serum creatinine was normal. On Day 28 [(b) (6)], progressive worsening of pre-existing anemia and new onset of renal insufficiency were reported. Creatinine increased to above the ULN at 90 µmol/L; hemoglobin, hematocrit, and further decreased compared to Day 10 values while MCV remained normal. LDH, AST, creatine kinase, and aldolase remained elevated. The patient experienced some nausea, shortness of breath, diarrhea and reduced appetite between Day 35 [(b) (6)] and Day 49 [(b) (6)]. On Day 49, the patient was hospitalized, and diagnoses of acute renal failure and hemolytic anemia were made. Lung and heart x-ray upon admission showed signs of cardiac insufficiency, and furosemide intravenous therapy was initiated. On the same day, treatment with study medication was discontinued. On Day 50 [(b) (6)] laboratory tests showed further decreased hemoglobin, red blood cell count, hematocrit, and MCV. Creatinine was further increased to 295 µmol/L. LDH was further increased to 920 U/L. CK and CRP remained high. Additional unplanned laboratory values on Day 50 included BUN 17.7 mmol/L, CRP 95.4 mg/L (reference range: 0 – 5) and serum myoglobin 1155 µg/L (reference range: 0 to 76). Local laboratory blood film showed schistocytes, ovalocytes and spherocytes. ANA was further elevated (1:640 compared to baseline), and anti-dsDNA antibodies were not detected. At the local laboratory, serum was positive for autoantibodies including anti-Jo1, anti-RNP anti anti-Ro52. Infection was considered but not confirmed; clostridium toxin and a viral antibody screen were negative. WBC count was within the normal range, neutrophil count was increased, and platelet count was within the normal range. Serum complement levels were low: C3 at 0.30 g/L (reference range: 0.90 to 1.80) and C4 at 0.08 g/L (reference range: 0.10 to 0.40). On Day 52, chest x-ray showed signs of both arterial and venous pulmonary hypertension, multiplied pulmonary interstitium, suspected incipient pulmonary fibrosis and significant cardiomegaly. Culture tests showed no evidence of A/B *Clostridium difficile* antigen and toxins. Further investigations showed that the anemia was hemolytic and consistent with autoimmune origin. Reticulocytes were 2% and haptoglobin was low (less than 0.06 g/L) (reference range: 0.3 to 2.0); direct antiglobulin (Coomb's) test was positive for IgG and C3d. Urinalysis showed protein 3+, blood 2+, 19 RBC/µL, 10 WBC/µL and 2 hyaline casts/µL. The RBC seen in urine casts suggested a possible nephritic syndrome. The patient did not report any significant cold exposure. There were no skin or neurological symptoms. In the past, the patient had occasionally been tested positive for circulating immune complexes ([(b) (6)], but negative in [(b) (6)]). Anti-Sm autoantibodies were detected in [(b) (6)], antineutrophil cytoplasmic antibodies (ANCAs) were detected in [(b) (6)], but tests were negative on Day 50. Serum myoglobin had been increased and Coomb's test was positive in [(b) (6)]. The patient

received treatment with RBC transfusion (2 units on Day 50 and 1 more later), plasmapheresis, hemodialysis and normal saline. Treatment with bosentan was stopped on Day 49 and methylprednisolone dose was increased. The hemolytic anemia was not resolved, and acute renal failure was deteriorating (creatinine 384 µmol/L on Day 52) and dialysis was commenced on Day 53. Platelet counts were 155 × 10^9/L at the time of admission on Day 49 and dropped to 136× 10^9/L on the second and 124 × 10^9/L on the third day of hospital stay. On Day 57, chest X-ray remained unchanged and x-ray of thoracic spine showed osteopenia mild sigmoid scoliosis, flat thoracic kyphosis. No signs of compression fractures or incipient deforming spondylosis. On Day 58 (b) (6), a renal biopsy was performed. The morphology showed protracted/recurrent severe damage of the endothelial cells of the arteries, arterioles and capillaries with fibrinoid necrosis, arterial occlusion with thrombotic microangiopathy and subsequent damage of the glomeruli and interstitium. The appearances resembled those of accelerated/malignant hypertension or atypical hemolytic uremic syndrome (HUS), but not direct endothelial drug toxicity. The kidney damage seems to be permanent such that the patient would require long term hemodialysis. Because of suspected HUS (low haptoglobin, positive Coomb's test, high LDH and elevated free serum hemoglobin), 4 plasmaphereses were performed, also for renal insufficiency, high myoglobin levels in serum secondary to myositis and right-side cardiac insufficiency secondary to pulmonary hypertension, hemodialysis therapy was initiated. On Day 65 (b) (6), the patient was discharged from hospital. There was clinical suspicion of an inborn error in complement.

> *Reviewer Comment: This isolated case appears to involve a complex interaction between the therapy (siponimod), a genetic deficiency in complement, and the patient's autoimmune disease. There is a possible role of siponimod, but no patients in the clinical trials of MS experienced a similar event, and so this may represent a unique interaction between several rare factors.*

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

For the MS trials A2201 and A2034, the study protocol required permanent discontinuation of siponimod therapy for the following:

- Diagnosis of macular edema
- Decrease in FEV1or FVC below 80% of baseline, persistent for 3 months regardless of symptoms
- FEV1 or FVC less than 60% of baseline at any visit
- Increase in ALT ≥ 5 x Upper Limit of Normal (ULN)
- Increase in AST ≥ 5 x ULN
- Histologically confirmed skin cancer
- Pregnancy
- Withdrawal of consent

- Start of another therapy for MS
- Worsening or concerning symptom in opinion of investigator with plausible association to study therapy (*e.g.,* cardiac, hematological, and neurological symptoms)

In the trials enrolling patients with MS, investigators encouraged patients who withdrew from study treatment to remain in the study and follow an abbreviated schedule of follow-up events.

Controlled Pool

In the controlled phases of trials conducted in MS, for siponimod 2 mg, the most common single preferred term reported as a reason for discontinuation was macular edema in 0.9% of patients treated with any siponimod dose and 2% with siponimod 2 mg. Pooling bradycardia and conduction defects revealed that these TEAEs were the most common reason for discontinuation in siponimod 2 mg (1.3%) or any siponimod treatment group (1.2%). Pooling liver transaminase elevation terms revealed that liver transaminase elevations were a frequent cause of discontinuation in patients treated with siponimod 2 mg (0.9%) or with any dose of siponimod (0.8%).

Table 18: Incidence of Most Frequent Treatment Emergent Adverse Events Leading to Study Drug Discontinuation in At Least 2 Patients) by Preferred Term, Controlled Pool, Safety Set (Safety Database 1)

Preferred Term	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Number of patients with at least one discontinuation AE	1 (2.0%)	5 (11.6%)	1 (2.4%)	92 (8.0%)	10 (20.0%)	109 (8.2%)	30 (4.9%)
Bradyarrhythmia[1]	1 (2.0%)	0	0	15 (1.3%)	0	16 (1.2%)	0
Macular edema[2]	0	0	0	12 (1.0%)	1 (2.0%)	13 (0.9%)	1 (0.2%)
Liver transaminase increased[3]	0	0	0	10 (0.9%)	1 (2.0%)	11 (0.8%)	0
ALT increased	0	0	0	6 (0.5%)	1 (2.0%)	7 (0.5%)	0
Atrioventricular block 2nd degree	0	0	0	5 (0.4%)	2 (4.0%)	7 (0.5%)	0
Bradycardia	1 (2.0%)	0	0	4 (0.3%)	0	5 (0.4%)	0
GGT increased	0	0	0	4 (0.3%)	0	4 (0.3%)	0
AST increased	0	0	0	3 (0.3%)	1 (2.0%)	4 (0.3%)	0
Depression	0	0	0	3 (0.3%)	0	3 (0.2%)	1 (0.2%)
Dizziness	0	0	0	3 (0.3%)	2 (4.0%)	5 (0.4%)	0

Preferred Term	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Fatigue	0	0	0	3 (0.3%)	0	3 (0.2%)	4 (0.7%)
Pulmonary function test decreased	0	0	0	3 (0.3%)	0	3 (0.2%)	0
Angina pectoris	0	0	0	2 (0.2%)	0	2 (0.2%)	0
Atrioventricular block 1st degree	0	0	0	2 (0.2%)	0	2 (0.2%)	0
CO diffusing capacity decreased	0	0	0	2 (0.2%)	0	2 (0.2%)	0
Hepatic enzyme increased	0	0	0	2 (0.2%)	0	2 (0.2%)	0
Malignant melanoma *in situ*	0	0	0	2 (0.2%)	0	2 (0.2%)	0
Edema peripheral	0	0	0	2 (0.2%)	1 (2.0%)	3 (0.2%)	0
Seminoma	0	0	0	2 (0.2%)	0	2 (0.2%)	0
Uveitis	0	0	0	2 (0.2%)	0	2 (0.2%)	0
Headache	0	0	0	1 (0.1%)	1 (2.0%)	2 (0.2%)	2 (0.3%)
Lymphopenia	0	0	0	1 (0.1%)	2 (4.0%)	3 (0.2%)	0
Multiple sclerosis relapse	0	1 (2.3%)	0	1 (0.1%)	0	2 (0.2%)	2 (0.3%)
Urinary tract infection	0	0	0	1 (0.1%)	0	0	2 (0.3%)
Insomnia	0	0	0	0	0	0	3 (0.5%)
Prostate cancer	0	0	0	0	0	0	2 (0.3%)

Source: SCS Appendix 1-Table 2.1-10.1

[1] includes preferred terms bradycardia and all conduction defect terms
[2] includes preferred terms macular edema and cystoid macular edema
[3] includes preferred terms AST/ALT/GGT increased, hepatic enzymes increased

Dose Initiation Discontinuation Reasons

Siponimod therapy is initiated by titration. Adverse events during this titration are of interest because Cardiac Disorder adverse events prompted the titration schedule as a means of mitigating cardiovascular events noted when siponimod had been initiated without a titration.

Table 19: Reason for Premature Discontinuation from Study A2304 During Dose Initiation, Controlled Pool, Safety Set (Safety Database 1)

Patient	Last Day of Study Treatment	Reason for Permanent Discontinuation
Standard Cardiac Monitoring Group		
(b) (6)	Day 9	Macular Edema
	Day 4	Dizziness
	Day 8	Hypersensitivity
	Day 7	Supraventricular Tachycardia
	Day 6	Panic Attack
	Day 3	Somnolence
	Day 3	Bradycardia
	Day 6	Physician Decision
	Day 7	Atrioventricular Block (first degree)
	Day 9	Physician Decision
	Day 6	Muscle Spasms, Burning Sensation, Pruritis, Muscle Tightness
Expanded Cardiac Monitoring Group		
(b) (6)	Day 5	Protocol Violation
	Day 1	Atrioventricular Black (Second Degree)
	Day 7	Malignant Melanoma *in situ*
	Day 5	Stroke
	Day 4	Sinus Bradycardia
	Day 6	Bradycardia

Source: SCS Appendix 3, Table 4-6

*Patients randomized to placebo

Narratives for Standard Cardiac Monitoring Group Discontinuations

Patient (b) (6) received the first dose of study medication on Day 1 (b) (6) The patient's mean blood pressure was 115.3/66.7 mmHg and pulse rate 63 BPM on Day 3 ((b) (6)), the patient experienced bradycardia. On the next day (b) (6), the patient's mean blood pressure was 113.3/68.3 mmHg and pulse rate was 50 BPM. No treatment was

reported for this event. Treatment with the study medication was permanently discontinued due the event (bradycardia), and the patient received the last dose on same day (b) (6). The event (bradycardia) was considered resolved on Day 5 (b) (6). The patient discontinued the study due to an adverse event and attended the End of Study visit.

Patient (b) (6) received the first dose of study medication on Day 1 (b) (6). On Day 1 (b) (6) the ECG tracings pre- and 3-hours post-dose on Day 1 (b) (6) were evaluated as normal. Flat T waves were observed at 6-hours post dose on Day 1. PR interval was maximum 195 milliseconds 3 hours post dose. The dose of the study medication was temporarily interrupted due to dosing error on Day 06 (b) (6). The study medication was restarted on Day 07 (b) (6). On Day 7 (b) (6) the ECGs pre-dose and at three hours and at six hours post-dose showed first degree atrioventricular block with PR intervals of 226 milliseconds, 209 milliseconds, and 246 milliseconds, respectively. The event was reported as an adverse event. Treatment with the study medication was permanently discontinued due the event (atrioventricular block first degree), and the patient received the last dose on Day 07 (b) (6). The event (atrioventricular block first degree) was considered resolved on the same day. An unscheduled ECG on Day 8 (b) (6) continued to show the first degree AVB with a PR interval of 201 milliseconds. The patient discontinued the study due to an adverse event and attended the End of Study visit.

Long-term Safety Pool

The most frequent adverse events leading to study drug discontinuation in the long-term safety database were as follows: macular edema (0.3 per 100 PY) and alanine aminotransferase increased (0.2 per 100 PY). If one pools all liver transaminase elevation reports, the IR for liver transaminase increase would become the most frequent discontinuation reason (n=17) with an IR of approximately 0.4 per 100 PY.

These figures represent the most up-to-date figures from the 120-day safety update with a cut-off date of December 31, 2017.

Table 20: Discontinuation for Adverse Events That Occurred for At Least Three Siponimod-treated Patients, Safety Databases 2 and 4

	Siponimod 2-10 mg* N=1737		Siponimod 2-10 mg** N=1737	
Preferred Term	**n (%)**	**IR/ 100 PY**	**n (%)**	**IR/100 PY**
At least one AE	180 (10.4%)	3.8	180 (10.4%)	4.1
Macular edema	14 (0.8%)	0.3	14 (0.8%)	0.3
Alanine aminotransferase increased	11 (0.6%)	0.2	11 (0.6%)	0.2
Atrioventricular block second degree	7 (0.4%)	0.1	7 (0.4%)	0.2
Fatigue	7 (0.4%)	0.1	7 (0.4%)	0.2
Aspartate aminotransferase increased	6 (0.3%)	0.1	6 (0.3%)	0.1
Breast cancer	6 (0.3%)	0.1	6 (0.3%)	0.1
Dizziness	6 (0.3%)	0.1	6 (0.3%)	0.1
Gamma-glutamyltransferase increased	6 (0.3%)	0.1	6 (0.3%)	0.1
Bradycardia	5 (0.3%)	0.1	5 (0.3%)	0.1
Lymphopenia	5 (0.3%)	0.1	5 (0.3%)	0.1
Depression	4 (0.2%)	0.1	4 (0.2%)	0.1
Dyspnea	4 (0.2%)	0.1	4 (0.2%)	0.1
Headache	4 (0.2%)	0.1	4 (0.2%)	0.1
Hepatic enzyme increased	4 (0.2%)	0.1	4 (0.2%)	0.1
Lymphocyte count decreased	4 (0.2%)	0.1	4 (0.2%)	0.1
Multiple sclerosis	4 (0.2%)	0.1	4 (0.2%)	0.1
Peripheral edema	4 (0.2%)	0.1	4 (0.2%)	0.1
Atrioventricular block first degree	3 (0.2%)	0.1	3 (0.2%)	0.1
CO diffusing capacity decreased	3 (0.2%)	0.1	3 (0.2%)	0.1
Pulmonary function test decreased	3 (0.2%)	0.1	3 (0.2%)	0.1
Urinary tract infection	3 (0.2%)	0.1	3 (0.2%)	0.1

Source: SCS 120-day Update Appendix 1-Table2.1-10.2

*Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.
**Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

Notes: A patient with multiple occurrences of an AE is counted only once in that AE category. Incidence rate (IR) is calculated by n/T, *i.e.,* the number of patients who reported at least one AE in this category, over the total patient-years of the population for that event. IR is expressed per 100 patient-years of the population.

Study A2304

In Study A2304, approximately 67.9% of patients randomized to siponimod and 62.3% randomized to placebo completed the trial on their randomized treatment. The most common reason overall for discontinuation in Study A2304 was perceived "lack of efficacy" (11.8%) as compared to 7.6% who discontinued due to an AE.

Table 21: Patients with Most Frequently Reported TEAEs Causing Study Drug Discontinuation, Study A2304

Preferred Term	Siponimod N=1099 n (%)	Placebo N=546 n (%)
Any patient with AE leading to discontinuation	84 (7.6%)	28 (5.1%)
Macular edema	11 (1.0%)	1 (0.2%)
Alanine Aminotransferase Increased	5 (0.5%)	0
Bradycardia	4 (0.4%)	0
Aspartate Aminotransferase Increased	3 (0.3%)	0
Depression	3 (0.3%)	1 (0.2%)
Dizziness	3 (0.3%)	0
Fatigue	3 (0.3%)	4 (0.7%)
Gamma-Glutamyltransferase Increased	3 (0.3%)	0
Pulmonary Function Test Decreased	3 (0.3%)	0
Angina Pectoris	2 (0.2%)	0
Atrioventricular Block First Degree	2 (0.2%)	0
Atrioventricular Block Second Degree	2 (0.2%)	0
Carbon Monoxide Diffusing Capacity Decreased	2 (0.2%)	0
Hepatic Enzyme Increased	2 (0.2%)	0
Malignant Melanoma *in situ*	2 (0.2%)	0
Peripheral Edema	2 (0.2%)	0
Seminoma	2 (0.2%)	0
Uveitis	2 (0.2%)	0

Source: Table 12-13, Study A2304 SCS

Study A2304EP

In the ongoing Extension Phase of Study A2304, as of the December 31, 2017 cut-off date, 50 additional patients (4.1%) had discontinued treatment due to AEs. The most frequently reported AE leading to discontinuation in these 50 patients was death (n=4).

Study A2201

In Study A2201, AEs were the most common reason for study drug discontinuation (13.3%

overall averaged across all doses). The most frequent AE leading to discontinuation was second degree AV block.

Table 22: All Adverse Events Causing Study Drug Discontinuation by Preferred Term and Treatment Dose in Study A2201, All Periods, Safety Set

	Siponimod 10 mg N=50 n (%)	Siponimod 2 mg N=49 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 0.25 mg N=51 n (%)	Placebo N=61 n (%)
Any AE leading to study drug discontinuation	10 (20.0%)	6 (12.2%)	1 (2.4%)	5 (11.6%)	1 (2.0%)	2 (3.3%)
Lymphopenia	2 (4.0%)	1 (2.0%)	0	0	0	0
AV block second degree	2 (4.0%)	3 (6.1%)	0	0	0	0
AV block	1 (2.0%)	0	0	0	0	0
Bradycardia	0	0	0	0	1 (2.0%)	0
Macular edema	1 (2.0%)	0	0	0	0	0
Face edema	1 (2.0%)	0	0	0	0	0
Non-cardiac chest pain	1 (2.0%)	0	0	0	0	0
Peripheral edema	1 (2.0%)	0	0	0	0	0
Chest pain	0	0	1 (2.4%)	0	0	0
Pyrexia	0	0	0	1 (2.3%)	0	0
Intentional overdose	0	1 (2.0%)	0	0	0	0
Lymphocyte count decreased	2 (4.0%)	0	0	0	0	0
ALT increased	1 (2.0%)	1 (2.0%)	0	0	0	0
AST increased	1 (2.0%)	0	0	0	0	0
Blood pressure diastolic increased	0	0	0	0	0	1 (1.6%)
Uterine leiomyoma	0	0	0	1 (2.3%)	0	0
Dizziness and Vertigo	2 (4.0%)	0	0	0	0	1 (1.6%)
Headache	1 (2.0%)	0	0	0	0	0
Multiple sclerosis relapse	0	0	0	1 (2.3%)	0	0
Optic neuritis	0	0	0	1 (2.3%)	0	0
Schizophreniform disorder	0	0	0	1 (2.3%)	0	0
Pruritus generalized	1 (2.0%)	0	0	0	0	0

Source: Table 12-14, Study 2201 CSR

Study A2201E

The incidence of AEs requiring discontinuation in the extension study A2201 was 9.2% (17 patients). The most common AE preferred term reported as a reason for study drug discontinuation was "headache" in approximately 3% of patients in the trial.

Table 23: All Adverse Events Causing Study Drug Discontinuation by Preferred Term and Treatment Dose in Study A2201, Extension Phase

Preferred Term	Siponimod 10/2 mg N=33 n (%)	Siponimod 2/2 mg N=29 n (%)	Siponimod 1.25/2 mg N=43 n (%)	Siponimod 0.5/2 mg N=29 n (%)	Siponimod 0.25/2 mg N=50 n (%)	All Patients N=184 n (%)
Number of patients with any AE leading to discontinuation	3 (9.1%)	5 (17.2%)	2 (4.7%)	2 (6.9%)	5 (10.0%)	17 (9.2%)
Headache	1 (3.0%)	1 (3.4%)	0	0	0	2 (1.1%)
Sinusitis	1 (3.0%)	0	0	0	0	1 (0.5%)
Electrocardiogram QT prolonged	1 (3.0%)	0	0	0	0	1 (0.5%)
Hepatic enzyme increased	1 (3.0%)	0	0	0	0	1 (0.5%)
Alanine aminotransferase increased	0	2 (6.9%)	0	0	0	2 (1.1%)
Central nervous system lesion	0	1 (3.4%)	0	0	1 (2.0%)	2 (1.1%)
Fatigue	0	1 (3.4%)	0	0	0	1 (0.5%)
Aspartate aminotransferase increased	0	1 (3.4%)	0	0	0	1 (0.5%)
Gamma-glutamyltransferase increased	0	1 (3.4%)	0	0	0	1 (0.5%)
Breast cancer	0	0	1 (2.3%)	0	1 (2.0%)	2 (1.1%)
Lymphocyte count decreased	0	0	1 (2.3%)	0	0	1 (0.5%)
Pancreatitis acute	0	0	0	1 (3.4%)	0	1 (0.5%)
Diabetes mellitus	0	0	0	1 (3.4%)	0	1 (0.5%)
Multiple sclerosis relapse	0	0	0	0	2 (4.0%)	2 (1.1%)
Colon cancer metastatic	0	0	0	0	1 (2.0%)	1 (0.5%)

Source: Study A2201E SCS, Table 12-9

Reviewer Comment: The reasons for discontinuations in the core and extension phases of Study A2201, studies undertaken in patients with relapsing MS, do not indicate a unique safety issue leading to discontinuation of siponimod in this population. Liver

transaminase elevations and MS relapses were the only events occurring in > 1 patient.

Study A2202
In a controlled trial of siponimod for patients with polymyositis and dermatomyositis, there were three discontinuations due to adverse events on treatment. A patient with polymyositis discontinued from the trial due to macular edema on active treatment with siponimod 2 mg. A patient with dermatomyositis discontinued from the trial during the placebo phase due to SAE of peritonitis.

Study X2205
In a controlled trial of siponimod for patients with polymyositis, there was one patient who discontinued the study because of three SAEs (kidney injury, hemolytic anemia, and hemolytic uremic syndrome). This case is discussed in Section 8.4.2.

Study X2206
In a controlled trial of siponimod for patients with active dermatomyositis, there were five patients who experienced eight AEs that led to discontinuation. Four of these patients are discussed in Section 8.4.2. The remaining patient not previously discussed discontinued the trial because of lymphopenia.

8.4.4. Significant Adverse Events

Adverse Events Leading to Treatment Modification/Dose Interruptions

Controlled Pool
During the controlled phase of MS trials, the applicant reported that 7.0% (80/1148) patients treated at the proposed marketing dose of 2 mg experienced a dose interruption of at least one day due to an adverse event as compared to 2.8% of patients in the placebo treatment group.

The most frequent AEs leading to a dose interruption in at least three patients in the siponimod 2 mg group were macular edema (n=9, 0.8%), herpes zoster (n=5, 0.4%), alanine aminotransferase increased (n=4, 0.3%), carbon monoxide diffusing capacity decreased (n=4, 0.3%), vomiting (n=4, 0.3%), and urinary tract infection (n=3, 0.3%).

Table 24: Incidence of Most Frequent Adverse Events Leading to Study Drug Interruption in At Least Two Patients at Any Treatment Dose, Controlled Pool (Safety Set)

Preferred Term	Siponimod 0.25mg N=51 n (%)	Siponimod 0.5mg N=43 n (%)	Siponimod 1.25mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10mg N=50 n (%)	Placebo N=607 n (%)
Patients with at least 1 AE leading to interruption	0	1 (2.3%)	0	80 (7.0%)	2 (4.0%)	17 (2.8%)
Macular Edema	0	0	0	9 (0.8%)	0	0
Herpes Zoster	0	0	0	5 (0.4%)	0	0
Alanine Aminotransferase Increased	0	0	0	4 (0.3%)	0	0
Carbon Monoxide Diffusing Capacity Decreased	0	0	0	4 (0.3%)	0	0
Vomiting	0	0	0	4 (0.3%)	0	1 (0.2%)
Urinary Tract Infection	0	0	0	3 (0.3%)	0	0
Appendicitis	0	0	0	2 (0.2%)	0	0
Fatigue	0	0	0	2 (0.2%)	0	0
Gastroenteritis	0	0	0	2 (0.2%)	0	0
Headache	0	0	0	2 (0.2%)	0	0
Malaise	0	0	0	2 (0.2%)	0	0
Nausea	0	0	0	2 (0.2%)	0	0
Seizure	0	0	0	2 (0.2%)	0	0

Source: SCS, Table 2-17

Long-term Safety Pool

Analysis of the long-term Safety Database 2, which includes safety data obtained for patients while on any dose of siponimod, revealed that 9.0% (157/1737) experienced an AE leading to interruption of siponimod. The most common AEs resulting in dose interruptions for at least 3 patients were lymphopenia (n=19), macular edema (n=12), and herpes zoster (n=9).

Table 25: Adverse Events Leading to Dose Interruption (At Least 3 Patients) Treated with Siponimod, Long-term Safety Pool (Safety Database 2)

	Siponimod 2-10 mg* N=1737
Preferred Term	**n (%*)**
Any AE leading to interruption	157 (9.0%)
Lymphopenia	19 (1.1%)
Macular edema	12 (0.7%)
Herpes zoster	9 (0.5%)
Urinary tract infection	6 (0.3%)
Alanine aminotransferase increased	5 (0.3%)
Vomiting	5 (0.3%)
Carbon monoxide diffusing capacity decreased	4 (0.2%)
Appendicitis	3 (0.2%)
Fatigue	3 (0.2%)
Gastroenteritis	3 (0.2%)
Nausea	3 (0.2%)
Seizure	3 (0.2%)
Trigeminal neuralgia	3 (0.2%)
Urosepsis	3 (0.2%)

Source: SCS, Table 2-18

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

120 Day Safety Update

The 120-day Safety Update added 7 patients; the overall frequency consequentially increased to 9.4% (164/1737) of patients who had dose interruptions because of an AE. The three most common AEs leading to study drug interruptions remained unchanged, lymphopenia (n=19), macular edema (n=12), and herpes zoster (n=9).

> *Reviewer Comment: The AEs leading to study drug interruptions were anticipated events based on prior observations of potentially serious AEs associated with S1P modulator therapy. The protocols for the MS trials mandated that study treatment be interrupted for severe lymphopenia, for symptoms and findings consistent with macular edema, changes in lung function tests, and for increased liver transaminases. Recrudescence of*

herpes zoster is a known AE associated with S1P therapy, as is increased risk of infection. Labeling for siponimod will reflect these risks and provide recommendations for interruption/discontinuation as appropriate.

Adverse Events by CTCAE Rating

Controlled Pool

In the controlled phases of MS trials, the most frequent events were Grade 1 and 2 events at all doses of siponimod. At the proposed maintenance dose of 2 mg, 76.4% (877/1148) patients experienced an AE that was Grade 1 or 2 in intensity. There were 125 patients (10.9%) with Grade 3 AEs. The most common Grade 3 AEs (reported by at least 4 patients on 2 mg siponimod) were urinary tract infection (n=9), alanine aminotransferase increased (n=8), angina pectoris (n=6), fall (n=5), basal cell carcinoma (n=4), second degree atrioventricular block (n=4), fatigue (n=4). There were 23 patients (2.0%) with Grade 4 serious events. These events were reported as Serious Adverse Events and are included in the data in Section 8.4.2. Fatal events are summarized in Section 8.4.1.

Table 26: Frequency of Adverse Events by CTCAE Grade, Controlled Phase (Safety Set)

CTCAE Grade	Siponimod 0.25mg N=51 n (%)	Siponimod 0.5mg N=43 n (%)	Siponimod 1.25mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10mg N=50 n (%)	Placebo N=607 n (%)
Grade 1	24 (47.1%)	15 (34.9%)	16 (38.1%)	434 (37.8%)	20 (40.0%)	209 (34.4%)
Grade 2	15 (29.4%)	15 (34.9%)	12 (28.6%)	443 (38.6%)	19 (38.0%)	221 (36.4%)
Grade 3	0 (0.0)	5 (11.6%)	2 (4.8%)	125 (10.9%)	8 (16.0%)	56 (9.2%)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	23 (2.0%)	0 (0.0)	7 (1.2%)
All Grades	41 (80.4%)	37 (86.0%)	30 (71.4%)	1027 (89.5%)	48 (96.0%)	494 (81.4%)
Missing	2 (3.9%)	2 (4.7%)	0 (0.0)	2 (0.2%)	1 (2.0%)	1 (0.2%)

Source: SCS Appendix 1-Table 2.1-4.1

Long-term Safety Pool

In the long-term safety pool (Safety Database 2), the applicant reported that 71.8% (1247/1737) of patients in trials of MS reported an AE that was Grade 1 or 2 in intensity. There were 267 patients (15.4%) patients who reported a Grade 3 event. The most common Grade 3 AEs were lymphopenia (n=25), urinary tract infection (n=18), fall (n=10), alanine aminotransferase increased (n=9), and headache (n=8). Grade 4 events were coded as SAEs and are discussed in 8.4.2.

Table 27: Frequency of Adverse Events by CTCAE Grade, Long-term Safety Set (Safety Databases 2 and 4)

CTCAE Grade	Siponimod 2-10 mg* N=1737 n (%)	Siponimod 2-10 mg** N=1737 n (%)
Grade 1	551 (31.7%)	552 (31.8%)
Grade 2	696 (40.1%)	692 (39.8%)
Grade 3	267 (15.4%)	262 (15.1%)
Grade 4	47 (2.7%)	47 (2.7%)
All Grades	1563 (90.0%)	1556 (89.6%)
Missing	2 (0.1%)	3 (0.2%)

Source: SCS Appendix 1-Table2.1-4.2

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

120-day Safety Update

The 120-day safety update provided 29 additional events of any grade to Safety Database 2. Approximately 27 Grade 1 events were recoded as Grade 2 or higher because of the obligation to record the worst CTCAE score when multiple occurrences of the same AE had different grades. The combined frequency of Grade 1 and 2 events remained consistent with the previous frequency (71.9% versus 71.8%). The frequency of Grade 3 AEs increased to 16.7%. The most common Grade 3 AEs were lymphopenia (n=25), urinary tract infection (n=22), fall (n=10), alanine aminotransferase increased (n=9), basal cell carcinoma (n=8), and headache (n=8). Grade 4 events occurred in 3.0% (n=52) of patients who received at least a single dose of siponimod 2 mg or 10 mg. grade 4 events were coded as SAEs and are discussed in Section 8.4.2. Deaths are discussed in Section 8.4.1.

Table 28: Frequency of Adverse Events by CTCAE Grade, Long-term Safety Pool 120-day Update (Safety Databases 2 and 4)

CTCAE Grade	Siponimod 2-10 mg* N=1737 n (%)	Siponimod 2-10 mg** N=1737 n (%)
Grade 1	524 (30.2%)	525 (30.2%)
Grade 2	724 (41.7%)	720 (41.5%)
Grade 3	290 (16.7%)	285 (16.4%)
Grade 4	52 (3.0%)	52 (3.0%)
All Grades	1592 (91.7%)	1583 (91.2%)
Missing	2 (0.1%)	2 (0.2%)

Source: 120-day Safety Update SCS Appendix 1-Table 2.1-4.2

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

> *Reviewer Comment: Overall, the most common events were Grades 1 and 2. In the long-term safety pool, lymphopenia, liver transaminase increases, infections, and basal cell carcinoma were expected based on experiences with S1P modulator therapy. Headaches occur in approximately 50% of the general population[11], and, therefore, headache is a common reported AE in all clinical trials. The presence of Grade 3 falls is an expected finding in association with MS as discussed in Sections 8.4.2 and 8.4.5.*

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported Treatment Emergent Adverse Events (TEAEs) in patients treated with siponimod 2 mg (the proposed marketing dose) were infections, headaches, falls, and hypertension.

Controlled Pool

In the controlled phases of clinical trials in MS, patients treated with any dose of siponimod reported TEAEs more often (88.7%) than patients in the placebo treatment arm (81.4%). Patients receiving siponimod 10 mg reported the highest frequency of adverse events (96.0%) among siponimod-treated patients, and there appeared to be evidence of a dose-dependent increase in most AEs with siponimod. Adverse events requiring concomitant therapy were reported in over half of patients (67.6%), but adverse events leading to study drug interruption

(6.2%) and discontinuation (8.2%) occurred in less than 10% of patients treated in trials of MS.

Table 29: Reviewer Table, Summary of Adverse Events, Controlled Pool, Safety Set (Safety Database 1)

	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 N (%)	Placebo N=607 n (%)
Treatment-Emergent AEs	41 (80.4%)	37 (86.0%)	30 (71.4%)	1027 (89.5%)	48 (96.0%)	1183 (88.7%)	494 (81.4%)
AEs leading to Study Drug Discontinuation	1 (2.0%)	5 (11.6%)	1 (2.4%)	92 (8.0%)	10 (20.0%)	109 (8.2%)	30 (4.9%)
AEs Leading to Study Drug Interruption	0	1 (2.3%)	0	80 (7.0%)	2 (4.0%)	83 (6.2%)	17 (2.8%)
AEs Requiring Concomitant Therapy	25 (49.0%)	29 (67.4%)	25 (59.5%)	796 (69.3%)	27 (54.0%)	902 (67.6%)	406 (66.9%)

Source: adae.xpt

For patients receiving siponimod in controlled trials, the highest incidences of TEAEs came from the Infections and Infestations and Nervous System Disorders SOCs. The largest disparities between siponimod-treated patients and placebo-treated patients were an 8% difference in the incidence of TEAEs in the Investigations SOC and a 4% difference in the frequency of TEAEs in the Gastrointestinal Disorders SOC.

Table 30: Incidence of Treatment Emergent Adverse Events by Primary System Organ Class, Controlled Pool, Safety Set (Safety Database 1)

Primary SOC	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Number of patients with at least one AE	41 (80.4%)	37 (86.0%)	30 (71.4%)	1027 (89.5%)	48 (96.0%)	1183 (88.7%)	494 (81.4%)
Infections and Infestations	20 (39.2%)	24 (55.8%)	18 (42.9%)	557 (48.5%)	18 (36.0%)	637 (47.8%)	301 (49.6%)
Nervous System Disorders	10 (19.6%)	15 (34.9%)	9 (21.4%)	442 (38.5%)	33 (66.0%)	509 (38.2%)	194 (32.0%)

Primary SOC	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Musculoskeletal and Connective Tissue Disorders	6 (11.8%)	11 (25.6%)	8 (19.0%)	296 (25.8%)	6 (12.0%)	327 (24.5%)	157 (25.9%)
Gastrointestinal Disorders	6 (11.8%)	11 (25.6%)	7 (16.7%)	279 (24.3%)	14 (28.0%)	317 (23.8%)	120 (19.8%)
General Disorders and Administration Site Conditions	6 (11.8%)	10 (23.3%)	8 (19.0%)	277 (24.1%)	15 (30.0%)	316 (23.7%)	122 (20.1%)
Investigations	6 (11.8%)	5 (11.6%)	3 (7.1%)	272 (23.7%)	9 (18.0%)	295 (22.1%)	86 (14.2%)
Injury, Poisoning and Procedural Complications	2 (3.9%)	5 (11.6%)	3 (7.1%)	241 (21.0%)	3 (6.0%)	254 (19.0%)	120 (19.8%)
Skin and Subcutaneous Tissue Disorders	6 (11.8%)	7 (16.3%)	7 (16.7%)	199 (17.3%)	8 (16.0%)	227 (17.0%)	102 (16.8%)
Psychiatric Disorders	6 (11.8%)	3 (7.0%)	2 (4.8%)	171 (14.9%)	1 (2.0%)	183 (13.7%)	88 (14.5%)
Vascular Disorders	2 (3.9%)	2 (4.7%)	1 (2.4%)	167 (14.5%)	4 (8.0%)	176 (13.2%)	67 (11.0%)
Cardiac Disorders	2 (3.9%)	5 (11.6%)	0	144 (12.5%)	17 (34.0%)	168 (12.6%)	62 (10.2%)
Respiratory, Thoracic and Mediastinal	9 (17.6%)	9 (20.9%)	3 (7.1%)	135 (11.8%)	11 (22.0%)	167 (12.5%)	79 (13.0%)
Neoplasms Benign, Malignant, and Unspecified	0	3 (7.0%)	1 (2.4%)	118 (10.3%)	3 (6.0%)	125 (9.4%)	47 (7.7%)
Eye Disorders	0	4 (9.3%)	1 (2.4%)	117	9 (18.0%)	131 (9.8%)	58 (9.6%)
Metabolism and Nutrition Disorders	1 (2.0%)	0	1 (2.4%)	88 (7.7%)	4 (8.0%)	94 (7.0%)	29 (4.8%)
Renal and Urinary Disorders	0	2 (4.7%)	1 (2.4%)	87 (7.6%)	0	90 (6.8%)	37 (6.1%)

Primary SOC	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Ear and Labyrinth Disorders	1 (2.0%)	2 (4.7%)	5 (11.9%)	61 (5.3%)	3 (6.0%)	72 (5.4%)	43 (7.1%)
Blood and Lymphatic System Disorders	0	1 (2.3%)	0	49 (4.3%)	6 (12.0%)	56 (4.2%)	10 (1.6%)
Reproductive System and Breast Disorders	3 (5.9%)	1 (2.3%)	0	38 (3.3%)	1 (2.0%)	43 (3.2%)	26 (4.3%)
Hepatobiliary Disorders	0	2 (4.7%)	0	27 (2.4%)	0	29 (2.2%)	5 (0.8%)
Endocrine Disorders	0	0	0	12 (1.0%)	0	12 (0.9%)	4 (0.7%)
Immune System Disorders	0	0	0	8 (0.7%)	0	8 (0.6%)	9 (1.5%)
Congenital, Familial and Genetic Disorders	0	0	0	5 (0.4%)	0	5 (0.4%)	0
Social Circumstances	0	0	0	3 (0.3%)	0	3 (0.2%)	4 (0.7%)
Product Issues	0	0	0	2 (0.2%)	0	2 (0.2%)	1 (0.2%)

Source: SCS Appendix 1-Table 2.1-2.1

As indicated in the following table, in controlled studies of patients with MS, the most commonly reported TEAEs for siponimod-treated patients by preferred term were headache, nasopharyngitis, urinary tract infections, and falls.

Table 31: Treatment Emergent Adverse Events That Occurred in ≥3% of Siponimod-treated Patients by Preferred Term, Controlled Pool, Safety Set (Safety Database 1)

Preferred Term	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Number of patients with at least one AE	41 (80.4%)	37 (86.0%)	30 (71.4%)	1027 (89.5%)	48 (96.0%)	1183 (88.7%)	494 (81.4%)
Headache	4 (7.8%)	9 (20.9%)	5 (11.9%)	173 (15.1%)	22 (44.0%)	213 (16.0%)	76 (12.5%)
Nasopharyngitis	8 (15.7%)	8 (18.6%)	9 (21.4%)	154 (13.4%)	7 (14.0%)	186 (13.9%)	87 (14.3%)
Urinary Tract Infection	2 (3.9%)	2 (4.7%)	3 (7.1%)	135 (11.8%)	2 (4.0%)	144 (10.8%)	83 (13.7%)
Fall	0	0	0	128 (11.1%)	0	128 (9.6%)	62 (10.2%)
Hypertension	1 (2.0%)	1 (2.3%)	1 (2.4%)	119 (10.4%)	1 (2.0%)	123 (9.2%)	44 (7.2%)
Increased Hepatic Transaminases Increased[1]	3 (5.9%)	0	1 (2.4%)	115 (10.0%)	7 (14.0%)	126 (9.4%)	14 (2.3%)
Fatigue	0	1 (2.3%)	4 (9.5%)	105 (9.1%)	8 (16.0%)	118 (8.9%)	56 (9.2%)
Upper Respiratory Tract Infection	0	3 (7.0%)	1 (2.4%)	95 (8.3%)	2 (4.0%)	101 (7.6%)	48 (7.9%)
Dizziness	0	5 (11.6%)	1 (2.4%)	80 (7.0%)	13 (26.0%)	99 (7.4%)	32 (5.3%)
Influenza	4 (7.8%)	1 (2.3%)	1 (2.4%)	77 (6.7%)	2 (4.0%)	85 (6.4%)	44 (7.2%)
Nausea	3 (5.9%)	2 (4.7%)	3 (7.1%)	76 (6.6%)	8 (16.0%)	92 (6.9%)	21 (3.5%)

Preferred Term	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Siponimod All Doses N=1334 n (%)	Placebo N=607 n (%)
Diarrhea	1 (2.0%)	1 (2.3%)	0	72 (6.3%)	1 (2.0%)	75 (5.6%)	26 (4.3%)
Back Pain	1 (2.0%)	3 (7.0%)	2 (4.8%)	69 (6.0%)	3 (6.0%)	78 (5.8%)	47 (7.7%)
Pain in Extremity	2 (3.9%)	2 (4.7%)	1 (2.4%)	61 (5.3%)	1 (2.0%)	67 (5.0%)	21 (3.5%)
Bradycardia	2 (3.9%)	2 (4.7%)	0	53 (4.6%)	14 (28.0%)	71 (5.3%)	16 (2.6%)
Arthralgia	0	2 (4.7%)	1 (2.4%)	52 (4.5%)	0	55 (4.1%)	37 (6.1%)
Depression	3 (5.9%)	0	1 (2.4%)	51 (4.4%)	0	55 (4.1%)	32 (5.3%)
Edema Peripheral	1 (2.0%)	0	0	50 (4.4%)	2 (4.0%)	53 (4.0%)	13 (2.1%)
Melanocytic Nevus	0	1 (2.3%)	1 (2.4%)	48 (4.2%)	2 (4.0%)	52 (3.9%)	19 (3.1%)
Muscle Spasticity	0	0	0	44 (3.8%)	0	44 (3.3%)	24 (4.0%)
Constipation	0	0	0	42 (3.7%)	2 (4.0%)	44 (3.3%)	22 (3.6%)
Cough	3 (5.9%)	4 (9.3%)	1 (2.4%)	40 (3.5%)	4 (8.0%)	52 (3.9%)	19 (3.1%)
Insomnia	1 (2.0%)	0	0	38 (3.3%)	0	39 (2.9%)	20 (3.3%)
Muscle Spasms	0	0	1 (2.4%)	37 (3.2%)	0	38 (2.8%)	19 (3.1%)
Bronchitis	0	3 (7.0%)	1 (2.4%)	36 (3.1%)	0	40 (3.0%)	16 (2.6%)
Contusion	0	1 (2.3%)	1 (2.4%)	35 (3.0%)	0	37 (2.8%)	17 (2.8%)

Source: SCS Appendix 1-Table 2.1-3.1.1

[1] includes Preferred Terms ALT Increased and GGT Increased

Table 32: Reviewer Table, Adverse Events Reported in ≥5% of Patients Taking Siponimod Using Customized Pooled Preferred Terms, Controlled Pool (Safety Database 1)

	Siponimod All Doses N=1334 n (%)	Siponimod 2 mg N=1148 n (%)	Placebo N=607 n (%)
Infections (all)[1]	645 (48.4%)	564 (49.1%)	303 (49.9%)
Upper respiratory infections[2]	368 (27.6%)	313 (27.3%)	175 (28.8%)
Falls and Balance Disturbances[3]	244 (18.3%)	225 (19.6%)	104 (17.1%)
Headaches	243 (18.2%)	199 (17.3%)	87 (14.3%)
Urinary tract infections	178 (13.3%)	167 (14.6%)	92 (15.2%)
Hypertension[4]	148 (11.1%)	143 (12.5%)	53 (8.7%)
Viral Infections (all)[5]	165 (12.4%)	141 (12.3%)	70 (11.5%)
Fatigue[6]	157 (11.8%)	139 (12.1%)	74 (12.2%)
Falls	132 (9.9%)	132 (11.5%)	64 (10.5%)
Elevated Liver Transaminases[7]	131 (9.8%)	120 (10.5%)	17 (2.8%)
Nausea and Vomiting	115 (8.6%)	96 (8.4%)	30 (4.9%)
Arrhythmia[8]	112 (8.4%)	91 (7.9%)	37 (6.1%)
Dizziness[9]	99 (7.4%)	80 (7.0%)	33 (5.4%)
Edema[10]	83 (6.2%)	79 (6.9%)	22 (3.6%)
Influenza	85 (6.4%)	77 (6.7%)	46 (7.6%)
Depression	76 (5.7%)	72 (6.3%)	39 (6.4%)
Diarrhea	75 (5.6%)	72 (6.3%)	26 (4.3%)
Bradycardia	90 (6.8%)	71 (6.2%)	20 (3.3%)
Back pain	80 (6.0%)	71 (6.2%)	49 (8.1%)
Joint Pain[11]	68 (5.1%)	63 (5.5%)	42 (6.9%)

Source: adae.xpt joined to adsl.xpt

[1] includes all preferred terms related to infections of any type or source
[2] includes upper respiratory tract infection, upper respiratory infection, nasopharyngitis
[3] includes falls, dizziness, gait disturbance, balance disturbance, difficulty walking
[4] includes blood pressure increased
[5] includes all preferred terms referencing infectious with a viral etiology
[6] includes asthenia, fatigue, malaise, weakness
[7] includes increased hepatic enzymes, increased AST/ALT/GGT
[8] includes all preferred terms that are cardiac arrhythmias
[9] includes dizziness and light-headedness
[10] includes peripheral and other forms of edema but not angioedema
[11] includes arthralgia, arthritis, arthrosis

Reviewer Comment: Despite a great deal of parity between the siponimod and placebo groups, this pooled analysis of most common preferred terms for TEAEs draws out some critical differences between siponimod and placebo TEAEs. Overall, this analysis demonstrates that the infection rate for all infections and for urinary tract infections specifically is approximately balanced, or even favors placebo, between the siponimod and placebo treatment groups. However, as expected based on reductions of circulating CD4+/CD8+ cells, viral infections were slightly more common in siponimod-treated patients. Influenza was more frequently reported in the placebo treatment group which was an unexpected finding because with another S1P modulator, influenza was more common than placebo. A customized grouped term for falls and disrupted balance was approximately 2% different between siponimod treatment and placebo treatment groups, and dizziness was increased 2% suggesting that siponimod is associated with more frequent falls because of more frequent dizziness or light-headedness. Finally, this analysis conforms that edema, headaches, and gastrointestinal symptoms will need to be highlighted as common mild symptoms associated with siponimod therapy as part of the clinical trial experience just as these symptoms were noted at similarly higher frequencies than placebo in the fingolimod development program.

Titration Pool

In the titration pool containing events recorded during titration of siponimod to target dose, 41.7% of patients reported at least one TEAE. The most frequently reported AEs were in the Nervous System Disorders and Cardiac Disorders SOCs. The most often reported TEAEs were headache (5.8%), dizziness (3.9%), bradycardia (3.9%), and nausea (3.6%).

Table 33: Treatment Emergent Adverse Events by System Organ Class and Preferred Term Occurring in At Least ≥ 2% of Patients, Titration Pool, Safety Set (Safety Database 3)

Primary SOC	**Siponimod All Doses N=1545 n (%)**
Number of patients with at least one AE	**645 (41.7%)**
Nervous System Disorders	**213 (13.8%)**
Headache	89 (5.8%)
Dizziness	60 (3.9%)
Cardiac Disorders	**132 (8.5%)**
Bradycardia	61 (3.9%)
General Disorders and Administration Site Conditions	**132 (8.5%)**
Gastrointestinal Disorders	**120 (7.8%)**

Primary SOC	Siponimod All Doses N=1545 n (%)
Nausea	56 (3.6%)
Infections and Infestations	**109 (7.1%)**
Musculoskeletal and Connective Tissue Disorders	**67 (4.3%)**
Skin and Subcutaneous Tissue Disorders	**51 (3.3%)**
Injury, Poisoning and Procedural Complications	**43 (2.8%)**
Vascular Disorders	**38 (2.5%)**
Psychiatric Disorders	**36 (2.3%)**
Investigations	**33 (2.1%)**

Source: SCS Appendix 1-Table 2.1-1.6

In the overall study population, the incidence of TEAEs was highest on Day 1 both for siponimod and placebo (14.2% vs. 11.2%, respectively) and Day 7 (6.9% vs. 6.4%, respectively). Not surprisingly, the most common TEAEs reported for these days were Cardiac Disorders (4.2% vs. 1.8% placebo on Day 1 and 3.1% vs. 1.8% placebo on Day 7); among them bradycardia was reported in 2.5% with siponimod vs. 1.5% in placebo on Day 1, and 2.0% vs. 1.1%, respectively, on Day 7. The second most commonly reported group of AEs were in the Nervous System Disorders SOC with 4.1% of patients in the siponimod group vs. 2.4% in the placebo group on Day 1 (most frequent were headache (1.6%) and dizziness (1.5%) vs. 2.4% in the placebo group (most frequent was headache (1.5%) and dizziness (0.4%)). The incidence of Nervous System Disorders on Day 7 was 1.5% vs. 1.6% in the siponimod and placebo groups, respectively, with headache 0.5% and dizziness 0.4% in the siponimod group, and 0.7% and 1.1%, respectively, in the placebo group.

The incidence of Cardiac Disorders in siponimod-treated patients in both cardiac risk groups is higher than with placebo. However, the frequency of TEAEs was reduced in the Standard Cardiac Monitoring group. Cardiac Disorders were reported for 9.8% of patients in the siponimod group vs. 4.6% of patients on placebo in the Expanded Cardiac Monitoring group; for the same period, the numbers in the Standard Cardiac Monitoring group were 7.0% in siponimod patients vs. 3.5% in placebo patients, with bradycardia the most common TEAE in either group.

The most common TEAEs between Day 1 and 6 were Nervous System Disorders (5.0%), most common was headache (1.7%); General Disorders (3.2%) with the most common complaint being fatigue (1.2%). The incidence of Cardiac disorders between Day 1 and Day 6 was 2.6% overall, and the most common was cardiac symptom reported was bradycardia reported in 0.6% of patients. After Day 7, Nervous System Disorders were reported for 4.5% of patients

(1.7% of patients reporting headache), Cardiac Disorders for 0.8% of patients, most common report was bradycardia (0.2%).

Within the first day of initiation of treatment, 16.3% of patients reported at least one TEAE. On this day, the most common SOCs were: Nervous System Disorders reported for 4.1% of patients, the most common preferred term was headache (1.9%); Cardiac Disorders were reported for 4.1% of patients, the most common preferred terms were bradycardia (2.1%) and sinus bradycardia (0.6%); and General Disorders reported for 2.8% of patients with the most common reported symptom being fatigue (1.6% of patients).

In the titration pool, atrioventricular block was reported in 14 patients (0.9%) as AVB first degree and in 5 patients (0.3%) as second-degree AV block (Mobitz I). All were asymptomatic, in one case the event led to study drug discontinuation. The only case (0.07%, 1/1545) of atrioventricular block second degree (Mobitz II) was recorded in a patient in whom the disorder was present prior to commencing study treatment and consequentially had been placed into the High-Risk Cardiac group for monitoring purposes.

> *Reviewer Comment: Given the short duration of titration and known effects of siponimod and S1P modulators on the heart, it is not surprising that bradycardia was a common event in the titration pool. Headache was not unexpected given the high headache frequency (~15%) observed in the controlled trials database, but dizziness appears to be an early, frequently reported TEAE. TEAEs in the Infections and Infestations SOC are not as prominent here because the lymphopenic effects of siponimod are beginning during titration but will not be fully realized in magnitude nor outcome in 7 days.*

Long-term Safety Pool

Data from the long-term safety pools largely recapitulated the TEAE findings from the controlled safety pool. In the long-term safety pool of patients, the overall frequency of TEAEs (90%) was comparable to the overall TEAE frequency of 89.5% reported for 2 mg siponimod in controlled trials. The rates of drug interruption and discontinuation rose from 6.2% and 8.2% to 9.0 and 9.6%, respectively.

Table 34: Treatment Emergent Adverse Event Categories, Long-term Safety Pool, Safety Databases 2 and 4

	Siponimod 2-10 mg* N=1737 n (%)	Siponimod 2-10 mg** N=1737 n (%)
Adverse Events	1563 (90.0%)	1556 (89.6%)
AEs Leading to Study Drug Discontinuation	166 (9.6%)	166 (9.6%)
AEs Leading to Study Drug Interruption	157 (9.0%)	154 (8.9%)
AEs Requiring Concomitant Therapy	1280 (73.7%)	1267 (72.9%)

Source: SCS Appendix-Table 2.1-14.2

The most frequently reported TEAEs in the long-term safety pools, as was the case in the controlled pool, came from the Infections and Infestations and Nervous System Disorders SOCs.

Table 35: Incidence of Treatment Emergent Adverse Events by Primary Organ Class, Long-term Safety Pools, Safety Set (Safety Databases 2 and 4)

Primary SOC	Siponimod 2-10 mg* N=1737 n (%)	Siponimod 2-10 mg** N=1737 n (%)
Number of patients with at least one AE	1563 (90.0%)	1556 (89.6%)
Infections and Infestations	955 (55.0%)	937 (53.9%)
Nervous System Disorders	707 (40.7%)	683 (39.3%)
Musculoskeletal and Connective Tissue Disorders	502 (28.9%)	486 (28.0%)
General Disorders and Administration Site Conditions	465 (26.8%)	442 (25.4%)
Investigations	462 (26.6%)	451 (26.0%)
Gastrointestinal Disorders	460 (26.5%)	441 (25.4%)
Injury, Poisoning and Procedural Complications	410 (23.6%)	400 (23.0%)
Skin and Subcutaneous Tissue Disorders	357 (20.6%)	338 (19.5%)
Psychiatric Disorders	300 (17.3%)	284 (16.4%)

Primary SOC	Siponimod 2-10 mg* N=1737 n (%)	Siponimod 2-10 mg** N=1737 n (%)
Vascular Disorders	263 (15.1%)	255 (14.7%)
Respiratory, Thoracic and Mediastinal Disorders	250 (14.4%)	237 (13.6%)
Neoplasms Benign, Malignant, and Unspecified	249 (14.3%)	236 (13.6%)
Cardiac Disorders	235 (13.5%)	232 (13.4%)
Eye Disorders	216 (12.4%)	207 (11.9%)
Blood and Lymphatic System Disorders	185 (10.7%)	183 (10.5%)
Metabolism and Nutrition Disorders	172 (9.9%)	166 (9.6%)
Renal and Urinary Disorders	156 (9.0%)	154 (8.9%)
Ear and Labyrinth Disorders	126 (7.3%)	118 (6.8%)
Reproductive System and Breast Disorders	86 (5.0%)	79 (4.5%)
Hepatobiliary Disorders	44 (2.5%)	44 (2.5%)
Endocrine Disorders	27 (1.6%)	25 (1.4%)
Immune System Disorders	21 (1.2%)	18 (1.0%)
Social Circumstances	8 (0.5%)	8 (0.5%)
Congenital, Familial and Genetic Disorders	7 (0.4%)	7 (0.4%)
Pregnancy, Puerperium, and Perinatal Conditions	5 (0.3%)	5 (0.3%)
Product Issues	2 (0.1%)	2 (0.1%)
Surgical and Medical Conditions	1 (0.1%)	1 (0.1%)

Source: SCS Appendix 1-Table 2.1-2.2

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

The following table summarizes TEAEs reported in 3% or more of patients in the long-term safety pools. The most frequent TEAEs by single preferred term remained nasopharyngitis, headache, urinary tract infection, and fall. Several TEAEs emerged such as herpes zoster, sinusitis, and cystitis which are expected sequelae of long-term the result of prolonged lymphocyte suppression; indeed, lymphopenia was reported as a TEAE in approximately 7% of patients in this long-term pool.

Table 36: Incidence of Treatment Emergent Adverse Events Occurring in ≥ 3% of Patients by Preferred Term, Long-term Safety Pools, Safety Set (Safety Databases 2 and 4)

Preferred Term	**Siponimod 2-10 mg* N=1737 n (%)**	**Siponimod 2-10 mg** N=1737 n (%)**
Number of patients with at least one AE	1563 (90.0%)	1556 (89.6%)
Nasopharyngitis	314 (18.1%)	295 (17.0%)
Headache	278 (16.0%)	266 (15.3%)
Urinary Tract Infection	258 (14.9%)	251 (14.5%)
Fall	209 (12.0%)	208 (12.0%)
Dizziness and Vertigo	210 (12.1%)	196 (11.3%)
Hypertension	185 (10.7%)	178 (10.2%)
Hepatic Transaminases Increased[1]	180 (10.4%)	174 (10.0%)
Fatigue	170 (9.8%)	161 (9.3%)
Upper Respiratory Tract Infection	151 (8.7%)	148 (8.5%)
Influenza	141 (8.1%)	137 (7.9%)
Back Pain	137 (7.9%)	128 (7.4%)
Nausea	126 (7.3%)	120 (6.9%)
Lymphopenia	123 (7.1%)	122 (7.0%)
Diarrhea	110 (6.3%)	101 (5.8%)
Arthralgia	98 (5.6%)	95 (5.5%)
Depression	98 (5.6%)	91 (5.2%)
Pain in Extremity	95 (5.5%)	90 (5.2%)
Hypercholesterolemia and Blood cholesterol increased	98 (5.6%)	94 (5.4%)
Melanocytic Nevus	93 (5.4%)	87 (5.0%)
Bradycardia	81 (4.7%)	90 (4.6%)
Edema Peripheral	81 (4.7%)	79 (4.5%)

Preferred Term	Siponimod 2-10 mg* N=1737 n (%)	Siponimod 2-10 mg** N=1737 n (%)
Cough	78 (4.5%)	72 (4.1%)
Muscle Spasticity	73 (4.2%)	72 (4.1%)
Contusion	71 (4.1%)	70 (4.0%)
Bronchitis	70 (4.0%)	66 (3.8%)
Insomnia	68 (3.9%)	58 (3.3%)
Constipation	66 (3.8%)	64 (3.7%)
Sinusitis	58 (3.3%)	52 (3.0%)
Cystitis	58 (3.3%)	56 (3.2%)
Herpes Zoster	57 (3.3%)	56 (3.2%)
Pyrexia	56 (3.2%)	46 (2.6%)
Vomiting	53 (3.1%)	51 (2.9%)
Muscle Spasms	52 (3.0%)	48 (2.8%)
Musculoskeletal Pain	52 (3.0%)	50 (2.9%)

Source: SCS Appendix 1-Table 2.1-3.2

[1] includes preferred terms ALT increased, GGT increased

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

> *Reviewer Comment: TEAEs reported in the long-term safety pool are consistent with TEAEs reported in the controlled pool.*

120-day Safety Update

The 120-day Safety Update provided 29 new TEAEs to the long-term databases. The overall frequency of AEs rose to approximately 91.7% of exposed patients.

Table 37: Treatment Emergent Adverse Event Categories, Long-term Safety Pools, 120-day Safety Update, Safety Set (Safety Databases 2 and 4)

	Siponimod	Siponimod

	2-10 mg* N=1737 n (%)	**2-10 mg** N=1737 n (%)**
Adverse Events	1592 (91.7%)	1585 (91.2%)
AEs Leading to Study Drug Discontinuation	180 (10.4%)	180 (10.4%)
AEs Leading to Study Drug Interruption	164 (9.4%)	161 (9.3%)
AEs Requiring Concomitant Therapy	1330 (76.6%)	1317 (75.8%)

Source: 120-day Safety Update SCS Appendix 1-Table 2.1-14.2

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

The additional TEAEs did not significantly alter the frequencies of overall SOCs as observed in the original database. The Infections and Infestations and Nervous System Disorders SOCs still provide the most frequently reported TEAEs.

Table 38: Incidence of Treatment Emergent Adverse Events by Primary System Organ Class, 120-day Update Long-term Safety Pools, Safety Set (Safety Databases 2 and 4)

Primary System Organ Class	**Siponimod 2-10 mg* N=1737 n (%)**	**Siponimod 2-10 mg** N=1737 n (%)**
Number of patients with at least one AE	1592 (91.7%)	1585 (91.2%)
Infections and Infestations	1004 (57.8%)	986 (56.8%)
Nervous System Disorders	737 (42.4%)	713 (41.0%)
Musculoskeletal and Connective Tissue Disorders	535 (30.8%)	519 (29.9%)
General Disorders and Administration Site Conditions	489 (28.2%)	466 (26.8%)
Investigations	499 (28.7%)	488 (28.1%)
Gastrointestinal Disorders	490 (28.2%)	471 (27.1%)

Primary System Organ Class	Siponimod 2-10 mg* N=1737 n (%)	Siponimod 2-10 mg** N=1737 n (%)
Injury, Poisoning and Procedural Complications	442 (25.4%)	432 (24.9%)
Skin and Subcutaneous Tissue Disorders	377 (21.7%)	358 (20.6%)
Psychiatric Disorders	331 (19.1%)	315 (18.1%)
Vascular Disorders	281 (16.2%)	273 (15.7%)
Respiratory, Thoracic and Mediastinal Disorders	265 (15.3%)	252 (14.5%)
Neoplasms Benign, Malignant, and Unspecified	276 (15.9%)	263 (15.1%)
Cardiac Disorders	250 (14.4%)	247 (14.2%)
Eye Disorders	226 (13.0%)	217 (12.5%)
Blood and Lymphatic System Disorders	205 (11.8%)	203 (11.7%)
Metabolism and Nutrition Disorders	200 (11.5%)	194 (11.2%)
Renal and Urinary Disorders	184 (10.6%)	182 (10.5%)
Ear and Labyrinth Disorders	134 (7.7%)	126 (7.3%)
Reproductive System and Breast Disorders	103 (5.9%)	96 (5.5%)
Hepatobiliary Disorders	53 (3.1%)	53 (3.1%)
Endocrine Disorders	28 (1.6%)	26 (1.5%)
Immune System Disorders	24 (1.4%)	21 (1.2%)
Social Circumstances	8 (0.5%)	8 (0.5%)
Congenital, Familial and Genetic Disorders	11 (0.6%)	11 (0.6%)
Pregnancy, Puerperium, and Perinatal Conditions	5 (0.3%)	5 (0.3%)
Product Issues	2 (0.1%)	2 (0.1%)
Surgical and Medical Conditions	2 (0.1%)	2 (0.1%)

Source: 120-day Safety Update SCS Appendix 1-Table 2.1-2.2

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

In the long-term safety databases, the most frequently reported TEAEs by preferred terms remain nasopharyngitis, urinary tract infection, and headache. Urinary tract infection increased in frequency relative to headache in this updated data set.

Table 39: Incidence of Treatment Emergent Adverse Events Occurring in >3% of Patients by preferred term, Long-term Safety Pools, 120-day Update, Safety Set (Safety Databases 2 and 4)

Preferred Term	Siponimod 2-10 mg* N=1737 n (%)	Siponimod 2-10 mg** N=1737 n (%)
Number of patients with at least one AE	1592 (91.7%)	1556 (91.2%)
Nasopharyngitis	329 (18.9%)	310 (17.8%)
Urinary Tract Infection	285 (16.4%)	278 (16.0%)
Headache	282 (16.2%)	270 (15.5%)
Fall	226 (13.0%)	225 (13.0%)
Dizziness and Vertigo	219 (12.6%)	205 (11.8%)
Hypertension	196 (11.3%)	189 (10.9%)
Hepatic Transaminases Increased[1]	199 (11.5%)	193 (11.1%)
Fatigue	178 (10.2%)	169 (9.7%)
Upper Respiratory Tract Infection	156 (9.0%)	153 (8.8%)
Back Pain	152 (8.8%)	148 (8.5%)
Influenza	152 (8.8%)	148 (8.5%)
Lymphopenia	139 (8.0%)	138 (7.9%)
Nausea	129 (7.4%)	123 (7.1%)
Diarrhea	117 (6.7%)	108 (6.2%)
Hypercholesterolemia and Blood cholesterol increased	113 (6.5%)	108 (6.2%)
Depression	110 (6.3%)	103 (5.9%)
Arthralgia	108 (6.2%)	105 (6.0%)
Pain in Extremity	100 (5.8%)	95 (5.5%)
Melanocytic Nevus	99 (5.7%)	93 (5.7%)
Edema Peripheral	90 (5.2%)	88 (5.1%)
Cough	84 (4.8%)	78 (4.5%)
Bradycardia	81 (4.7%)	80 (4.6%)
Bronchitis	80 (4.6%)	76 (4.4%)

Preferred Term	Siponimod 2-10 mg* N=1737 n (%)	Siponimod 2-10 mg** N=1737 n (%)
Insomnia	78 (4.5%)	68 (3.9%)
Muscle Spasticity	77 (4.4%)	76 (4.4%)
Constipation	76 (4.4%)	74 (4.3%)
Contusion	73 (4.2%)	72 (4.1%)
Herpes Zoster	65 (3.7%)	64 (3.7%)
Muscle Spasms	61 (3.5%)	57 (3.3%)
Sinusitis	61 (3.5%)	55 (3.2%)
Cystitis	60 (3.5%)	58 (3.3%)
Pyrexia	59 (3.4%)	49 (2.8%)
Vomiting	54 (3.1%)	52 (3.0%)
Anxiety	53 (3.1%)	50 (2.9%)
Musculoskeletal Pain	53 (3.1%)	51 (2.9%)

Source: 120-day Safety Update SCS Appendix 1-Table 2.1-3.2

[1] includes preferred terms ALT increased, GGT increased

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

> *Reviewer Comment: The 120-day safety update data do not provide evidence of significant new safety concerns.*

Study A2304

In the controlled portion of the pivotal Phase 3 trial in SPMS, TEAEs were reported in 88.7% of patients randomized to siponimod and in 81.5% of patients randomized to placebo treatment.

Approximately half of patients in either siponimod or placebo treatment experienced AEs from the Infections and Infestations SOC.

Patients in the siponimod treatment groups experienced >5% more AEs from the Nervous System Disorders and Investigations SOCs than patients in placebo treatment as indicated in

the following table:

Table 40: Incidence of Treatment Emergent Adverse Events by Primary System Organ Class, Study 2304, Controlled Pool, Safety Set

Primary System Organ Class	Siponimod N=1099 n (%)	Placebo N=546 n (%)
Number of patients with at least one AE	**975 (88.7%)**	**445 (81.5%)**
Infections and Infestations	539 (49.0%)	268 (49.1%)
Nervous System Disorders	416 (37.9%)	175 (32.1%)
Musculoskeletal and Connective Tissue Disorders	289 (26.3%)	149 (27.3%)
Gastrointestinal Disorders	269 (24.5%)	110 (20.1%)
General Disorders and Administration Site Conditions	268 (24.4%)	110 (20.1%)
Investigations	263 (23.9%)	80 (14.7%)
Injury, Poisoning and Procedural Complications	238 (21.7%)	114 (20.9%)
Skin and Subcutaneous Tissue Disorders	188 (17.1%)	93 (17.0%)
Psychiatric Disorders	169 (15.4%)	83 (15.2%)
Vascular Disorders	160 (14.6%)	60 (11.0%)
Cardiac Disorders	130 (11.8%)	55 (10.1%)
Respiratory, Thoracic, and Mediastinal Disorders	117 (10.6%)	71 (10.3%)
Neoplasms Benign, Malignant, and Unspecified	113 (10.3%)	45 (8.2%)
Eye Disorders	111 (10.1%)	54 (9.9%)
Metabolism and Nutrition Disorders	85 (7.7%)	28 (5.1%)
Renal and Urinary Disorders	84 (7.6%)	37 (6.8%)
Ear and Labyrinth Disorders	55 (5.0%)	38 (7.0%)
Blood and Lymphatic System Disorders	47 (4.3%)	10 (1.8%)
Reproductive System and Breast Disorders	36 (3.3%)	24 (4.4%)
Hepatobiliary Disorders	27 (2.5%)	4 (0.7%)
Endocrine Disorders	11 (1.0%)	4 (0.7%)
Immune System Disorders	8 (0.7%)	7 (1.3%)
Congenital, Familial, and Genetic Disorders	5 (0.5%)	0
Social Circumstances	3 (0.3%)	3 (0.5%)
Product Issues	1 (0.2%)	1 (0.2%)

Source: CSR Study A2304 Table 12.3.1-1.2

The most frequently reported TEAEs in Study A2304 were headache, nasopharyngitis, urinary tract infection, and fall. The table below provides a summary of TEAEs occurring in ≥3% of

patients.

Table 41: Incidence of Treatment Emergent Adverse Events Occurring in ≥3% of Patients, Study A2304, Controlled Phase, Safety Set

Preferred Term	Siponimod N=1099 n (%)	Placebo N=546 n (%)
Patients with at least 1 AE	975 (88.7%)	445 (81.5%)
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%)
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%)
ALT 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%)
Melanocytic nevus	47 (4.3%)	17 (3.1%)
GGT increased	43 (3.9%)	6 (1.1%)
Muscle Spasticity	43 (3.9%)	23 (4.2%)
Constipation	41 (3.7%)	22 (4.0%)
Insomnia	38 (3.5%)	19 (3.5%)
Muscle Spasms	37 (3.4%)	19 (3.5%)
Bronchitis	36 (3.3%)	16 (2.9%)
Contusion	35 (3.2%)	15 (2.7%)
Cough	35 (3.2%)	18 (3.3%)
Vomiting	33 (3.0%)	13 (2.4%)
Vertigo	25 (2.3%)	26 (4.8%)
Gait disturbance	24 (2.2%)	22 (4.0%)

Oropharyngeal pain	20 (1.8%)	17 (3.1%)
Paresthesia	18 (1.6%)	20 (3.7%)

Source: CSR Study A2304 Table 14.3.1-1.3

Study A2201

In a controlled clinical trial of siponimod in patients with RMS, 85.1% (range: 69.0%-98.0%) of patients exposed to siponimod doses ranging from 0.25-10 mg reported TEAEs.

As was the case in the pooled MS trial population, the most frequently reported TEAEs in the controlled phases of Study A2201 were from the Nervous System Disorders and Infections and Infestations SOCs.

Table 42: Incidence of Treatment Emergent Adverse Events by Primary System Class and Treatment, Study A2201, All Periods, Safety Set

Primary SOC	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=49 n (%)	Siponimod 10 mg N=50 n (%)	Placebo N=61 n (%)
Nervous System Disorders	9 (17.6%)	15 (34.9%)	9 (21.4%)	24 (49.0%)	32 (64.0%)	13 (21.3%)
Infections and Infestations	17 (33.3%)	27 (62.8%)	17 (40.5%)	16 (32.7%)	20 (40.0%)	32 (52.5%)
Cardiac Disorders	2 (3.9%)	5 (11.6%)	0	11 (22.4%)	17 (34.0%)	7 (11.5%)
General Disorders and Administration Site Conditions	5 (9.8%)	10 (23.3%)	7 (16.7%)	7 (14.3%)	15 (30.0%)	12 (19.7%)
Gastrointestinal Disorders	6 (11.8%)	11 (25.6%)	7 (16.7%)	8 (16.3%)	14 (28.0%)	10 (16.4%)
Eye Disorders	0	4 (9.3%)	1 (2.4%)	5 (10.2%)	11 (22.0%)	4 (6.6%)
Respiratory, Thoracic And Mediastinal Disorders	9 (17.6%)	6 (14.0%)	3 (7.1%)	13 (26.5%)	9 (18.0%)	4 (6.6%)
Investigations	6 (11.8%)	5 (11.6%)	3 (7.1%)	7 (14.3%)	9 (18.0%)	4 (6.6%)
Skin and Subcutaneous Tissue Disorders	5 (9.8%)	7 (16.3%)	6 (14.3%)	9 (18.4%)	8 (16.0%)	7 (11.5%)
Blood and Lymphatic System Disorders	0	1 (2.3%)	0	2 (4.1%)	6 (12.0%)	0
Musculoskeletal and Connective Tissue Disorders	6 (11.8%)	11 (25.6%)	7 (16.7%)	4 (8.2%)	6 (12.0%)	7 (11.5%)
Metabolism and Nutrition Disorders	0	0	1 (2.4%)	1 (2.0%)	4 (8.0%)	1 (1.6%)
Vascular Disorders	2 (3.9%)	1 (2.3%)	0	2 (4.1%)	4 (8.0%)	5 (8.2%)

Primary SOC	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=49 n (%)	Siponimod 10 mg N=50 n (%)	Placebo N=61 n (%)
Ear and Labyrinth Disorders	1 (2.0%)	1 (2.3%)	5 (11.9%)	6 (12.2%)	3 (6.0%)	4 (6.6%)
Injury, Poisoning and Procedural Complications	1 (2.0%)	5 (11.6%)	3 (7.1%)	3 (6.1%)	3 (6.0%)	6 (9.8%)
Neoplasms Benign, Malignant and Unspecified	0	3 (7.0%)	1 (2.4%)	4 (8.2%)	3 (6.0%)	3 (4.9%)
Psychiatric Disorders	4 (7.8%)	3 (7.0%)	2 (4.8%)	2 (4.1%)	1 (2.0%)	5 (8.2%)
Endocrine Disorders	0	0	0	1 (2.0%)	0	0
Hepatobiliary Disorders	0	2 (4.7%)	0	0	0	1 (1.6%)
Immune System Disorders	0	0	0	0	0	1 (1.6%)
Psychiatric Disorders	1 (2.0%)	0	0	0	0	0
Renal and Urinary Disorders	0	2 (4.7%)	1 (2.4%)	1 (2.0%)	0	0
Reproductive System and Breast Disorders	3 (5.9%)	1 (2.3%)	0	0	0	0

Source: Study A2201 CSR PT-Table 14.3.1-1.1

Reviewer Comment: The similarity between the safety findings in Study A2201 and the data from Trial A2304 conducted in patients with active SPMS, suggests that there is enough overlap in the RMS and active SPMS populations to generate conclusions from the combined pool that apply to both RMS and active SPMS patient populations. Indeed, the active SPMS population enrolled in Study A2304 was demographically like the enrolled population in Study A2201 and many of these SPMS patients were still experiencing relapses prior to, and during, the trial (see Dr. David Jones' Clinical Review of Efficacy). In our current understanding of active SPMS, this progressive form of MS emerges in patients initially diagnosed with RMS, and thus it is not unreasonable to expect considerable overlap in AEs reported in the RMS and active SPMS populations. The currently marketed approved S1P modulator, fingolimod, is indicated for RMS, which lends further confidence to the hypothesis that siponimod, which appears quite similar to fingolimod with respect to safety findings, can be used with similar expectations of relative safety in either RMS or active SPMS patients.

The most frequently reported TEAEs in the controlled phases of this trial in patients with RMS were headache, bradycardia, dizziness, and nasopharyngitis. Other TEAEs anticipated for a S1P modulator (lymphopenia, macular edema, elevated transaminases, and hypertension) were also reported at expected frequencies.

Table 43: Most Frequent (≥3% in Any Group) Treatment Emergent Adverse Events by Preferred Term and Treatment, Study A2201, All Periods, Safety Set

Preferred term	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=49 n (%)	Siponimod 10 mg N=50 n (%)	Placebo N=61 n (%)
Patients with at least 1 AE	**38 (74.5%)**	**37 (86.0%)**	**29 (69.0%)**	**48 (98.0%)**	**48 (96.0%)**	**49 (80.3%)**
Headache	5 (9.8%)	8 (18.6%)	5 (11.9%)	15 (30.6%)	23 (46.0%)	5 (8.2%)
Bradycardia	2 (3.9%)	2 (4.7%)	0	3 (6.1%)	14 (28.0%)	2 (3.3%)
Dizziness	0	5 (11.6%)	1 (2.4%)	5 (10.2%)	13 (26.0%)	6 (9.8%)
Lymphopenia[1]	0	0	1 (2.4%)	2 (4.1%)	9 (18.0%)	0
Nasopharyngitis	7 (13.7%)	11 (25.6%)	8 (19.0%)	6 (12.2%)	9 (18.0%)	8 (13.1%)
Fatigue	0	1 (2.3%)	4 (9.5%)	4 (8.2%)	8 (16.0%)	5 (8.2%)
Nausea	3 (5.9%)	2 (4.7%)	3 (7.1%)	2 (4.1%)	8 (16.0%)	2 (3.3%)
Liver transaminases increased[2]	3	0	1 (2.4%)	5 (10.2%)	5 (10.0%)	0
Cough	3 (5.9%)	4 (9.3%)	1 (2.4%)	5 (10.2%)	4 (8.0%)	1 (1.6%)
Sinusitis	0	1 (2.3%)	3 (7.1%)	2 (4.1%)	4 (8.0%)	1 (1.6%)
Back pain	1 (2.0%)	3 (7.0%)	2 (4.8%)	2 (4.1%)	3 (6.0%)	3 (4.9%)
Migraine	3 (5.9%)	0	0	2 (4.1%)	3 (6.0%)	1 (1.6%)
AV block 1st degree	0	1 (2.3%)	0	0	3 (6.0%)	0
Chills	0	0	0	0	3 (6.0%)	0
Vertigo	1 (2.0%)	1 (2.3%)	3 (7.1%)	6 (12.2%)	2 (4.0%)	3 (4.9%)
Upper respiratory tract infection	0	3 (7.0%)	1 (2.4%)	4 (8.2%)	2 (4.0%)	7 (11.5%)
Influenza	2 (3.9%)	1 (2.3%)	1 (2.4%)	4 (8.2%)	2 (4.0%)	4 (6.6%)
AV block 2nd degree	0	0	0	3 (6.1%)	2 (4.0%)	2 (3.3%)
Urinary tract infection	1 (2.0%)	2 (4.7%)	3 (7.1%)	2 (4.1%)	2 (4.0%)	2 (3.3%)
Melanocytic nevus	0	1 (2.3%)	1 (2.4%)	2 (4.1%)	2 (4.0%)	3 (4.9%)
Oropharyngeal pain	2 (3.9%)	2 (4.7%)	0	2 (4.1%)	2 (4.0%)	1 (1.6%)
Eye pain	0	0	0	2 (4.1%)	2 (4.0%)	2 (3.3%)
Oral herpes	1 (2.0%)	1 (2.3%)	2 (4.8%)	1 (2.0%)	2 (4.0%)	3 (4.9%)
Constipation	0	0	0	1 (2.0%)	2 (4.0%)	0
Hypercholesterolemia	0	0	1 (2.4%)	0	2 (4.0%)	1 (1.6%)
Paresthesia	0	2 (4.7%)	0	0	2 (4.0%)	0
Edema peripheral	1 (2.0%)	1 (2.3%)	0	0	2 (4.0%)	1 (1.6%)

Preferred term	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=49 n (%)	Siponimod 10 mg N=50 n (%)	Placebo N=61 n (%)
Hypotension	1 (2.0%)	1 (2.3%)	0	0	2 (4.0%)	0
Dry mouth	0	1 (2.3%)	0	0	2 (4.0%)	1 (1.6%)
Muscular weakness	0	0	0	0	2 (4.0%)	1 (1.6%)
Temperature intolerance	0	0	0	0	2 (4.0%)	0
Somnolence	1 (2.0%)	0	1 (2.4%)	4 (8.2%)	1 (2.0%)	1 (1.6%)
Diarrhea	1 (2.0%)	1 (2.3%)	0	2 (4.1%)	1 (2.0%)	3 (4.9%)
Palpitations	0	0	0	2 (4.1%)	1 (2.0%)	1 (1.6%)
Sinus bradycardia	0	0	0	2 (4.1%)	1 (2.0%)	1 (1.6%)
Dyspnea	3 (5.9%)	1 (2.3%)	1 (2.4%)	1 (2.0%)	1 (2.0%)	1 (1.6%)
Pharyngitis	2 (3.9%)	0	1 (2.4%)	1 (2.0%)	1 (2.0%)	3 (4.9%)
Ecchymosis	0	2 (4.7%)	0	1 (2.0%)	1 (2.0%)	1 (1.6%)
Cystitis	1 (2.0%)	0	0	1 (2.0%)	1 (2.0%)	2 (3.3%)
Pyrexia	1 (2.0%)	7 (16.3%)	1 (2.4%)	0	1 (2.0%)	4 (6.6%)
Vomiting	0	3 (7.0%)	1 (2.4%)	0	1 (2.0%)	2 (3.3%)
Pain in extremity	2 (3.9%)	2 (4.7%)	1 (2.4%)	0	1 (2.0%)	0
Dry eye	0	2 (4.7%)	1 (2.4%)	0	1 (2.0%)	0
Hypoesthesia	0	0	1 (2.4%)	0	1 (2.0%)	2 (3.3%)
Asthenia	0	2 (4.7%)	0	0	1 (2.0%)	3 (4.9%)
Toothache	0	1 (2.3%)	0	2 (4.1%)	0	3 (4.9%)
Aphthous stomatitis	0	0	0	2 (4.1%)	0	0
Pruritus	0	1 (2.3%)	3 (7.1%)	1 (2.0%)	0	1 (1.6%)
Abdominal pain	0	0	2 (4.8%)	1 (2.0%)	0	1 (1.6%)
C-reactive protein increased	1 (2.0%)	2 (4.7%)	0	1 (2.0%)	0	0
Myalgia	1 (2.0%)	2 (4.7%)	0	1 (2.0%)	0	0
Visual impairment	0	2 (4.7%)	0	1 (2.0%)	0	2 (3.3%)
Erythema	0	2 (4.7%)	0	1 (2.0%)	0	0
Bronchitis	0	3 (7.0%)	1 (2.4%)	0	0	0
Arthralgia	0	2 (4.7%)	1 (2.4%)	0	0	2 (3.3%)
Acne	1 (2.0%)	1 (2.3%)	1 (2.4%)	0	0	2 (3.3%)
Depression	2 (3.9%)	0	1 (2.4%)	0	0	2 (3.3%)
Dyspepsia	1 (2.0%)	2 (4.7%)	0	0	0	0

Preferred term	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=49 n (%)	Siponimod 10 mg N=50 n (%)	Placebo N=61 n (%)
Hyperthermia	1 (2.0%)	2 (4.7%)	0	0	0	0
Respiratory tract infection	1 (2.0%)	2 (4.7%)	0	0	0	0
Abdominal pain lower	0	2 (4.7%)	0	0	0	0
Anxiety	1 (2.0%)	1 (2.3%)	0	0	0	2 (3.3%)
Abdominal pain upper	0	1 (2.3%)	0	0	0	2 (3.3%)
Dry skin	2 (3.9%)	0	0	0	0	0
Epicondylitis	0	0	0	0	0	2 (3.3%)
Hot flush	0	0	0	0	0	2 (3.3%)
Hypoesthesia oral	0	0	0	0	0	2 (3.3%)

Source: Study A2201 CSR PT-Table 14.3.1-1.1

[1] includes preferred terms lymphocyte decreased, leukopenia, lymphopenia
[2] includes preferred terms ALT increased, GGT increased

Reviewer Comment: The most frequently reported TEAEs (headache, lymphopenia, dizziness, nasopharyngitis) align with the frequently reported TEAEs in the pooled trial data from all patients with MS. Bradycardia is overrepresented as a TEAE relative to the findings in Study A2304 because of the lack of titration in Period 1 of Study A2201 increasing cardiac AE frequency, especially bradycardia. Two notable absences from the most frequently reported TEAEs in Study A2034 are falls and urinary tract infections; however, these two AEs would be anticipated more frequently in patients with progressive form of MS who will have much higher rates of neurogenic urinary retention requiring catheterization (a significant UTI risk factor)[8] and will have more advanced disability predisposing to falls.[12]

Study A2202

In Study A2202, a controlled trial of siponimod as a therapy for polymyositis and dermatomyositis, 75.0% of patients treated with siponimod, and 80.0% of patients treated with placebo reported TEAEs.

Table 44: Treatment Emergent Adverse Events in All Patients by System Organ Classes

	Siponimod 10 mg N=16 n (%)	Placebo N=10 n (%)
All Patients with AEs	12 (75.0%)	8 (80.0%)
Nervous System Disorders	8 (50.0%)	2 (20.0%)
Gastrointestinal Disorders	6 (37.5%)	4 (40.0%)
Musculoskeletal and Connective Tissue Disorders	6 (37.5%)	2 (20.0%)
Respiratory, Thoracic, and Mediastinal Disorders	2 (12.5%)	4 (40.0%)
Eye Disorders	2 (12.5%)	2 (20.0%)
Infections and Infestations	3 (18.8%)	1 (10.0%)
Skin and Subcutaneous Disorders	3 (18.8%)	1 (10.0%)
General Disorders and Administrative Site Conditions	3 (18.8%)	0
Vascular Disorders	2 (12.5%)	1 (10.0%)
Cardiac Disorders	1 (6.3%)	0
Hepatobiliary Disorders	0	1 (10.0%)
Injury, Poisoning, and Procedural Complications	1 (6.3%)	1 (10.0%)
Neoplasms Benign, Malignant, and Unspecified	1 (6.3%)	0

Source: Study A2202 CSR Table 14.3.1-1.1

The most common TEAE for siponimod-treated patients in this study was headache (25%). Other TEAEs occurred in two or fewer patients.

Table 45: Treatment Emergent Adverse Events in All Patients, Study A2202

Preferred Term	Siponimod 10 mg N=16 n (%)	Placebo N=10 n (%)
Patients with at least one AE	**12 (75.0%)**	**8 (80.0%)**
Headache	4 (25.0%)	2 (20.0%)
Oropharyngeal pain	0 (0.0%)	4 (40.0%)
Diarrhea	2 (12.5%)	1 (10.0%)
Arthralgia	1 (6.3%)	1 (10.0%)

Preferred Term	**Siponimod 10 mg N=16 n (%)**	**Placebo N=10 n (%)**
Hypertension	2 (12.5%)	0 (0.0%)
Myalgia	2 (12.5%)	0 (0.0%)
Nausea	1 (6.3%)	1 (10.0%)
Pyrexia	2 (12.5%)	0 (0.0%)
Tremor	2 (12.5%)	0 (0.0%)
Abdominal pain upper	1 (6.3%)	0 (0.0%)
Aphthous stomatitis	0 (0.0%)	1 (10.0%)
Back pain	0 (0.0%)	1 (10.0%)
Basal cell carcinoma	1 (6.3%)	0 (0.0%)
Bronchitis	1 (6.3%)	0 (0.0%)
Cataract	0 (0.0%)	1 (10.0%)
Cholelithiasis	0 (0.0%)	1 (10.0%)
Conjunctivitis	1 (6.3%)	0 (0.0%)
Cough	1 (6.3%)	0 (0.0%)
Dental caries	1 (6.3%)	0 (0.0%)
Dermatitis	0 (0.0%)	1 (10.0%)
Dizziness	1 (6.3%)	0 (0.0%)
Dysgeusia	1 (6.3%)	0 (0.0%)
Dysphagia	1 (6.3%)	0 (0.0%)
Frequent bowel movements	1 (6.3%)	0 (0.0%)
Gastroesophageal reflux disease	1 (6.3%)	0 (0.0%)
Hematoma	0 (0.0%)	1 (10.0%)
Hemorrhoids	0 (0.0%)	1 (10.0%)
Intervertebral disc compression	1 (6.3%)	0 (0.0%)
Intervertebral disc protrusion	1 (6.3%)	0 (0.0%)
Macular edema	0 (0.0%)	1 (10.0%)
Mechanical urticaria	1 (6.3%)	0 (0.0%)
Neck pain	1 (6.3%)	0 (0.0%)
Edema peripheral	1 (6.3%)	0 (0.0%)
Oral herpes	1 (6.3%)	0 (0.0%)
Pain in extremity	1 (6.3%)	0 (0.0%)
Palpitations	1 (6.3%)	0 (0.0%)
Periorbital edema	0 (0.0%)	1 (10.0%)
Peritonitis	0 (0.0%)	1 (10.0%)
Productive cough	1 (6.3%)	0 (0.0%)

Preferred Term	Siponimod 10 mg N=16 n (%)	Placebo N=10 n (%)
Rash	1 (6.3%)	0 (0.0%)
Rhinorrhea	1 (6.3%)	0 (0.0%)
Rosacea	1 (6.3%)	0 (0.0%)
Salivary hypersecretion	1 (6.3%)	0 (0.0%)
Sciatica	1 (6.3%)	0 (0.0%)
Skin mass	1 (6.3%)	0 (0.0%)
Spinal compression fracture	1 (6.3%)	1 (10.0%)
Tinea versicolor	1 (6.3%)	0 (0.0%)
Vision blurred	1 (6.3%)	0 (0.0%)
Visual acuity reduced	0 (0.0%)	1 (10.0%)

Source: Study A2202 CSR Table 14.3.1-1.1

Study X2205

In Study X2205, a controlled trial of siponimod in patients with polymyositis, during Period 1 of this trial, a total of 12 (85.7%) patients overall experienced at least one TEAE. During Period 2, in which six patients continued with open label 2 mg siponimod and three placebo patients switched to open label siponimod 2 mg, a total of 6 (66.7%) patients experienced at least one TEAE.

Table 46: Reviewer Table, Incidence of Adverse Events by Primary System Organ Class, Periods 1 and 2, Study X2205, Safety Set

	Siponimod 2 mg N=7 n (%)	Siponimod 2 mg/ 2 mg N=6 n (%)	Placebo/ Siponimod 2 mg N=3 n (%)	Siponimod 10 mg N=2 n (%)	Placebo N=5 n (%)
All Patients with AEs	6 (85.7%)	4 (66.7%)	2 (66.7%)	2 (100.0%)	4 (80.0%)
Nervous System Disorders	2 (28.6%)	0	0	1 (50.0%)	3 (60.0%)
General Disorders and Administrative Site Conditions	3(42.9%)	1 (16.7%)	0	1 (50.0%)	1 (20.0%)
Gastrointestinal Disorders	1 (14.3%)	0	1 (33.3%)	1 (50.0%)	1 (20.0%)

	Siponimod 2 mg N=7 n (%)	Siponimod 2 mg/ 2 mg N=6 n (%)	Placebo/ Siponimod 2 mg N=3 n (%)	Siponimod 10 mg N=2 n (%)	Placebo N=5 n (%)
Eye Disorders	2 (28.6%)	1 (16.7%)	1 (33.3%)	1 (50.0%)	0
Investigations	1 (14.3%)	0	1 (33.3%)	0	1 (20.0%)
Infections and Infestations	0	1 (16.7%)	1 (33.3%)	1 (50.0%)	1 (20.0%)
Blood and Lymphatic System Disorders	1 (14.3%)	0	0	0	0
Cardiac Disorders	0	0	0	0	1 (20.0%)
Injury, Poisoning, and Procedural Complications	0	0	0	0	1 (20.0%)
Psychiatric Disorders	1 (14.3%)	0	0	0	0
Renal and Urinary Disorders	1 (14.3%)	0	0	0	0
Reproductive System and Breast Disorders	1 (14.3%)	0	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders	1 (14.3%)	0	0	0	0
Musculoskeletal and Connective Tissue Disorders	1 (14.3%)	2 (33.3%)	1 (33.3%)	0	0
Hepatobiliary Disorders	0	1 (16.7%)	0	0	0
Skin and Subcutaneous Tissue Disorders	0	1 (16.7%)	0	0	0

Sources: CSR Study X2205, Tables 12-1 and 12-2

Overall, headache was the most common TEAEs (4 patients, 28.6%), followed by dizziness (3 patients, 21.4%), abdominal pain upper and nausea (2 patients each, 14.3%). All the other TEAEs are reported in only 1 patient across treatment arms.

Table 47: Incidence of Treatment-Emergent Adverse Events by Preferred Term, Period 1, Study X2205, Safety Set

Preferred Term	Siponimod 2 mg N=7 n (%)	Siponimod 10 mg N=2 n (%)	Placebo N=5 n (%)
Patients with at least one AE	**6 (85.7%)**	**2 (100.0%)**	**4 (80.0%)**
Headache	2 (28.6%)	0	2 (40.0%)
Dizziness	0	1 (50.0%)	2 (40.0%)
Abdominal pain upper	1 (14.3%)	0	1 (20.0%)
Nausea	1 (14.3%)	0	1 (20.0%)
Acute kidney injury	1 (14.3%)	0	0
Asthenia	1 (14.3%)	0	0
Back pain	1 (14.3%)	0	0
Benign prostatic hyperplasia	1 (14.3%)	0	0
Carbon monoxide diffusing capacity decreased	0	0	1 (20.0%)
Cardiac murmur	1 (14.3%)	0	0
Cataract	1 (14.3%)	0	0
Cerebral artery stenosis	0	0	1 (20.0%)
Chest discomfort	0	1 (50.0%)	0
Depression	1 (14.3%)	0	0
Diarrhea	1 (14.3%)	0	0
Epicondylitis	0	0	1 (20.0%)
Eye pain	0	1 (50.0%)	0
Fatigue	0	0	1 (20.0%)
Feeling cold	1 (14.3%)	0	0
Hemolytic anemia	1 (14.3%)	0	0
Hemolytic uremic syndrome	1 (14.3%)	0	0
Myalgia	1 (14.3%)	0	0
Nasopharyngitis	0	0	1 (20.0%)
Ocular hyperemia	1 (14.3%)	0	0
Palpitations	0	0	1 (20.0%)
Pyrexia	1 (14.3%)	0	0
Rhinorrhea	1 (14.3%)	0	0

Preferred Term	Siponimod 2 mg N=7 n (%)	Siponimod 10 mg N=2 n (%)	Placebo N=5 n (%)
Urinary tract infection	0	1 (50.0%)	0
Vomiting	0	1 (50.0%)	0

Source: CSR Study X2205, Table 12-3

Table 48: Incidence of Treatment Emergent Adverse Events by Preferred Term, Period 2, Study X2205, Safety Set

Preferred Term	Siponimod 2mg/2mg N=6 n (%)	Placebo/ Siponimod 2mg N=3 n (%)
Patients with at least one AE	4 (66.7%)	2 (66.7%)
Upper respiratory tract infection	1 (16.7%)	1 (33.3%)
Cataract	0	1 (33.3%)
Cholelithiasis	1 (16.7%)	0
Diarrhea	0	1 (33.3%)
Fatigue	1 (16.7%)	0
GGT increased	0	1 (33.3%)
Musculoskeletal pain	1 (16.7%)	0
Pain in extremity	1 (16.7%)	0
Papule	1 (16.7%)	0
Polymyositis	0	1 (33.3%)
Spinal pain	1 (16.7%)	0
Vitreous detachment	1 (16.7%)	0

Source: CSR Study X2205, Table 12-4

Reviewer Comment: Most TEAEs in this study were mild in intensity. The TEAEs in Period 1 were shared in both placebo and siponimod treatment arms. In Period 2, a vitreous detachment event was noted as mild and was not associated with macular edema. The patient with hemolytic-uremic syndrome, a SAE, was discussed in Section 8.4.4. There was a second SAE, dizziness, that led to study discontinuation. The TEAEs in this study provide additional confirmatory data concerning the adverse event profile of siponimod and present no new concerning events.

Study X2206

In Study X2206, a controlled trial of siponimod in patients with active dermatomyositis, the most commonly affected primary SOCs during Period 1 of the trial were Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, Nervous System Disorders (each SOC n=6, 35.3%), followed by General Disorders and Administration Site Conditions (n=5, 29.4%).

Table 49: Incidence of Treatment Emergent Adverse Events by System Organ Class, Period 1, Study X2206, Safety Set

	Siponimod 0.5 mg N=4 n (%)	Siponimod 2 mg N=4 n (%)	Siponimod 10 mg N=4 n (%)	Placebo N=5 n (%)
Subjects with at least one AE	1 (25.0%)	4 (100.0%)	4 (100.0%)	2 (40.0%)
Infections and Infestations	0	4 (100.0%)	1 (25.0%)	1 (20.0%)
Musculoskeletal and Connective Tissue Disorders	1 (25.0%)	2 (50.0%)	3 (75.0%)	0
Nervous System Disorders	1 (25.0%)	2 (50.0%)	3 (75.0%)	0
General Disorders and Administration Site Conditions	0	2 (50.0%)	3 (75.0%)	0
Eye Disorders	1 (25.0%)	2 (50.0%)	1 (25.0%)	0
Skin and Subcutaneous Tissue Disorders	1 (25.0%)	1 (25.0%)	0	2 (40.0%)
Gastrointestinal Disorders	0	1 (25.0%)	2 (50.0%)	0
Injury, Poisoning and Procedural Complications	0	1 (25.0%)	2 (50.0%)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (25.0%)	0	2 (50.0%)	0
Investigations	0	1 (25.0%)	1 (25.0%)	0
Ear and Labyrinth Disorders	0	0	1 (25.0%)	0
Neoplasms Benign, Malignant and Unspecified	0	1 (25.0%)	0	0
Vascular Disorders	0	0	1 (25.0%)	0

Source: CSR Study X2206, Table 12-2

Overall, in Period 1 of this trial, among all patients exposed to siponimod, fatigue, headache and nasopharyngitis were the most common TEAEs, each of these AEs was reported by three (17.6%) patients.

Table 50: Incidence of Treatment Emergent Adverse Events by Preferred Term, Period 1, Study X2206, Safety Set

	Siponimod 0.5 mg N=4 n (%)	Siponimod 2 mg N=4 n (%)	Siponimod 10 mg N=4 n (%)	Placebo N=5 n (%)
Subjects with at least one AE	**1 (25.0%)**	**4 (100.0%)**	**4 (100.0%)**	**2 (40.0%)**
Fatigue	0	1 (25.0%)	2 (50.0%)	0
Headache	0	1 (25.0%)	2 (50.0%)	0
Nasopharyngitis	0	3 (75.0%)	0	0
Arthralgia	0	1 (25.0%)	1 (25.0%)	0
Asthenia	0	0	2 (50.0%)	0
Diarrhea	0	1 (25.0%)	1 (25.0%)	0
Muscle spasms	1 (25.0%)	0	1 (25.0%)	0
Muscular weakness	0	2 (50.0%)	0	0

Source: CSR Study X2206, Table 12-4

A total of 9 (52.9%) patients experienced at least one AE during Period 2, with the most commonly affected primary SOCs being Nervous System Disorders and Skin and Subcutaneous Tissue Disorders (each n=4, 23.5%), followed by gastrointestinal Disorders and Infections and Infestations (each n=3, 17.6%).

Table 51: Treatment Emergent Adverse Events by Primary System Organ Class, Study X2206, Period 2, Safety Set

Primary SOC	Placebo / Siponimod 2 mg N=5 n (%)	Siponimod 0.5 mg / Siponimod 2 mg N=4 n (%)	Siponimod 2 mg / Siponimod 2 mg N=4 n (%)	Siponimod 10 mg / Siponimod 2 mg N=4 n (%)
Subjects with at least one AE	2 (40.0%)	1 (25.0%)	4 (100.0%)	2 (50.0%)
Nervous System Disorders	0	0	3 (75.0%)	1 (25.0%)
Skin and Subcutaneous Tissue Disorders	1 (20.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)
Gastrointestinal Disorders	0	1 (25.0%)	1 (25.0%)	1 (25.0%)
Infections and Infestations	0	1 (25.0%)	2 (50.0%)	0
Investigations	1 (20.0%)	0	0	1 (25.0%)
Respiratory, Thoracic and Mediastinal Disorders	0	0	2 (50.0%)	0
Cardiac Disorders	0	0	1 (25.0%)	0
Ear and Labyrinth Disorders	0	0	1 (25.0%)	0
Eye Disorders	0	0	1 (25.0%)	0
General Disorders and Administration Site Conditions	0	0	1 (25.0%)	0
Injury, Poisoning and Procedural Complications	0	0	0	1 (25.0%)
Musculoskeletal and Connective Tissue Disorders	0	0	1 (25.0%)	0
Psychiatric Disorders	0	0	1 (25.0%)	0
Surgical and Medical Procedures	0	0	1 (25.0%)	0

Source: CSR Study X2206, Table 12-3

In Period 2, the most common TEAEs reported were headache (n=3, 17.6%) and syncope (n=2, 11.8%). These events were reported only in patients treated with siponimod 2 mg and 10 mg.

Table 52: Treatment Emergent Adverse Events by Preferred Term, Period 2, Study X2206, Safety Set

	Placebo / Siponimod 2 mg N=5 n (%)	Siponimod 0.5 mg / Siponimod 2 mg N=4 n (%)	Siponimod 2 mg / Siponimod 2 mg N=4 n (%)	Siponimod 10 mg / Siponimod 2 mg N=4 n (%)
Subjects with at least one AE	**2 (40.0%)**	**1 (25.0%)**	**4 (100.0%)**	**2 (50.0%)**
Headache	0	0	2 (50.0%)	1 (25.0%)
Syncope	0	0	1 (25.0%)	1 (25.0%)

Source: CSR Study X2206, Table 12-5

Reviewer Comment: The TEAEs from Study X2206 provide confirmation of common AEs from the pivotal trials in MS and no other new AEs of concern.

Clinical Pharmacology Studies

In the single dose studies, 45.4% of all siponimod-treated and 24.4% of all placebo-treated subjects reported at least one TEAE. All but a few of the TEAEs (>95%) were reported to be mild in severity. In the multiple dose studies, 52.8% of all siponimod-treated and 22.9% of placebo-treated subjects reported at least one TEAE. Most of the reported TEAEs (>90%) were mild in severity.

For the single and multiple dose studies conducted in healthy subjects (0.1 to 75 mg and 0.3 to 20 mg, respectively), the most frequently reported TEAEs were headache (32.3% and 20.8%, respectively), dizziness (12.1% and 5.7%, respectively) and nausea (5.5% and 4.2%, respectively). Cardiac disorders with frequencies ≥ 2% only occurred in subjects receiving single doses of siponimod and included bradycardia (4.3%) and AV block second degree (Mobitz I, 2:1 or 3:2 conduction) (3.4%).

8.4.6. Laboratory Findings

General Chemistry Results

A review of electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, P), random glucose, albumin, and amylase values did not reveal consistent evidence of treatment effects of siponimod at any dose on these parameters' lab test results in the clinical trials of MS during either the controlled or extension phases. Mean changes in lab results were generally similar by treatment, with notable exceptions being lymphocyte counts, hepatic transaminases, and cholesterol (discussed further below). Shift analyses of general chemistry values did not reveal significant trends

associated with treatment except as noted below.

Hematology

Siponimod treatment is associated with a dose dependent treatment reduction in total white blood cell and absolute lymphocyte counts. The reductions in lymphocyte counts were consistent and persistent while patients remained on treatment. The decrease in white blood cells is greatest within the subpopulation of CD4+ lymphocytes. The reductions in other lymphocyte-related parameters were largely consistent and sustained throughout the entire period of measurement. Platelet counts suggested a trend toward small reductions but with large variability.

Hematology mean changes from baseline in total white blood cell, absolute lymphocyte, absolute neutrophil, and platelet counts at months 1, 6, 12, 18, and 24 by treatment, are presented in the following table:

Table 53: Mean Changes from Baseline to Indicated Endpoints in Total White Blood Cell, Absolute Lymphocyte, Absolute Neutrophil, and Platelet Counts, Controlled Pool, Safety Set

	Siponimod 0.25mg (N = 51) Mean ± SD	Siponimod 0.5mg (N = 43) Mean ± SD	Siponimod 1.25mg (N = 42) Mean ± SD	Siponimod 2mg (N = 1148) Mean ± SD	Siponimod 10mg (N = 50 Mean ± SD)	Placebo (N = 607) Mean ± SD
Total White Blood Cells ($x10^9$/L)						
Month 1	-1.08 ± 1.53	-1.05 ± 1.43	-1.52 ± 1.83	-1.65 ± 1.51	-0.97 ± 1.72	+0.05 ± 1.80
Month 6		-0.44 ± 1.54		-1.70± 1.67	-1.54 ± 1.36	+0.26 ± 1.81
Month 12				-1.71 ± 1.56		+0.31 ± 1.97
Month 18				-1.57 ± 1.82		+0.34 ± 1.93
Month 24				-1.70 ± 1.70		+0.18 ± 1.93
Absolute Lymphocytes ($x10^9$/L)						
Month 1	-0.50 ± 0.44	-0.87± 0.44	-1.11 ± 0.37	-1.23 ± 0.52	-1.40 ± 0.56	+0.04 ± 0.40
Month 6		-0.96 ± 0.54		-1.26 ± 0.55	-1.62 ± 0.61	+0.08 ± 0.44
Month 12				-1.26 ± 0.54		+0.09 ± 0.47
Month 18				-1.27 ± 0.52		+0.11 ± 0.44
Month 24				-1.26 ± 0.54		+0.06 ± 0.47
Absolute Neutrophils ($x10^9$/L)						
Month 1	-0.43 ± 1.08	-0.23 ± 1.36	-0.46 ± 1.62	-0.43 ± 1.34	+0.18 ± 1.64	-0.03 ± 1.67
Month 6		-0.67 ± 1.27		-0.43 ± 1.47	-0.15 ± 1.47	+0.13 ± 1.68
Month 12				-0.45 ± 1.38		+0.16 ± 1.85
Month 18				-0.32 ± 1.69		+0.160 ± 1.79
Month 24				-0.44 ± 1.49		+0.09 ± 1.71
Platelet Count ($x10^9$/L)						

	Siponimod 0.25mg (N = 51) Mean ± SD	Siponimod 0.5mg (N = 43) Mean ± SD	Siponimod 1.25mg (N = 42) Mean ± SD	Siponimod 2mg (N = 1148) Mean ± SD	Siponimod 10mg (N = 50 Mean ± SD)	Placebo (N = 607) Mean ± SD
Month 1	-7.98 ± 33.83	-11.58 ± 27.58	-0.52 ± 50.56	-7.16 ± 35.34	-10.66 ± 34.84	+4.46 ± 36.46
Month 6		-18.15 ± 29.98		-8.75 ± 38.44	-4.89 ± 25.65	-0.48 ± 39.89
Month 12				-12.55 ± 41.66		-2.03 ± 39.73
Month 18				-13.33 ± 44.08		-4.19 ± 42.15
Month 24				-16.67 ± 50.12		-9.57 ± 38.04

Source: SCS Appendix 1-Table 3.5-1.1

An analysis of new or worsening abnormalities based on CTCAE grade confirmed that virtually all patients on treatment with siponimod experienced a decrease in lymphocytes. Siponimod was associated with low grade anemic events without an increase in anemia that required transfusion or was life-threatening.

Table 54: Reviewer Table, Number of Patients with New or Worsening Abnormalities by CTCAE Grade, Safety Database 2

Abnormality	Siponimod 2-10 mg* N=1737	Placebo N=607
White Blood Cell Count Decreased		
Grade 1: <LLN - 3.0 x 10^9/L	602/1621 (37.1%)	49/584 (8.4%)
Grade 2: <3.0 - 2.0 x10^9/L	360/1705 (21.1%)	7/607 (1.2%)
Grade 3: <2.0 - 1.0 x 10^9/L	28/1710 (1.6%)	0
Grade 4: <1.0 x 10^9/L	0	0
All Grades	990/1710 (57.9%)	56/607 (9.2%)
Lymphocyte Count Decreased		
Grade 1: <LLN x 0.8 x 10^9/L	28/1543 (1.8%)	29/584 (5.0%)
Grade 2: <0.8 - 0.5 x 10^9/L	249/1598 (15.6%)	18/603 (3.0%)
Grade 3: <0.5 - 0.2 x 10^9/L	1185/1634 (72.5%)	3/606 (0.5%)
Grade 4: <0.2 x 10^9/L	158/1656 (9.5%)	1/607 (0.2%)
All Grades	1620/1657 (97.8%)	51/607 (8.4%)
Neutrophil Count Decreased		
Grade 1: <LLN - 1.5 x 10^9/L	69/1701 (4.1%)	4/605 (0.7%)
Grade 2: <1.5 - 1.0 x 10^9/L	58/1706 (3.4%)	10/607 (1.6%)
Grade 3: <1.0 - 0.5 x 10^9/L	5/1709 (0.3%)	0
Grade 4: <0.5 x 10^9/L	0	0
All Grades	132/1710 (7.7%)	14/607 (2.3%)

Abnormality	Siponimod 2-10 mg* N=1737	Placebo N=607
Platelet Cell Count Decreased		
Grade 1: <LLN-75.0 x 10^9/L	123/1661 (7.4%)	31/594 (5.2%)
Grade 2: <75.0 - 50.0 x 10^9/L	3/1708 (0.2%)	1/607 (0.2%)
Grade 3: <50.0 - 25.0 x 10^9/L	2/1708 (0.1%)	0
Grade 4: <25.0 x 10^9/L	2/1708 (0.1%)	1/607 (0.2%)
All Grades	130/1708 (7.6%)	33/607 (5.4%)
Anemia		
Grade 1: <LLN - 100 g/L	202/1601 (12.6%)	48/567 (8.5%)
Grade 2: <100 - 80 g/L	21/1701 (1.2%)	4/603 (0.7%)
Grade 3: <80 - 65 g/L transfusion indicated	4/1710 (0.2%)	2/607 (0.3%)
Grade 4: Life-threatening consequences	0	0
All Grades	227/1710 (13.3%)	54/607 (8.9%)

Sources: adae.xpt, 120-day Safety Update SCS

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

Reviewer Comment: Siponimod's effects on lymphocytes appear consistent with those of the other approved S1P therapy, fingolimod. In comparison to siponimod's reduction in WBC at 12 months (-1.71), in MS clinical trials, fingolimod 0.5 mg treatment yielded a -2.20 mean WBC change at 12 months. Considering the changes in absolute lymphocytes, siponimod (-1.26) and fingolimod (-1.33) appeared to have similar treatment effects at 12 months. Fingolimod treatment yielded a mean reduction in absolute neutrophils of -0.73 as compared to the decrease noted with siponimod of -0.45; this reduction is not predicted to create a clinically significant neutropenia, and there were no cases of neutropenia (<0.5x10^9 neutrophils/L) reported in the controlled patient pool. A small decrease in platelet count (with large variability) was noted with fingolimod and is noted with siponimod treatment; this small decrease in circulating platelets is of uncertain clinical significance but did not appear to predispose to bleeding diatheses. Siponimod appeared to increase likelihood of CTCAE Grade 1-2 anemic events without a difference in transfusion or life-threatening events; a hemoglobin shift analysis did not demonstrate a difference between siponimod from placebo treatments.

The percent change in the subtypes of lymphocytes from baseline are shown in the following table:

Table 55: Reviewer Table, Summary of Percent Change from Baseline, White Blood Cell Subtypes, Controlled Phase, Study A2304, Safety Set

	Siponimod 2 mg N=1099	Placebo N=546
	% Change from Baseline ± SD	% Change from Baseline ± SD
Total White Blood Cell Count		
Month 1	-23.05 ± 19.91	+3.78 ± 26.27
Month 3	-25.10 ± 22.36	+5.68 ± 25.87
Month 6	-23.42 ± 22.42	+7.47 ± 26.09
Month 12	-23.80 ± 20.38	+7.74 ± 30.85
Month 18	-22.06 ± 23.54	+8.88 ± 27.90
Month 24	-24.26 ± 22.17	+5.04 ± 29.02
Absolute Lymphocyte Count		
Month 1	-66.95 ± 14.67	+4.93 ± 23.53
Month 3	-69.73 ± 16.36	+7.13 ± 26.77
Month 6	-69.19 ± 15.35	+8.15 ± 27.34
Month 12	-69.10 ± 14.98	+8.10 ± 28.92
Month 18	-69.57 ± 14.18	+9.13 ± 26.51
Month 24	-70.32 ± 16.26	+5.24 ± 29.21
Absolute Neutrophil Count		
Month 1	-9.76 ± 31.08	-0.63 ± 39.78
Month 3	-11.46 ± 34.08	+1.51 ± 37.64
Month 6	-9.81 ± 34.03	+2.61 ± 37.61
Month 12	-10.31 ± 32.28	+3.24 ± 42.26
Month 18	-7.67 ± 38.66	+3.36 ± 40.57
Month 24	-10.41 ± 34.55	+0.51 ± 45.70
CD4+ Lymphocyte Count		
Month 1	-90.18 ± 14.66	+9.18 ± 64.96
Month 3	-91.28 ± 17.12	+10.50 ± 67.67
Month 6	-91.35 ± 24.90	+10.32 ± 69.07
Month 12	-91.22 ± 20.00	+10.00 ± 71.21
Month 18	-92.00 ± 13.18	+14.37 ± 81.14
Month 24	-89.52 ± 25.01	+14.26 ± 96.79
CD8+ Lymphocyte Count		
Month 1	-65.46 ± 23.24	+12.29 ± 71.92
Month 3	-70.16 ± 23.45	+11.71 ± 76.73

	Siponimod 2 mg N=1099	Placebo N=546
	% Change from Baseline ± SD	**% Change from Baseline ± SD**
Month 6	-70.44 ± 23.12	+12.15 ± 73.11
Month 12	-69.61 ± 36.73	+10.79 ± 67.40
Month 18	-71.43 ± 23.81	+16.36 ± 75.00
Month 24	-71.50 ± 24.94	+10.32 ± 78.72
Absolute Monocyte Count		
Month 1	+10.20 ± 34.18	+3.01 ± 36.49
Month 3	+5.09 ± 34.28	+1.26 ± 38.04
Month 6	+9.16 ± 35.75	+6.27 ± 39.40
Month 12	+11.48 ± 31.22	+6.48 ± 37.66
Month 18	+10.91 ± 38.30	+9.44 ± 34.98
Month 24	+6.35 ± 31.90	+5.73 ± 37.81
Absolute Eosinophil Count		
Month 1	-10.79 ± 60.43	+5.15 ± 55.66
Month 3	-17.27 ± 69.21	+2.19 ± 70.66
Month 6	-20.00 ± 65.79	+3.24 ± 72.16
Month 12	-14.39 ± 75.04	+9.70 ± 65.30
Month 18	-10.37 ± 96.07	+16.67 ± 79.09
Month 24	-14.62 ± 72.77	+0.78 ± 56.82
Absolute Basophil Count		
Month 1	-75.61 ± 28.29	+5.26 ± 52.11
Month 3	-78.57 ± 24.05	+17.95 ± 50.53
Month 6	-78.57 ± 23.81	+23.68 ± 50.53
Month 12	-92.86 ± 23.33	+25.64 ± 45.38
Month 18	-75.61 ± 22.44	+26.31 ± 53.68
Month 24	-75.61 ± 29.51	+13.89 ± 63.89

Source: Tables 14.3-2.1.1 and 14.3-2.1.2 CSR, Study A2304

Reviewer Comment: The decrease in total white blood cell counts associated with siponimod therapy appears driven largely by a reduction in lymphocytes and, more specifically, by an approximate reduction of 70% and 90% in CD8+ and CD4+ lymphocytes, respectively. An approximate 10% decline in absolute neutrophil count occurs with high variability. The reduction in lymphocytes is a likely explanation for the increased risk of infection noted in these studies, and the large decline in CD4+ and CD8+ cell counts are risk factors for the appearance of opportunistic infections and the reactivation of latent infections. The decreased absolute basophil count is of unclear clinical significance and had been noted in association with fingolimod therapy. See Section 8.5.1. for further discussion of lymphopenia.

Lymphocyte Recovery

Limited numbers of patients in the controlled portion of trials in MS were observed after discontinuation of siponimod for recovery of lymphocyte counts. Based on the data observed up to 4+ weeks after discontinuation, recovery occurs during weeks 1-4, and the greatest increase in lymphocyte count between Weeks 1 and 2. Most patients' counts appear to return to baseline values within 4 weeks of discontinuation.

Table 56: Absolute Lymphocyte Count After Discontinuation of Siponimod By Visit Window and Treatment, Controlled Pool, Safety Set

Visit Window		Baseline		Post-Baseline	Change from Baseline
Treatment	**Dose N**	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Week 1 Follow-up					
Siponimod	**0.25mg (N = 51)**	8	2.21 ± 0.84	1.69 ± 0.79	-0.52 ± 0.26
Siponimod	**0.5mg (N = 43)**	16	1.67 ± 0.47	0.74 ± 0.32	-0.93 ± 0.317
Siponimod	**1.25mg (N = 42)**	5	1.77 ± 0.55	0.63 ± 0.32	-1.15 ± 0.25
Siponimod	**2mg (N = 1148)**	403	1.74 ± 0.52	0.56 ± 0.33	-1.18 ± 0.53
Siponimod	**10mg (N = 50)**	9	1.78 ± 0.55	0.34 ± 0.22	-1.44 ± 0.60
Week 2 Follow-up					
Siponimod	**0.25mg (N = 51)**	4	2.21 ± 0.28	1.60 ± 0.94	-0.60 ± 0.75
Siponimod	**0.5mg (N = 43)**	3	2.01 ± 0.63	1.74 ± 1.18	-0.28 ± 0.67
Siponimod	**1.25mg (N = 42)**	4	1.83 ± 0.69	1.22 ± 0.55	-0.61 ± 0.80
Siponimod	**2mg (N = 1148)**	41	1.83 ± 0.71	1.15 ± 0.55	-0.68 ± 0.64
Siponimod	**10mg (N = 50)**	9	1.84 ± 0.61	1.42 ± 0.61	-0.42 ± 0.59
Week 3 Follow-up					
Siponimod	**0.5mg (N = 43)**	4	2.00 ± 0.49	2.10 ± 0.63	+0.10 ± 0.56

Visit Window		Baseline		Post-Baseline	Change from Baseline
Treatment	**Dose N**	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Siponimod	**1.25mg (N = 42)**	1	1.29	1.40	+0.11
Siponimod	**2mg (N = 1148)**	31	1.92 ± 0.81	1.62 ± 0.68	-0.30 ± 0.65
Siponimod	**10mg (N = 50)**	5	1.54 ± 0.35	0.94 ± 0.29	-0.59 ± 0.33
Week 4 Follow-up					
Siponimod	**1.25mg (N = 42)**	1	1.58	1.98	+0.40
Siponimod	**2mg (N = 1148)**	42	1.65 ± 0.48	1.48 ± 0.60	-0.17 ± 0.44
Siponimod	**10mg (N = 50)**	4	1.48 ± 0.51	1.25 ± 0.45	-0.24 ± 0.48
>Week 4 Follow-up					
Siponimod	**0.25mg (N = 51)**	6	2.03 ± 0.50	1.70 ± 0.46	-0.34 ± 0.36
Siponimod	**0.5mg (N = 43)**	32	1.73 ± 0.46	1.77 ± 0.54	+0.04 ± 0.36
Siponimod	**1.25mg (N = 42)**	4	1.63 ± 0.30	1.85 ± 0.36	+0.22 ± 0.17
Siponimod	**2mg (N = 1148)**	253	1.82 ± 0.57	1.56 ± 0.59	-0.25 ± 0.47
Siponimod	**10mg (N = 50)**	37	1.78 ± 0.53	1.68 ± 0.46	-0.10 ± 0.39

Source: Table 3.5-1.1 SCS Appendix 1

Table 57: Frequency of Abnormalities in Lymphocyte Count Decreased, Neutrophil Count Decreased, and White Blood Cell Count Decreased by CTCAE Grade and Visit Window, Controlled Pool, Safety Set

	Siponimod 0.25 mg	Siponimod 0.5 mg	Siponimod 1.25 mg	Siponimod 2 mg	Siponimod 10 mg	Placebo
Follow-up Week 1						
Grade 1 Events	0/8 (0)	2/16 (12.5%)	0/5 (0)	3/395 (0.8%)	0/9 (0)	1/203 (0.5%)
Grade 2 Events	1/8 (12.5%)	1/16 (6.3%)	0/5 (0)	27/401 (6.7%)	0/9 (0)	1/207 (0.5%)
Grade 3 Events	0/8 (0)	1/16 (6.3%)	1/5 (20.0%)	107/403 (26.6%)	1/9 (11.1%)	0/207
Grade 4 Events	0/8 (0)	0/16 (0)	0/5 (0)	1/403 (0.2%)	0/9 (0)	0/207 (0)
Follow-up Week 2						
Grade 1 Events	0/4 (0)	0/3 (0)	0/4 (0)	0/40 (0)	0/9 (0)	1/16 (6.3%)
Grade 2 Events	0/4 (0)	0/3 (0)	0/4 (0)	1/40 (0)	0/9 (0)	1/17 (5.9%)
Grade 3 Events	1/4 (25.0%)	0/3 (0)	0/4 (0)	4/41 (9.8)	0/9 (0)	0/18 (0)
Grade 4 Events	0/4 (0)	0/3 (0)	0/4 (0)	0/41 (0)	0/9 (0)	0/18 (0)
Follow-up Week 3						
Grade 1 Events	0/0 (0)	0/4 (0)	0/1 (0)	0/30 (0)	0/5 (0)	0/11 (0)
Grade 2 Events	0/0 (0)	0/4 (0)	0/1 (0)	0/31 (0)	0/5 (0)	1/11 (9.1%)
Grade 3 Events	0/0 (0)	0/4 (0)	0/1 (0)	0/31 (0)	0/5 (0)	0/12 (0)
Grade 4 Events	0/0 (0)	0/4 (0)	0/1 (0)	0/31 (0)	0/5 (0)	0/12 (0)
Follow-up Week 4						
Grade 1 Events	0/0 (0)	0/0 (0)	0/1 (0)	0/40 (0)	0/4 (0)	0/14 (0)
Grade 2 Events	0/0 (0)	0/0 (0)	0/1 (0)	0/42 (0)	0/4 (0)	0/15 (0)
Grade 3 Events	0/0 (0)	0/0 (0)	0/1 (0)	0/42 (0)	0/4 (0)	0.15 (0)

	Siponimod 0.25 mg	Siponimod 0.5 mg	Siponimod 1.25 mg	Siponimod 2 mg	Siponimod 10 mg	Placebo
Grade 4 Events	0/0 (0)	0/0 (0)	0/1 (0)	0/42 (0)	0/4 (0)	0/15 (0)

Source: Table 3.3-2.1 SCS 120-day Update, Appendix 1

Reviewer Comment: Significant lymphocyte recovery beginning 1 week after discontinuation would be predicted based on siponimod's half-life (approximately 36 hours). Recovery appears to continue through and beyond 4 weeks post-discontinuation. It is unclear which lymphocytes are released from lymph node reserves and whether there are deficiencies in subpopulations of lymphocytes that exist during or after restoration of normal range total white blood counts because there were no investigations after discontinuation of lymphocyte subtypes beyond neutrophils. In fingolimod, there is a severe exacerbation of symptoms noted in a fraction of patients 3-6 months after discontinuation that is suspected to be related to lymphocyte count recovery. (b) (4)

Shift Analyses of Hematologic Results

Shift analyses of hematologic values based on CTC grades were unremarkable other than the dose dependent white blood cell, absolute lymphocyte, CD4+, and CD8+ counts associated with siponimod therapy (data not shown).

Hemoglobin shift analysis performed in Study A2304 confirmed that most events in the siponimod treated patients were low grade, not life-threatening, events, and the distributions of events between the siponimod and placebo treatment arms were similar.

Table 58: Hemoglobin Shift Table Based on CTCA Grade During Study by Parameter and Treatment, Study A2304, Controlled Pool, Safety Set

Treatment		Worst Value on Study Treatment				
	Baseline	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Siponimod 2 mg N=1148						
Grade 0	1053 (92.8%)	961 (84.7%)	90 (7.9%)	2 (0.2%)	0	0
Grade 1	76 (6.7%)	8 (0.7%)	59 (5.2%)	9 (0.8%)	0	0
Grade 2	6 (0.5)	0	0	3 (0.3%)	3 (0.3%)	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
All Grades	1135 (100%)	969 (85.4%)	149 (13.1%)	14 (1.2%)	3 (0.3%)	0

Treatment		Worst Value on Study Treatment				
	Baseline	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Placebo N=607						
Grade 0	567 (93.4%)	517 (85.2%)	48 (7.9%)	2 (0.3%)	0	0
Grade 1	36 (5.9%)	7 (1.2%)	25 (4.1%)	2 (0.3%)	2 (0.3%)	0
Grade 2	4 (0.7%)	0	0	4 (0.7%)	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
All Grades	607 (100%)	524 (86.3%)	73 (12.0%)	8 (1.3%)	2 (0.3%)	0

Source: SCS Appendix 1, Table 3.3-4

Clinical Chemistry

Liver Transaminases
Siponimod is associated with an increase in liver transaminases, most frequently, alanine aminotransferase (ALT). When observed, the elevations in liver transaminases were typically within 1-3x the upper limit of normal (ULN). The increased values persisted during treatment. Elevated transaminases during treatment returned to baseline values within 3 months of discontinuation of siponimod. There were no cases meeting Hy's law criteria.

MS Controlled Pool
In the siponimod 2 mg group, 45.9% of patients had raised ALT (>1 x ULN) on at least one occasion post-baseline, with 5.6% having ALT of 3x ULN and with 1 patient (0.1%) having ALT of >10 x ULN. In the placebo group 12.4% of patients had ALT >1 x ULN, 1.3% had ALT >3 x ULN and 1 patient (0.2%) had an ALT >10 x ULN.

In the siponimod 2 mg group, 20.8% of patients had an elevated AST (>1 x ULN) on at least one occasion post-baseline, with 1.1% having AST of 3 x ULN and 1 patient (0.1%) with AST of >10 x ULN. In the placebo group, 4.6% of patients had AST >1 x ULN, 0.8% had AST >3 x ULN and no patients had an AST >10 x ULN.

In the siponimod 2 mg treatment group, 29.2% of patients had an elevated GGT >1 x ULN, 10.1% of patients had an GGT >3 x ULN, and 3.1% had a GGT >5 x ULN. In the placebo group, 6.1% of patients had GGT >1 x ULN, 1.7% had GGT >5 x ULN, and no patients had GGT >10 x ULN.

In the 2 mg siponimod treatment group, 14.8% of patients experienced an increased alkaline phosphatase >1 x ULN compared to 6.5% of placebo treated patients.

Patients experienced an increased total bilirubin in both siponimod and placebo treatment

arms in the controlled studies pool. In the siponimod 2 mg treatment group, 22 patients (1.9%) had total bilirubin > 1.5 x ULN. In the placebo group, the proportion who had raised total bilirubin (> 1.5 ULN) was similar (8 patients, 1.3%).

There were no cases reported which indicated serious hepatotoxicity (*i.e.,* satisfying Hy's Law) in any of the siponimod treatment groups or in the placebo group for the controlled trial data.

The distribution of patients with liver parameter abnormalities in controlled trials of siponimod is presented in the following table:

Table 59: Reviewer Table, Distribution of Patients with Liver Parameter Abnormalities, Controlled Pool, Safety Set

Parameter	Finding	Siponimod 0.25mg N=51 n/m (%)	Siponimod 0.5mg N = 43 n/m (%)	Siponimod 1.25mg N=42 n/m (%)	Siponimod 2mg N=1148 n/m (%)	Siponimod 10mg N=50 n/m (%)	Placebo N=607 n/m (%)
ALT	>1× ULN	10/50 (20.0%)	11/43 (25.6%)	13/42 (31.0%)	520/1134 (45.9%)	21/47 (44.7%)	75/607 (12.4%)
	>3 × ULN	2/50 (4.0%)	0	1/42 (2.4%)	63/1134 (5.6%)	3/47 (6.4%)	8/607 (1.3%)
	>5 × ULN	1/50 (2.0%)	0	0	14/1134 (1.2%)	1/47 (2.1%)	4/607 (0.7%)
	>8 × ULN	0	0	0	5/1134 (0.4%)	1/47 (2.1%)	1/607 (0.2%)
	>10 × ULN	0	0	0	1/1134 (0.1%)	0	1/607 (0.2%)
	>20 × ULN	0	0	0	0	0	0
AST	>1 × ULN	7/50 (14.0%)	3/43 (7.0%)	4/42 (9.5%)	236/1134 (20.8%)	14/47 (29.8%)	28/607 (4.6%)
	>3 × ULN	0	0	0	12/1134 (1.1%)	0	5/607 (0.8%)
	>5 × ULN	0	0	0	5/1134 (0.4%)	0	1/607 (0.2%)
	>8 × ULN	0	0	0	2/1134 (0.2%)	0	0
	>10 × ULN	0	0	0	1/1134 (0.1%)	0	0

Parameter	Finding	Siponimod 0.25mg N=51 n/m (%)	Siponimod 0.5mg N = 43 n/m (%)	Siponimod 1.25mg N=42 n/m (%)	Siponimod 2mg N=1148 n/m (%)	Siponimod 10mg N=50 n/m (%)	Placebo N=607 n/m (%)
	>20 × ULN	0	0	0	0 (0%)	0	0
GGT	**>1 × ULN**	4/46 (8.7%)	2/42 (4.8%)	4/40 (10.0%)	317/1087 (29.2%)	12/45 (26.7%)	36/587 (6.1%)
	>3 × ULN	2/50 (4.0%)	2/43 (4.7%)	0	114/1129 (10.1%)	4/47 (8.5%)	10/606 (1.7%)
	>5 × ULN	1/50 (2.0%)	0	0	35/1134 (3.1%)	1/47 (2.1%)	0
	>20 × ULN	0	0	0	0	0	0
Alkaline Phosphatase	**>1 × ULN**	4/50 (8.0%)	3/42 (7.1%)	0	163/1098 (14.8%)	2/45 (4.4%)	38/584 (6.5%)
	>3 × ULN	0	0	0	7/1134 (0.6%)	0	1/607 (0.2%)
	>5 × ULN	0	0	0	0	0	0
	>20 × ULN	0	0	0	0	0	0
Total Bilirubin	**>1.5 × ULN**	1/50 (2.0%)	0	0	22/1134 (1.9%)	0	8/607 (1.3%)
	>2 × ULN	0	0	0	8/1134 (0.7%)	0	1/607 (0.2%)
	>3 × ULN	0	0	0	2/1134 (0.2%)	0	0
Hy's Law	**ALT or AST >3x ULN & BILI >2x ULN**	0	0	0	0	0	0

Source: SCS Appendix 1-Table 3.4-1.1

m: Number of patients at risk (patients having at least one post-baseline measurement for the laboratory test under consideration. n = Number of patients.

Reviewer Comment: There appears to be a dose-dependent effect of siponimod on increased AST, ALT, and GGT. Transaminase elevation was expected based on prior experience with fingolimod, and these findings are consistent with the transaminase

findings in fingolimod controlled trials. Patients who discontinued siponimod due to elevated transaminases did not require further treatment. The applicant provided data on follow-up transaminase values after discontinuation that demonstrated a return to baseline within 3-12 months of discontinuation (follow-up data are provided below). There were no reported cases of liver necrosis, fulminant liver failure, or deaths due to hepatitis (or suspected hepatic causes) in the siponimod clinical program. Labeling for siponimod will recommend baseline liver transaminase testing and follow-up to mitigate risks of drug-induced liver injury.

Table 60: Summary of Mean Changes in Liver Transaminases by Visit and Treatment, Controlled Pool, Safety Set (Safety Database 1)

	Siponimod 2 mg N=1148	**Placebo N=546**
	Mean Change from Baseline ± SD (U/L)	**Mean Change from Baseline ± SD (U/L)**
Alanine Aminotransferase		
Month 1	+10.74 ± 13.40	0.11 ± 13.12
Month 3	+15.23 ± 24.54	-0.43 ± 13.25
Month 6	+16.00 ± 22.46	-0.07 ± 13.12
Month 12	+16.67 ± 21.85	-0.08 ± 13.69
Month 18	+16.20 ± 22.17	-0.40 ± 11.34
Month 24	+15.85 ± 21.56	+0.08 ± 10.76
Last Study Assessment	+17.65 ± 26.39	+0.02 ± 12.48
Follow-up Month 1	+10.66 ± 42.41	8.44 ± 63.98
Follow-up Month 3	+0.78 ± 15.08	-3.19 ± 14.03
Follow-up Month 6	+0.78 ± 15.08	-3.19 ± 14.03
Follow-up Month 12	-3.50 ± 6.81	-1.33 ± 2.08
Aspartate Aminotransferase		
Month 1	+4.36 ± 11.58	-0.15 ± 6.74
Month 3	+6.31 ± 12.31	-0.26 ± 7.32
Month 6	+6.44 ± 10.97	-0.09 ± 6.52
Month 12	+6.93 ± 12.69	-0.02 ± 7.95
Month 18	+6.26 ± 10.36	+0.33 ± 6.43
Month 24	+6.17 ± 10.74	+0.22 ± 5.99
Last Study	+6.72 ± 13.13	-0.42 ± 6.58

	Siponimod 2 mg N=1148	Placebo N=546
	Mean Change from Baseline ± SD (U/L)	**Mean Change from Baseline ± SD (U/L)**
Assessment		
Follow-up Month 1	+4.74 ± 27.97	+4.74 ± 34.74
Follow-up Month 3	-0.13 ± 8.29	-2.46 ± 7.57
Follow-up Month 6	-0.65 ± 3.54	-2.46 ± 4.77
Follow-up Month 12	-3.25 ± 6.65	-2.33 ± 2.08
Gamma Glutamyl Transferase		
Month 1	+12.92 ± 30.99	-0.15 ± 11.30
Month 3	+29.56 ± 53.47	-0.37 ± 9.67
Month 6	+36.19 ± 51.62	+0.55 ± 12.37
Month 12	+43.69 ± 59.20	-0.17 ± 11.60
Month 18	+46.72 ± 54.31	+2.39 ± 17.42
Month 24	+48.75 ± 53.26	+2.11 ± 12.60
Last Study Assessment	+43.25 ± 59.90	+1.46 ± 17.24
Follow-up Month 1	+27.47 ± 58.38	0.61 ± 17.93
Follow-up Month 3	+8.36 ± 28.93	-3.30 ± 19.70
Follow-up Month 6	+1.47 ± 4.64	+3.54 ± 10.72
Follow-up Month 12	+1.50 ± 1.29	-0.67 ± 4.73

Source: SCS Appendix 1, Table 3.5-1.1

Reviewer Comment: There are clear increases in AST, ALT, and GGT sustained throughout siponimod 2 mg therapy. The elevations begin within 1 month of therapy and decline within 12 months off therapy. The clinical significance of these elevated transaminase levels is unclear. A baseline transaminase evaluation and a repeat evaluation on therapy are of obvious necessity for patients taking siponimod therapy and proposed labeling appears to include sufficient guidance in this matter.

Long-term Safety Pool

In the Long-term Safety Databases of patients taking at least one dose of siponimod 2-10 mg,

49.7% of patients had an elevated ALT (>1 x ULN) on at least one occasion, as compared to 45.9% of siponimod 2 mg treated patients in the controlled pool; with 6.0% having ALT of 3x ULN and with 2 patients (0.1%) having an ALT of >10 x ULN.

With respect to AST, 24.0% of patients in the Long-term Safety Databases had raised AST (> 1 x ULN), with 1.1% having AST of 3x ULN and 1 patient (0.1%) having an AST of >10 x ULN.

In siponimod treated patients in the Long-term Safety Databases, 32.4% of patients had a GGT >1 x ULN, 11.4% had a GGT >3 x ULN, and 3.0% had a GGT >5 x ULN.

In the Long-term Safety Pool, 2.0% of patients had total bilirubin >1.5 x ULN.

There were no patients with transaminase values meeting Hy's Law criteria in the Long-term Safety Pool.

Distributions of patients with hepatic parameter abnormalities is shown in the following table:

Table 61: Reviewer Table, Distribution of Patients with Liver Parameter Abnormalities, Long-term Safety Databases 2 and 4

Parameter		Siponimod 2-10 mg* N=1737	Siponimod 2-10 mg** N=1737
ALT	**n**	1709	1707
	No abnormalities	859 (50.3%)	872 (51.1%)
	>1 × ULN	850 (49.7%)	835 (48.9%)
	>3 × ULN	103 (6.0%)	100 (5.9%)
	>5 × ULN	23 (1.3%)	22 (1.3%)
	>10 × ULN	2 (0.1%)	1 (0.1%)
	>20 × ULN	0	0/1707 (0)
AST	**n**	1709	1707
	No abnormalities	1299 (76.0%)	1315 (77.0%)
	>1 × ULN	410 (24.0%)	392 (23.0%)
	>3 × ULN	18 (1.1%)	17 (1.0%)
	>5 × ULN	8 (0.5%)	7 (0.4%)
	>10 × ULN	1 (0.1%)	1 (0.1%)
	>20 × ULN	0	0
GGT	**n**	1709	1707
	No abnormalities	1178/1709 (68.9%)	1187/1707 (69.5%)
	>1 × ULN	531/1637 (32.4%)	520/1624 (32.0%)
	>3 × ULN	194/1704 (11.4%)	192/1699 (11.3%)
	>5 × ULN	52/1709 (3.0%)	52/1707 (3.0%)
	>20 × ULN	0	0

Parameter		Siponimod 2-10 mg* N=1737	Siponimod 2-10 mg** N=1737
Alkaline Phosphatase	**n**	1709	1707
	No abnormalities	1430/1709 (83.7%)	1431/1709 (83.8%)
	>1 × ULN	279/1643 (17.0%)	276/1640 (16.8%)
	>3 × ULN	10/1709 (0.6%)	10/1707 (0.6%)
	>5 × ULN	0	0
	>20 × ULN	0	0
Total Bilirubin	**n**	1709	1707
	>1.5 × ULN	35 (2.0%)	34 (2.0%)
	>2 × ULN	11 (0.6%)	11 (0.6%)
	>3 × ULN	3 (0.2%)	3 (0.2%)
Hy's Law	**n**	1709	1707
	Met criteria	0	0

Source: Table 3.4-2.2a SCS

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

Box plot figures showing mean ALT and AST changes by visit window in the Long-term Safety Database are as follows:

Figure 1: Applicant Figure, Box Plot of Mean ALT by Visit Window, Safety Database 2

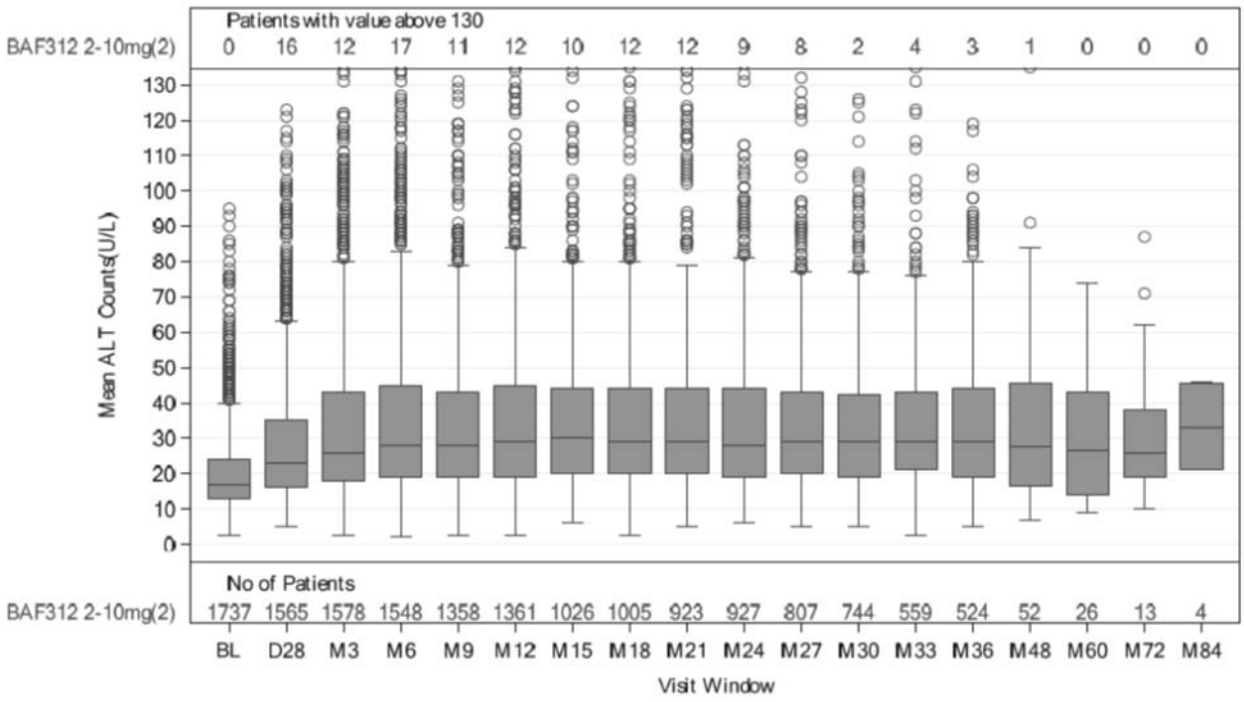
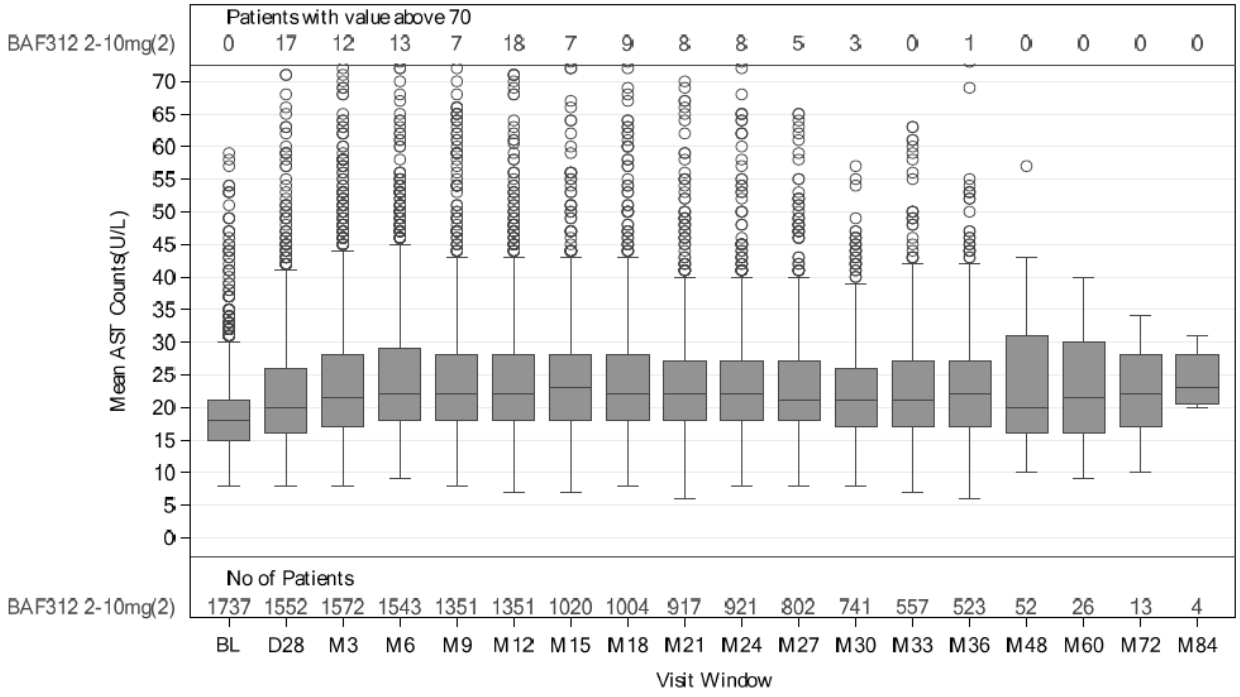


Figure 2: Applicant Figure, Box Plot of Mean AST Counts by Visit Window, Safety Database 2



Reviewer Comment: The findings in the Long-term Safety Databases are consistent with the observed hepatic parameter abnormalities in the Controlled Pool and confirm a risk of elevated transaminases associated with siponimod therapy at 2 mg maintenance doses. The clinical significance of these elevated values is unclear.

120-day Update of Long-term Safety Pool

The 120-day Update provided additional data that led to small increases in percentages of patients experiencing elevated hepatic values.

In the 120-day Update of Safety Database 2, there were 50.7 % (up from 49.7%) of patients who experienced an ALT > 1 x upper limit of normal (ULN)) on at least one occasion post-baseline; with 6.2% (up from 6.0%) having ALT of >3 x ULN. There were no new reported cases of patients having an ALT of >10 x ULN.

In the 120-day Safety Database 2, there was a 0.8% increase (24.8% versus 24.0%) of patients who had AST >1 x ULN. There were no changes in the numbers of patients with AST increased 3 x ULN and 10 x ULN.

The frequency of patients with a GGT > 1 x ULN rose from 32.4% to 32.9%. The frequency of

patients with GGT > 3 x ULN rose from 3.0% to 3.3%.

Increased total bilirubin >1.5 x ULN occurred in 2.2% of patients, a small increase over the 2.0% of patients in the original database.

> *Reviewer Comment: The additional data in the 120-day Safety Update do not change the prior conclusions regarding risk of elevated hepatic parameters associated with siponimod therapy.*

Renal Function

MS Controlled Pool

In the controlled pool of patients in MS trials, serum creatinine levels were reduced over 24 months in siponimod 2 mg treatment group and in the placebo treatment group. New abnormal renal findings on testing were common in both the siponimod (563/1316, 42.8%) and placebo treatment 295/607, 48.6%) groups. Symptomatic renal changes were much less common, with 1.0% of patients in the siponimod 2 mg group experiencing a new renal symptom as compared to 0.5% in the placebo treatment group. Creatinine clearance changes were noted in both siponimod and placebo treated patients. At Month 12, the change from baseline in creatinine clearance (by the Cockcroft-Gault method) was +0.392 mL/min for siponimod 2 mg and -1.28 mL/min for placebo. At Month 12, the change from baseline in creatinine clearance (by the Modification of Diet in Renal Disease (MDRD) method) was +1.42 mL/min for siponimod 2 mg and -0.575 mL/min for placebo.

Table 62: Mean Change from Baseline in Serum Creatinine, Controlled Pool, Safety Set

	Siponimod 0.25 mg (N = 51)	**Siponimod 0.5 mg (N = 43)**	**Siponimod 1.25 mg (N = 42)**	**Siponimod 2 mg (N = 1148)**	**Siponimod 10 mg (N = 50)**	**Placebo (N = 607)**
Mean Change ± SD						
Serum Creatinine (µmol/L)						
Month 1	-0.04 ± 7.30	-0.88 ± 5.91	-0.14 ± 6.12	-1.26 ± 9.21	+0.57 ± 7.00	+0.47 ± 8.38
Month 3	+0.93 ± 7.72	-0.78 ± 6.36	+1.30 ± 7.30	-1.58 ± 9.57	+0.20 ± 8.03	-0.07 ± 8.60
Month 6		+0.09 ± 8.24		-1.13 ± 10.06	+1.32 ± 6.12	-0.19 ± 8.89
Month 12				-1.24 ± 10.19		-0.04 ± 9.36
Month 18				-0.67 ± 10.59		-0.19 ± 9.90
Month 24				-1.71 ± 7.83		-0.04 ± 8.71

Source: SCS Appendix 1-Table 3.5-1.1

Renal changes determined by clinical or laboratory criteria during controlled phase of trials in MS are summarized in the following table:

Table 63: Summary of Renal Events, Controlled Pool, Safety Set

	Siponimod 0.25 mg N=51 n/m (%)	Siponimod 0.5 mg N = 43 n/m (%)	SIPONIMOD 1.25 mg N=42 n/m (%)	Siponimod 2 mg N=1148 n/m (%)	Siponimod 10 mg N=50 n/m (%)	Placebo N=607 n/m (%)
Patients with New Renal Finding	5/50 (10%)	3/43 (7.0%)	2/42 (4.8%)	548/1134 (48.3%)	5/47 (10.6%)	295/607 (48.6%)
SCr increase ≥ 25% and < 50% from baseline	5/50 (10.0%)	3/43 (7.0%)	2/42 (4.8%)	100/1134 (8.8%)	5/47 (10.6%)	65/607 (10.7%)
SCr increase ≥ 50% from baseline	0	0	0	14/1134 (1.2%)	0	12/607 (2.0%)
New onset proteinuria	0	0	0	267/1134 (23.6%)	0	134/607 (22.1%)
New onset glycosuria	0	0	0	37/1134 (3.3%)	0	14/607 (2.3%)
New onset hematuria	0	0	0	321/1134 (29.5%)	0	187/562 (33.3%)
Dysuria	0	0	0	11/1134 (1.0%)	0	3/607 (0.5%)
Oliguria/Anuria	0	0	0	0	0	0

Source: SCS Appendix 1 Table 3.5-3.1

Long-term Safety Pool

In the Long-term Safety pool of patients with MS, over 36 months of observation, the mean serum creatinine reduction observed was approximately 1 µmol/L. Approximately 40% of patients treated with siponimod in the long-term safety databases experienced a new renal test finding, and approximately 1% experienced a new renal symptom. Creatinine clearance changes were noted in siponimod treated patients. At Month 36, the change from baseline in creatinine clearance (by the Cockcroft-Gault method) was -0.85 mL/min for all patients treated with at least one dose of siponimod 2 mg (Safety Database 2). At Month 36, the change from baseline in creatinine clearance (by the MDRD method) was +0.43 mL/min for patients treated with at least one dose of siponimod 2 mg.

Table 64: Mean Change from Baseline in Serum Creatinine, Long-term Safety Pool (Safety Databases 2 and 4)

Visit	Siponimod 2-10 mg* N=1737 Mean Change (µmol/L) ± SD	Siponimod 2-10 mg** N=1737 Mean Change (µmol/L) ± SD
Month 1	-1.05 ± 8.52	-1.10 ± 8.60
Month 3	-1.15 ± 8.71	-1.22 ± 8.8
Month 6	-0.91 ± 9.30	-0.86 ± 9.35
Month 12	-0.88 ± 9.37	-0.93 ± 9.35
Month 18	-0.79 ± 12.53	-0.72 ± 10.93
Month 24	-1.79 ± 9.73	-1.64 ± 9.85
Month 30	-0.54 ± 22.21	-0.58 ± 21.92
Month 36	-0.87 ± 13.22	-0.87 ± 13.09

Source: SCS Appendix 1 Tables 3.5-2.2 and 2.2a

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

Table 65: Summary of Renal Events, Long-term Safety Pool, Safety Databases 2 and 4

	Siponimod 2-10 mg* N=1737	Siponimod 2-10 mg** N=1737
Patients with New Renal Finding	684/1709 (40.0%)	676/1708 (39.6%)
SCr increase ≥ 25% and < 50% from baseline	198/1709 (11.6%)	191/1708 (11.2%)
SCr increase ≥ 50% from baseline	29/1709 (1.7%)	66/1705 (3.9%)
New onset proteinuria	289/1395 (20.7%)	289/1393 (20.7%)
New onset glycosuria	66/1707 (3.9%)	66/1705 (3.9%)
New onset hematuria	358/1349 (26.5%)	358/1347 (26.6%)
Dysuria	15/1709 (0.9%)	15/1708 (0.9%)
Oliguria/Anuria	15/1709 (0.9%)	15/1708 (0.9%)

Source: SCS Appendix 1 Tables 3.5-3.2 and 3.5-3.2a

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who

received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

120-day Update

In the 120-day Safety Update to the Long-term Safety Pool data, the mean change at 36 months in serum creatinine increased slightly to -1.07± 12.66 µmol/L for all patients who received at least one dose of siponimod. The revised data did not change for new events as 40% of patients treated with siponimod in the updated long-term safety databases experienced a new renal test finding, and approximately 1% experienced a new renal symptom. In the revised data, at Month 36, the change from baseline in creatinine clearance (by the Cockcroft-Gault method) was -0.38 mL/min for all patients treated with at least one dose of siponimod 2 mg (Safety Database 2). In the revised data, at Month 36, the change from baseline in creatinine clearance (by the MDRD method) was +1.01 mL/min for patients treated with at least one dose of siponimod 2 mg.

> *Reviewer Comment: The clinical significance of a mean decline of approximately 1* µmol/L *in serum creatinine with a small change in creatinine clearance are unclear. One potential concern would be that these findings are associated with a loss of muscle mass associated with progression of disability, but placebo-treated patients, who accumulated significant more disability, showed increased serum creatinine and decreased creatinine clearance which would not be expected with muscle atrophy. New onset of renal-related events as indicated by a new laboratory or clinical finding were largely balanced between the siponimod and placebo treatment groups, suggesting that siponimod is not associated with renal pathology that is producing a total breakdown in filtration capacity. There were also no trends with serum urea to suggest a deleterious kidney function change in either the siponimod or placebo treatment arms.*

Urinalysis

Study A2304

Shift analyses of parameters from urinalysis tests performed during study visits in Study A2304 showed no significant differences in parameters between patients treated with siponimod and patients treated with placebo.

The following table shows shift analyses at visit month 12 (the visit with the largest sample size from each treatment group) for urinalysis parameters.

Table 66: Reviewer Table, Urinalysis Shift Analysis, Month 12, Study A2304, Controlled Phase, Safety Set

	Baseline	Negative	Positive
Leukocyte Esterase			
Siponimod			
Negative	525/1099 (47.8%)	396/1099 (36.0%)	129/1099 (11.7%)
Positive	365/1099 (33.2%)	154/1099 (14.0%)	211/1099 (19.2%)
Total	890/1099 (81.0%)	550/1099 (50.0%)	340/1099 (30.9%)
Placebo			
Negative	271/546 (49.6%)	204/546 (37.4%)	67/546 (12.3%)
Positive	164/546 (30.0%)	69/546 (12.6%)	95/546 (17.4%)
Total	435/546 (79.7%)	273/546 (50.0%)	162/546 (29.7%)
Urine Bilirubin			
Siponimod			
Negative	880/1099 (80.1%)	873/1099 (79.4%)	7/1099 (0.6%)
Positive	10/1099 (0.9%)	9/1099 (0.8%)	1/1099 (0.1%)
Total	890/1099 (81.0%)	882/1099 (80.3%)	8/1099 (0.7%)
Placebo			
Negative	431/546 (78.9%)	426/546 (78.0%)	5/546 (0.9%)
Positive	4/546 (0.7%)	3/546 (0.5%)	1/546 (0.2%)
Total	435/546 (79.7%)	429/546 (78.6%)	6/546 (1.1%)
Urine Blood			
Siponimod			
Negative	622/1099 (56.6%)	532/1099 (48.4%)	90/1099 (8.2%)
Positive	268/1099 (24.4%)	166/1099 (15.1%)	102/1099 (9.3%)
Total	890/1099 (81.0%)	698/1099 (62.5%)	192/1099 (17.5%)
Placebo			
Negative	296/546 (54.2%)	252/546 (46.2%)	44/546 (8.1%)
Positive	139/546 (25.5%)	61/546 (11.2%)	78/546 (14.3%)
Total	435/546 (79.7%)	313/546 (57.3%)	122/546 (22.3%)
Urine Glucose			
Siponimod			
Negative	881/1099 (80.2%)	872/1099 (79.3%)	9/1099 (0.8%)
Positive	9/1099 (0.8%)	6/1099 (0.5%)	3/1099 (0.3%)
Total	890/1099 (81.0%)	878/1099 (19.9%)	12/1.1 (1.1%)
Placebo			
Negative	431/546 (78.9%)	426/546 (78.0%)	5/546 (0.9%)

	Baseline	Negative	Positive
Positive	4/546 (0.7%)	3/546 (0.5%)	1/546 (0.2%)
Total	435/546 (79.7%)	429/546 (78.6%)	6/546 (1.1%)
Urine Ketones			
Siponimod			
Negative	802/1099 (73.0%)	752/1099 (68.4%)	50/1099 (4.5%)
Positive	88/1099 (8.0%)	79/1099 (7.2%)	9/1099 (0.8%)
Total	890/1099 (81.0%)	831/1099 (75.6%)	59/1099 (5.4%)
Placebo			
Negative	386/546 (70.7%)	356/546 (65.2%)	30/546 (5.5%)
Positive	49/546 (9.0%)	41/546 (7.5%)	8/546 (1.5%)
Total	435/546 (79.7%)	397/546 (72.7%)	38/546 (7.0%)
Urine Protein			
Siponimod			
Negative	785/1099 (71.4%)	737/1099 (67.1%)	48/1099 (4.4%)
Positive	105/1099 (9.6%)	80/1099 (7.3%)	25/1099 (2.3%)
Total	890/1099 (81.0%)	817/1099 (74.3%)	73/1099 (6.6%)
Placebo			
Negative	398/546 (72.9%)	372/546 (68.1%)	26/546 (4.8%)
Positive	37/546 (6.8%)	34/546 (6.2%)	3/546 (0.5%)
Total	435/546 (79.7%)	406/546 (74.4%)	29/546 (5.3%)
Urobilinogen			
Siponimod			
Negative	877/1099 (79.8%)	858/1099 (78.1%)	19/1099 (1.7%)
Positive	13/1099 (1.2%)	8/1099 (0.7%)	5/1099 (0.5%)
Total	890/1099 (81.0%)	866/1099 (78.8%)	24/1099 (2.2%)
Placebo			
Negative	429/546 (78.6%)	412/546 (75.5%)	17/546 (3.1%)
Positive	6/546 (1.1%)	6/546 (1.1%)	0
Total	435/546 (79.7%)	418/546 (76.6%)	17/546 (3.1%)

Source: CSR Study A2304 Table 14.3-2.1.6

Reviewer Comment: Shift analysis and summaries of change from baseline in urinalysis parameters from Studies A2304 and A2201 (not shown) did not demonstrate treatment effects for any dose of siponimod as compared to placebo. There were no differences in leukocyte esterase or white blood cell content of urine from siponimod-treated patients as compared to placebo-treated patient samples to provide an explanation for the increased urinary tract infection rate associated with siponimod treatment (see Section 8.4.5).

Cholesterol and Triglycerides

Controlled Pool

In the controlled phases of trials in MS, mean total cholesterol levels in the siponimod 2 mg group gradually increased from baseline through 36 months. Change from baseline to last assessment on study drug was +0.35 mmol/L for 2 mg siponimod. The proportion of patients with abnormally high total cholesterol was higher in 2 mg siponimod (35.6% All grades) compared to placebo (23.9%).

There was an increase in mean difference in triglyceride serum levels in the 2 mg siponimod group from baseline to a peak at Month 9 of +0.16 mmol/L. The change from baseline to last assessment for the 2 mg siponimod treatment group was +0.08 mmol/L. The proportion of patients with abnormally high triglycerides was higher in the 2mg siponimod group (35.8% encompassing all grades) compared with placebo (29.0%).

Shift analyses for cholesterol, not triglycerides, demonstrated a sustained change from baseline to higher total cholesterol.

There was limited follow-up data, but what data were captured suggest that within two months of discontinuation total cholesterol levels were decreasing but had not yet returned to baseline (data not shown).

Table 67: Mean Change by Dose, Controlled Pool, Safety Set

	Siponimod 0.25 mg (N = 51)	Siponimod 0.5 mg (N = 43)	Siponimod 1.25 mg (N = 42)	Siponimod 2 mg (N = 1148)	Siponimod 10 mg (N = 50)	Placebo (N = 607)
Mean Change ± SD						
Total Cholesterol (mmol/L)						
Month 1	+2.33 ± 0.58	+1.00 ± 0.00		+0.10 ± 0.65	-0.14 ± 2.91	-0.01 ± 0.58
Month 3	-0.27 ± 1.61	+2.67 ± 2.25	+1.00 ± 1.41	+0.21 ± 0.71	+0.63 ± 3.0	0.00 ± 0.75
Month 6		+2.33 ± 1.53		+0.20 ± 0.72	+3.00 ± 2.00	+0.04 ± 0.68
Month 12				+0.33 ± 0.82		-0.07 ± 0.73
Month 18				+0.40 ± 0.96		-0.01 ± 0.74
Month 24				+0.38 ± 0.97		+0.12 ± 0.78
Month 30				+0.43 ± 0.84		+0.16 ± 0.74
Month 36				+0.45 ± 0.75		+0.05 ± 1.00
Triglycerides (mmol/L)						
Month 1	+0.08 ± 0.41	0.00 ± 0.48	+0.02 ± 0.58	+0.19 ± 0.60	+0.27 ± 0.64	+0.01 ± 0.61
Month 3	+0.17 ± 0.50	+0.03 ± 0.84	-0.11 ± 0.68	+0.07 ± 0.61	+0.31 ± 0.56	-0.04 ± 0.61

	Siponimod 0.25 mg (N = 51)	Siponimod 0.5 mg (N = 43)	Siponimod 1.25 mg (N = 42)	Siponimod 2 mg (N = 1148)	Siponimod 10 mg (N = 50)	Placebo (N = 607)
Mean Change ± SD						
Month 6		0.00 ± 0.60		+0.10 ± 0.66	+0.30 ± 0.56	+0.06 ± 0.63
Month 12				+0.12 ± 0.88		-0.04 ± 0.66
Month 18				+0.13 ± 1.31		+0.06 ± 0.68
Month 24				+0.03 ± 0.65		-0.05 ± 0.70
Month 30				+0.10 ± 0.73		+0.25 ± 0.73
Month 36				+0.19 ± 0.44		0.00 ± 0.93

Source: SCS Appendix 1 Table 3.5-1.1

Table 68: Total Cholesterol Shift by CTCAE Grade During Study, Controlled Pool, Safety Set

Baseline		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Grade	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Grade 0	511/1097 (46.6%)	194/1097 (17.7%)	310/1097 (28.3%)	6/1097 (0.5%)	0	1/1097 (0.1%)
Grade 1	557/1097 (50.8%)	12/1097 (1.1%)	474/1097 (43.2%)	70/1097 (6.4%)	1/1097 (0.1%)	0
Grade 2	19/1097(1.7%)	0	3/1097 (0.3%)	13/1097 (1.2%)	1/1097 (0.1%)	2/1097 (0.2%)
Grade 3	0	0	0	0	0	0
Grade 4	10/1097 (0.9%)	0	0	0	0	10 (0.9%)
Total	1097 (100.0%)	206/1097 (18.8%)	787/1097 (71.7%)	89/1097 (8.1%)	2/1097 (0.2%)	13/1097 (1.2%)
Missing	51/1148					

Source: SCS Appendix 1 Table 3.4-3

Adverse Events

In the Controlled Pool Safety Set (Safety Database 1), combining the preferred term of "hypercholesterolemia" with the preferred term "blood cholesterol increased" yielded a combined frequency of 4.2% (48/1148 patients) with an incidence rate (IR) of 2.7/100 PY for the 2 mg siponimod treatment group as compared to 3.0% (18/607 patients) with an IR of 2.1/100 PY in the placebo treatment group. However, the frequency of the adverse event "low density lipoprotein increased" was reported more often in placebo-treated patients (8/607, 1.3%, IR=0.9/100 PY) than it was in siponimod-treated patients (9/1148, 0.8%, IR=0.5/100 PY). The TEAE "high density lipoprotein decreased" was reported at similar frequencies in the two treatment groups (0.1% in siponimod vs. 0.2% in placebo, IR for both treatment groups=0.1/100 PY.)

In the Controlled Pool Safety Set (Safety Database 1), "hypertriglyceridemia" (preferred term) and "blood triglycerides increased" yielded a combined frequency of 0.4% (5/1148 patients) with an IR of 0.4/100 PY and 2/1148 patients in the siponimod 2 mg treatment group and 0.7% (4/607) with an IR of 0.4/100 PY in the placebo treatment group.

In the Controlled Pool Safety Set (Safety Database 1), the terms "hyperlipidemia" and "dyslipidemia" (which can refer to either triglycerides or cholesterol) were reported in 0.4% (5/1148 patients) and 0.2% (2/1148 patients), respectively, in the siponimod 2 mg treatment group versus 0.2% (1/607 patients) and 0/607, respectively, in the placebo treatment group.

There were no SAEs and no treatment discontinuations due to any of these lipid-related TEAEs.

> *Reviewer Comment: The sustained elevations in serum total cholesterol appear to occur coincidentally with an increase in reported events of elevated cholesterol associated with siponimod 2 mg. However, specific events related to known risk factors, elevated low density lipoprotein and decreased high density lipoprotein, did not differ in frequency between treatments. The triglyceride elevations do not appear to confer a similar increased association with TEAEs related to high triglycerides.*

Long-term Safety Pool

Increased total cholesterol and triglyceride values were observed in the Long-term Safety Pool at all visits. Findings were comparable to what was observed in the Controlled Pool.

Visit	**Siponimod 2-10 mg* N=1737 Mean Change (mmol/L) ± SD**	**Siponimod 2-10 mg** N=1737 Mean Change (mmol/L) ± SD**
Total Cholesterol		
Month 1	+0.12 ± 0.80	+0.13 ± 0.76
Month 3	+0.21 ± 0.92	+0.29 ± 0.88
Month 6	+0.26 ± 0.91	+0.23 ± 0.99
Month 12	+0.31 ± 0.99	+0.32 ± 1.03
Month 18	+0.36 ± 1.31	+0.36 ± 1.28
Month 24	+0.29 ± 1.32	+0.30 ± 1.31
Month 30	+0.36 ± 1.36	+0.25 ± 1.42
Month 36	+0.30 ± 1.38	+0.19 ± 1.49
Triglycerides		
Month 1	+0.19 ± 0.61	+0.20 ± 0.62
Month 3	+0.08 ± 0.62	+0.08 ± 0.62

Visit	Siponimod 2-10 mg* N=1737 Mean Change (mmol/L) ± SD	Siponimod 2-10 mg** N=1737 Mean Change (mmol/L) ± SD
Month 6	+0.11 ± 0.65	+0.11 ± 0.64
Month 12	+0.11 ± 0.80	+0.12 ± 0.80
Month 18	+0.13 ± 1.08	+0.13 ± 1.09
Month 24	+0.10 ± 0.67	+0.10 ± 0.68
Month 30	+0.14 ± 0.83	+0.15 ± 0.81
Month 36	+0.13 ± 0.72	+0.12 ± 0.72

Sources: Tables 3.5-1.2, 3.5-1.2 and 3.5-1.2, 3.5-1.2a

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

Adverse Events

In the long-term safety set with broadest exposure (Safety Database 2), combining the preferred term of "hypercholesterolemia" with the preferred term "blood cholesterol increased" yielded a combined frequency of 5.6% (98/1737 patients) with an IR of 2.5/100 PY. The TEAE "low density lipoprotein increased" was report in 1.0% (18/1737) of patients (IR=0.4/100 PY). The TEAE "high density lipoprotein decreased" was reported in 3/1737 patients (0.2%, IR=0.1/100 PY).

In the long-term safety set with broadest exposure (Safety Database 2), "hypertriglyceridemia" (preferred term) and "blood triglycerides increased" yielded a combined frequency of 0.6% (11/1737 patients) with an IR of 0.4/100 PY.

In the long-term safety pool with the broadest exposure (Safety Database 2), the terms "hyperlipidemia" and "dyslipidemia" (which can refer to either triglycerides or cholesterol) were reported in 0.7% (12/1737 patients) and 0.4% (7/1148 patients), respectively, in the siponimod 2 mg treatment group.

<u>120-day Safety Update</u>

The revised data in the 20-day Safety Update did not significantly change the total cholesterol and triglyceride data from the original SCS. The observed increased values persisted at very similar mean changes at all visits.

Adverse Events
In the updated long-term safety pool with the broadest exposure (Safety Database 2), combining the preferred term of "hypercholesterolemia" with the preferred term "blood cholesterol increased" yielded a combined frequency of 6.5% (113/1737 patients) with an IR of 2.5/100 PY. The AEs "low density lipoprotein increased" occurred in 21/1737 patients (1.2%, IR=0.4/100 PY) and "high density lipoprotein decreased" remained unchanged, occurring in 3/1737 (0.2%, IR=0.1/100 PY).

In the updated long-term safety set with broadest exposure (Safety Database 2), "hypertriglyceridemia" (preferred term) and "blood triglycerides increased" yielded a combined frequency of 0.7% (12/1737 patients) with an IR of 0.3/100 PY.

In the updated long-term safety pool with the broadest exposure (Safety Database 2), the terms "hyperlipidemia" and "dyslipidemia" (which can refer to either triglycerides or cholesterol) were reported in 0.7% (12/1737 patients) and 0.6% (11/1148 patients), respectively, in the siponimod 2 mg treatment group.

> *Reviewer Comment: The long-term safety pool elevated cholesterol findings remained consistent with the controlled pool data. Increased total cholesterol is a risk factor for cerebrovascular and cardiovascular disease and associated with increased risk of myocardial infarction and stroke. While the total cholesterol increases were small and associated with large variability, they were sustained throughout treatment. There was a >5% frequency of elevated cholesterol-related events during long-term siponimod therapy. However, analysis of the adverse events related to the sub-components of the total cholesterol linked with increased risk of vascular disease, increased low density lipoprotein and decreased high density lipoprotein, revealed no real differences between siponimod and placebo, and the reported frequencies of these events in the long-term safety pool fail to justify a definitive conclusion of siponimod treatment being associated with a change in cholesterol parameters associated with disease risk.*

8.4.7. Vital Signs

Based on prior experience with S1P modulators, there was an expectation that the predominant changes in vital signs associated with siponimod administration would be diminished heart rate and small but sustained increases in systolic and diastolic blood pressure readings. Bradycardia and hypertension were confirmed in the safety pool. No other unanticipated vital sign changes were elucidated.

Heart Rate
Siponimod's action on S1P receptors in cardiac tissues has a known effect of acutely reducing heart rate during treatment initiation and can be associated with the induction of cardiac

conduction block. For Study A2304, the applicant implemented a titration schedule (see Section 8.1) designed to mitigate the cardiac effects of siponimod therapy initiation. Patients in Study A2304 were also divided in Standard Cardiac Risk and High Cardiac Risk groups with closer monitoring in the latter group (see Section 8.3.3.) The applicant investigated heart rate changes during the first seven days of siponimod administration. Overall, some heart rate reduction occurred after each dose on each day of treatment, but the greatest reduction and most bradycardic events (see Section 8.5.2.) occurred on Day 1.

Controlled Pool

In Study A2304, the initial 0.25 mg dose of siponimod yielded significant reductions in heart rates with a maximum mean reduction achieved at 4 hours post-first dose of -5.30 beats per minute relative to the baseline resting heart rate.

Table 69: Change in Heart Rate from Baseline Pre-Dose Rate, Study A2304, Safety Set

Change in HR from pre-dose (BPM)	Siponimod 0.25 mg N=1099		Placebo N=546	
	n	Mean Change (SD)	n	Mean Change (SD)
1-hour post-dose	981	-1.67 (7.15)	483	-1.16 (6.74)
2 hours post-dose	976	-3.56 (7.50)	481	-0.79 (7.71)
3 hours post-dose	978	-5.22 (7.79)	481	-0.23 (7.58)
4 hours post-dose	977	-5.30 (7.67)	480	+0.76 (7.68)
5 hours post-dose	973	-5.12 (7.72)	479	+0.54 (7.61)
6 hours post-dose	968	-4.81 (7.26)	477	+0.43 (7.34)

Source: CSR Study A2304-Table 14.3-3.2.1

At Day 6 of the titration, when patients had reached the maintenance dose of 2 mg, the heart rate reductions after the seventh dose more modest, with a maximum mean reduction in heart rate achieved at 3 hours post-dose of -3.08 BPM.

Table 70: Change in Heart Rate from Pre-Dose Heart Rate, Study A2304, Safety Set

Change in HR from pre-dose (BPM)	Siponimod 2 mg N=954		Placebo N=546	
	n	Mean Change (SD)	n	Mean Change (SD)
1-hour post-dose	954	-1.60 (5.55)	473	-1.76 (6.59)
2 hours post-dose	953	-2.97 (6.41)	470	-1.95 (7.64)
3 hours post-dose	953	-3.08 (6.85)	472	-2.00 (7.65)
4 hours post-dose	950	-2.26 (6.68)	472	-0.32 (7.39)
5 hours post-dose	947	-1.75 (6.56)	471	-0.35 (7.53)
6 hours post-dose	945	-0.90 (6.32)	468	-0.17 (7.60)

Source: CSR Study A2304 Table 14.3-3.2.2

Study A2304 had an Expanded Cardiac Monitoring option for patients meeting specific eligibility criteria related to baseline cardiovascular findings that might confer higher risk of a cardiovascular AE (see Section 8.3.3). Two patients in the siponimod treatment group had heart rates <40 BPM at screening; both patients were assigned to the Expanded Cardiac Monitoring group.

One of these two patients, Patient (b) (6), was enrolled with pre-dose first degree AV block (PR interval= 267 msec) and bradycardia of 35 BPM 5 hours after the first dose on Day 1; other findings in the patient included second degree AV block Mobitz I noted on ECG at Hour 3 after first dose. The AV block and bradycardia findings were asymptomatic and were reported as SAEs. This patient discontinued study drug and was hospitalized for observation. The AV block and heart rate < 40 BPM resolved without further treatment within 2 days.

Patient (b) (6) was assigned to Expanded Cardiac Monitoring group had a pre-dose baseline bradycardia on mobile cardiac telemetry (minimum hourly rate of 34 BPM) but had a measured heart rate of over 60 BPM in vital sign assessments. The patient had a history of treatment with mitoxantrone which was deemed an additional risk factor warranting Expanded Cardiac Monitoring. On Day 1 of siponimod therapy initiation, the patient had asymptomatic bradycardia with minimum hourly rates as measured by mobile cardiac telemetry of 43 BPM. On Day 2 the mobile cardiac telemetry measured a minimum hourly rate of 37 BPM. On Day 3 and Day 4 mobile cardiac telemetry measured minimum hourly heart rates of 37 and 32 BPM, respectively. Mobile cardiac telemetry captured one incidence of bradycardia to 20 BPM in the evening of Day 3. The mobile telemetry observations were not accompanied by any significant reductions in blood pressure. Due to these findings, study drug was discontinued permanently on Day 4. On Day 24, the patient had a pacemaker implanted for a diagnosis of idiopathic sinus disease.

During Study A2304, there were two additional patients reported with new onset bradycardia at Day 7. These patients were not in the Expanded Cardiac Monitoring group.

Patient (b) (6) had a heart rate of 39 BPM noted 3 hours post-dose on Day 7. The bradycardia was asymptomatic and was not treated. The patient remained in the trial on study drug.

Patient (b) (6) experienced symptomatic bradycardia on Day 7 in the study. The patient had a heart rate of 48 BPM on vital sign assessment, confirmed by ECG at 46 BPM, and the bradycardia was accompanied by new-onset chest pain. A diagnosis of angina pectoris was not confirmed, ECG did not reveal findings consistent with myocardial injury, and a subsequent myocardial perfusion scan was normal. The symptoms resolved within 24 hours without treatment, and study drug was discontinued.

Long-term Safety Pool and 120-day Safety Update

The overall findings for heart rate reduction in patients completing titration to the 2 mg siponimod dose in Study A2304 demonstrated 2 out of 985 (0.2%) of patients with a new sustained heart rate of < 40 BPM, and 58/982 patients (5.9%) with a new sustained heart rate of < 50 BPM. The frequencies in the placebo treated group for HR < 40 BPM was 0/485 patients and for < 50 BPM 6/484 (1.2%). A single patient in Study A2304 (1/984, 0.1%) had a sustained heart rate > 120 BPM as did a patient (1/485, 0.2%) in the placebo treatment group.

The overall mean change in heart rate over the first month of treatment was less than 1 BPM and is summarized in the following table:

Table 71: Change in Heart Rate from Baseline to 28 Days, Long-term Safety Pool (Safety Database 2)

Heart Rate	Siponimod 2-10 mg* N=1560 Heart Rate (BPM) Baseline	Siponimod 2-10 mg** N=1560 Heart Rate (BPM) Day 28	Change from Baseline N=1560 Heart Rate (BPM)
Mean ± SD	72.94 ± 10.38	73.01 ± 9.95	+0.07
Median	72.33	72.00	-0.33
Min	46.30	46.00	-0.30
Max	122.70	159.30	-26.6

Source: SCS, Table 4.1-1.2

However, as the following table demonstrates, the frequencies of new onset of heart rates < 60 BPM from baseline to last recorded (minimum 90-day exposure) exceed 25% of the entire safety population exposed to siponimod, indicating that there exists a persistent subset of patients with significantly diminished heart rates with recordings lower than 40 BPM.

Table 72: New Onset of Heart Rate Changes, Long Term Safety Pool, Safety Set (Safety Database 2)

Pulse Rate (BPM)	N	Siponimod 2-10 mg n (%)
< 40	1720	9 (0.5)
<50	1716	65 (3.8)
<60	1572	388 (24.7)
>100	1697	77 (4.5)
>120	1719	4 (0.2)

Source: SCS Table 4-2, 120-Day Safety Update, page 47

Reviewer Comment: Siponimod exposure reduces patients' heart rates, with 462 out of 1737 (26.6%) patients exposed in the entire development program experiencing a new heart rate < 60 BPM. The applicant claims that the titration schedule reduces symptomatic bradycardia, which appears to be the case as the overall rate of the AE of bradycardia was 4.8% in non-titrated patients versus 4.0% in the titration pool (see Section 8.4.2 and 8.4.5 for further discussion of bradycardia as an AE), but the titration schedule does not prevent new onset of bradycardia nor does it eliminate all risk of severe bradycardia and symptomatic bradycardia. Approximately 6% of patients who titrated to the 2 mg siponimod dose experienced new heart rates < 50 BPM after titration, and there were two patients with symptomatic bradycardia events noted in successfully titrated patients. Therefore, the titration schedule appears to reduce the frequency of bradycardia, but bradycardia with symptoms still occurs in association with siponimod administration. For patients with histories of abnormal rhythms, there is a clear risk of exacerbating underlying cardiac issues, and for these patients first dose monitoring appears necessary. See Section 8.5.2 for further discussion of bradycardia.

Systolic Blood Pressure

Controlled Pool

In Study A2304, treatment with 2 mg siponimod was associated with a consistent increase in systolic blood pressure relative to patients' baseline blood pressure measurements. At six months, a mean increase in systolic blood pressure of +3.01 mmHg was present in the siponimod 2 mg group and a mean decrease of −0.84 mmHg occurred in the placebo-treated group. At twelve months, the mean systolic blood pressure rose by +3.73 mmHg in the siponimod 2 mg group, and the mean decrease in systolic blood pressure was −0.61 mmHg in the placebo group. After one year of therapy, the increase in systolic blood pressure decreased from the peak mean value at Month 12. The mean changes were +2.98 mmHg at eighteen months and +3.02 mmHg at 24 months. The overall observed increase from baseline reading to the last recorded blood pressure at end of treatment with 2 mg siponimod was +3.47 mmHg.

Table 73: Reviewer Table, Mean Systolic Blood Pressure Changes, Safety Set, Study A2304

Treatment Month	Siponimod 2 mg N=1126		Placebo N=607	
	n	Mean Change (SD)	n	Mean Change (SD)
Month 1	1126	+1.48 (11.75)	607	-1.12 (11.84)
Month 3	1093	+2.47 (12.65)	593	-0.99 (12.88)
Month 6	1042	+3.01 (12.44)	557	-0.84 (13.12)
Month 12	896	+3.73 (12.96)	435	-0.61 (13.38)

Treatment Month	Siponimod 2 mg N=1126		Placebo N=607	
	n	Mean Change (SD)	n	Mean Change (SD)
Month 18	583	+2.98 (13.31)	274	-0.65 (14.08)
Month 24	357	+3.02 (13.46)	151	+0.80 (14.94)
End of Treatment	1122	+3.47 (12.95)	602	-0.48 (13.47)

Source: Source: SCS Appendix 1-Table 4.1-1.1]

There was a greater percentage of patients with a new (not present at baseline) systolic blood pressure reading >140 mmHg in the siponimod 2 mg group (29.6%) versus the placebo group (24.1%). As a result, a larger proportion of patients in the 2 mg siponimod patient pool reported hypertension (119 patients, 10.4%) as compared to placebo patients (44 patients, 7.2%).

For markedly hypertensive systolic blood pressure readings (>160 mmHg, or >180 mmHg) there did not appear to be a treatment effect as the frequencies of these hypertensive readings were similar between patients in the siponimod 2 mg (5.5%) and placebo (5.3%) groups.

Long-term Safety Pool

In Safety Database 2, the trend observed in the A2304 Study towards a consistent increase in systolic blood pressure was maintained, though numbers after 48 months of exposure are small (see table below).

Table 74: Systolic Blood Pressure Mean Changes from Baseline by Visit, Long-term Safety Pool, Safety Set (Safety Database 2)

	Siponimod 2-10 mg* N = 1737	Systolic Blood Pressure Change from Baseline (mmHg)
Treatment Month	**n**	**Mean (SD)**
Month 1	1658	+1.50 (11.402)
Month 3	1662	+2.64 (12.399)
Month 6	1589	+2.76 (12.262)
Month 12	1383	+3.52 (12.781)
Month 24	943	+3.07 (12.577)
Month 36	663	+2.98 (13.008)
Month 48	248	+2.89 (13.139)
Month 60	125	+3.97 (14.059)
Month 72	60	+4.54 (11.500)
Month 84	7	+5.76 (14.321)

Source: SCS, Table 4.1-1.2

*Safety Database 2: Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

> *Reviewer Comment: An increase in systolic blood pressure of approximately 4-6mmHg is not expected to confer a significant increase in cardiovascular risk for patients taking siponimod. The increased risk of new hypertension associated with siponimod will be described on labeling and is readily treated with antihypertensive therapy. An increased risk of developing hypertension does not introduce a significant change to the risk-benefit considerations of siponimod for the indication of the treatment of multiple sclerosis.*

Diastolic Blood Pressure

Controlled Pool

There was an elevation in diastolic blood pressure associated with siponimod therapy. At six months, the mean increase in diastolic blood pressure was +1.27 mmHg in the siponimod 2 mg group while patients in the placebo group experienced a mean decrease of −0.30 mmHg. As with systolic blood pressure, the peak mean increases in diastolic blood pressure occurred at Month 12 of 2 mg siponimod treatment. At one year, the mean increase in diastolic blood pressure in the siponimod 2 mg group was +1.36 mmHg; the mean decrease in the placebo group was −0.78 mmHg. The mean diastolic blood pressure increase declined with longer durations of siponimod therapy. At eighteen months, the mean increase in the 2 mg siponimod treatment group was +0.45 mmHg, and at twenty-four months, the mean increase in diastolic blood pressure in the siponimod 2 mg group was +0.11 mmHg. The mean change from baseline to last recorded diastolic blood pressure in the 2 mg siponimod group was +0.96 mmHg.

Table 75: Reviewer Table, Diastolic Blood Pressure Changes, Safety Set, Study A2304

Treatment Month	Siponimod 2 mg N=1126		Placebo N=607	
	n	Mean Change ± SD	n	Mean Change ± SD
Month 1	1126	+0.60 ± 8.81	607	-0.27 ± 8.00
Month 3	1093	+0.77 ± 9.09	593	-0.21 ± 8.56
Month 6	1042	+1.27 ± 9.41	557	-0.30 ± 8.84
Month 12	896	+1.36 ± 9.75	435	-0.78 ± 8.86
Month 18	583	+0.45 ± 9.28	274	-0.06 ± 9.09
Month 24	357	+0.11 ± 9.90	151	+0.08 ± 9.20
End of Treatment	1122	+0.96 (9.67)	602	-0.47 (9.11)

Source: SCS Appendix 1-Table 4.1-1.1]

Reviewer Comment: A mean increase in diastolic blood pressure of approximately 1 mmHg over two years is not expected to be of great clinical significance.

Long-term Safety Pool

Table 76: Diastolic Blood Pressure Mean Changes from Baseline by Visit, Long-term Safety Pool, Safety Set (Safety Database 2)

	Siponimod 2-10 mg* N = 1737	**Diastolic Blood Pressure Change from Baseline (mmHg)**
Treatment Month	**n**	**Mean ± SD**
Month 1	1561	+0.6 ± 8.6
Month 3	1659	+0.9 ± 8.7
Month 6	1579	+1.0 ± 9.0
Month 12	1365	+1.1 ± 9.5
Month 24	912	+0.7 ± 9.8
Month 36	538	+0.4 ± 10.1
Month 48	70	-0.1 ± 10.8
Month 60	46	+0.6 ± 10.5
Month 72	33	-0.2 ± 8.1
Month 84	4	+6.4 ± 5.5

Source: SCS Appendix 1, Table 4.1-1.2

*Safety Database 2: Safety data of all patients receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

Body Weight

Controlled Pool

Weight changes in patients who received 2 mg siponimod were not markedly different from weight changes observed in the placebo treatment group. There was, however, a higher frequency of reported AE of weight gain in siponimod-treated patients relative to placebo in controlled trials of MS (see Section 8.4.5.)

Table 77: Weight Changes in Siponimod and Placebo Treatment Groups, Safety Database 2

Weight Change	**Siponimod 2 mg n=1071**	**Placebo n=574**
≥7% decrease from baseline	118 (11.0%)	67 (11.7%)

≥7% increase from baseline	156 (14.6%)	76 (13.2%)

Source: SCS Appendix 1, Table 4.1-2.2

Long-term Safety Pool

On average, patients in the long-term safety pool gained less than 1 kg. At month 1, mean weight gain in Safety Database 2 for patients treated with siponimod was 0.69 ± 5.22 kg. At month 78, the mean weight gain was 0.62 ± 4.76 kg.

8.4.8. Electrocardiograms (ECGs)

Controlled Pool

As expected because of the bradycardic effects of siponimod, electrocardiogram (ECG) monitoring of patients in Study A2304 revealed an increase in the number of patients with new finding of PR interval prolongation or prolonged QTcF. Over one third (35.7%) of patients in the siponimod treatment group had a new ECG finding during the titration period as opposed to 31.8% of patients in the placebo treatment group. The most common new ECG findings for patients in the siponimod group were first degree AV block, sinus bradycardia, and flattened T waves. The ECG data are summarized below.

Table 78: ECG Intervals: Number and Percentage of Patients Meeting New QTcF or PR Interval Criteria, Controlled Pool, Safety Set (Safety Database 1)

ECG Parameters	Siponimod 2 mg N=1148 n/patients at risk (%)	Placebo N=607 n/patients at risk (%)
PR (millisecond, msec)		
New ≥200 msec	63/1116 (5.6%)	20/597 (2.7%)
New ≥230 msec	26/1143 (2.3%)	1/605 (0.2%)
New ≥300 msec	2/1146 (0.2%)	0/606
QTcF (msec)		
New >430 (male) or new >450 (female)	148/1108 (13.4%)	40/584 (6.8%)
New >450 (male) or new >470 (female)	14/1142 (1.2%)	8/604 (1.3%)
New >480 msec	1/1145 (0.1%)	1/605 (0.2%)

ECG Parameters	Siponimod 2 mg N=1148 n/patients at risk (%)	Placebo N=607 n/patients at risk (%)
New >500 msec	1/1146 (0.1%)	0/606
Change from baseline >30 msec	185/1146 (16.1%)	67/606 (11.1%)
Change from baseline >60 msec	3/1146 (0.3%)	1/606 (0.2%)

Source: SCS, Table 4-8

First degree AV block on ECGs was seen slightly more frequently in the siponimod 2 mg group compared to the placebo groups at baseline (3.7% versus 3.0%) and remained more frequent at post-baseline visits up to Month 24 (4.0% versus 2.9%).

Atrial premature complexes or ventricular premature complexes were observed with similar incidence in siponimod 2 mg and placebo treatment groups at Month 12 (ectopy frequency was 1.3% in both groups) and higher in siponimod versus placebo at Month 24 (ectopy frequency 3.0% versus 0.5%).

Depressed ST segment was reported in a less than 2% of patients between the siponimod 2 mg and placebo groups at Baseline (1.5% versus 1.6%), Month 12 (1.9% versus 1.3%) and Month 24 (1.7% versus 1.5%).

Four patients (three in the siponimod 2 mg group, one in the placebo group) had ECG findings suggestive of myocardial infarction at Month 12; these patients also had similar findings at baseline. ECGs at Month 3 revealed myocardial infarction findings for 6 patients in the siponimod group and one in the placebo group. In the safety reporting in the Controlled pool, only one patient in the 2 mg siponimod group was reported with findings consistent with myocardial infarction (Patient (b) (6)) and one patient was reported with new myocardial infarction in the placebo group. TEAEs that were subcategorized as events related to ischemic heart disease were observed in 8 siponimod 2 mg patients (0.7%) and 5 patients (0.8%) receiving placebo. Of these reported AEs, myocardial infarction/acute coronary syndrome was reported as an SAE in two patients receiving siponimod 2 mg and in one placebo patient. Myocardial infarction risk is discussed in Section 8.5.6.

The Expanded Cardiac Monitoring group had a higher incidence of any ECG findings at Day 1 before initial dose (~25%) compared to Standard Cardiac Monitoring group with more extensive cardiac assessments (~8%). Newly detected ECG findings at any time post-first dose were also more common in the Expanded Cardiac Monitoring group (49.1% siponimod, 37.4% placebo) than in patients in the Standard Cardiac Monitoring group who had more extensive cardiac assessments (24.7% siponimod, 18.9% placebo). The most common findings were sinus

bradycardia (12.3% versus 2.4% placebo in the Expanded Cardiac Monitoring group, and 5.4% versus 1.3% placebo in the group.

The ECG findings in the extensive cardiac assessment monitoring group are summarized in the following table:

Table 79: Summary of Patients with ECG Findings, Study A2304, Safety Set (Subset with Extensive Cardiac Assessments)

Finding	Siponimod Any Dose N=982 n/m (%)	Placebo N=485 n/m (%)
Any findings	**351 (35.7%)**	**154 (31.8%)**
Sinus Bradycardia	92 (9.4%)	10 (2.1%)
1st Degree AV Block	86 (8.8%)	21 (4.3%)
T waves flat	66 (6.7%)	33 (6.8%)
T wave inversion	41 (4.2%)	15 (3.1%)
ST depression	36 (3.7%)	16 (3.3%)
Left anterior fascicular block	32 (3.3%)	19 (3.9%)
Premature atrial complexes	29 (3.0%)	14 (2.9%)
Intraventricular conduction delay, nonspecific	25 (2.5%)	11 (2.3%)
Premature ventricular complex	11 (1.1%)	14 (2.9%)
Right bundle branch block	11 (1.1%)	6 (1.2%)
Sinus tachycardia	9 (0.9%)	20 (4.1%)
T waves biphasic	8 (0.8%)	3 (0.6%)
Incomplete right bundle branch block	6 (0.6%)	1 (0.2%)
Ectopic supraventricular rhythm	5 (0.5%)	8 (1.6%)
Left atrial enlargement	5 (0.5%)	0
Inferior wall myocardial infarction*	4 (0.4%)	2 (0.4%)
Other	3 (0.3%)	3 (0.6%)
Atrial fibrillation	2 (0.2%)	0
Left bundle branch block	2 (0.2%)	0
Low QRS voltage	2 (0.2%)	0
QTcB prolongation >500 msec	2 (0.2%)	0
Septal myocardial infarction*	2 (0.2%)	0
QTcF prolongation >500 msec	1 (0.1%)	0
Wolff-Parkinson-White syndrome	1 (0.1%)	1 (0.2%)
Left ventricular hypertrophy	0	1 (0.2%)
ST elevation	0	1 (0.2%)
Supraventricular tachycardia	0	1 (0.2%)

Source: SCS, Table 4-15

*These findings had been noted on baseline ECG

Reviewer Comment: The ability of ECG to capture significant new ECG findings with clinical consequences justifies that ECG monitoring as proposed in labeling for patients

with pre-existing cardiac risk factors is sufficient as opposed to more extensive monitoring Holter or mobile telemetry.

Long-term Safety Pool

There were patients in the long-term safety pool who experienced new PR intervals ≥300 msec or a new change from baseline in QTcF >60 msec. Of the patients in the long-term safety pool, 3 (0.2%) patients in the siponimod 2-10 mg broad group had new PR intervals ≥300 msec. A total of 9 (0.5%) patients in the siponimod 2-10 mg broad group had a >60 msec change from baseline in QTcF.

Table 80: ECG Intervals: Number and Percentage of Patients Meeting New QTcF or PR Interval Criteria, Long-term Safety Pool, Safety Set (Safety Databases 2 and 4)

ECG Parameters	Siponimod 2-10 mg* N=1737 n/patients at risk (%)	Siponimod 2-10 mg** N=1737 n/patients at risk (%)
PR (msec)		
New ≥200 msec	101/1689 (6.0%)	95/1603 (5.9%)
New ≥230 msec	36/1724 (2.1%)	34/1635 (2.1%)
New ≥300 msec	3/1727 (0.2%)	2/1638 (0.1%)
QTcF (msec)		
New >430 (male) or new >450 (female)	256/1663 (15.4%)	234/1575 (14.9%)
New >450 (male) or new >470 (female)	33/1720 (1.9%)	30/1631 (1.8%)
New > 480 msec	1/1727 (0.1%)	1/1638 (0.1%)
New >500 msec	1/1727 (0.1%)	1/1638 (0.1%)
Change from baseline >30 msec	330/1727 (19.1%)	293/1638 (17.9%)
Change from baseline >60 msec	9/1727 (0.5%)	8/1638 (0.5%)

Source: SCS, Table 4-9

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

120-day Safety Update

There were three new additional reports added to the long-term safety database. For QTcF, there were 2 new reports of change from baseline >30 msec and a value of 403 msec was reported for a male patient.

Table 81: ECG Intervals: Number and Percentage of Patients Meeting New QTcF or PR Interval Criteria, Long-term Safety Pool 120-day Update, Safety Set (Safety Databases 2 and 4)

ECG Parameters	Siponimod 2-10 mg* N=1737 n/patients at risk (%)	Siponimod 2-10 mg** N=1737 n/patients at risk (%)
PR (msec)		
New ≥200 msec	101/1689 (6.0%)	95/1603 (5.9%)
New ≥230 msec	36/1724 (2.1%)	34/1635 (2.1%)
New ≥300 msec	3/1727 (0.2%)	2/1638 (0.1%)
QTcF (msec)		
New >430 (male) or new >450 (female)	257/1663 (15.4%)	234/1575 (14.9%)
New >450 (male) or new >470 (female)	33/1720 (1.9%)	30/1631 (1.8%)
New > 480 msec	2/1727 (0.1%)	2/1638 (0.1%)
New >500 msec	1/1727 (0.1%)	1/1638 (0.1%)
Change from baseline >30 msec	330/1727 (19.1%)	293/1638 (17.9%)
Change from baseline >60 msec	9/1727 (0.5%)	8/1638 (0.5%)

Source: SCS 120-day Safety Update, Table 4-4

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

> *Reviewer Comment: The ECG data appear to demonstrate that while there is a twofold risk of a new QTcF of > 430 msec, there are no clinically significant effects of siponimod on QT interval, confirming the negative Thorough QT Study findings.*

Mobile Cardiac Telemetry (MCT)

Controlled Phase

MCT was used during titration to provide a complete monitoring experience for patients initiating siponimod therapy. MCT demonstrated that at the end of the first day of dose initiation, heart rate decreased by a mean of five-six beats per minute after the first dose, decreasing on subsequent days and finally reaching the maximum difference from baseline to minimum heart rate on Day 5. Thereafter, minimum mean hourly heart rate slowly increased.

The applicant performed a *post hoc* analysis of dose initiation MCT extreme heart rate data showed that the peak incidence of minimum heart rates of less than 50 BPM and less than 40 BPM occurred on Day 4 and Day 5, which corresponds to the maximum decrease from baseline. Newly detected minimum heart rates less than 40 BPM occurred in 6.8% of siponimod patients and in 1.8% of placebo patients. All patients with heart rates less than 40 BPM were asymptomatic. No heart rate less than 30 BPM was captured in any of the groups except one patient in the Expanded Cardiac Monitoring group with a history of previous treatment with mitoxantrone and pre-dose baseline bradycardia on MCT who experienced an asymptomatic HR of 20 BPM observed in the titration period.

There were no new Mobitz II atrioventricular blocks, no higher degree blocks, and no complete AV blocks observed by MCT in the siponimod group during dose initiation at any time after first dose. The incidence of Mobitz I AV block during dose initiation, based on MCT, was low and was not markedly different between the siponimod and placebo groups. Incidence of pauses defined as T ≥ 3 sec was low; there were 6 events (1.0%) in the Standard Cardiac Monitoring group and 1 event in Expanded Cardiac Monitoring group (0.4%) and none on placebo. Pauses of at least 3 seconds infrequently occurred on Days 1-6; these were observed at any time (Day 1 to Day 6) post first dose in seven siponimod patients (newly detected any time post first dose) and in no placebo patients.

The MCT findings, other than findings of clinical interest, were mostly asymptomatic and observed in higher incidence in the Expanded Cardiac Monitoring group. These findings were not correlated with symptoms such as syncope or dizziness.

MCT detected sinus bradycardia in 8.8% of siponimod patients (20 patients) and 2.7% of placebo patients (3 patients) in the Expanded Cardiac Monitoring group, and 5.7% of siponimod patients (35 patients) and 0.6% of placebo patients (2 patients) in the Standard Cardiac Monitoring group, respectively. Sinus bradycardia was most often detected at Days 4-5 of titration. By contrast, 1st degree atrioventricular block was most often noted on Day 3 of titration. The observed events were not associated with symptoms and did not occur coincidentally with reported TEAEs.

The incidence of 2nd degree AV block Mobitz type I was 0.7% versus 0.2% with placebo treatment, with frequencies of 1.6% in the Expanded Cardiac Monitoring and 0.3% in the Standard Cardiac Monitoring groups, respectively.

Holter Monitoring

Controlled Phase
The number of patients with interpretable Holter data was low (<20% of patients overall) which limits conclusions from Holter monitoring. However, Holter monitoring appeared to corroborate the more expansive MCT results in that the incidence of Mobitz type I atrioventricular block was low and similar between both siponimod and placebo treatment groups. No new incidences of second degree Mobitz type II atrioventricular blocks, higher degree block or complete AV blocks were recorded via Holter monitoring.

The incidence of Holter findings at any time post first dose was lower in the siponimod group relative to placebo in the Expanded Cardiac Monitoring group (11.2% siponimod, 31.1% placebo) and higher in the Standard Cardiac Monitoring group in the siponimod group than placebo (23.2% siponimod, 11.9% placebo). Most of these findings were related to ectopy, such as frequent ventricular premature complexes (VPC) and non-sustained ventricular tachycardia.

The following table provided by the applicant summarizes the findings captured by the MCT and ECG/Holter/ECG monitoring:

Table 82: Applicant Table, Summary of MCT/Holter Cardiac Monitoring Findings for Standard and Expanded Cardiac Monitoring Group, Controlled Pool, Safety Set (Safety Database 1)

Category	Expanded Cardiac Monitoring Group		Standard Cardiac Monitoring Group		All Patients	
	Siponimod N=358	Placebo N=174	Siponimod N=741	Placebo N=372	Siponimod N=1099	Placebo N=546
Number of patients with available AEs*	26 (7.3%)	7 (4.0%)	76 (10.3%)	26 (7.0%)	102 (9.3%)	33 (6.0%)

Category	Expanded Cardiac Monitoring Group		Standard Cardiac Monitoring Group		All Patients	
	Siponimod N=358	Placebo N=174	Siponimod N=741	Placebo N=372	Siponimod N=1099	Placebo N=546
Number of patients with available MCT	247	124	624	314	871	438
HR<40 bpm	18 (7.3%)	0	9 (1.4%)	0	27 (3.1%)	0
Pause	2 (0.8%)	0	6 (1.0%)	0	8 (0.9%)	0
HR<40 bpm and AE irrespective of time	0	0	1 (0.2%)	0	1 (0.1%)	0
Pause and HR<40bpm	1 (0.4%)	0	2 (0.3%)	0	3 (0.3%)	0
Pause and HR<40bpm and AV Block 2 Mobitz I	0	0	0	0	0	0
Pause and HR<40bpm and AV Block 2 Mobitz I and AE irrespective of time	0	0	0	0	0	0
Pause and HR<40bpm and AV Block 2 Mobitz I and AE within 1 day of finding	0	0	0	0	0	0
Number of patients with available MCT/Holter/ECG	358	174	740	372	1098	546
Pause	11 (3.1%)	1	10 (1.4%)	0	21 (1.9%)	1
Pause and AE irrespective of time	0	0	2 (0.3%)	0	2 (0.2%)	0
Pause and AV Block 2 Mobitz I	4 (1.1%)	1	3 (0.4%)	0	7 (0.6%)	1
Pause and AV Block 2 Mobitz I and AE irrespective of time	0	0	0	0	0	0
Pause and AV Block 2 Mobitz I and AE within 1 day of finding	0	0	0	0	0	0
AV Block 2nd degree Mobitz I**	9 (2.5%)	1	5 (0.7%)	2	14 (1.3%)	3
AV Block 2nd degree Mobitz I and AE irrespective of time	0	0	0	0	0	0
AV Block 2nd degree Mobitz I and AE within 1 day of finding	0	0	0	0	0	0

Source: SCS Appendix 3, Table 4-4

*AEs with the following preferred terms were included: dizziness, presyncope, syncope, angina pectoris, chest discomfort, chest pain, palpitations, hypotension, orthostatic hypotension,

fatigue, and fall.
**Based on MCT and Holter assessment, but also including one patient who had Mobitz I reported on the AE eCRF page.

Reviewer Comment: The titration did appear to eliminate second degree heart block as there were no new cases of symptomatic 2nd degree AV block after titration was implemented. Extensive cardiac monitoring via MCT and Holter monitors did not elucidate more clinically relevant findings than ECG, and so ECG appears sufficient to capture the information needed to make decisions regarding continuing treatment. Given the similarity of siponimod to fingolimod, it is reasonable to assume that patients are at risk of significant cardiac rhythm disturbances with siponimod initiation. The dose titration instituted for siponimod does appear to mitigate risk for patients without a history of cardiac disease because the rates of any events in this group were low and the events that were present were obviously symptomatic or transient, and labeling can address these situations and ensure safety during initial dosing in most patients. Patients with a prior history of arrhythmia or cardiac disease should undergo first dose monitoring with a pre- and post-dose ECG. Because of the observed peak heart rate reduction noted on Day 1, a pre-treatment ECG and an ECG at 6 hours post-first dose are needed for high risk patients to address safety concerns associated with persistent 1st degree AV block or persistent sinus bradycardia. Recommendations regarding symptomatic bradycardia, heart block, prolonged QTc interval, and interactions with other arrhythmia-inducing therapies should mirror fingolimod labeling as well.

8.4.9. **QT**

Based on nonclinical and previous clinical experience with siponimod and with a drug having a similar mechanism of action, fingolimod, the applicant provided a Thorough QT (TQT) Study entitled, "A randomized, double-blind, parallel-group, placebo- and moxifloxacin-controlled multiple-dose study to assess the QT interval after oral administration of siponimod in healthy subjects." The primary objective of this TQT Study was "[t]o assess if the placebo-corrected, baseline-adjusted mean QTcF (ΔΔQTcF) at therapeutic and supratherapeutic doses of siponimod exceeds the regulatory threshold level of concern of 5 milliseconds as evidenced by an upper bound of a one-sided 95% CI for the largest mean QTc effect of 10 milliseconds."

The applicant states that, "[the] thorough QT study at therapeutic (2 mg) and supratherapeutic (10 mg) doses demonstrated no significant direct QT prolonging effect of siponimod. Hence, siponimod is not associated with an arrhythmogenic potential related to QT prolongation. In addition, the results of the pooled categorical QTc analysis across... studies were consistent with those of the dedicated thorough QT study."

The Division's Interdisciplinary Review Team for QT Studies provided a consultation and

reached the same general conclusion as follows: "The thorough QT study investigating the effects of therapeutic (2 mg) and supratherapeutic (10 mg) doses of siponimod on cardiac repolarization, as assessed by the time-matched, baseline- and placebo-corrected QTcF (ΔΔQTcF), demonstrated no direct QT prolonging effect of siponimod. Siponimod is not associated with an arrhythmogenic potential related to QT prolongation."

In the TQT study, categorical analysis revealed no treatment-emergent QTcF values above 480 milliseconds and no QTcF increases from baseline of more than 60 milliseconds on any of the on-treatment assessment days.

The applicant reported no cases of sudden death, Torsade de pointes, ventricular flutter, ventricular fibrillation, or seizures throughout the clinical development program.

Reviewer Comment: Refer to the Interdisciplinary Review Team for QT Studies consultation for further comments regarding the TQT Study findings. The Interdisciplinary Review Team for QT Studies has provided feedback regarding recommended labeling language for siponimod based on the findings in the TQT Study.

8.4.10. Immunogenicity

Siponimod does not appear to provoke an immune response directed against its structure. Anti-drug antibodies have not been observed.

However, because siponimod lowers circulating numbers of lymphocytes, the potential effects of siponimod on the immune response/immunogenicity of selected vaccines were investigated in a dedicated study. Non-inferior responder rates demonstrated that concomitant siponimod treatment did not compromise the efficacy of a PPV-23 vaccination (T cell-independent response) and therefore no siponimod treatment interruption is required. The efficacy of quadrivalent influenza vaccination (T cell-dependent vaccine) is not compromised if siponimod treatment is paused 1 week prior until 4 weeks after vaccination.

Reviewer comment: The applicant has proposed language for how the findings of the immune response studies will be described in labeling. This reviewer agrees with the applicant's proposed language because it is consistent with other current labeling language.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Infections

Controlled Pool

The incidences of Infections and Infestations SOC TEAEs were similar in the siponimod 2 mg and placebo treatment groups (48.8%, 49.8%, respectively) in the controlled pool. Furthermore, a customized search pooling preferred terms related to all infection types demonstrated equivalence in pooled infection terms between patients treated with any siponimod dose and placebo. Urinary tract and upper respiratory infection frequencies were also similar between siponimod and placebo treatment groups in this custom analysis (see Section 8.4.5.)

Siponimod is associated with lymphopenia, and postmarketing experience with another S1P modulator revealed an association with reactivation of herpes viruses and opportunistic infections seen in the immune compromised state. Therefore, the applicant provided additional analyses of infections of specific concern.

In the controlled pool, fungal infections (based on risk search terms defined by high level group terms) were reported for 3.7% of patients in the siponimod 2 mg and for 3.1% of patients in the placebo treatment group. The most common identified fungal infections were cutaneous. Tinea versicolor and onychomycosis were reported in 0.5% and 0.4% of siponimod-treated patients as compared to 0.2% and 1.2% of placebo-treated patients.

> *Reviewer Comment: There does not appear to be an imbalance in common fungal infections between the siponimod and placebo treatment groups.*

Varicella reactivation was more common in the siponimod treatment group (2.9%, OR=4.5, IR=1.6) as compared to the placebo treatment group (0.7%). There was a SAE of varicella zoster of the ear leading to varicella meningitis reported as a SAE. There were no herpes-related deaths in the siponimod treatment groups in controlled studies. Herpes viral infections (other than varicella virus re-activation) were reported 4.6% (52/1148) of patients in the siponimod 2 mg group and in 3.0% (18/607) patients in the placebo group. Oral herpes was reported for 19 (1.7%) and 13 (2.1%) patients in the siponimod 2 mg and placebo groups, respectively. Herpes simplex was reported for 4 (0.3%) and 2 (0.3%) patients in the siponimod 2 mg and placebo groups, respectively.

There was, not surprisingly, a relationship between lymphocyte count and frequencies of infections. For the siponimod treated group, there was a higher frequency of patients (53.0%) with at least one measured lymphocyte count in the lowest category ($<0.4 \times 10^9$/L) at any time on siponimod treatment who experienced one or more infections.

There were no cases of cryptococcal meningitis nor progressive multifocal leukoencephalopathy reported in the controlled safety pool.

> *Reviewer Comment: Siponimod appears to be associated with the same increased incidence of herpes virus infection reactivation and varicella recrudescence observed in*

another S1P modulator, fingolimod. Therefore, labeling for siponimod should state the risk of serious reactivation of herpes infections observed with fingolimod and should provide the same guidance as the fingolimod labeling regarding verifying varicella titer and vaccination of antibody negative patients before initiating siponimod.

Long-term Safety Pool

As expected, infections remained common in the long-term safety pool, with 55.4% (962/1737) of patients reporting a preferred term within a broad search of infection-related terms.

Fungal skin infection frequency in the long-term safety pool decreased from the controlled pool to 1.2%.

There were additional reports of herpetic virus reactivation, including varicella zoster virus, but the overall incidence rates for herpetic reactivation events other than varicella remained the same at 1.4 per 100 PY while the varicella reactivation IR increased from 1.6 to 1.8 per 100PY.

There were no new cases of other opportunistic infections noted.

120-day Safety Update

Infection frequencies in the updated safety pool data remained stable with 58.2% (1011/1637) of patients in the safety database experiencing an infection-related event.

Skin fungal infection frequency remained 1.2%.

There were nine more patients with events consistent with varicella virus reactivation added to the safety database, but the incidence rate for these events remained 1.8 per 100 PY. For all herpetic infections other than varicella, the incidence rate was 1.3 per 100 PY.

The 120-day update did not provide any opportunistic infection cases. A case of cryptococcal meningitis was reported in a patient taking siponimod in a MedWatch report form filed after the 120-day update.

Reviewer Comment: The infection risk associated with siponimod appears like that of the approved S1P modulator, fingolimod. The similarity of the overall infection frequencies between siponimod and placebo suggest that immune function remains despite relative lymphopenia and most patients are at low risk of opportunistic infections when administered the 2 mg siponimod dose. However, given the evidence of varicella virus reactivation and the addition of a late breaking report of cryptococcal meningitis, it does appear that siponimod is associated with enough immune suppression to be associated with herpes virus recrudescence and, rarely, opportunistic infections. Labeling can provide appropriate guidance regarding the overall infection risks and Warnings and

Precautions regarding reactivation of varicella virus and acquiring serious opportunistic infections anticipated in the postmarketing setting.

8.5.2. Lymphopenia

Controlled Pool

There is a discussion of lymphocyte findings during the controlled phases of clinical trials in Section 8.4.6.

Long-term Safety Pool and 120-day Safety Update

Siponimod reduces the number of S1P receptors on lymphocyte cell membranes and thereby prevents egress of lymphocytes from lymphatic reserves. Fingolimod, an approved S1P modulator, causes persistent reductions in circulating lymphocyte numbers by the same mechanism. Therefore, it was expected that the serum absolute lymphocyte counts in patients would be reduced by siponimod therapy, and such was the case. For the long-term safety pools, absolute lymphocyte counts were reduced at Day 28 for siponimod at any studied dose and remained reduced from Day 28 until the latest follow-up recorded for patients who remained on therapy. In the siponimod 2 mg treatment group, the change from baseline in absolute lymphocytes counts was −1.227 $x10^9$/L compared to +0.043 $x10^9$/L for the placebo group at Day 28. The onset of the reduction can occur on Day 1 and peaks in Weeks 2-3 (see Section 8.4.6.)

Absolute lymphocyte count data were provided in the 120-day safety update for lymphocyte values up through Month 84, albeit with small numbers of subjects, and the mean reduction in circulating lymphocyte number remained approximately 1 $x10^9$/L across the 84 weeks of monitoring.

Table 83: Absolute Lymphocyte Count Change from Baseline to Day 28, Long-term Safety Pool, Safety Set (Safety Database 4)

	Baseline	Day 28	Mean Change from Baseline to Day 28
N	1643	1643	1643
Mean	1.73 $x10^9$/L	0.56 $x10^9$/L	-1.17 $x10^9$/L
SD	0.61	0.29	+0.57
Median	1.70 $x10^9$/L	0.10 $x10^9$/L	-1.10 $x10^9$/L
Min	0.17 $x10^9$/L	0.50 $x10^9$/L	-3.94 $x10^9$/L
Max	4.55 $x10^9$/L	3.80 $x10^9$/L	+1.30 $x10^9$/L

Source: Table 3.5-1.2 120-day Update SCS

Table 84: Absolute Lymphocyte Count Change from Baseline to Month 84, Long-term Safety Pool, Safety Set, (Safety Database 4)

	Baseline	Month 84	Change from Baseline to Month 84
n	4	4	4
Mean	1.62x10^9/L	0.69 x10^9/L	-0.93 x10^9/L
SD	0.30	0.34	0.30
Median	1.67 x10^9/L	0.96 x10^9/L	-1.23 x10^9/L
Min	1.41 x10^9/L	0.38 x10^9/L	-0.94 x10^9/L
Max	1.92 x10^9/L	1.12 x10^9/L	-0.60 x10^9/L

Source: Table 3.5-1.2 120-day Update SCS

Almost all patients in the long-term safety pools reported "lymphocyte count decreased" (98.7%; all grades in the broadest long-term safety pool), the majority (73.2%) had CTCAE grade 3 (count <0.5 - 0.2 x10^9/L lymphocytes. Grade 4 lymphopenia < 0.2 x10^9/L lymphocytes) was noted in 10.4 % of patients in the long-term safety pool. Lymphopenia was reported as AE in 11.6% (202/1737) of siponimod patients.

Table 85: Reviewer Table, Lymphopenia Adverse Events, Safety Databases 2 and 4

Preferred Term	Siponimod 2-10 mg (including titration) N=1737		Siponimod 2-10 mg (not including titration) N=1737	
	n (%)	IR	n (%)	IR
Lymphopenia	139 (8.0)	3.1 (2.6, 3.7)	138 (7.9)	3.2 (2.7, 3.8)
Lymphocyte count decreased	68 (3.9)	1.5 (1.1, 1.9)	68 (3.9)	1.6 (1.2, 2.0)

Source: 120-day Update SCS Appendix 1-Table 2.1-13.2a, Table 2.1-13.2

The applicant performed a comparison of the overall incidence of the patients with findings in the Infections and Infestations SOC in conjunction with patients' nadir lymphocyte count and found a 64.8% frequency of events with lymphocyte counts <0.4 x10^9/L lymphocytes, a frequency of 46.5% with 0.4-0.6 x10^9/L lymphocytes, and a 48.6% frequency with >0.6 x10^9/L lymphocytes. There was no obvious correlation between lymphocyte counts and serious adverse events of infection.

After discontinuation of siponimod, recovery of lymphocyte counts occurs beginning in the second week, which coincides with a duration greater than five half-lives, assuming a half-life for siponimod of approximately 36 hours.

Reviewer Comment: Reduction in serum lymphocyte count is a direct consequence of S1P

modulation and this reduction in white blood cells is presumed to be part of siponimod's mechanism of action. The observed reduction in serum lymphocytes associated with siponimod therapy is similar in quantity and quality the reduction noted with the approved S1P modulator, fingolimod. Cases of lymphopenia leading to discontinuation were rare and are discussed in Section 8.4.3. Neutropenia was not observed in association with siponimod. There is a known and expected increase in certain types of infections associated with this reduction. Lymphopenia should be a listed Warning and Precaution on the labeling for siponimod to educate patients and prescribers about the risk. The applicant provided baseline lymphocyte count and monitoring recommendations, and I agree with their proposal. The increased risk of infections caused by lymphopenia can be mitigated partially with labeling directed at prescribers and consumers warning for increased awareness of infection risk.

8.5.3. **Bradycardia/Bradyarrhythmia**

S1P modulators are associated with significant bradycardia and rhythm disturbances with initial dosing because of interaction with S1P1 receptors in cardiac muscle that mediate heart rate. In Study A2304, the applicant selected the siponimod dose of 2 mg daily and instituted a 6-day titration schedule to achieve this maintenance dose to reduce the frequency and risks of serious cardiac symptoms associated with first dose. In Period 1 of Study A2201, the doses of 0.5 mg, 2 mg, and 1 mg had been initiated without titration but due to bradyarrhythmic effects, later in Study 2201, titration schemes were implemented to mitigate the cardiac effects. All patients starting their initial exposure or restarting after a 4 day or longer interruption, would follow the same titration procedure as follows:

Day 1: 0.25 mg
Day 2: 0.25 mg
Day 3: 0.50 mg
Day 4: 0.75 mg
Day 5: 1.25 mg
Day 6 (maintenance dose): 2 mg

On Day 1, patients were monitored in the clinic for at least the first six hours after taking the first dose of study drug (Day 1) with hourly heart rate and blood pressure measurements. Additionally, a surface 12 lead ECG was taken at three- and six-hours post-dose. After six hours of observation, patients could be discharged if the effect on heart rate was within pre-defined limits, the patient was asymptomatic, and the six-hour ECG did not show any new relevant abnormalities. Patients not meeting the per protocol predefined criteria had to be observed longer until criteria were met (even if it required overnight hospitalization). Patients were required to continue titration and return to clinic on Day 7 when the same observations as on Day 1 were performed for at least the first 6 hours after taking the Day 7 dose of study drug.

During the titration period data for extensively monitored patients were collected in all patients for Day 1 through Day 7 by MCT (every day collection) or Holter ECG (Day 1, Day 4, Day 7), if use of MCT was not feasible at that particular site. To prevent unblinding, monitoring after the first intake of the study drug was performed under the responsibility of an independent physician referred to as the First Dose Administrator. This physician reviewed vital signs during 6-hour monitoring, post-dose ECG, assessed discharge criteria at 6 hours post-dose, and managed cardiac events when they occurred. The investigator/treating physician was informed of any SAEs that may have occurred, remaining otherwise blinded to the cardiac events happening on the first day.

Overall, as indicated in the following table, most cardiac conduction-related TEAEs of specific concern occurred within a week of initiation of siponimod therapy. As expected based on prior experience with other S1P modulators and findings in siponimod specifically in prior trials, bradycardia (4.4% siponimod, 2.6% placebo) and sinus bradycardia (1.3% siponimod, 0.2% placebo) were the most frequently reported TEAE in each treatment group from Days 1 to 7. In Study A2304, a search of the combined AE terms “bradyarrhythmia” and “bradycardia” revealed that 7.4% of patients in the siponimod treatment group and 2.9% in the placebo treatment group experienced reports of these events during dose initiation.

Table 86: S1P Modulator Specific Cardiac Treatment Emergent AEs of Interest by Week until Day 28, Study A2304, Controlled Pool, Safety Set

Treatment Group Preferred Term	**Day 1-7 n (%)**	**Day 8-14 n (%)**	**Day 15-21 n (%)**	**Day 22-28 n (%)**
Siponimod 2 mg (N=1099)				
Number of patients with any AE up to Day 28	321 (29.2%)	170 (15.5%)	122 (11.1%)	134 (12.2%)
Bradycardia	48 (4.4%)	0	0	0
Sinus bradycardia	14 (1.3%)	0	0	0
Heart rate decreased	4 (0.4%)	0	0	0
Syncope	1 (0.1%)	2 (0.2%)	0	0
Atrioventricular block first degree	10 (0.9%)	0	0	1 (0.1%)
Atrioventricular block second degree	5 (0.5%)	1 (0.1%)	0	0
Placebo (N=546)				
Number of patients with any AE up to Day 28	128 (23.4%)	68 (12.5%)	59 (10.8%)	60 (11.0%)
Bradycardia	14 (2.6%)	0	0	0

Treatment Group Preferred Term	Day 1-7 n (%)	Day 8-14 n (%)	Day 15-21 n (%)	Day 22-28 n (%)
Sinus bradycardia	1 (0.2%)	0	0	0
Atrioventricular Block First Degree	1 (0.2%)	0	0	0
Atrioventricular block second degree	0	0	0	0

Source: SCS Table 4-17

Reviewer Comment: The expectation with titration was that bradycardia and related events would be reduced, which as discussed elsewhere appeared to be the outcome of titration. However, TEAEs related to bradycardia still occur at a higher rate than placebo and appear confined largely to the period immediately after initiation of therapy. One concern regarding the observed increased signal for falls and injuries was that patients would fall due to syncope. The two cases of syncope noted on Days 8-14 were not associated with falls or injuries. In both cases, ECGs obtained with the events showed no changes from baseline. The recurrent case of 1st degree AV block noted in one patient was asymptomatic and resolved on subsequent ECGs. It appears that the titration makes persistent, high degree, AV block highly unlikely.

Patient symptoms reported during siponimod initiation occurred during first dose administration and were mild. Headache, fatigue and dizziness were the most common TEAEs reported in the siponimod 2 mg group on Day 1 of dose initiation, which were all reported at lower frequencies on Days 2-7. There were 15 patients (1.3%) in the siponimod 2 mg group in the Controlled Pool who discontinued due to bradyarrhythmia and bradycardia or related symptoms including hypotension and malaise. Out of these patients, 11 (1.0%) discontinued due to reports of bradyarrhythmia and bradycardia, five (0.4%) patients due to second degree AV block Mobitz I, two (0.2%) patients due to first degree AV block, and 4 (0.3%) due to bradycardia. There were no patients in the placebo treatment group who discontinued due to any of these cardiac AEs.

Table 87: Frequency of Treatment Emergent Events with Start Dates During Dose Initiation, by Day and Preferred Term, Study A2304, Controlled Pool, Safety Set

Treatment group Preferred term	Day 1 n (%)	Day 2 n (%)	Day 3 n (%)	Day 4 n (%)	Day 5 n (%)	Day 6 n (%)	Day 7 n (%)
Siponimod 2 mg (N=1099)							
Number of patients with at least one AE	156 (14.2%)	56 (5.1%)	25 (2.3%)	45 (4.1%)	32 (2.9%)	21 (1.9%)	76 (6.9%)
Angina pectoris	0	0	0	1 (0.1%)	0	0	0

Treatment group **Preferred term**	**Day 1** **n (%)**	**Day 2** **n (%)**	**Day 3** **n (%)**	**Day 4** **n (%)**	**Day 5** **n (%)**	**Day 6** **n (%)**	**Day 7** **n (%)**
Palpitations	1 (0.1%)	3 (0.3%)	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	2 (0.2%)
Chest discomfort	1 (0.1%)	1 (0.1%)	0	0	1 (0.1%)	0	0
Fatigue	16 (1.5%)	7 (0.6%)	1 (0.1%)	4 (0.4%)	0	0	4 (0.4%)
Dizziness/Postural Dizziness	16 (1.5%)	6 (0.6%)	0	5 (0.5%)	2 (0.2%)	2 (0.2%)	4 (0.4%)
Headache	18 (1.6%)	8 (0.7%)	3 (0.3%)	1 (0.1%)	3 (0.3%)	2 (0.2%)	6 (0.5%)
Presyncope	0	0	0	1 (0.1%)	0	0	0
Syncope	0	0	0	1 (0.1%)	0	0	0
Fall	1 (0.1%)	0	2 (0.2%)	2 (0.2%)	1 (0.1%)	1 (0.1%)	0
Hypotension	2 (0.2%)	1 (0.1%)	0	0	0	0	0
Orthostatic hypotension	1 (0.1%)	0	0	2 (0.2%)	0	0	0
Placebo (N=546)							
Number of patients with at least one AE	61 (11.2%)	31 (5.7%)	11 (2.0%)	14 (2.6%)	9 (1.6%)	11 (2.0%)	35 (6.4%)
Palpitations	0	0	0	0	0	0	1 (0.2%)
Chest discomfort	0	0	0	0	0	1 (0.2%)	0
Fatigue	3 (0.5%)	3 (0.5%)	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	0
Dizziness/Postural Dizziness	2 (0.4%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	2 (0.4%)	0	6 (1.1%)
Headache	8 (1.5%)	3 (0.5%)	2 (0.4%)	4 (0.7%)	2 (0.4%)	0	4 (0.7%)
Fall	2 (0.4%)	0	0	0	0	1 (0.2%)	1 (0.2%)
Hypotension	0	0	0	0	0	0	1 (0.2%)

Source: SCS Appendix 1-Table 2.1-15.1

> *Reviewer Comment: >98% of reported symptom AEs were CTCAE 1-2. Fatigue and dizziness were discordant between treatment groups. Headache frequency was similar between the two groups. Dizziness appears to remain associated with siponimod treatment long-term whereas reports of fatigue and related terms are not markedly different between placebo and siponimod treated patients in the entire controlled pool database (see Section 8.4.5.)*

Cardiac Risk Categorization

In Study 2304 core phase and extension, patients were classified according to pre-existing cardiac risks including observations at screening.

A total of 1471 out of 1645 (89.4%) of patients had extensive cardiac monitoring at treatment initiation. This "Expanded Cardiac Monitoring" group was comprised of 358 patients (32.6%). Additionally, 628 patients (57.1%) of the Standard Cardiac Monitoring group also had extensive monitoring before implementation of a protocol amendment by which 6 hours post-dose monitoring on Day 1 and Day 7 was no longer required for patients with no cardiac risk (referred to as the "Standard Cardiac Monitoring" group).

> *Reviewer Comment: The applicant proposed the first protocol amendment for Study A2304 in April 2014 to the Division and shared the safety data available at that time and the Data Monitoring Committee's recommendation to end the 6 hours post dose monitoring for Standard Cardiac Monitoring patients on Days 1 and 7. The Division agreed to the amendment because the safety data presented demonstrated a much lower risk of atrioventricular block and symptomatic cardiac events for Standard Cardiac Monitoring patients. The Division agreed to the amendment and the amendment was implemented on May 26, 2014.*

As summarized previously, the initial 0.25 mg dose of siponimod is associated with heart rate reduction. After first dose, siponimod was associated with a decline in sitting pulse on Day 1 that began as early as 1 hour after dosing, reaching its maximal decrease after 3-4 hours on Day 1. The maximal decline from pre-dose values in mean sitting pulse was −5.3 beats per minute. There is some reduction in the siponimod treatment effect on heart rate, but not total accommodation. On Day 7, when patients received their second dose of siponimod at the 2 mg maintenance dose, the maximal decline at 3 hours post-dose in the siponimod treatment group was a mean change of −3.08 beats per minute.

The reductions in sitting pulse observed at the initiation of siponimod treatment attenuated with chronic 2 mg treatment. In many patients, the heart rates return to baseline rates within 4 weeks of initiation (See Section 8.4.7.)

Table 88: Comparison of Changes in Heart Rates between Expanded and Standard Cardiac Monitoring Groups, Study A2304, Controlled Phase, Safety Set (Safety Database 1)

Change in HR from pre-dose (BPM)	Expanded Cardiac Monitoring Group		Standard Cardiac Monitoring Group	
	Siponimod N=358 Mean ± SD	Placebo N=174 Mean ± SD	Siponimod N=741 Mean ± SD	Placebo N=373 Mean ± SD
Day 1 Pre-dose (BPM)	70.64	71.11	73.91	74.29
1-hour post-dose	-1.53 ± 6.63	-0.69 ± 6.51	-1.75± 7.42	-1.41 ± 6.85
2 hrs. post-dose	-3.30 ± 7.31	-0.70 ± 7.01	-3.71 ± 7.60	-0.84 ± 8.07
3 hrs. post-dose	-4.87 ± 7.71	-0.64 ± 7.62	-5.41 ± 7.83	0.00 ± 7.56
4 hrs. post-dose	-4.64 ± 7.70	1.35 ± 7.56	-5.68 ± 7.63	0.45 ± 7.73
5 hrs. post-dose	-4.62 ± 7.83	1.27 ± 7.46	-5.40 ± 7.65	0.15 ± 7.68
6 hrs. post-dose	-4.60 ± 7.16	1.04 ± 7.03	-4.93 ± 7.31	0.10 ± 7.49
Day 7 Pre-dose (BPM)	66.35	71.92	69.34	75.06
1-hour post-dose	-1.66 ± 5.55	-2.02 ± 6.22	-1.57± 5.56	-1.62 ± 6.78
2 hrs. post-dose	-2.52 ± 6.45	-1.72 ± 7.66	-3.22 ± 6.38	-2.07 ± 7.63
3 hrs. post-dose	-2.84 ± 7.02	-2.16 ± 7.54	-3.21 ± 6.76	-1.92 ± 7.72
4 hrs. post-dose	-1.80 ± 6.49	-0.90 ± 6.82	-2.51 ± 6.78	-0.01 ± 7.67
5 hrs. post-dose	-1.63 ± 6.26	-0.10 ± 7.16	-1.81 ± 6.71	-0.49 ± 7.74
6 hrs. post-dose	-0.63 ± 6.42	-0.06 ± 7.34	-1.04 ± 6.27	-0.23 ± 7.74

Source: SCS Appendix 3, Table 4-1

In Study A2304, during the first 7 days of treatment, 4.4% patients in the siponimod treatment group versus 2.6% patients in the placebo group reported bradycardia in a visit vital signs assessment. Bradycardia was reported in 51 (4.4%) patients treated with siponimod 2 mg in the first 3 months of treatment; bradycardia was reported for less than 1% of patients in each time interval after 3 months. In the placebo group, bradycardia was reported in 16 (2.6%) patients in the first 3 months and was not reported for any patients after 3 months.

An analysis of treatment emergent adverse events in Study A2304 showed a low frequency of bradycardic events in the titration period. In the first seven days of treatment, sinus bradycardia was reported in 1.3% of siponimod treated patients versus 0.2% placebo-treated patients. Sinus bradycardia was reported in 16 (1.4%) siponimod 2 mg patients in the first 3 months of treatment, and for zero patients each time interval after 3 months. In the placebo group, sinus bradycardia was reported in 3 (0.5%) patients in the first 3 months and in 2 (0.3%) patients in the greater than 12-month interval. In Study A2304, bradycardia and sinus

bradycardia were reported in 48 (4.4%) and 14 (1.3%) patients treated with siponimod 2 mg in the first 7 days of treatment and for no patients from days 8 to 28. By comparison, in Study A2201, prior to instituting titration, the frequency of bradycardia was as high as 28% and sinus bradycardia frequency was over 4%.

Along with vital sign monitoring, there were ECG evaluations performed in patients during dose initiation and titration. Changes in QTcF parameters were the most common new findings based on the ECG studies. Specifically, the most common (~10%) observed change from baseline was a change of greater than 30 msec and a new QTcF interval or greater than 430 msec (male) or new greater than 450 msec (female) in patients treated with siponimod. The incidence of clinically relevant QTcF changes was low and only 3 patients experienced QTcF increases from baseline of more than 60 msec. Sinus bradycardia, first degree AV block (PR prolongation), and flat T waves (which were of no clinical significance) were noted less frequently. PR interval prolongation was more common (82/986 or 8.3%) in the siponimod treatment group as compared to the placebo group (14/485 or 2.9%); none of the PR prolongations were associated with symptoms. Most of these observed changes, including bradycardia and 1st degree atrioventricular block, were asymptomatic and did not require additional treatment. In Study A2201, before titration, there were five patients with 2nd degree atrioventricular block with symptomatic bradycardia, four of these were reported as SAEs.

> *Reviewer Comment: The titration regimen appears to reduce the magnitude of the bradycardia associated with siponimod in all patients. The reduction in bradycardic events in titrated versus un-titrated patients suggests the 6-day titration achieved the goal of reducing cardiac disorder events related to bradycardia. The frequencies of atrioventricular block were also reduced by titration and the elimination of more severe symptomatic blocks is encouraging.*

The Expanded Cardiac Monitoring group had more findings before (as expected) and after initial treatment with siponimod. The Expanded Cardiac Monitoring group had a higher incidence of any findings at Day 1 pre-dose (~25%) compared to Standard Cardiac Monitoring group with extensive cardiac assessments (~8%). The incidence of QTcF and PR interval abnormalities was higher in patients in the Expanded Cardiac Monitoring group (0.3-16.1%) compared with the Standard Cardiac Monitoring group (0-10.1%).

Newly detected ECG findings at any time post-first dose were more common in the Expanded Cardiac Monitoring group (49.1% siponimod, 37.4% placebo) than in patients in the Standard Cardiac Monitoring group who had extensive cardiac assessments (24.7% in siponimod treatment versus 18.9% in placebo treatment). The most common finding was sinus bradycardia (12.3% versus 2.4% placebo in the Expanded Cardiac Monitoring group, and 5.4% versus 1.3% placebo in the Standard Cardiac Monitoring group.

MCT monitoring provided a fuller picture of the Expanded Cardiac Monitoring group's experience with siponimod during titration. In comparison to Standard Cardiac Monitoring group, the Expanded Cardiac Monitoring Group experienced more sustained bradycardia and atrioventricular block.

Table 89: Cardiac Monitoring Findings in Standard and Expanded Cardiac Monitoring, Study A2304, Safety Set (Subsets of Patients with Standard and Expanded Cardiac Monitoring)

	AV Block Mobitz I		Pause ≥ 3 seconds		Hourly Minimum of 5 min. average HR <50 BPM		Hourly Minimum of 5 min. average HR <40 BPM	
	Siponimod n/m (%)	Placebo n/m (%)	Siponimod n/m (%)	Placebo n/m (%)	Siponimod n/m (%)	Placebo n/m (%)	Siponimod n/m (%)	Placebo n/m (%)
Expanded Cardiac Monitoring group								
Day 1 pre-dose	0	0	0	0	11/201 (5.5%)	2/101 (2.0%)	0	0
Any day Post-dose	4/247 (1.6%)	0	1/246 (0.4%)	0	78/191 (40.8)	17/97 (17.5%)	17/244 (7.0%)	0
Day 1 post-dose	0	0	0	0	61/247 (24.7%)	18/121 (14.9%)	2/247 (0.8%)	0
Day 2	0	0	0	0	76/244 (31.1%)	20/121 (16.5%)	1/244 (0.4%)	0
Day 3	2/244 (0.8%)	0	0	0	95/244 (38.9%)	16/124 (12.9%)	4/244 (1.6%)	0
Day 4	1/242 (0.4%)	0	1/242 (0.4%)	0	99/242 (40.9%)	15/123 (12.2%)	7/242 (2.9%)	0
Day 5	1/238 (0.4%)	0	0	0	105/238 (44.1%)	19/121 (15.7%)	10/238 (4.2%)	0
Day 6	1/234 (0.4%)	0	1/234 (0.4%)	0	83/234 (35.5%)	13/119 (10.9%)	7/234 (3.0%)	0
Standard Cardiac Monitoring group								
Day 1 pre-dose	0	0	0	0	3/542 (0.6%%)	0	0	0
Any day PD*	2/624 (0.3%)	1/314 (0.3%)	6/623 (1.0%)	0	1166/558 (29.7%)	20/272 (7.4%)	9/624 (1.4%)	0
Day 1 post-dose	1/622 (0.2%)	0	0	0	74/622 (11.9%)	16/314 (5.1%)	1/622 (0.2%)	0

	AV Block Mobitz I		Pause ≥ 3 seconds		Hourly Minimum of 5 min. average HR <50 BPM		Hourly Minimum of 5 min. average HR <40 BPM	
	Siponimod n/m (%)	Placebo n/m (%)	Siponimod n/m (%)	Placebo n/m (%)	Siponimod n/m (%)	Placebo n/m (%)	Siponimod n/m (%)	Placebo n/m (%)
Day 2	1/621 (0.2%)	0	0	0	101/621 (16.3%)	18/312 (5.8%)	3/621 (0.5%)	0
Day 3	2/621 (0.3%)	0	0	0	136/621 (21.9%)	22/310 (7.1%)	6/621 (1.0%)	0
Day 4	2/613 (0.3%)	1/302 (0.3%)	2/613 (0.3%)	0	146/613 (23.8%)	25/302 (8.3%)	5/613 (0.8%)	0
Day 5	1/604 (0.2%)	0	2/604 (0.3%)	0	146/604 (24.2%)	19/299 (6.4%)	6/604 (1.0%)	0
Day 6	1/587 (0.2%)	0	2/587 (0.3%)	0	115/587 (19.6%)	19/291 (6.5%)	6/587 (1.0%)	0

Source: SCS Appendix 3, Table 4-3

Despite the higher frequency of captured events, patients in the Expanded Cardiac Monitoring group were managed safely with the existing protocol monitoring. The following table summarizes the experiences with patients in the Expanded Cardiac Monitoring group monitored on site during Study A2304:

Table 90: Overview of "In-House" Treatment Initiation Monitoring Experience, Study A2304, Safety Set (Subset of Patients with Extensive Cardiac Monitoring)

Criteria	Siponimod N=962 n/m (%)	Placebo N=470 n/m (%)
Day 1		
Required monitoring beyond 6 hours	86/962 (8.9%)	19 (4.0%)
Low HR	58/962 (6.0%)	10 (2.1%)
Decreasing HR	22/962 (2.3%)	7 (1.5%)
Symptoms related to decreased HR	0	0
Treatment emergent ECG abnormalities	6/962 (0.6%)	2 (0.4%)
Discharged but returned for additional monitoring due to symptomatic event on Day 2	3/962 (0.3%)	1 (0.2%)

Criteria	Siponimod N=962 n/m (%)	Placebo N=470 n/m (%)
Day 7		
Required monitoring beyond 6 hours	42/946 (4.4%)	16 (3.5%)
Low HR	27/946 (2.9%)	9 (2.0%)
Decreasing HR	12/ 946 (1.3%)	7 (1.5%)
Symptoms related to decreased HR	1/946 (0.1%)	0
Treatment emergent ECG abnormalities	0	0
Discharged but returned for additional monitoring due to symptomatic event on Day 8	0	0

Source: SCS, Table 4-16

Reviewer comment: The results of the cardiac risk subgroup analyses appear to show that siponimod can be initiated safely by titration in most patients without a need for in-house observation. The observed abnormalities and incidence of cardiovascular-related safety events in the Standard Cardiac Risk subgroup were consistent with the prior data that led to the Division waiving the need for first dose monitoring in the Standard risk patients. The specific findings above refer to the higher risk patients with history of cardiac problems and justify monitoring after first dose of siponimod. Significant bradycardia, defined as new heart rates <40-50 BPM, were observed at a consistently higher frequency in the Expanded Cardiac Monitoring group in comparison to the Standard Cardiac Monitoring group, and nearly 10% of these patients needed monitoring beyond 6-hour vs 4% needing monitoring beyond 6 hours in the placebo group. Additionally, patients in the Expanded Cardiac Monitoring group showed a higher incidence of clinically notable abnormalities at initial dosing, both pre- and post-dose, for most parameters. For example, in the Expanded Cardiac Monitoring group, 2nd degree atrioventricular block Mobitz type I was observed more often in the first day of treatment in the Expanded Cardiac Monitoring group. Patients with underlying cardiac disease (including any patients with atrioventricular conduction delays) require more observation on treatment initiation. Since the largest mean decreases in heart rate were observed on Day 1, post-dose observation on Day 1 for 6-hours is recommended in patients with labeling defined underlying cardiac disease or risk factors such as a history of bradycardia. On Day 7 the need for monitoring beyond 6 hours had declined to 4.4% vs. 3.5% in placebo. To explore this approximately 1% difference, a review of the discharge protocol provides clarity. In order to be discharged without further monitoring, the following criteria had to be met:

"Monitoring beyond 6 hours was required according to the study protocol if any one of the following discharge criteria was not met:

- *heart rate was at least 50 bpm or maximally 10 bpm lower than the baseline value;*
- *heart rate was not the lowest value measured during the observation period;*
- *there were no symptoms related to decreased heart rate;*
- *ECG at 6 hours did not show any new significant treatment-emergent ECG abnormalities; other than sinus bradycardia, not observed at the pre-dose ECG."*

At Day 7, no patients met criteria 3 or 4 to justify further monitoring. There were no patients who had ECG changes that justified additional monitoring, and there were no patients with symptomatic events that required monitoring beyond Day 7. On review, this "need for monitoring" was enforced on Day 7 because patients were experiencing bradycardia, which was expected with this therapy, and, as noted previously, patients in the higher risk monitoring group had greater reduction in their heart rates than the standard risk group. Therefore, these restrictive criteria regarding heart rate on Day 7 do not appear to be useful for inclusion on labeling, and there does not appear to be justification for ECG monitoring on Day 7 for either the standard or higher cardiac risk patients.

8.5.4. **Macular Edema**

Prior experience with a S1P modulator led to routine ophthalmological assessments in the siponimod studies. Macular edema was confirmed by ophthalmologist assessment.

Reviewer Comment: The applicant did not provide any of the original ophthalmology scans or photographs for review. The Division of Transplant and Ophthalmology Products (DTOP) reviewer made an Information Request on 01/04/2018 for the original data, but the applicant indicated that the original OCT data and photographs were stored at local sites and were not retained in the applicant's study archives. Therefore, we are entirely reliant on the diagnosis of macular edema made by the applicant's ophthalmologists.

Controlled Pool

The applicant reported that in the controlled pool of patients in MS trials, macular edema (including cystoid macular edema) appeared as a treatment-emergent AE in 20 (1.7%) patients [Odds Ratio of 10.7 vs. Placebo] in the siponimod 2 mg group and in one patient (0.2%) in the placebo treatment group. When new onset macular edema was noted in the siponimod 2 mg dose group, it was unilateral in 14/20 patients and associated with new visual impairment in 9/20 patients.

Macular edema was a SAE for 3 (0.3%) patients in the siponimod 2 mg treatment group and reported as a SAE in no other siponimod or placebo treated patients. There were 11 patients (1.0%) who discontinued siponimod 2 mg treatment and one patient who discontinued siponimod 10 mg because of macular edema.

A search for all TEAEs of macular edema using the broadest search terms yielded 21 cases across all doses of siponimod. Two of the cases in the 2 mg siponimod exposure group were coded as "cystoid" macular edema; these two cases are included among "macular edema (any)" events in the table below.

Table 91: Adverse Events of Macular Edema, Controlled Pool, Safety Set (Safety Database 1)

	Siponimod 0.25mg N=51 n (%)	**Siponimod 0.5mg N=43 n (%)**	**Siponimod 1.25mg N=42 n (%)**	**Siponimod 2 mg N=1148 n (%)**	**Siponimod 10mg N=50 n (%)**	**Placebo N=607 n (%)**
Macular Edema (any)	0	0	0	20 (1.7%)	1 (2.0%)	1 (0.2%)
Cystoid Macular Edema	0	0	0	2 (0.2%)	0	0

Source: SCS Appendix 1 Table 2.1-13.1.1

> *Reviewer Comment: The current labeling for the approved non-specific S1P receptor modulator fingolimod includes a quoted frequency of 0.5% at the marketed dose of 0.5 mg meaning that the risk of macular edema associated with siponimod 2 mg (1.7%) is more than three-fold higher despite a claim of siponimod having greater S1P receptor selectivity to reduce, among other outcomes, increased vascular permeability (the surmised etiology of macular edema in exposed patients.)*

Macular edema occurred most frequently (14 patients out of 20) in the first four months after initiation of siponimod 2 mg (with no reported cases in the placebo population during the same duration of treatment), but some cases of macular edema TEAEs were reported to have onsets more than a year after start of siponimod therapy. The timing of onset for patients with new macular edema are described in the following table:

Table 92: Reviewer Table, Timing of Onset of Macular Edema, Siponimod 2 mg, Controlled Pool, Safety Set

Onset Relative to Siponimod Start	Siponimod 2 mg N=20 with macular edema
Months 1-3	4 (20%)
Months 4-6	10 (50%)
Months 5-8	0
Months 9-12	4 (20%)
Months >12	2 (10%)

Source: SCS Listing 2.1-3.2

Reviewer Comment: In proposed labeling from the applicant, the applicant suggested a baseline ophthalmic examination (b) (4) *Furthermore, in consultation with DTOP, it was their opinion that because every reported case of macular edema was symptomatic (most often, visual loss)* (b) (4) *Instead, the DTOP consultants suggested language for labeling that would direct patients to seek out urgent medical examination in response to any change in vision. This reviewer agrees that* (b) (4) *However, this reviewer still advocates for a baseline ophthalmological examination as being necessary to provide a baseline for future comparison and to identify other findings thus removing the possibility for uncertainty in a future examination if findings were present before therapy began.*

The study protocol allowed for patients with a history of uveitis and diabetes mellitus, independent risk factors associated with increased risk of macular edema, to enroll in the A2304 trial. Of the 20 patients on siponimod 2 mg with an AE of macular edema, two patients (10%) who experienced macular edema had a medical history of diabetes mellitus or uveitis. In addition, there were three patients (15%) with AEs of macular edema which was preceded by a history of increased intraocular pressure, retinal detachment or diabetes mellitus. A patient in the 10 mg siponimod treatment condition had a prior history of uveitis and optic neuritis of the right eye and experienced an AE of macular edema.

Reviewer Comment: The higher rates of macular edema noted in patients exposed to siponimod with histories of diabetes mellitus or uveitis would seem to suggest these predisposing factors substantially increase the risk of macula edema beyond the treatment effect of siponimod. Whether increase risk exists with the approved S1P modulator

fingolimod is the subject of an ongoing postmarketing study and definitive results of this study are pending. Labeling proposed by the applicant described an increased risk in patients with uveitis and diabetes mellitus. The consultation from DTOP disagreed with the proposed labeling and disagrees with the conclusion that there is increased risk in these patient populations. This reviewer acknowledges the difficulties in interpreting safety data from three patients in these sub-populations who would have a higher risk regardless of treatment. This reviewer defers to the expert reviewer on this matter. The pending fingolimod trial results may provide some clarification of the risk for a similar therapy to inform labeling of siponimod.

Long-term Safety Pool

In the long-term safety pool, 25 (1.4%) patients (IR of 0.6 per 100 PY) had an AE of macular edema. These 25 patients include the 21 patients identified in the controlled pool with the addition of four cases.

Table 93: Adverse Events of Macular Edema, Long-term Safety Pool, Safety Databases 2 and 4

Preferred Term	Siponimod 2-10 mg* N=1737 n (%)		Siponimod 2-10 mg** N=1737 n (%)	
	n (%)	IR	n (%)	IR
Macular Edema	23 (1.4%)	0.6	23 (1.4%)	0.6
Cystoid Macular Edema	2 (0.1%)	0.0	2 (0.1%)	0.0
Macular Edema (any)	25 (1.4%)	0.6	25 (1.4%)	0.6

Sources: adae.xpt, SCS Appendix 1-Table 2.1-13.2, Table 2.1-13.2a

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

Of the four additional cases, two cases had an onset of macular edema within the first 6 months of treatment, one patient at approximately 12 months of commencing siponimod therapy and one experienced macular edema 24 months after commencing siponimod.

Table 94: Reviewer Table, Timing of Onset of Macular Edema, Siponimod 2 mg, Long-term Safety Pool (Safety Database 2)

Onset Relative to Siponimod Start	Siponimod 2 mg N=24 with macular edema
Months 1-3	4 (16.7%)
Months 4-6	12 (50%)
Months 5-8	0
Months 9-12	5 (20.8%)
Months >12	3 (12.5%)

120-day Update

There was an additional case in the 120-day Safety Update labeled as "asymptomatic retinal edema" reported in the Long-term Safety Database. Including this case would change the overall frequency of "macular edema (any)" AE to 1.5% (25/1737 patients) and the IR would remain 0.6. The description of the case as being asymptomatic makes it unlikely to be the macular edema.

Reviewer Comment: Macular edema associated with siponimod appears to be a more significant safety issue than was the case with the approved S1P modulator, fingolimod. The frequency of macular edema observed in the long-term safety databases with siponimod is nearly three-fold higher than fingolimod's associated risk, and the timing of onset of macular edema appears more variable in siponimod (b) (4) *because the onsets are dispersed over years of therapy. Please refer to the consultation from DTOP regarding conclusions and recommendations with respect to the management of the risk of macular edema.*

8.5.5. Respiratory Effects

Controlled Pool

In the controlled pool, asthma, obstructive airway disorder, and terms related to airway restriction were reported as AEs in ten (0.9%) patients treated with siponimod 2 mg and in two (0.3%) placebo-treated patients (Odds Ratio=2.7). Asthma was the most common reported restrictive airway-related event in five patients (0.4%) in the 2 mg siponimod treatment group and in one patient (0.2%) in placebo treatment.

Cough and related terms were reported as TEAEs in 52 patients (3.9%, Odds Ratio=1.3) treated with siponimod (any dose) and 19 patients (3.1%) treated with placebo. Dyspnea and exertional dyspnea occurred in 26 patients (2.0%, Odds Ratio=1.1) in the whole siponimod treatment group as compared to 13 patients (1.8%) in the placebo treatment group.

None of the cough, asthma, bronchospasm, or bronchoconstriction AEs were reported as serious AEs. There was a single case of dyspnea listed as a SAE. There were two notable discontinuations due to Respiratory, Thoracic, and Mediastinal TEAEs in the controlled pool. One patient discontinued treatment in the siponimod 2 mg group due to dyspnea and another patient discontinued siponimod 2 mg treatment due to cough.

In Study A2304, pulmonary assessments were performed that included forced expiratory volume (FEV1), forced vital capacity, and carbon monoxide diffusing capacity (DLCO).

In the siponimod 2 mg group, there was a reduction in FEV1 that peaked at 15 months of treatment. In the siponimod 2 mg treatment group, 9.2% of patients had FEV1 below 80% at any visit as compared to 6.4% of placebo patients. At 2 consecutive visits, 3.0% of siponimod-treated patients and 2.4% of placebo-treated patients had FEV1 values below 80% and 2 siponimod patients had FEV1 findings below 60%.

FVC results showed a similar reduction associated with siponimod treatment that peaked at 15 months of treatment.

FEV1/FVC did not vary across 36 months for either the siponimod or placebo treatment groups.

DLCO reductions were more variable than FEV1 and FVC reductions associated with siponimod therapy. DLCO changes below 80% compared to baseline at any visit were reported in 21.7% of siponimod and 10.9% placebo patients and DLCO changes below 60% of baseline values at any visit were reported in 3.6% of patients in the siponimod group and 1.8% of placebo patients. There were 69 (7.8%) siponimod-treated patients and 11 (2.5%) placebo patients who had DLCO values below 80% at 2 consecutive visits 3 months apart. Mean changes from baseline for absolute DLCO values (siponimod, placebo) were −0.4 and 0.6 mL/min/mmHg at Day 28, −1.5 and 1.6 mL/min/mmHg at Month 6, and −1.5 and 0.1 mL/min/mmHg at Month 12. There were no AEs obviously associated with the observed reductions in DLCO.

Table 95: Respiratory Parameters by Treatment Group, Study A2304, Controlled Pool, Safety Set

	Siponimod 2 mg N=1061	Placebo N=525
	Percent Change from Baseline ± SD	**Percent Change from Baseline ± SD**
FEV1		
Month 1	+1.7% ± 7.4	+9.1% ± 7.6
Month 3	-1.9% ± 8.0	+0.5% ± 9.1
Month 6	-2.7% ± 9.9	+0.4% ± 11.9
Month 12	-2.8% ± 10.1	-0.7% ± 10.2
Month 15	-4.3% ± 10.6	-2.8% ± 8.9
Month 18	-4.0% ± 10.7	-0.3% ± 9.4
Month 24	-2.8% ± 10.8	+0.1% ± 13.3
Month 30	-3.3% ± 11.4	-1.1% ± 14.0
Month 36	-2.9% ± 11.6	+8.1% ± 16.1
FVC		
Month 1	+2.4% ± 6.1	+11.9% ± 13.1
Month 3	-1.0% ± 8.3	+0.7% ± 8.9
Month 6	-1.0% ± 8.7	+0.9% ± 9.1
Month 12	-1.6% ± 10.3	+0.6% ± 10.8
Month 15	-2.7% ± 10.6	-0.3% ± 9.6
Month 18	-2.3% ± 11.3	-1.0% ± 7.9
Month 24	-1.3% ± 11.2	-0.2% ± 14.0
Month 30	-1.5% ± 10.8	-0.3% ± 14.3
Month 36	-1.0% ± 10.6	+4.7% ± 9.5
FEV1/FVC		
Month 1	0.0% ± 0.0	0.0% ± 0.1
Month 3	0.0% ± 0.1	0.0% ± 0.1
Month 6	0.0% ± 0.1	0.0% ± 0.1
Month 12	0.0% ± 0.1	0.0% ± 0.1
Month 15	0.0% ± 0.1	0.0% ± 0.1
Month 18	0.0% ± 0.1	0.0% ± 0.1
Month 24	0.0% ± 0.1	0.0% ± 0.1
Month 30	0.0% ± 0.1	0.0% ± 0.1
Month 36	0.0% ± 0.1	0.0% ± 0.2
DLCO		
Month 1	-12.4% ± 32.2	-12.0% ± 31.2
Month 3	+2.2% ± 53.4	+6.1% ± 50.3

	Siponimod 2 mg N=1061	**Placebo N=525**
	Percent Change from Baseline ± SD	**Percent Change from Baseline ± SD**
Month 6	-9.3% ± 14.0	+5.0% ± 12.5
Month 12	-1.9% ± 56.8	+12.1% ± 87.3
Month 15	-3.4% ± 38.8	-3.4% ± 12.7
Month 18	-7.5% ± 16.4	+0.4% ± 12.4
Month 24	+1.3% ± 55.7	+2.5% ± 23.4
Month 30	-2.7% ± 33.9	+3.0% ± 33.2
Month 36	-10.2% ± 15.1	+5.4% ± 37.7

Sources: Study A2304 CSR Tables 14.3-5.1.2, 14.3-5.1.3

Reviewer Comment: There were more frequent reports of cough and dyspnea in patients treated with siponimod compared to placebo treated patients. The origin of these TEAEs appears to be related to siponimod-associated persistent reductions in FEV1 and FVC. The reduction in these respiratory parameters is greatest at 15 months of treatment and persist until at least 36 months. Whether these changes are permanent or return to baseline with discontinuation are not clear. On recommendation of the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) consultants, a postmarketing study of these parameters will be requested to study this phenomenon and examine persistence of this airway restriction. Please see consult from DPARP regarding the pulmonary findings associated with siponimod.

Long-term Safety Pool

Respiratory AEs associated with siponimod treatment in the Long-term Safety Pool are summarized in the following table:

Table 96: Reviewer Table, Incidence of Airway Restriction Adverse Events, Long-term Safety Pool, Databases 2 and 4

Preferred Term	Siponimod 2-10 mg* N=1737 n (%)		Siponimod 2-10 mg** N=1737 n (%)	
	n (%)	IR	n (%)	IR
Cough	78 (4.5%)	2.0	72 (4.1%)	1.9
Dyspnea and Exertional Dyspnea	33 (1.9%)	0.8	30 (1.7%)	0.8
Airway Restriction***	20 (1.2%)	0.5	19 (1.1%)	0.5
Asthma	8 (0.5%)	0.2	8 (0.5%)	0.2
Obstructive Airways Disorder	4 (0.2%)	0.1	4 (0.2%)	0.2

Sources: adae.xpt, SCS Appendix 1-Table 2.1-13.2 and 2.1-13.2a

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

***Includes asthma, obstructive airways disorder, wheezing, forced expiratory volume decreased, hyperventilation, hypoxia

120-day Safety Update

The 120-day Safety Update included several new AEs of cough and dyspnea and one additional AE related to airway restriction. The updated summary of AEs is as follows:

Table 97: Reviewer Table, Incidence of Airway Restriction Adverse Events, 120-day Safety Update, Long-term Safety Pool, Databases 2 and 4

Preferred Term	Siponimod 2-10 mg* N=1737 n (%)		Siponimod 2-10 mg** N=1737 n (%)	
	n (%)	IR	n (%)	IR
Cough	84 (4.8%)	1.9	78 (4.5%)	1.8
Dyspnea and Exertional Dyspnea	34 (2.0%)	0.7	31 (1.8%)	0.7
Airway Restriction***	21 (1.2%)	0.5	20 (1.2%)	0.5
Asthma	8 (0.5%)	0.2	8 (0.5%)	0.2
Obstructive Airways Disorder	4 (0.2%)	0.1	4 (0.2%)	0.2

Sources: adae.xpt, 120-day Safety Update Table 2-16

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

** (Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

***Includes asthma, obstructive airways disorder, wheezing, forced expiratory volume decreased, hyperventilation, hypoxia

Reviewer Comment: The long-term safety data confirm that cough and dyspnea are common AEs associated with siponimod treatment and increase in frequency with longer treatment.

8.5.6. Hypertension

Hypertension occurred more frequently in controlled studies with an approved S1P modulator, fingolimod. It is assumed that the effects on blood vessel permeability that result from S1P exposure will yield some degree of elevated blood pressure regardless of how specific the S1P modulator may be.

Controlled Pool

At Month 6 there was a mean increase in systolic BP of +3.01 mmHg in the siponimod 2 mg group and a mean decrease of −0.84 mmHg in the placebo group. At Month 12 the mean increase in systolic BP was +3.73 mmHg in the siponimod 2 mg group and the mean decrease was −0.61 mmHg in the placebo group. After Month 12 through Month 30, the increase in mean systolic BP in the siponimod 2 mg group remained between +2.76 and +4 mmHg. There were small elevations in diastolic BP. At Month 6 there was a mean increase in diastolic BP of +1.27 mmHg in the siponimod 2 mg group and a mean decrease of −0.30 mmHg in the placebo group. At Month 12 the mean increase in diastolic BP in the siponimod 2 mg group was 1.36 mmHg and the mean decrease in the placebo group was −0.78 mmHg. At Month 18 and Month 24 mean increases in diastolic BP in the siponimod 2 mg group were relatively smaller in magnitude (+0.45 mmHg and +0.11 mmHg, respectively).

Notably high (>160 mmHg, or >180 mmHg) systolic BP was seen for a comparable percentage of patients in the siponimod 2 mg and placebo groups. There were more patients with notable high systolic BP >140 mmHg in the siponimod 2 mg group (29.6%) versus the placebo group (24.1%). Notably high (>90, >100 or >110 mmHg) diastolic BP was seen in similar percentages of patients in the siponimod 2 mg (24.5%, 6.8%, 0.9%) and placebo (24.6%, 6.8%, 0.5%) treatment groups.

In the Controlled Pool (Safety Database 1), more patients were noted with the TEAE of hypertension (based on the broadest risk search terms for “hypertension”) in the siponimod 2 mg treatment group (140/1148 patients, 12.2%) than in the placebo treatment group (53/607, 8.7%). Hypertension AE reporting appeared to parallel the blood pressure changes (which were present by six months) with most AEs noted within 3-6 months of initiating treatment. Thereafter frequencies of hypertension AEs in both siponimod and placebo treatment groups declined and there was a trend toward systolic blood pressure elevations becoming smaller in magnitude but without a return to baseline.

Long-term Safety Pool

As observed in the controlled phase, mean SBP increased during the first 12 months of treatment with siponimod 2 mg in the long-term safety pools. After Month 12 through Month 72, the change from baseline in mean SBP in long-term safety database with the longest duration of observation (Safety Database 2) remained stable between +3 and +4.5 mmHg. Increase in mean DBP was +1.28 mmHg at Month 12. From Month 12 to Month 72 the mean increase ranged from +0.41 to +1.83 mmHg.

Notably high (>160 mmHg, or >180 mmHg) systolic BP occurred with a higher frequency than in the controlled pool for patients treated with 2 mg siponimod. There were more patients with notable high systolic BP >140 mmHg in the siponimod 2 mg group (34.2%) versus the controlled pool group (29.6%). Notably high (>90, >100 or >110 mmHg) diastolic BP was seen in higher

percentages of patients in the long-term siponimod 2 mg (31.6%, 8.2%, 1.3%) group versus the controlled pool (24.5%, 6.8%, 0.9%).

Frequency of TEAEs broadly defined for "hypertension" in the long-term pool increased from 12.2% to 12.7% (220/1737 patients). The incidence rate of hypertension in the long-term safety pool of 6.0 per 100PY is lower than the incidence rate in the controlled pool (8.8 per 100PY).

120-day Safety Update

Analysis of data through month 84 demonstrated that the mean systolic blood pressure increased during the first 12 months of treatment with siponimod in the updated long-term safety pools. After Month 12, the change from baseline in mean systolic blood pressure in Safety Database 2 remained stable between +3 and +4.5 mmHg. Increases in mean DBP were small; mean increase of 1.35 mmHg at Month 12. After Month 12, the mean increase remained stable at less than +2 mmHg. There were limited observations available past Month 72 but there appeared to be a trend toward a diminution in the blood pressure increases with increasing duration of exposure. Whereas the frequency of broadly defined hypertension AEs increased to 13.2% (229/1737 patients), the overall incidence rate of hypertension TEAEs declined from the prior calculated value to 5.5 per 100 PY.

> *Reviewer Comment: The observed, sustained, increases in systolic and diastolic blood pressure readings, along with the higher than placebo frequency of hypertension and related TEAEs associated with siponimod during controlled clinical trials, are comparable to those that led to a specific Warning and Precautions statement for hypertension on the labeling of the approved S1P modulator, fingolimod. Hypertension is a known, modifiable risk factor of myocardial infarction and stroke. There are many therapies approved for the treatment of hypertension. A similar Warning and Precautions statement to inform consumers and prescribers of the risk of hypertension associated with siponimod is justified by the findings in the controlled and long-term safety data from the trials submitted in this application.*

8.5.7. Embolic and Thrombotic Events

Controlled Pool

As noted in Sections 8.4.1. and 8.4.2., there was a mismatch between deaths and SAEs due to strokes/transient ischemic attacks, embolic events, and myocardial infarction in siponimod treatment compared with placebo treatment.

The applicant provided a customized NMQ broad search for "thromboembolic events" and identified 34 TEAEs. A customized search performed by this reviewer focusing on cerebral and myocardial thrombotic events captured the same 34 AEs. Within these 34 events in the controlled pool safety database (Safety Database 1), there were seven TEAEs classified as

ischemic cerebrovascular events (two transient ischemic attacks, one embolic stroke, four strokes) and two SAEs of myocardial infarction occurring in patients treated with siponimod. A broader search of the controlled pool safety database for TEAEs consistent with an acute thrombotic event yielded 34 TEAEs for patients in the siponimod 2 mg and placebo treatment groups in the Controlled Pool. There were no TEAEs related to thromboembolic searches in patients treated with 0.25 mg, 0.5 mg, 1.25 mg, or 10 mg siponimod.

The following table summarizes the thrombotic adverse event findings:

Table 98: Applicant Table, Incidence of Treatment Emergent Adverse Events by Broad SMQ, Controlled Pool, Safety Set (Safety Database 1)

Adverse Events	**Siponimod 2 mg N=1148 n (%) Odds Ratio**	**Siponimod All Doses N=1334 n (%) Odds Ratio**	**Placebo N=607 n (%)**
Thromboembolic, custom query (all)†	34 (3.0%) **1.2**	34 (2.6%) **1.0**	15 (2.5%)
Hemorrhagic central nervous system vascular conditions (SMQ) (broad)	3 (0.3%) **0.8**	3 (0.2%) **0.8**	2 (0.3%)
Ischemic central nervous system vascular conditions (SMQ) (broad)	7 (0.6%)	7 (0.5%)	0
Embolic and thrombotic events, arterial (SMQ)	7 (0.6%) **3.7**	7 (0.5%) **3.2**	1 (0.2%)
Ischemic heart disease (SMQ) (broad)	8 (0.7%) **0.8**	8 (0.6%) **0.8**	5 (0.8%)

Sources: adae.xpt, SCS Appendix 1-Table 2.1-13.1.1, SCS Table 2-26

† includes preferred terms: brain injury, dysarthria, hemiparesis, hemiplegia, intracranial aneurysm, monoparesis, paraparesis, cerebrovascular accident, hemorrhagic stroke, putamen hemorrhage, subarachnoid hematoma, subdural hematoma, brainstem infarctions, cerebral ischemia, ischemic stroke, transient ischemic attack, acute myocardial infarction, myocardial infarction, peripheral arterial occlusive disease, acute coronary syndrome, angina pectoris, coronary artery disease, electrocardiogram T wave abnormal, and myocardial ischemia.

The odds ratios for thromboembolic events, hemorrhagic central nervous system events, and ischemic heart disease events, are 1.0 or less, arguing against a systemic higher risk of these events in association with siponimod therapy. There were eight patients (0.7%) in the

siponimod treatment group and five placebo-treated patients (0.8%) identified by the ischemic heart disease-related AEs search. Within this group were two patients in the siponimod 2 mg treatment group and one placebo treatment group patient with SAEs of myocardial infarction or acute coronary syndrome, and coronary artery disease were present in the family or personal histories of these patients.

> *Reviewer Comment: There does not appear to be clear increase in risk for myocardial infarction or hemorrhagic strokes associated with siponimod. One of the cases of hemorrhagic central nervous system events was a subdural hematoma suffered secondary to a fall, and this narrative is included among the falls with serious injuries summarized in Section 8.4.2.*

The central nervous system ischemic and arterial thrombotic events have no correlate in the placebo treatment group and would represent an estimated incidence rate of 2.0 per 100 PY for all events and 0.4 per 100 PY for strokes. Review of the narratives for these events suggests there were risk factors for strokes in most, but not all, cases.

Of the seven patients with ischemic cerebrovascular events, the two patients who experienced transient ischemic attacks had significant risk factors for stroke. One of these patients (Patient (b) (6)) was being treated for longstanding hyperlipidemia. The other patient was taking medroxyprogesterone (which can predispose to stroke) for gynecological reasons, and after the transient ischemic attack, she experienced a deep vein thrombosis leading to discontinuation of therapy, strong evidence of a hypercoagulable state.

<u>Transient Ischemic Attack</u>

1. Patient (b) (6) was a 56-year-old woman diagnosed with multiple sclerosis in (b) (6) with conversion to SPMS in (b) (6). The patient had no prior history of MS therapies before siponimod. The patient had a comorbid diagnosis of depression and hypercholesterolemia. Concomitant medications included sertraline for depressive syndrome, paracetamol for pain due to MS, diclofenac for left heel pain, atorvastatin and pravastatin to control cholesterol levels, alphacaine for broken tooth, acetylleucine for vertigo, fusidate sodium and betamethasone for facial erythema, and loperamide for diarrhea. The patient received the first dose of study medication on Day 1 (b) (6). On Day 400 (b) (6), the patient was hospitalized with a transient ischemic attack which lasted for 20 minutes. The patient experienced transient aphasia and decrease in binocular acuity which lasted for less than one hour. The patient's CT scan was unremarkable. Treatment included acetylsalicylate. The event (transient ischemic attack) was considered resolved on the same day (b) (6). Treatment with the study medication was temporarily interrupted due to the event on Day 401 (b) (6) and the patient was discharged from the hospital. Treatment with study medication was restarted on the following day (b) (6). On Day 404 (b) (6),

doppler ultrasound of neck vessels did not show any remarkable findings or plaques. Blood flow was symmetrical. The patient received the last dose of the study medication on Day 887 (b) (6) and completed the study.

2. Patient (b) (6) was a 47-year-old woman with MS diagnosed in (b) (6) and SPMS in (b) (6) There was no history of other treatments for MS. The patient has depression, tinea versicolor, and metrorrhagia. Concomitant medications included piracetam, citalopram and clonazepam for depression, tolperisone for spasticity of limb and MS, irbesartan for hypertension, pantoprazole and famotidine as gastric ulcer prophylaxis and gastroesophageal reflux disease, and medroxyprogesterone acetate for metrorrhagia. The patient received the first dose of study medication on Day 1 (b) (6). On Day 67 (b) (6), the patient was reported to have experienced a mild transient ischemic attack. The report of this attack was mentioned within a report of an event on Day 604 (deep vein thrombosis) and the original case report form provides no additional detail for the transient ischemic attack event because it was filed retrospectively.

Out of the additional five cases, four patients had significant co-existing risk factors for stroke, specifically, hypertension (Patients (b) (6) and (b) (6)), hyperlipidemia (Patient (b) (6)), diabetes mellitus (Patient (b) (6)), and a patent foramen ovale with atrial septal defect (Patient (b) (6).

Reviewer Comment: The rates of pre-existing hypertension, hyperlipidemia, and diabetes mellitus were balanced between siponimod and placebo treatment. Patent foramen ovale is an uncommonly found risk factor for stroke that would not be expected to be balanced between treatment groups. Therefore, four cases of stroke would remain unbalanced against no placebo patients.

The remaining patient had a stroke associated with two transient ischemic attacks (Patient (b) (6)) beginning on Day 5 of siponimod therapy. There were no blood pressure readings for this patient that were hypertensive, and she had no preexisting medical conditions to raise her risk aside from her age (58 years old) and her diagnosis of MS.[13]

Reviewer Comment: A case of stroke with multiple TIAs during titration of siponimod is very concerning for an exposure associated risk of a significant medical event.

1. (Brainstem stroke) Patient (b) (6) was a 55-year-old man with MS diagnosed in (b) (6) with conversion to SPMS in (b) (6) Prior disease-modifying treatment for MS included interferon beta-1b, which was discontinued in (b) (6) due to an unspecified reason, and interferon beta-1a, which was discontinued on (b) (6), due to lack of efficacy. The patient's medical history included atrial septal defect (b) (6) gout, sinus

bradycardia, fatigue, benign prostatic hyperplasia, post procedural fistula, hyperuricemia, and cyst removal (in (b) (6)). Concomitant medications included enoxaparin sodium for stroke and thrombosis prophylaxis, pantoprazole sodium sesquihydrate as prophylaxis, clopidogrel for stroke prophylaxis, methylprednisolone sodium succinate for MS relapse, citalopram and tamsulosin for MS symptoms, and allopurinol for hyperuricemia. The patient also underwent a spinal laminectomy for disc prolapse and cervical cyst removal. The patient received the first dose of study medication on Day 1 ((b) (6)). On Day 105 ((b) (6)), the patient had dizziness, severe ataxia, and dysarthria and was hospitalized. He was diagnosed with a brain stem infarction. On the same day ((b) (6)), MRI showed no infarction. The study medication was temporarily interrupted due to the event (brain stem infarction) on the same day ((b) (6)). The patient underwent physiotherapy for ataxia and the clinical symptoms of dysarthria improved the next day ((b) (6)). Siponimod was restarted on the same day ((b) (6)). On the same day ((b) (6)), his lumbar puncture revealed oligoclonal bands and extra intracranial ultrasound revealed no atherosclerosis and stenosis. Assuming relapse, the patient started treatment with methylprednisolone. Due to no change in clinical symptoms after start of treatment the patient underwent a repeat MRI on Day 111 ((b) (6)), which confirmed brain stem (pontine) infarction and an electrocardiogram (ECG) showed sinus rhythm without atrial fibrillation. On Day 112 ((b) (6)), transesophageal echocardiography showed patent foramen ovale (PFO) and atrial septal aneurysm. It was reported that, the patient was diagnosed with brain stem infarction due to cardiac embolism. Treatment for the event (brain stem infarction) included acetylsalicylic acid and simvastatin for vessel stabilization and enoxaparin as prophylaxis. The event (brain stem infarction) was considered resolved on the same day ((b) (6)). The patient was discharged from the hospital the next day ((b) (6)). On Day 119 ((b) (6)), he underwent PFO occlusion without complication, atrial septal defect repair for PFO, and was treated with acetylsalicylic acid and clopidogrel. The patient received the last dose of the study medication on Day 128 ((b) (6)). The patient discontinued the study due to patient's/guardian's decision and attended the End of Study visit.

2. (Stroke) Patient (b) (6) was a 52-year-old woman with multiple sclerosis diagnosed in (b) (6) and SPSM diagnosed in (b) (6) Prior disease-modifying treatments for MS included interferon beta 1b, discontinued in (b) (6) and glatiramer acetate, discontinued on (b) (6), both due to lack of efficacy. The patient's medical history included breast cancer (b) (6) hypertension and type 2 diabetes mellitus (both since (b) (6)), back pain, and depression. Concomitant medications included ramipril and nebivolol for hypertension, tilidine-naloxone combination for lumbago, metformin for diabetes mellitus, citalopram for depression, ibuprofen, and fampridine. At screening ((b) (6)), the patient's blood pressure was 144/90 mmHg and heart rate 67 BPM. The patient's baseline body mass index (BMI) was 25.7 (weight: 70 kg, height 165 cm).

The patient's ECG and Holter/MCT findings at screening/baseline were normal. The patient received the first dose of the study medication on Day 1 ([(b) (6)]). On Day 92 ([(b) (6)]) and on Day 182 ([(b) (6)]), during her third month and six-month study visits, patient's glycosylated hemoglobin (HbA1c) and blood triglycerides levels were high. HbA1c were 6.6% and 6.5% respectively (RR: 3.5 to 6%). The blood triglycerides were 2.55 mmol/L and 2.67 mmol/L respectively (RR: 0 to 2.25 mmol/L). On Day 227 ([(b) (6)]), the patient developed temporary right hemiparesis with persistent global aphasia, left side hemiparesis immediately after thrombolytic therapy, and speech impairment. On the same day ([(b) (6)]), the patient was hospitalized with a diagnosis of cerebrovascular accident. The patient had cerebral infarctions in the right medullary layer and the left PICA (posterior inferior cerebellar artery) territory with embolic stroke pattern. On the same day, the patient's contrast cranial CT and CT angiography of the intracranial and extracranial cerebral vessels showed considerable leukoencephalopathy, bilateral thalamic defects, ventrolisthesis of cervical vertebra 3 (CV) and CV 4, and degenerative changes of the cervical spine. On the following day ([(b) (6)]), the patient's ECG showed sinus rhythm with 1st degree AV block, lumbar and cervical spinal syndrome. There was pronounced leukoencephalopathy. On Day 228 ([(b) (6)]) the study medication was temporarily interrupted due to the event (cerebrovascular accident). Motor function examination showed severe right hemiparesis, normal tendon reflexes, and positive right pyramidal signs. On Day 232 ([(b) (6)]), the patient's neurocranial MRI angiography with contrast showed relatively recent infarctions in the right medullary layer and in the left PICA territory, extensive leukoencephalopathy, and multiple foci in the basal ganglia. The pronounced diffusion disorders and the lacking enhancement argue against acute MS foci. On Day 234 ([(b) (6)]), the patient's trans-esophageal echocardiography showed suspected persisting foramen ovale and thrombi in left atrium and left atrial appendage. On Day 235 ([(b) (6)]), the patient's sleep deprivation EEG with hyperventilation showed evidence of right frontotemporal focal lesion obscured by artifact, and towards the end fatigue with signs of reduced vigilance was noted. Treatment included thrombolytic therapy with alteplase solution, acetylsalicylic acid, and simvastatin. The patient was discharged from the hospital on Day 239 ([(b) (6)]) with improved general conditions and slight residual deterioration of gait disorder. The event (cerebrovascular accident) was considered resolved on Day 276 ([(b) (6)]). The study medication restart date was not reported and the day of last dose of study medication was reported as Day 227 ([(b) (6)]). The patient attended the End of Study visit.

3. (Stroke) Patient [(b) (6)]7 was a 57-year-old man diagnosed with MS in [(b) (6)] and SPMS in [(b) (6)]. Prior disease modifying treatment for MS included glatiramer acetate, discontinued in [(b) (6)] due to unspecified reasons. The patient's medical history included malignant melanoma ([(b) (6)]), torticollis, seborrheic keratosis, dermoid cyst, lentigo, melanocytic nevus, photodermatosis, and hypertonic bladder. Concomitant medications

included fluorouracil for actinic keratosis, baclofen for leg stiffness, ibuprofen for tooth pain, solifenacin succinate for overactive bladder, ondansetron for nausea prophylaxis, senna and docusate sodium for constipation prophylaxis, naproxen sodium and paracetamol for generalized pain, cannabis sativa for MS symptoms, acetylsalicylic acid for cardiovascular health, botulinum toxin type a for dystonia, fampridine for MS, bupropion for depression, atorvastatin for high LDL, and lorazepam as sleep aid. The patient received the first dose of study medication on Day 1 ((b) (6)). On Day 188 ((b) (6)), the patient presented with word finding difficulty, right hemifield visual loss, headache, emesis, and was hospitalized. He also experienced fatigue. On the same day, the patient's ECG, CT pulmonary angiogram, and head CT scan showed negative findings and a score of 9 on the National Institutes for Health Stroke Scale. The patient's MRI showed acute left thalamic stroke and was diagnosed with cerebrovascular accident (thalamic infarction). Treatment included acetylsalicylic acid, paracetamol, heparin, and diazepam. No action was taken with the study medication due to the event. The event (cerebrovascular accident) was considered resolved on Day 189 ((b) (6)) and the patient was discharged from the hospital to rehab facility after 1 week. The patient received the last dose of the study medication on Day 579 ((b) (6)) and completed the study.

4. (Stroke) Patient (b) (6) was a 58-year-old woman with MS diagnosed in (b) (6) and SPMS diagnosed in (b) (6) Her medical history included anxiety. At baseline ((b) (6)), the patient's blood pressure was 110/60 mmHg and pulse rate 70 BPM. The patient received the first dose of siponimod on Day 1 ((b) (6)). On Day 5 ((b) (6)), the patient felt sick and experienced symptoms including motor deficit and difficulty in speaking/expressive aphasia. On the same day, the patient was diagnosed with an ischemic stroke which led to hospitalization. The patient was treated with acetylsalicylic acid, betahistine, and pramiracet. Treatment with study medication was permanently discontinued due the event (ischemic stroke) and the patient received the last dose on (b) (6)). The patient was discharged from the hospital on Day 8 ((b) (6)). The ischemic stroke was considered resolved on Day 382 ((b) (6)). The patient discontinued the study due to adverse event (ischemic stroke) and attended the End of Study visit.

5. (Stroke) Patient (b) (6) was a 59-year-old woman with multiple sclerosis diagnosed in (b) (6) and SPMS diagnosed in (b) (6). Prior disease-modifying treatment for MS included human normal immunoglobulin, which was discontinued on in (b) (6) due to lack of efficacy. The patient's medical history included appendicectomy ((b) (6)) and arterial hypertension (diagnosed in (b) (6)). Concomitant medications included enalapril maleate-hydrochlorothiazide, rilmenidine, doxazosin, and atenolol-chlorthalidone for arterial hypertension, diclofenac and tramadol for right coxalgia, valaciclovir as herpes prophylaxis, tizanidine, baclofen, and amantadine sulfate for MS, multivitamin

supplement, and potassium chloride for potassium deficiency. At baseline ([(b) (6)]), the patient's SBP/DBP was 150/96 mmHg, 150/95 mmHg, and 147/92 mmHg. The patient received the first dose of study medication (placebo) on Day 1 ([(b) (6)]). Due to disease progression, the patient began open-label treatment with siponimod on Day 545 ([(b) (6)]). On Day 573 ([(b) (6)]), the patient's SBP/DBP was 171/93 mmHg, 170/92 mmHg, and 169/90 mmHg. On Day 578 ([(b) (6)]), the patient was hospitalized due to a cerebrovascular accident (stroke with aphasia). Echocardiography showed mild sclerosis of aortic valve and mitral valve, and sonography of extracranial arteries showed flat, fibrous bifurcation plaques. On the same day, the patient underwent lysis therapy. The patient was treated with doxazosin, acetylsalicylic acid, and atorvastatin calcium. The event (cerebrovascular accident) was considered resolved on Day 580 ([(b) (6)]) and the patient was discharged from the hospital on the next day ([(b) (6)]). On Day 600 ([(b) (6)]), the patient experienced a transient ischemic attack and was hospitalized. The patient was treated with clopidogrel. The event (transient ischemic attack) was considered resolved on the same day ([(b) (6)]). On Day 701 ([(b) (6)]), patient experienced a second transient ischemic attack, which was considered resolved the same day. No treatment was reported for this event. Treatment with the study medication was permanently discontinued due to the transient ischemic attack. The patient received the last dose of open-label siponimod treatment on [(b) (6)]. The patient discontinued the study due to transient ischemic attack and attended the End of Study visit.

Peripheral Vascular Events

For the sake of completeness, there were a total of three non-serious TEAEs (two grade 1 events and one event grade 2) of peripheral vascular events ("arteriopathy obliterans" of lower limbs, obliterative atherosclerosis of unknown site, and arterial insufficiency both feet) reported in three patients (PIDs [(b) (6)], respectively) randomized to siponimod. Two patients received treatment (acetylsalicylic acid in one and unspecified medication in the other) and none in the third reported case, and no action was taken with the study drug for these events. No cases were reported in placebo-treated patients.

Reviewer Comment: There was one case without traditional risk factors that appeared to associate a thromboembolic event directly to siponimod therapy. The MS diagnosis would have elevated her risk above that of the healthy population, but the fact that the event occurred within 5 days of starting siponimod therapy creates a temporal coincidence. It is possible that the rise in blood pressure associated with initiating siponimod therapy (see Section 8.4.7.) may cause an unavoidable (but in most cases transient) risk of thromboembolic events in a subset of patients who otherwise do not have predisposing factors such as hyperlipidemia, hypertension, or diabetes mellitus. These events, when considered together and patient risk factors are accounted for, do

not change this reviewer's risk-benefit assessment of siponimod. The peripheral vascular events were mild and mitigated with appropriate treatments and do not change the risk-benefit assessment for siponimod. On the current labeling for the approved S1P modulator, fingolimod, there is a Section 6 comment regarding ischemic strokes and peripheral vascular occlusive disease reported during premarketing clinical trials without an establishment of causal relationship. A similar labeling warning for siponimod would be appropriate given the uncertainty of the relationship between the events discussed herein and siponimod.

Long-term Safety Pool

In the long-term safety pool (broad), TEAEs categorized as "embolic and thrombotic events" by Standardized MedDRA Query were reported in 62 (3.6%) siponimod 2 mg and 10 mg patients (IR=1.5-1.6 per 100 PY) with 28 additional cases to those included in the 2 mg group of the controlled pool. This incidence rate would represent a reduction from that observed in the controlled pool for all embolic and thrombotic events (IR=2.0 per 100 PY).

There were five new cases of related to ischemic cerebrovascular conditions compared to the controlled pool that were added from the A2304 extension study. Of the five new cases, three cases (two patients with transient ischemic attacks and one patient with a lacunar infarct) had significant underlying risk factors: hyperlipidemia (all cases), hypertension (all cases), coronary artery disease (one case), and smoking (one case). A fourth patient with longstanding history of hypertension experienced a stroke approximately four weeks after switching from off placebo to siponimod in the open label extension trial. The patient subsequently had two further episodes of TIA leading to permanent discontinuation of siponimod. In the other case (a patient who had been randomized to placebo in the double-blind period), a carotid artery occlusion was noted during screening prior to the patient receiving siponimod that was subsequently deemed to be the etiology of the patient's stroke.

Table 99: Incidence of Treatment Emergent Adverse Events by Broad SMQ, Long-term Safety Pool, Safety Set (Safety Databases 2 and 4)

Adverse Events	Siponimod 2-10 mg* N=1737		Siponimod 2-10 mg** N=1737	
	n (%*)	Incidence Rate/100 PY	n (%*)	Incidence Rate/100 PY
Embolic and thrombotic events custom query (all)	62 (3.6%)	1.5	61 (3.5%)	1.6
Hemorrhagic central nervous system vascular conditions (SMQ) (broad)	9 (0.5%)	0.2	9 (0.5%)	0.2
Ischemic central nervous system vascular conditions (SMQ) (broad)	12 (0.7%)	0.3	12 (0.7%)	0.3
Embolic and thrombotic events, arterial (SMQ)	13 (0.7%)	0.3	13 (0.7%)	0.3
Ischemic heart disease (SMQ) (broad)	18 (1.0%)	0.4	18 (1.0%)	0.5

Sources: adae.xpt, SCS Appendix 1-Table 2.1-13.2, Table 2.1-13.2a, SCS Table 2-27

*(Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

**(Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability)

120-day Safety Update

The safety update provided by the applicant added eight new patients with new events. There were three patients with hemorrhagic central nervous system conditions, two patients with ischemic strokes, one patient with a retinal thrombus, one patient with a myocardial infarction, and one patient with an arterial embolus.

The two new ischemic strokes reported were confounded by concurrent risk factors. Patient (b) (6) who had longstanding hypertension experienced a stroke associated with dehydration in the setting of a worsening pneumonia. The second new stroke was a lacunar stroke reported in a patient with history of atrial fibrillation.

Table 100: Incidence of Treatment Emergent Adverse Events by Broad SMQ, 120-Day Safety Update, Safety Set (Safety Databases 2 and 4)

Adverse Events	Siponimod 2-10 mg* N=1737		Siponimod 2-10 mg** N=1737	
	n (%*)	Incidence Rate/100 PY	n (%*)	Incidence Rate/100 PY
Embolic and thrombotic events custom query (all)	68 (3.9%)	1.5	67 (3.9%)	1.5
Hemorrhagic central nervous system vascular conditions (SMQ) (broad)	12 (0.7%)	0.3	12 (0.7%)	0.2
Ischemic central nervous system vascular conditions (SMQ) (broad)	16 (0.9%)	0.3	16 (0.9%)	0.3
Embolic and thrombotic events, arterial (SMQ)	15 (0.9%)	0.3	15 (0.9%)	0.3
Ischemic heart disease (SMQ) (broad)	19 (1.1%)	0.4	19 (1.1%)	0.4

Sources: adae.xpt, 120-day Safety Update SCS Appendix 1-Tables 2.1-13.2 and 2.1-13.2a

*(Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

**(Safety Database 4) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability)

> *Reviewer Comment: The additional events in the long-term safety pool suggests a risk thromboembolic events in patients exposed to siponimod that cannot be totally accounted for by concurrent confounding risk factors. Labeling should describe these risks in the clinical trials.*

8.5.8. Seizures

Controlled Pool

As noted in Section 8.4.2, the most frequent SAEs associated with siponimod treatment in the controlled pool were seizures and related terms (10 patients, 0.9%); there were no patients in the placebo treated group with SAEs of seizure or related terms.

One patient in the siponimod treatment group discontinued siponimod because of a seizure; this patient notably had concomitant treatment with fampridine which can increase risk of seizures. No placebo treatment patients discontinued therapy due to seizures.

There was a single death in a patient with seizures in the setting of longstanding epilepsy with repeated head trauma due to post-ictal loss of tone leading to several falls (discussed in Section 8.4.1.)

At enrollment, epilepsy was noted in the medical histories of 16/1148 (1.4%) of patients in the siponimod 2 mg treatment group and in 7/607 (1.2%) of patients in the placebo treatment group.

The applicant provided a SMQ search term analysis to investigate TEAEs like seizure and related terms that I was able to confirm in a search of the controlled pool safety database.

There were 19 patients (1.7%) who experienced seizures (or an event related to seizures or epilepsy) in the siponimod 2 mg treatment group. There was an additional case of a patient with a seizure in the 0.25 mg treatment group.

Table 101: Incidence of Treatment Emergent Adverse Events of Seizures, Controlled Pool, Safety Set (Safety Database 1)

	Siponimod 0.25 mg N=51 n (%) [Odds Ratio]	**Siponimod 2 mg N=1148 n (%) [Odds Ratio]**	**Siponimod All Doses N=1334 n (%) [Odds Ratio]**	**Placebo N=607 n (%)**
Seizures (Convulsions SMQ, broad)	1 (2.0%) **[4.0]**	19 (1.7%) **[3.4]**	20 (1.5%) **[3.0]**	3 (0.5%)
Epilepsy (PT)	0	10 (0.9%) **[2.7]**	10 (0.8%) **[2.5]**	2 (0.3%)
Seizure (PT)	1 (2.0%) **[11.9]**	5 (0.4%) **[2.7]**	6 (0.5%) **[2.2]**	1 (0.2%)
Partial Seizures (PT)	0	3 (0.3%)	3 (0.2%)	0
Generalized Tonic-Conic Seizure (PT)	0	2 (0.2%)	2 (0.2%)	0
Myoclonic Epilepsy (PT)	0	1 (0.1%)	1 (0.1%)	0

Sources: adae.xpt, SCS Appendix 1-Table2.1-13.1.1

There are two TEAEs (reported in Patients (b) (6) and (b) (6)) represented in the table above that were later re-coded as “leg cramps.”

> *Reviewer Comment: This reviewer is very skeptical of the re-coding of these two events. There is an obvious visual difference between a seizure and leg cramps. The difference between these phenomena is sufficiently large to provide reasonable doubt that a trained medical professional would confuse these two clinically distinct events in two separate patients. The provided clinical reports do not provide sufficient detail to support a clear justification for the re-coding of these events as "leg cramps." The inclusion of these patients would not change this reviewer's conclusions regarding a possible association of siponimod with seizures.*

Excluding the two patients whose seizures were apparently leg cramps, in the 17 patients receiving siponimod 2 mg with reported seizures and related events there were six patients who had a history of epilepsy reported in their medical histories and confirmed by prophylactic treatment with anticonvulsants, prior to commencing siponimod. A history of epilepsy could be an obvious confounding diagnosis for seizures, but it should be noted that the number of patients with histories of epilepsy at enrollment were balanced between the siponimod (16 patients, 1.4%) and placebo treatment (7 patients, 1.2%) groups, and, thus, given this pre-exposure balance, it is quite concerning that more patients experienced seizures in the siponimod treatment group than in the placebo condition.

> *Reviewer Comment: Two cases out of the remaining twelve cases are incorrectly coded. A patient experienced a TEAE of "epilepsy" reported two days following a stroke. The stroke provided a plausible etiology and timing for the reported seizure which was almost certainly a provoked ictal event and direct consequence of the stroke and thus not an "epileptic" event which, by definition, requires the cause to be idiopathic. Upon review of the report for the TEAE coded as "myoclonic epilepsy," this event appears to be miscoded because the incident was described as nocturnal ballistic movements in a patient with a history of restless leg syndrome in a patient without other convincing history of myoclonic epilepsy events.*

Thus, excluding the two cases with apparent miscoding, there are nine patients (9/1334) who experienced their first seizures while receiving any siponimod treatment (0.7%, Odds Ratio=1.4 overall vs. the placebo treatment group.) If we add back the two patients with recoding of their events as leg cramps, the frequency would rise to nearly 0.8% and the Odds Ratio would rise to 1.6 vs. placebo treatment.

Less than half of the new onsets of seizures in these nine patients occurred within the first six months of treatment with siponimod. First seizures in non-epileptic patients occurred between Days 44 and 899 of treatment relative to initiation of siponimod. The distribution of events was as follows:

1-3 months: n=2

3-6 months: n=2
6-30 months: n=5

These nine patients with new diagnosis of epilepsy during siponimod treatment continued in study with no further seizures reported. Seven of these patients were treated with an anticonvulsant.

> *Reviewer Comment: Epilepsy is twice more common in the worldwide population of patients with MS than healthy peers,[14] and seizures in patients with MS may have an incidence of over 5% or higher over a patient's lifespan.[15] The risk of a patient with MS being diagnosed with epilepsy increases with longer durations of MS.[14,15] There were no gross imbalance between siponimod (1.4%) and placebo (1.2%) treatment groups with respect to patients who were enrolled with a pre-treatment diagnosis of epilepsy or seizures, and the ultimate difference in frequencies between groups, 0.2% matches the baseline imbalance between the two treatment groups. Furthermore, it is surprisingly nevertheless that the epilepsy incidence and prevalence reported in the literature (up to 5%, and up to 7%, respectively)[9,14,15] are 5-fold higher than the enrollment baseline rates in both treatment groups (1.4% and 1.2%, respectively) and ten-fold more frequent than the observed frequencies of epilepsy in either treatment group. This disconnect between the reported and observed rates of epilepsy is recapitulated in other clinical trial databases of patients with MS, suggesting that either the published population rates of epilepsy are exaggerated or that the clinical trial population is not reflective of the general MS population with respect to epilepsy risk. Regardless, there is a mismatch with an Odds Ratio of approximately 2.0 favoring an association of siponimod with seizures. There is no clear mechanism for siponimod to promote seizure activity; S1P receptors are not known to be involved in epileptic kindling or seizure propagation. In fact, some reports suggest S1P modulation may prevent seizures in animal models of epilepsy.[16,17] Half of the patients who experienced seizures in the siponimod group had a history of epilepsy, some notably refractory to treatment. Seizures are a stochastic event and the observed mismatch could be a statistical anomaly. Regardless of the data in this trial, seizures/epilepsy are common complications of MS. The applicant proposes labeling for fingolimod describes a possible association of seizure with similar event rates and on review similar concerns were raised with this other S1P modulator. This reviewer agrees with the applicant's labeling recommendation to report the seizure frequencies in the siponimod and placebo treatment groups within the description of the clinical trials experience. There is insufficient data presently to ascertain whether siponimod or S1P modulators in general are associated with epilepsy and disentangling this issue in the postmarketing setting would require a rigorous, longitudinal commitment by multiple applicants to determine whether a given treatment is associated with an increase or whether the demographics of epilepsy in MS that are published are not representative of the clinical trial populations.*

Long-term Safety Pool

In long-term safety pool, analysis of Safety Databases 2 and 4 revealed that seizures were reported in 35 (2.0%) of patients treated with siponimod 2 mg, an addition of 16 cases compared to the treatment group with seizures in the controlled pool.

The long-term safety pool frequency of 2.0% is an increase from the 1.7% in the controlled pool. This increase was unique to seizures. Other SAEs in Nervous System Disorders SOC such as multiple sclerosis relapses remained stable at similar frequencies in the long-term safety pool. However, the incidence rate of seizures declined from 1.1/100 PY in the controlled pool to 0.9/100 PY in the long-term safety pool.

Eight of the additional sixteen patients with seizures had no prior history of epilepsy or seizures. The range in time to onset for the events in the additional 16 cases was 24 to 1097 days after initiation of siponimod.

> *Reviewer Comment: The frequency and incidence rates of seizure still do not match reportedly higher rates of 5% or greater in the patient population with MS. The lack of alignment in frequencies between clinical trials and population research is puzzling. The time to onset appears increasingly less convincingly linked to initiation of siponimod therapy.*

120-day Safety Update

The updated long-term safety pool included an additional seven patients with seizures and related phenomena. The frequency of seizures in the long-term safety pool rose from 2.0% to 2.4% (42 patients/1737 patients). The incidence rate for seizures in the long-term safety pool remained 0.9/100 PY.

Several of these additional cases had unusual confounding factors. One case was reported as multiple hospitalizations with seizures and status epilepticus in a patient with a new diagnosis of mitochondrial epileptic encephalopathy due to a *POLG1* mutation. One patient had a seizure coincident with a serious head injury causing a subdural hemorrhage, a provoked, non-epileptic seizure. A case was recoded as “muscle spasm” after an original coding as “toe seizure.”

Two of the seven new cases of seizure occurred in patients with no prior history of epilepsy. The range of exposure durations from initiation of siponimod therapy in these seven new cases was 21 to 29 months.

> *Reviewer Comment: Epilepsy occurs in patients with MS likely because of the repeated inflammatory injury adjacent to and within regions that can be kindled. The relative lack of epileptic events in the placebo group in controlled studies suggests an association between*

siponimod exposure and seizures, and the continued rise in epilepsy frequency in the long-term safety pool affirms the possible relationship. Still, despite a slow rise in frequency, the lack a biologically plausible mechanism, the absence of a clear temporal relationship to treatment initiation, and the fact that the observed frequency of seizures remains less than half the predicted rates based on what is reported in the general MS population creates uncertainty about the strength and magnitude of the association between siponimod and seizures. It is noteworthy that in the Agency's review of clinical safety for the approved S1P modulator fingolimod that there was a similar frequency of seizures in fingolimod-treated patients that was higher than placebo-treated patients but lacking a clear temporal association with treatment start that invited speculation by the reviewer and the applicant about a potential relationship. I would advocate that labeling for siponimod adopt the same approach as with fingolimod, reporting of the data without an explicit endorsement of a potential association.

8.5.9. **Suicidality**

Controlled Pool

Depression and suicide are always a concern with drug development. The applicant performed a review of preferred terms related to suicide and the results were largely confirmed by this reviewer's customized search. The incidence of TEAEs in the category of "suicidality" (based on a customized search) was 8.3% in siponimod treatment group (with an Odds Ratio relative of 1.0 vs. placebo) and 8.7% in placebo treatment group. A higher rate of the TEAE of depression in the placebo group explained the overall higher frequency for suicidality in placebo-treated patients. The incidence rate for suicidality terms (defined by SMQ) was 1.5/100 PY.

There was a single suicidal death in the database in a 55-year-old man with a history of depression and recent initiation of a depression treatment associated with increase suicide risk; this case is discussed in Section 8.4.1. There were no suicidality related events in the 10 mg siponimod treatment group and so this group is not depicted on the table below.

Table 102: Frequency of Treatment Emergent Adverse Events of Suicidality (≥5 patients in any treatment group), Controlled Pool, Safety Set (Safety Database 1)

Risk name Preferred term	Siponimod 0.25 mg N=51 n (%) [Odds Ratio]	Siponimod 0.5 mg N=43 n (%) [Odds Ratio]	Siponimod 1.25 mg N=42 n (%) [Odds Ratio]	Siponimod 2 mg N=1148 n (%) [Odds Ratio]	Siponimod Any Dose N=1334 n (%) [Odds Ratio]	Placebo N=607 n (%)
Suicidality (custom)*	3 (5.9%) **[0.7]**	1 (2.3%) **[0.2]**	2 (4.8%) **[0.5]**	96 (8.3%) **[1.0]**	102 (7.6%) **[0.9]**	53 (8.7%)
Depression (PT)	3 (5.9%) **[1.1]**	0	1 (2.4%) **[0.4]**	51 (4.4%) **[0.8]**	55 (4.1%) **[0.8]**	32 (5.3%)
Depressed mood (PT)	0	0	0	15 (1.3%) **[1.1]**	15 (1.1%) **[0.9]**	7 (1.2%)
Suicide attempt (PT) and suicidal behavior (PT)	0	0	0	9 (0.8%) **[1.6]**	9 (0.7%) **[1.4]**	3 (0.5%)
Suicidal ideation	0	0	0	5 (0.4%) **[2.7]**	5 (0.3%) **[1.5]**	1 (0.2%)
Columbia suicide severity rating scale abnormal (PT)	0	0	0	1 (0.1%)	1 (0.1%)	0

Source: adae.xpt, SCS Appendix 1 Table 2.1-9.1.1b

*includes preferred terms in Suicide/Self-injury SMQ and addition of Columbia suicide severity rating scale abnormal.

Reviewer Comment: While the overall rate of suicide-associated TEAEs is balanced between the siponimod and placebo treatment groups, suicidal ideation, occurred significantly more often (Odds Ratio=2.7) in patients in the 2 mg siponimod treatment group than placebo. As evidenced by the combination of suicide attempt and suicidal behavior, there was a mismatch between patients attempting suicide favoring siponimod. A custom search for overdose and completing suicide in a custom search (four siponimod-treated vs. no placebo-treated patients). Depression is more frequently reported in the placebo treatment group and does not provide an explanation for the mismatch in suicidal ideation in the siponimod-treatment group. There are confounding factors in interpreting the increased suicide behavior risk. The number of events reported in all treatment groups is small. Placebo treatment group patients reported suicidal ideation and behaviors at a lower rate that predicted in the MS population, where estimates of suicidal thoughts may be prevalent in 22-29% of patients and suicide rates may be 7.5x greater in patients with MS as compared with the general population.[18] It is also notable that the patient attempting overdose in Study A2201 had a history of anxiety and depression that predated siponimod,

and experienced exacerbation of anxiety with siponimod initiation (this case is included below.) The case of a completed suicide, discussed in Section 8.4.1., had significant confounding features including depression and recent initiation of a SSRI. A role for siponimod cannot be ruled out completely, however.

Intentional Overdose

Patient (b) (6) was a 39-year-old man with relapsing remitting multiple sclerosis was enrolled in study CBAF312A2201. The patient entered the core phase of the study on (b) (6) and received the first dose of study medication on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6). The patient had 2 relapses in the last two years prior to randomization and 1 relapse in the year prior to randomization. His last relapse prior to randomization was on (b) (6). The patient did not receive any treatment for MS relapse. At baseline, his EDSS score was 3.0. The patient's medical history included deafness in the right ear since birth since (b) (6), chicken pox in (b) (6) reactive depression since (b) (6) treated with citalopram and quetiapine fumarate and underwent psychotherapy, pollakiuria since (b) (6) treated with trospium and oxybutynin, baker cyst since (b) (6), and melanocytic nevus (benign mole) since (b) (6). The patient did not have a history of diabetes mellitus or evidence of retinopathy prior to study start. At the time of screening the patient was not an active smoker. The patient did not have a history of liver disease or risk factors for liver disease. During the study, the patient received corticosteroid treatment for MS relapses from (b) (6) to (b) (6). On Day 2 until Day 20, the patient complained of mild dyspnea at night, occurring at rest. The patient reported that he was anxious on these days; the investigator commented that psychosomatic dyspnea seemed a possible diagnosis. No action was taken with the study medication due to this event. On Day 20, the patient took 41 tablets of study medication (intentional overdose) in an attempted suicide and then at about four hours after ingestion drove himself to the hospital. The patient received charcoal and was monitored. He did not experience bradycardia or dyspnea. He was transferred to a psychiatric ward. The study medication was permanently discontinued due to the event (intentional overdose) on the same day (Day 20). Laboratory exams on Day 20 revealed an increase of transaminases (ALT at 90 U/l, AST at 52 U/l) and a normal white blood count ($7.26x10^9$ /L). On Day 25, during hospitalization, the patient was diagnosed with hypothyroidism. No treatment was given for these events. The patient was discharged from the hospital on Day 30 and his treatment with quetiapine commenced on Day 38 (b) (6). The patient completely recovered from the suicide attempt on Day 41 (b) (6). The repeat LFTs on Day 37 showed a further increase in the ALT to 137 U/L (>2XULN) and AST to 66 U/L, which then decreased on Day 128: ALT to 87 U/L and AST to 50 U/L. On Day 38, the patient's pulmonary function tests (PFTs), i.e. the FEV1 and the FVC were noted to be less than 80% of the baseline predicted value. FEV1 was 71% and FVC was 59% of the baseline predicted values. The PFTs improved to greater than 80% of the predicted baseline values in the subsequent visits. On Day 38, the patient's visual acuity (VA) in the right and left eye was assessed as 1.00 versus a baseline value of 1.20 assessed on (b) (6). The patient prematurely discontinued

the study due to the event (intentional overdose, [suicide attempt]), and received the last dose of study medication on Day 20 (b) (6). The patient did not enter the extension phase of the study.

Long-term Safety Pool

In the long-term safety pool, the incidence rate for suicidality terms (as defined by SMQ) was reduced (4.3 per 100 PY) relative to what had been observed in the controlled pool (5.7 per 100 PY), a change driven by the larger number of total events in this pool than by a change in underlying frequency of suicide-related events. Suicidality events in the long-term safety pool are summarized in the following table:

Table 103: Frequency of Treatment Emergent Adverse Events of Suicidality (≥5 patients in any treatment group), Long-term Safety Pool, Safety Set (Safety Databases 2 and 4)

Search Term Preferred Term	Siponimod 2-10 mg* N=1737		Siponimod 2-10 mg** N=1737	
	n (%)	Incidence Rate/100 PY	n (%)	Incidence Rate/100 PY
Suicidality (NMQ)	164 (9.4%)	4.3	157 (9.0%)	4.3
Depression (PT)	98 (5.6%)	2.5	91 (5.2%)	2.4
Depressed mood (PT)	21 (1.2%)	0.5	21 (1.2%)	0.5
Suicidal ideation (PT) and Columbia suicide severity rating scale abnormal (PT)	10 (0.6%)	0.2	10 (0.6%)	0.3
Suicide attempt and Suicidal behavior (PT)	9 (0.5%)	0.2	9 (0.5%)	0.3

Source: 120-day Update SCS Appendix 1, Table 2.1-13.2

* Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.
**Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability)

Reviewer Comment: The frequencies of suicide-related TEAEs in the long-term safety pool were largely consistent with the controlled pool. Notable differences include depression increased in frequency 4.4% to 5.6%, but depressed mood remained

unchanged. The previously identified potential concerns about suicidal ideation and behavior appear to remain relevant for long-term therapy.

120 Day Safety Update

The 120-safety update provided 18 new "suicidality" search-related events summarized in the following table:

Search Term Preferred Term	**Siponimod 2-10 mg* N=1737**		**Siponimod 2-10 mg** N=1737**	
	n (%)	**Incidence Rate/100 PY**	**n (%)**	**Incidence Rate/100 PY**
Suicidality (NMQ)	182 (10.5%)	4.2	175 (10.1%)	4.2
Depression (PT)	110 (6.6%)	2.4	103 (5.2%)	2.4
Depressed mood (PT)	22 (1.3%)	0.5	22 (1.3%)	0.5
Suicidal ideation (PT) and Columbia suicide severity rating scale abnormal (PT)	10 (0.6%)	0.2	10 (0.6%)	0.3
Suicide attempt and Suicidal behavior (PT)	12 (0.7%)	0.2	12 (0.7%)	0.3

Source: 120-day SCS Table 2.1-1.2

* Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.
**Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability)

Reviewer Comment: These additional events suggest a potential risk of suicidal thinking and behaviors in siponimod-treated patients, but the frequencies observed in the controlled and long-term pools for suicide-related issues such as depression and suicidal ideation are markedly less than the estimates in the population with MS which may be as high as 30% for these phenomena.[19] Any suggestion of a relationship between siponimod, suicidal ideation, and suicidal behavior relies on few events and lacks a clear relationship to treatment that outstrips the general risk of the population with MS. While labeling for other therapies used in MS has warnings for depression, there does not appear to sufficient evidence in this therapy to warrant a similar warning.

8.5.10. Liver Injury

Please refer to Section 8.4.6. for discussion of the liver transaminase changes associated with siponimod therapy and for recommendations regarding labeling.

8.5.11. Cholesterol

Please refer to Section 8.4.6. for discussion of changes in serum total cholesterol associated with siponimod therapy and recommendations regarding labeling.

8.6. Safety Analyses by Demographic Subgroups

A comparison of findings in controlled, long-term safety, and 120-safety update data for demographic subgroups revealed similar findings to the analysis of the entire population. Some subgroup populations in the controlled pool were small and represented very few patients' data. Therefore, in most cases, the updated, long-term database findings will be presented and discussed to ensure any summary conclusions are based upon the broadest dose exposure and longest durations of study for all exposed patients.

The applicant's analyses did not provide comparator groups and so it is not possible to determine if any observed risk differences are due to the demographic factor alone or due to treatment effects that vary by the demographic factor.

8.6.1. Duration of Exposure: Gender and Age

In the long-term safety pool (Safety Database 2), the overall mean durations of exposure to siponimod were 32.32 months for men and 31.66 months for women.

In the long-term safety pool, the mean duration of exposure to siponimod was comparable between males and females in the age groups of 31 to 45 years, 46 to 55 years and >55 years of age. Mean duration of exposure to siponimod was higher in males than females in the 18 to 30 years age group, but the number of total patients in this age group was small. It is unusual to have patients with SPMS diagnosed before age 35 years, because SPMS is not typically diagnosed until more than a decade after an initial diagnosis of RMS that typically occurs in the second or third decade of life.[20] Thus, patients with SPMS will be, on average, in their late thirties to mid-forties. It is therefore notable that there were 281/677 (41.5%) men and 444/1060 (41.9%) women < 45 years old in this safety database because that means over 40% of patients with MS in these studies were younger and earlier in the anticipated disability progression based on what is known and published from natural history studies than would be predicted for a typical SPMS population.[20]

This table summarizes the exposure by gender in the broadest safety database with the longest duration of exposure, Safety Database 2:

Table 104: Duration of Exposure by Age Group and Gender, Long-term Safety Pool, Safety Set (Safety Database 2)

	Men		Women	
	n	Mean Duration of Siponimod Exposure (months)	n	Mean Duration of Siponimod Exposure (months)
Ages	677	32.32	1060	31.66
18-30 years	27	41.83	64	36.91
31-45 years	254	33.08	380	35.19
46-55 years	290	31.52	429	29.86
>55 years	106	30.26	187	26.82

Source: 120-day Safety Update SCS Appendix 1-Table 1.2-2.2

8.6.2. Duration of Exposure: Race

In Safety Database 2, mean exposure for white patients was longest in duration whereas for patients identified as Asian (n=43) and Black/African American (n=11) had siponimod exposure durations that were shorter. In the long-term safety pool, the mean exposure to siponimod was 32.21 months, 26.73 months and 26.92 months for the White, Asian and Black/African American subgroups, respectively.

> *Reviewer Comment: The small numbers of Asian and Black/African American patients is a reflection of the established demographics of MS, a disease overwhelming diagnosed in white patients with significantly lower worldwide prevalence in Asian and Black patients by comparison.[21] The small numbers of minority patients with MS included in any MS development program are unavoidable and should provide caution regarding broad generalization of all study findings to minority patients.*

8.6.3. Duration of Exposure: CYP2C9 genotype

CYP2C9 is the major metabolizing enzyme of siponimod and exists in the population in isoforms that differ in processing capabilities based on genotype. Out of 1737 patients, 1475 (84.9%) had *1/*1, *1/*2, or *2/*2 genotypes (so-called, “extensive metabolizers”). Mean exposure to the siponimod in Safety Database 2 was 32.14 months and 31.14 months for the extensive

metabolizer (*1/*1, *1/*2, *2/*2) and "poor metabolizer" (*1/*3, *2/*3) subgroups, respectively. The applicant recommends siponimod be contraindicated for *3/*3 genotype patients due to their inability to process siponimod; the *3/*3 genotype was not studied in large numbers nor with any depth.

> *Reviewer Comment: Most white patients worldwide have the *1/*1, *1/*2, or *2/*2 genotypes,[21] an observation reflected in the clinical trial genotype data. The comparable durations of exposures between these groups are sufficiently close to provide meaningful conclusions, however. This reviewer agrees with the contraindication for *3/*3 genotype patients because of the manifold risks of their profound lack of metabolization of siponimod.*

8.6.4. **Adverse Events: Gender**

Considering all patients exposed to siponimod, the proportion of patients with at least one AE was 91.1% and 92.0% for male and female patients, respectively. In the siponimod 2 mg group during controlled trial phases, the exposure adjusted incidence rate (expressed per 100 patient-years) for patients with any AE was higher for women (277.0) than for men (229.3) whereas in placebo treatment groups, the incidence rate was not as disparate between men (184.3) and women (181.3).

In the long-term safety database, the percentage of patients with an AE was similar in both genders for most SOCs. The largest differences in percentage of AEs between male and female patients existed in the following SOCs: Nervous System Disorders (36.2%, 46.4%, respectively) with headache (12.1%, 18.9%) and dizziness (6.1%, 9.7%) being the most common listed preferred terms; Musculoskeletal and Connective Tissue Disorders (26.3%, 33.7%) with back pain (6.8%, 10.0%) the most common preferred term; Gastrointestinal Disorders (23.5%, 31.2%) with nausea showing the most striking discrepancy (4.1%, 9.5%) between genders.

While most AEs were comparable between genders, differences of ≥ 5% in the percentage of male and female patients with AEs were observed for the following PTs in Safety Database 2: bradycardia (7.7%, 2.7%), nausea (4.1%, 9.5%), urinary tract infection (11.7%, 19.4%) GGT increased (8.6%, 3.5%) and headache (12.1%, 18.9%). Alanine aminotransferase increased was reported in 8.9% of male and 4.2% of female patients.

Table 105: Incidence of Adverse Events in Men and Women Exposed to Siponimod, Long-term Safety Set (Safety Database 2)

	Siponimod 2-10 mg* All Males N=677	Siponimod 2-10 mg* All Females N=1060
Number of Patients with at Least One AE	617 (91.1%)	975 (92.0%)
Blood and Lymphatic System Disorders	59 (8.7%)	146 (13.8%)
Lymphopenia	49 (7.2%)	90 (8.5%)
Cardiac Disorders	121 (17.9%)	129 (12.2%)
Bradycardia	52 (7.7%)	29 (2.7%)
Eye Disorders	90 (13.3%)	136 (12.8%)
Gastrointestinal Disorders	159 (23.5%)	331 (31.2%)
Diarrhea	40 (5.9%)	77 (7.3%)
Constipation	31 (4.6%)	45 (4.2%)
Nausea	28 (4.1%)	101 (9.5%)
General Disorders & Administration Site Conditions	172 (25.4%)	317 (29.9%)
Fatigue	61 (9.0%)	117 (11.0%)
Pyrexia	30 (4.4%)	29 (2.7%)
Peripheral Edema	29 (4.3%)	61 (5.8%)
Gait Disturbance	21 (3.1%)	27 (2.5%)
Asthenia	20 (3.0%)	31 (2.9%)
Hepatobiliary disorders	23 (3.4%)	30 (2.8%)
Infections and Infestations	366 (54.1%)	638 (60.2%)
Nasopharyngitis	126 (18.6%)	203 (19.2%)

	Siponimod 2-10 mg* All Males N=677	**Siponimod 2-10 mg* All Females N=1060**
Urinary tract infection	79 (11.7%)	206 (19.4%)
Influenza	56 (8.3%)	96 (9.1%)
Upper respiratory tract infection	53 (7.8%)	103 (9.7%)
Bronchitis	23 (3.4%)	57 (5.4%)
Herpes zoster	19 (2.8%)	46 (4.3%)
Pharyngitis	16 (2.4%)	31 (2.9%)
Injury, Poisoning and Procedural Complications	153 (22.6%)	289 (27.3%)
Fall	69 (10.2%)	157 (14.8%)
Contusion	24 (3.5%)	49 (4.6%)
Investigations	215 (31.8%)	284 (26.8%)
Alanine aminotransferase increased	60 (8.9%)	44 (4.2%)
Gamma-glutamyltransferase increased	58 (8.6%)	37 (3.5%)
Lymphocyte count decreased	19 (2.8%)	49 (4.6%)
Blood cholesterol increased	16 (2.4%)	24 (2.3%)
Metabolism and Nutrition Disorders	80 (11.8%)	120 (11.3%)
Hypercholesterolemia	37 (5.5%)	36 (3.4%)
Musculoskeletal and Connective Tissue Disorders	178 (26.3%)	357 (33.7%)
Back Pain	46 (6.8%)	106 (10.0%)
Arthralgia	34 (5.0%)	74 (7.0%)
Muscle Spasms	28 (4.1%)	33 (3.1%)

	Siponimod 2-10 mg* All Males N=677	**Siponimod 2-10 mg* All Females N=1060**
Pain in extremity	22 (3.2%)	78 (7.4%)
Musculoskeletal pain	22 (3.2%)	31 (2.9%)
Neoplasms Benign, Malignant and Unspecified	96 (14.2%)	180 (17.0%)
Melanocytic nevus	36 (5.3%)	63 (5.9%)
Nervous System Disorders	245 (36.2%)	492 (46.4%)
Headache	82 (12.1%)	200 (18.9%)
Dizziness	41 (6.1%)	103 (9.7%)
Muscle spasticity	30 (4.4%)	47 (4.4%)
Paresthesia	15 (2.2%)	29 (2.7%)
Trigeminal neuralgia	14 (2.1%)	23 (2.2%)
Psychiatric Disorders	116 (17.1%)	215 (20.3%)
Depression	41 (6.1%)	69 (6.5%)
Insomnia	22 (3.2%)	56 (5.3%)
Anxiety	18 (2.7%)	35 (3.3%)
Renal and Urinary Disorders	75 (11.1%)	109 (10.3%)
Reproductive System and Breast Disorders	26 (3.8%)	77 (7.3%)
Respiratory, Thoracic and Mediastinal Disorders	98 (14.5%)	167 (15.8%)
Cough	30 (4.4%)	54 (5.1%)
Skin and Subcutaneous Tissue Disorders	145 (21.4%)	232 (21.9%)
Actinic keratosis	19 (2.8%)	24 (2.3%)

	Siponimod 2-10 mg* All Males N=677	Siponimod 2-10 mg* All Females N=1060
Rash	16 (2.4%)	24 (2.3%)
Eczema	16 (2.4%)	24 (2.3%)
Seborrheic dermatitis	14 (2.1%)	24 (2.3%)
Vascular Disorders	90 (13.3%)	191 (18.0%)
Hypertension	70 (10.3%)	126 (11.9%)

Source: 120-day SCS Appendix 1-Table 2.1-1.5a

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

Reviewer Comment: The proposed labeling includes data and language regarding frequencies of for the most frequent and most disparate AEs (headache, nausea, urinary tract infections, increased liver transaminases, falls) listed in the preceding table, and thus provides adequate notice to patients of both genders of the risks associated with siponimod. The difference in urinary tract infections between men and women is not consistent with the literature[8] than shows equal rates of urinary tract infection between male and female patients with MS, but there did appear to be a disparity in the rates of catheterization in enrolled men versus women that could explain the difference.

8.6.5. Adverse Events: Age

In the updated Safety Database 2, the proportion of patients with at least one AE was 90.6% and 92.4% for patients in the ≤ 45 years and > 45 years subgroups. For most SOCs, the percentage of patients with an AE was similar in both age groups. There were differences in the percentages of patients with AEs for the ≤45 years and >45 years age groups in the SOCs of Blood and Lymphatic System Disorders (15.9%, 8.9%, respectively) with lymphopenia the most common PT (10.6%, 6.1%), Injury, Poisoning and Procedural Complications (21.2%, 28.5%) primarily due to falls (8.4%, 16.3%), Musculoskeletal and Connective Tissue Disorders (25.7%, 34.5%) with back pain the most common preferred term (7.0%, 10.0%) and Vascular Disorders (10.5%, 20.3%,) primarily due to hypertension (7.3%, 14.1%).

Differences of ≥ 5% in the percentage of patients ≤ 45 years and >45 years of age with AEs were

observed for the following preferred terms: fall (8.4%, 16.3%) and hypertension (7.3%, 14.1%).

Table 106: Frequency of Most Frequent Treatment Emergent Adverse Events (>2%) by Primary System Organ Class, Preferred Term, and Age, Safety Set (Safety Database 2)

	Siponimod 2-10 mg* Age ≤ 45 years N=725	Siponimod 2-10 mg* Age > 45 years N=1060
Number of Patients with at Least One AE	657 (90.6%)	935 (92.4%)
Blood and Lymphatic System Disorders	115 (15.9%)	90 (8.9%)
Lymphopenia	77 (10.6%)	32 (6.1%)
Cardiac Disorders	109 (15.0%)	141 (13.9%)
Bradycardia	49 (6.8%)	32 (3.2%)
Ear and Labyrinth Disorders	59 (8.1%)	75 (7.4%)
Vertigo	32 (4.4%)	43 (4.2%)
Eye Disorders	95 (13.1%)	131 (12.9%)
Gastrointestinal Disorders	203 (28.0%)	287 (28.4%)
Diarrhea	41 (5.7%)	76 (7.5%)
Constipation	30 (4.1%)	46 (4.5%)
Nausea	54 (7.4%)	75 (7.4%)
General Disorders & Administration Site Conditions	192 (26.5%)	297 (29.3%)
Fatigue	73 (10.1%)	105 (10.4%)
Pyrexia	31 (4.3%)	28 (2.8%)
Peripheral Edema	23 (3.2%)	67 (6.6%)
Asthenia	16 (2.2%)	35 (3.5%)
Infections and Infestations	415 (57.2%)	589 (58.2%)

	Siponimod 2-10 mg* Age ≤ 45 years N=725	**Siponimod 2-10 mg* Age > 45 years N=1060**
Nasopharyngitis	157 (21.7%)	172 (17.0%)
Urinary tract infection	107 (14.8%)	178 (17.6%)
Influenza	73 (10.1%)	79 (7.8%)
Upper respiratory tract infection	64 (8.8%)	92 (9.1%)
Sinusitis	31 (4.3%)	30 (3.0%)
Bronchitis	30 (4.1%)	50 (4.9%)
Injury, Poisoning and Procedural Complications	154 (21.2%)	288 (28.5%)
Fall	61 (8.4%)	165 (16.3%)
Contusion	24 (3.3%)	49 (4.8%)
Investigations	207 (28.6%)	288 (28.5%)
Alanine aminotransferase increased	55 (7.6%)	49 (4.8%)
Gamma-glutamyltransferase increased	42 (5.8%)	53 (5.2%)
Lymphocyte count decreased	36 (5.0%)	32 (3.2%)
Metabolism and Nutrition Disorders	74 (10.2%)	126 (12.5%)
Hypercholesterolemia	32 (4.4%)	41 (4.1%)
Musculoskeletal and Connective Tissue Disorders	186 (25.7%)	349 (34.5%)
Back Pain	51 (7.0%)	101 (10.0%)
Arthralgia	39 (5.4%)	69 (6.8%)
Muscle Spasms	20 (2.8%)	41 (4.1%)
Pain in extremity	34 (4.7%)	66 (6.5%)

	Siponimod 2-10 mg* Age ≤ 45 years N=725	Siponimod 2-10 mg* Age > 45 years N=1060
Musculoskeletal pain	15 (2.1%)	38 (3.8%)
Neoplasms Benign, Malignant and Unspecified	111 (15.3%)	165 (16.3%)
Melanocytic nevus	47 (6.5%)	52 (5.1%)
Nervous System Disorders	295 (40.7%)	442 (43.7%)
Headache	135 (18.6%)	147 (14.5%)
Dizziness	63 (8.7%)	81 (8.0%)
Muscle spasticity	24 (3.3%)	53 (5.2%)
Psychiatric Disorders	132 (18.2%)	199 (19.7%)
Depression	46 (6.3%)	64 (6.3%)
Insomnia	31 (4.3%)	47 (4.6%)
Anxiety	24 (3.3%)	29 (2.9%)
Renal and Urinary Disorders	73 (10.1%)	111 (11.0%)
Reproductive System and Breast Disorders	53 (7.3%)	50 (4.9%)
Respiratory, Thoracic and Mediastinal Disorders	107 (14.8%)	158 (15.6%)
Cough	31 (4.3%)	53 (5.2%)
Skin and Subcutaneous Tissue Disorders	163 (22.5%)	214 (21.1%)
Vascular Disorders	76 (10.5%)	205 (20.3%)
Hypertension	53 (7.3%)	143 (14.1%)

Source: 120-day SCS Appendix 1-Table 2.1-1.5b

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

Reviewer Comment: Many of the increased frequencies of TEAEs with advanced age are known epiphenomena independent of siponimod exposure. For example, the diagnosis of hypertension increases with advancing age. However, there is a significant mismatch in the frequency of falls between patients younger than 45 (8.4%) and patients older than 45 (16.3%). Dizziness (8.7% and 8.0%) and vertigo (4.4% and 4.2%) TEAE frequencies remained stable across the age cut-off, and so it does not appear older patients experience more vertiginous phenomena that would raise fall risk. The increase in falls observed for patients > 45 years old is consistent with published data showing increasing fall risk in older, more disabled patients with SPMS.[10] In Section 8.6.9, there is a greater risk of certain types of injuries in falls in older patients, a finding consistent with the published literature[10] with the caveat that there is not a linear relationship between injury risk associated with falls and EDSS score worsening,[12] a finding that explains the paradoxical lower EDSS score average in patients with SAEs of serious injuries. (b) (4)

8.6.6. **Adverse Events: Race**

In Safety Database 2, the proportion of patients with at least one AE was 91.7%, 93.0% and 90.9% for White, Asian and Black subgroups respectively. The differences noted between the White and either Asian or Black subgroups in SOC and preferred terms cannot be meaningfully interpreted because of how small the Black and Asian subgroups are in comparison to the White subgroup.

8.6.7. **Adverse Events: CYP2C9 genotype**

CYP2C9 is the major metabolizing enzyme of siponimod and exists in the population in isoforms that differ in processing capabilities based on genotype. The *1 allele produces a CYP2C9 enzyme with the highest processing capability, and thus *1/*1 patients will have the most enzyme activity of any genotype. Other alleles commonly found in the population, *2 and *3 (among others) have reduced enzyme activity. Patients with *1/*2 will have an approximate 40% reduction in CYP2C9 enzyme activity over *1/*1. The *3 allele produces a CYP2C9 isoform with very little enzymatic activity. Patients with *1/*3 will have 75% less enzymatic activity than patients with the *1/*1 genotype, and *3/*3 will have 90% or greater reduction in CYP2C9 activity (see the Clinical Pharmacology Review for further discussion of CYP2C9 enzyme isoforms as they relate to siponimod.)

Because CYP2C9 is the primary metabolizing enzyme of siponimod, there is a concern that patients with poor metabolization of siponimod may experience larger frequencies of AEs because of higher than expected exposure. The proportions of patients with at least one AE reported in Safety Database 2 were comparable between the extensive metabolizer (*1/*1, *2/*1, *2/*2) patient population (91.5%) and the poor metabolizer (*1/*3, *2/*3) population (92.6%), and there were no overall differences between the frequencies of the most frequent AEs in these subgroups in the controlled pool.

Though overall findings in SOCs and preferred terms were largely similar, there were some notable exceptions. Infections and Infestations TEAEs were 7.5% less frequent in the poor metabolizer population. There were differences in the incidences of macular edema: 1.0%, IR=0.4/100 PY and 3.1%, IR=1.2/100 PY between the extensive and poor metabolizer subgroups, respectively. There was a trend toward increased frequency of hypertension reported in poor metabolizer subgroups; otherwise, percentage differences between subgroups were less than 5%.

Table 107: Reviewer Table, Frequency of Most Frequent Treatment Emergent Adverse Events (>2%) by Primary System Organ Class, Preferred Term and Genotype, Long-term Safety Pool, Safety Set (Safety Database 2)

SOC **Preferred Term**	**Siponimod** **2-10 mg*** **Extensive Metabolizer** **(*1/*1, *2/*1, *2/*2)** **N=1475**	**Siponimod** **2-10 mg*** **Poor Metabolizer** **(*1/*3, *2/*3)** **N=257**
Number of Patients with at Least One AE	1350 (91.5%)	238 (92.6%)
Blood and Lymphatic System Disorders	172 (11.7%)	33 (12.8%)
Lymphopenia	119 (8.1%)	20 (7.8%)
Cardiac Disorders	217 (14.7%)	32 (12.5%)
Bradycardia	71 (4.8%)	9 (3.5%)
Ear and Labyrinth Disorders	109 (7.4%)	24 (9.3%)
Vertigo	60 (4.1%)	14 (5.4%)
Eye Disorders	186 (12.6%)	39 (15.2%)

SOC **Preferred Term**	**Siponimod** **2-10 mg*** **Extensive Metabolizer** **(*1/*1, *2/*1, *2/*2)** **N=1475**	**Siponimod** **2-10 mg*** **Poor Metabolizer** **(*1/*3, *2/*3)** **N=257**
Macular Edema	<2%	8 (3.1%)
Gastrointestinal Disorders	422 (28.6%)	67 (26.1%)
Nausea	111 (7.5%)	17 (6.6%)
Diarrhea	98 (6.6%)	19 (7.4%)
Constipation	72 (4.9%)	<2%
General Disorders & Administration Site Conditions	417 (28.3%)	69 (26.8%)
Fatigue	145 (9.8%)	32 (12.5%)
Peripheral Edema	72 (4.9%)	16 (6.2%)
Pyrexia	54 (3.7%)	<2%
Asthenia	44 (3.0%)	6 (2.3%)
Hepatobiliary Disorders	43 (2.9%)	10 (2.9%)
Infections and Infestations	869 (58.9%)	132 (51.4%)
Nasopharyngitis	287 (19.5%)	40 (15.6%)
Urinary tract infection	248 (16.8%)	35 (13.6%)
Influenza	133 (9.0%)	19 (7.4%)
Upper respiratory tract infection	130 (8.8%)	35 (13.6%)
Bronchitis	68 (4.6%)	12 (4.7%)
Injury, Poisoning and Procedural Complications	381 (25.8%)	61 (23.7%)
Fall	195 (13.2%)	31 (12.1%)

SOC Preferred Term	Siponimod 2-10 mg* Extensive Metabolizer (*1/*1, *2/*1, *2/*2) N=1475	Siponimod 2-10 mg* Poor Metabolizer (*1/*3, *2/*3) N=257
Contusion	58 (3.9%)	15 (5.8%)
Investigations	429 (29.1%)	70 (27.2%)
Alanine aminotransferase increased	89 (6.0%)	15 (5.8%)
Gamma-glutamyltransferase increased	81 (5.5%)	14 (5.4%)
Lymphocyte count decreased	61 (4.1%)	7 (2.7%)
Metabolism and Nutrition Disorders	169 (11.5%)	30 (11.7%)
Hypercholesterolemia	64 (4.3%)	9 (3.5%)
Musculoskeletal and Connective Tissue Disorders	463 (31.4%)	72 (28.0%)
Back Pain	134 (9.1%)	18 (7.0%)
Arthralgia	92 (6.2%)	16 (6.2%)
Pain in extremity	87 (5.9%)	13 (5.1%)
Muscle Spasms	52 (3.5%)	9 (3.5%)
Musculoskeletal pain	44 (3.0%)	9 (3.5%)
Neoplasms Benign, Malignant and Unspecified	237 (16.1%)	39 (15.2%)
Melanocytic nevus	87 (5.9%)	12 (4.7%)
Nervous System Disorders	634 (43.0%)	102 (39.7%)
Headache	249 (16.9%)	32 (12.5%)
Dizziness	123 (8.3%)	21 (8.2%)
Muscle spasticity	71 (4.8%)	6 (2.3%)

SOC Preferred Term	Siponimod 2-10 mg* Extensive Metabolizer (*1/*1, *2/*1, *2/*2) N=1475	Siponimod 2-10 mg* Poor Metabolizer (*1/*3, *2/*3) N=257
Psychiatric Disorders	276 (18.7%)	53 (20.6%)
Depression	85 (5.8%)	25 (9.7%)
Insomnia	61 (4.1%)	17 (6.6%)
Anxiety	47 (3.2%)	6 (2.3%)
Renal and Urinary Disorders	171 (11.6%)	13 (5.1%)
Reproductive System and Breast Disorders	84 (5.7%)	19 (7.4%)
Respiratory, Thoracic and Mediastinal Disorders	229 (15.5%)	35 (13.6%)
Cough	76 (5.2%)	7 (2.7%)
Dyspnea	30 (2.0%)	<2%
Skin and Subcutaneous Tissue Disorders	329 (22.3%)	46 (17.9%)
Rash	36 (2.4%)	<2%
Eczema	32 (2.2%)	7 (2.7%)
Vascular Disorders	242 (16.4%)	39 (15.2%)
Hypertension	166 (11.3%)	30 (11.7%)

Source: 120-day SCS Appendix 1-Table 2.1-1.5d

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

Reviewer Comment: The small number of patients in the poor metabolizer group precludes definitive conclusions. There does appear to be a higher frequency of known TEAEs

associated with siponimod, dyspnea and macular edema, reported in poor metabolizers versus extensive metabolizers. The applicant proposes dose adjustments for poor metabolizers based on pharmacokinetic and pharmacodynamic data to ensure exposure that will be equally as effective and as safe as the 2 mg dose will be in extensive metabolizers. This reviewer agrees that poor metabolizers should have a maintenance dose lower than extensive metabolizers to ensure safe dosing. Genotype information will need to be included in safety reports and monitored for any systematic patterns of AEs in the postmarketing setting.

8.6.8. Serious Adverse Events: Gender

In Safety Database 2, the proportion of patients with at least one SAE was 24.8% for male patients and 22.4% for female patients. In the SOC of Infections and infestations, the frequencies of SAEs was 6.4% for men and 3.9% for women. Urinary tract infection was the most disparate preferred term under the Infections and Infestations SOC, reported for 2.5% and 1.4%, male and female patients respectively.) In the other SOCs, the incidence of SAEs was comparable for male and female patients.

Reviewer Comment: There were small (<5%) differences between men and woman on some SAEs but no clear pattern nor clinically significant differences are apparent. The AEs that were most discrepant between men and women were less so in the SAE database. The difference in the Infections and Infestations SOC appears to be a statistical consequence of the relatively smaller population of men yielding more events with fewer observations and not a true clinical difference.

8.6.9. Serious Adverse Events: Age

In the controlled pool of patients treated with siponimod 2 mg, there was a higher incidence rate of SAEs in the >45-year-old age group (141 patients; 14.4/100 PY) than in the ≤45-year-old age group (52 patients; 8.6/100 PY). The difference was due to a higher incidence of Infections and Infestations (24 patients, 2.2/100 PY versus 9 patients, 1.4/100 PY) and Nervous System Disorders (28 patients, 2.6/100 PY versus 11 patients, 1.7/100 PY) in the older age group.

In Safety Database 2, the proportion of patients with at least one SAE was 19.0% and 26.4% for patients in the ≤ 45 years and > 45 years subgroups, respectively. For most SOCs, the incidence of SAEs was comparable for the age-related subgroups. The SOCs with the highest differences in frequency of SAEs reported for patients in the ≤ 45 years and > 45 years subgroups are included in the following table:

Table 108: Incidence of Serious Adverse Events by Age Subgroup, Long-term Safety Pool, Safety Set (Safety Database 2)

	Siponimod 2-10 mg* Age ≤ 45 years N=725	Siponimod 2-10 mg* Age > 45 years N=1060
Number of Patients with at least 1 SAE	**138 (19.0%)**	**267 (26.4%)**
Infections and Infestations	**32 (4.4%)**	**52 (5.1%)**
Urinary tract infection	13 (1.8%)	19 (1.9%)
Appendicitis	0	4 (0.4%)
Pneumonia	3 (0.4%)	4 (0.4%)
Influenza	2 (0.3%)	1 (0.1%)
Pyelonephritis	2 (0.3%)	0
Upper respiratory tract infection	2 (0.3%)	2 (0.2%)
Urosepsis	2 (0.3%)	0
Injury, Poisoning and Procedural Complications	**19 (2.6%)**	**42 (4.2%)**
Laceration	3 (0.4%)	4 (0.4%)
Concussion	1 (0.1%)	6 (0.6%)
Fall	1 (0.1%)	5 (0.5%)
Neoplasms Benign, Malignant and Unspecified	**13 (1.8%)**	**48 (4.7%)**
Basal cell carcinoma	3 (0.4%)	23 (2.3%)
Breast cancer	2 (0.3%)	4 (0.4%)
Nervous System Disorders	**37 (5.1%)**	**59 (5.8%)**
Epilepsy and Seizures[1]	7 (1.0%)	9 (0.9%)
Multiple Sclerosis Relapse[2]	4 (0.6%)	5 (0.5%)
Syncope	1 (0.1%)	5 (0.5%)
Stroke	0	4 (0.4%)
Transient ischemic attack	0	3 (0.2%)

Source: 120-day SCS Appendix 1-Table 2.1-8.2.2b

* (Safety Database 2) Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

[1] includes preferred terms epilepsy, generalized seizure, partial complex seizure, seizure
[2] includes multiple sclerosis relapse, multiple sclerosis, and secondary progressive multiple sclerosis

Reviewer Comment: The large difference in fall-related SAEs between the two age groups mirrors the nearly two-fold difference in non-serious fall AEs observed between the older and younger subgroups. The difference in quality of the Nervous System SOC events appears to recapitulate the different SAE risks that are associated with aging. The prevalence of TIA and strokes increases approximately three-fold with each decade lived, and patients with MS are at overall higher risk for stroke at any age.[22] The appearance of neurovascular events in patients with MS older than age 45 years old is therefore not unexpected.

8.6.10. Serious Adverse Events: Race

In Safety Database 2, the proportions of patients with at least one SAE were 23.6%, 20.9% and 27.3% for White, Asian and Black subgroups, respectively. Three patients experienced at least 1 SAE in the Black subgroup. 9 patients experienced at least 1 SAE in the Asian subgroup. The SAEs in the Black subgroup included unique events of asthenia, gait disturbance urinary tract infection, craniocerebral injury, and seizure. In the Asian subgroup, the SAEs included bradycardia, influenza, femoral neck fracture, increased bilirubin, pulmonary function test decreased, multiple sclerosis relapse (n=2), secondary progressive multiple sclerosis, and dizziness.

Reviewer Comment: The paucity of patients and events in the Black and Asian subgroups precludes any substantial interpretation of the racial subgroup findings other than confirming the presence in these subgroups of the same high frequency SAEs observed in the overall study population such as urinary tract infection, femoral neck fracture, and multiple sclerosis relapse.

8.6.11. Serious Adverse Events: Genotype

In Safety Database 2, the proportions of patients with at least one SAE were 23.2% in both the extensive (*1/*1, *2/*1, *2/*2) and poor (*3/*1, *2/*3) metabolizer subgroups. The poor metabolizer subgroup experienced only 60 SAEs (as compared to 343 in the larger, extensive metabolizer group). The following table provides a summary of potential SAEs identified as most common or of concern for siponimod from updated long-term safety database.

Table 109: Reviewer Table, Incidence of Serious Adverse Events, Genotype Subgroups, Long-term Safety Pool, Safety Set (Safety Database 2)

SOC Preferred Term	Siponimod 2-10 mg* Extensive Metabolizer (*1/*1, *2/*1, *2/*2) N=1475	Siponimod 2-10 mg* Poor Metabolizer (*1/*3, *2/*3) N=257
Patients with at least 1 SAE	**343 (23.3%)**	**60 (23.3%)**
Blood and Lymphatic System Disorders	**4 (0.3%)**	**3 (1.2%)**
Lymphopenia	1 (0.1%)	0
Cardiac Disorders	**18 (1.2%)**	**3 (1.2%)**
Bradycardia	6 (0.4%)	0
AV block 2nd degree	5 (0.3%)	1 (0.4%)
Eye Disorders	**8 (0.5%)**	**1 (0.4%)**
Macular edema	2 (0.1%)	1 (0.4%)
Gastrointestinal Disorders	**22 (1.5%)**	**3 (1.2%)**
General Disorders	**12 (0.8%)**	**2 (0.8%)**
Infections and Infestations	**73 (4.9%)**	**11 (4.3%)**
Urinary tract infection	28 (1.9%)	4 (1.6%)
Pneumonia	6 (0.4%)	1 (0.4%)
Injury, Poisoning, and Procedural Complications	**51 (3.5%)**	**10 (3.9%)**
Falls	6 (0.4%)	0
Laceration	5 (0.3%)	2 (0.8%)
Concussion	4 (0.3%)	3 (1.2%)
Investigations	**24 (1.6%)**	**6 (2.3%)**

SOC Preferred Term	Siponimod 2-10 mg* Extensive Metabolizer (*1/*1, *2/*1, *2/*2) N=1475	Siponimod 2-10 mg* Poor Metabolizer (*1/*3, *2/*3) N=257
ALT/AST/GGT increased	8 (0.5%)	4 (1.6%)
Neoplasms Benign, Malignant, and Unspecified	**50 (3.4%)**	**11 (4.3%)**
Basal cell carcinoma	24 (1.6%)	2 (0.8%)
Breast cancer	5 (0.3%)	1 (0.4%)
Nervous System Disorders	**85 (5.8%)**	**11 (4.3%)**
Epilepsy and Seizures[1]	14 (0.9%)	1 (0.4%)
Syncope	6 (0.4%)	0
Stroke[2]	3 (0.2%)	1 (0.4)
Respiratory, Thoracic, and Mediastinal Disorders	**9 (0.6%)**	**1 (0.4%)**
Dyspnea	1 (0.1%)	0
Vascular Disorders	**8 (0.5%)**	**1 (0.4%)**
Hypertension	1 (0.1%)	0

Source: 120-day SCS Appendix 1-Table 2.1-8.2.2c and 2.1-8.2.2d

*Safety Database 2: Safety data collected while on any dose of siponimod in all patients who received at least one dose of 2 mg or 10 mg.

[1] includes preferred terms epilepsy, partial complex seizure, generalized seizure, seizure
[2] includes preferred terms cerebrovascular accident, brainstem infarct

Reviewer Comment: The frequency of SAEs known to be associated with siponimod therapy did not show a consistent pattern of increased risk for the poor metabolizer genotype with the exception of macular edema being more frequent in poor metabolizers, as had been noted for TEAEs. Epilepsy and seizures were less frequent in poor metabolizers, adding some more ambiguity to the hypothetical association of siponimod and increased seizure risk because if siponimod is associated with seizures the prediction would be more events in the

poor metabolizer patients due to higher exposure. Some sample sizes were too small to interpret, and caution is advised with most comparisons because of the small size of the patient pool. Reports made during postmarketing experience will indicate genotype of patients to assist in clarifying whether any increased risk of siponimod-associated SAEs exists for the poor metabolizer subgroup.

8.7. Specific Safety Studies/Clinical Trials

All clinical trial data are discussed in the preceding sections. There were no safety trials conducted aside from the Clinical Pharmacology Studies summarized in Section 8.2.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

S1P modulators like siponimod appear to be associated with increased risk of certain malignancies, specifically, cutaneous malignancies. Preclinical data do not suggest an increased risk of malignancies with siponimod. Lymphoma which was noted in female mice at high doses; however, there was no increase in lymphoma incidence was observed in the rat carcinogenicity study, nor was lymphoma observed in a 52-week monkey study.

Controlled Pool

In the controlled pool of the trials in MS, there was an observed lower overall malignancy risk among siponimod treatment condition patients compared to placebo treatment group patients. Malignancies, based on risk search terms defined by the SMQ "Malignant or unspecified tumors," were reported as TEAEs in 22 (1.7%) patients [Odds ratio 0.7 vs. placebo-treated patients] exposed to any dose of siponimod compared to 14 (2.3%) placebo patients. The malignancy rate for siponimod-treated patients was 1.3/100PY (22/1758.81PY) compared to 1.7/100PY (14/835.28PY) in placebo-treated patients.

The following table summarizes all malignancies reported in the Controlled Pool of patients.

Table 110: Reviewer Table, Incidence of All Malignancies, Controlled Pool, Safety Set (Safety Database 1)

	Siponimod 0.5mg N=43 n (%) [Odds Ratio]	Siponimod 2 mg N=1148 n (%) [Odds Ratio]	Siponimod All Doses N=1334 n (%) [Odds Ratio]	Placebo N=607 n (%)
Patients with any "Malignant or Unspecified Tumors" (SMQ)	1 (2.3%) [1.0]	21 (1.8%) [0.8]	22 (1.7%) [0.7]	14 (2.3%)
All patients with cutaneous malignancies[1]	1 (2.3%) [2.0]	15 (1.3%) [1.0]	16 (1.2%) [0.9]	8 (1.3%)
Basal cell carcinoma[2]	1 (2.3%) [2.0]	13 (1.1%) [1.0]	14 (1.1%)	7 (1.2%)
Malignant melanoma *in situ*	0	2 (0.2%)	2 (0.2%)	0
Seminoma	0	2 (0.2%)	2 (0.2%)	0
Squamous cell carcinoma[3]	0	2 (0.2%)	2 (0.2%)	0
Bowen's disease	0	1 (0.1%) [0.5]	1 (0.1%)	1 (0.2%)
Breast cancer	0	1 (0.1%) [0.5]	1 (0.1%)	1 (0.2%)
Endometrial cancer	0	1 (0.1%)	1 (0.1%)	0
Gastrointestinal melanoma	0	1 (0.1%)	1 (0.1%)	0
Keratoacanthoma	0	1 (0.1%)	1 (0.1%)	0
Lung adenocarcinoma	0	1 (0.1%) [0.5]	1 (0.1%)	1 (0.2%)

Source: SCS Appendix 1-Table 2.1-13.1.1

Note: there were no malignancies reported among patients in the siponimod 0.25 mg, 1.25 mg, or 10 mg treatment groups

[1] includes cases of basal cell carcinoma, malignant melanoma *in situ*, squamous cell carcinoma, Bowen's disease, and keratoacanthoma
[2] includes a case of "skin cancer" later reclassified as basal cell carcinoma
[3] includes preferred terms squamous cell carcinoma and lip squamous cell carcinoma

The most frequently identified malignancies in the siponimod studies were skin cancers (16 patients, 1.2%), largely because there had been an observed increased risk of cutaneous malignancies in the fingolimod development program, and, as a result, the siponimod development program included skin surveys by dermatologists as part of the routine study visits. However, most of these cancerous lesions were identified at early visits whereas the increased risk associated with fingolimod emerged in postmarketing studies. Thus, it was not surprising that overall in the controlled trial phase, there was no difference in frequency of cutaneous malignancies overall between the incidence of cutaneous malignancies in the siponimod (1.2%) and placebo treatment groups (1.3%). Likewise, the rate of any skin cancer was approximately equal in siponimod-exposed patients 0.91/100PY (16/1758.81PY) compared to 0.96/100PY (8/835.28PY) in placebo-treated patients.

Among the cutaneous malignancies identified in the controlled clinical trials, basal cell carcinoma was the most common skin malignancy and was reported with a similar incidence in the siponimod-exposed (1.1%, 14 patients) and placebo (1.2%, 7 patients) groups. Nine of the sixteen reported cases with cutaneous malignancies in the siponimod treatment group had pre-existing histories of other skin malignancies, or they had significant risk factors such as smoking or sunlight/ultraviolet light exposure.

There were mismatches in some cutaneous malignancies between the siponimod and placebo treatment groups but with small numbers of cases. Malignant melanoma related events (including a case of gastrointestinal melanoma) were reported in three patients (0.3%) in the siponimod treatment group; there were no reported cases in the placebo group. Skin squamous cell carcinoma was reported in two siponimod-exposed patients (0.2%) compared to no reported cases in placebo-treated patients.

> *Reviewer Comment: The labeling for the approved S1P modulator, fingolimod, includes a specific Warnings and Precautions statement citing an increased risk of basal cell carcinoma and melanoma. A Warnings and Precautions entry for cutaneous malignancies is not justified for siponimod based on the nearly equal frequencies and rates between siponimod and placebo treatments. However, given the high degree of similarity between siponimod and fingolimod, there is an expectation of a rise in skin cancers and perhaps other malignancies in the postmarketing setting. I recommend enhanced reported of malignancies to ascertain whether siponimod confers the same increased risk of skin cancers as fingolimod.*

Aside from cutaneous malignancies, the only cancer noted in more than one patient was seminoma, in two male patients in the siponimod treatment group, for an overall incidence rate of approximately 0.003/100 man-years (2/~692 man-years). Seminoma accounts for approximately 2% of all malignant cancers in men and is the most common cancer worldwide in men ages 15-40 years old.[23] The overall testicular incidence rates among non-Hispanic white men in European countries and the United States is around 5-6 per 100,000 men.[24] Therefore, having two diagnosed cases in a pool of 239 men would represent an unexpectedly high number of patients with seminomas in a non-Hispanic, white male population.

> *Reviewer Comment: Seminomas are a common cancer in men, but the observed rate in siponimod-treated men is out of proportion to what would be predicted (even using the highest estimates for populations) and is therefore of concern. It is reassuring that no more cases of seminoma nor other germ cell line tumors emerged in the long-term safety database. Nonclinical findings did not raise concern of an increased rate of testicular cancer. Nevertheless, this reviewer would advise increased pharmacovigilance for any reports of seminomas in the postmarketing setting.*

There were two cases of breast cancer reported in Study A2304 during the controlled phase, yielding an incidence rate of IR of 0.1 per 100 PY. Patient (b) (6) was diagnosed seven months after a patient had been randomized to siponimod 2 mg. The second case was diagnosed in a patient five month after she had been randomized to placebo treatment. Both patients discontinued their study treatments. The siponimod-treated patient narrative is included here.

<u>Breast Cancer</u>
Patient (b) (6) was diagnosed with MS (b) (6) and diagnosed with secondary progressive multiple sclerosis on (b) (6). The patient had not had previous therapy for MS. The patient's medical history included menarche (at the age of 11 years, (b) (6)), cholecystectomy ((b) (6)), breast cyst ((b) (6), ongoing), menopause ((b) (6)), carpal tunnel syndrome, venous angioma of brain, and trigeminal neuralgia. Her concomitant medications included carbamazepine, gabapentin, baclofen, and lidocaine as needed for trigeminal neuralgia. She received the first dose of study medication on Day 1 (b) (6). On Day 141 (b) (6), the patient was hospitalized due to aggravation of trigeminal neuralgia. The patient continued receiving carbamazepine and baclofen. The patient also received gabapentin. No action was taken with the study medication due to this event. On an unspecified date in (b) (6), the patient was found to have a tumor in the left breast. On Day 233 (b) (6) an ultrasonogram revealed the presence of cysts in the right breast (biggest cyst size was of 5 × 8 mm) along with a hypo-echogenic lesion of 5.5 ×7 mm and suspected adenoid cystic carcinoma (second irregular, blurred boundaries 22 × 35 × 46 mm) in the left breast

extending in milk ducts, and the next focus-near to breast areola showed irregular hypoechogenic focus 9 × 13 × 13 m. In the left arm pit-lymph nodes were not enlarged. On an unspecified date in (b) (6), the patient underwent a left breast biopsy. Treatment included doxorubicin, dexamethasone, and docetaxel. The study medication was permanently discontinued siponimod due to breast cancer and the last dose was received on Day 252 (b) (6). Chemotherapy was planned every month, for six cycles, followed by mammectomy. On (b) (6), histopathological findings showed infiltrative breast cancer [G2 NST WHO (b) (6) invasive CA of no special type receptors with ER-90%, cells/3, TS 8/8 (positive), PR: 80% cells/3, TS 8/8 (positive), PR: 80% cells/3, TS 8/8 (positive) and HER-2-1 (negative)]. The Investigator reported the histological typing of cancer as hormonal sensitive, without over expression HER-2 invasive carcinoma of non-specific type. The patient discontinued the study due to breast cancer and attended the End-of-Study visit. The event trigeminal neuralgia had not resolved and the event (breast cancer) was resolving at the time of last reporting.

Long-term Safety Pool

Analysis of the largest safety pools (Safety Databases 2 and 4) did not demonstrate an increase in malignancy-related events in all siponimod-treated patients (1.2 per 100 PY) as compared to 1.3 per 100 PY in the siponimod-treated patient group in the controlled pool.

Table 111: Reviewer Table, Incidence of Malignancies in Long-Term Safety Pool, Safety Set (Safety Databases 2 and 4)

Preferred terms	Siponimod 2-10 mg* N=1737		Siponimod 2-10 mg** N=1737	
	n (%*)	IR	n (%*)	IR
Patients with any "Malignant or Unspecified Tumors" (SMQ)	48 (2.8%)	1.2	48 (2.8%)	1.3
Basal cell carcinoma	25 (1.4%)	0.6	25 (1.4%)	0.7
Breast cancer	4 (0.2%)	0.1	4 (0.2%)	0.1
Bowen's disease	2 (0.1%)	0.0	2 (0.1%)	0.1
Colon cancer metastatic	2 (0.1%)	0.0	2 (0.1%)	0.1
Malignant melanoma *in situ*	2 (0.1%)	0.0	2 (0.1%)	0.1
Seminoma	2 (0.1%)	0.0	2 (0.1%)	0.1
Squamous cell carcinoma	2 (0.1%)	0.0	2 (0.1%)	0.1
Central nervous system lymphoma	1 (0.1%)	0.0	1 (0.1%)	0.0
Colon cancer stage IV	1 (0.1%)	0.0	1 (0.1%)	0.0

Preferred terms	Siponimod 2-10 mg* N=1737		Siponimod 2-10 mg** N=1737	
	n (%*)	IR	n (%*)	IR
Colorectal cancer	1 (0.1%)	0.0	1 (0.1%)	0.0
Endometrial cancer	1 (0.1%)	0.0	1 (0.1%)	0.0
Gastrointestinal melanoma	1 (0.1%)	0.0	1 (0.1%)	0.0
Glioma	1 (0.1%)	0.0	1 (0.1%)	0.0
Intraductal proliferative breast lesion	1 (0.1%)	0.0	1 (0.1%)	0.0
Keratoacanthoma	1 (0.1%)	0.0	1 (0.1%)	0.0
Lip squamous cell carcinoma	1 (0.1%)	0.0	1 (0.1%)	0.0
Lung adenocarcinoma	1 (0.1%)	0.0	1 (0.1%)	0.0
Renal cancer	1 (0.1%)	0.0	1 (0.1%)	0.0
Skin cancer	1 (0.1%)	0.0	1 (0.1%)	0.0
Squamous cell carcinoma of the vagina	1 (0.1%)	0.0	1 (0.1%)	0.0
Testicular cancer	1 (0.1%)	0.0	1 (0.1%)	0.0

Source: SCS Appendix 1

As was the case in the Controlled Pool, the largest number of reported malignancies in the Long-term Safety Pools were skin malignancies. As a S1P modulator, siponimod presumably has a mechanism of action sufficiently like that of fingolimod that the risk of cutaneous malignancies observed in postmarketing will be similar. This would mean that siponimod would be associated with skin malignancies (mainly squamous cell carcinoma and melanoma), the available data for siponimod do not suggest an increase of such malignancies. However, the applicant notes that the number of events of any type of malignancy to date, and the duration of follow-up, is relatively limited and does not permit conclusions currently on any potential long-term risk. The most parsimonious assumption would be to assume the same risk for siponimod as fingolimod, and therefore provide labeling in line with this assumed increased risk of cutaneous malignancies.

A second case of breast cancer was identified in the Long-term Pool.

Patient (b) (6), 1 42-year-old woman, received her first dose of siponimod 1.25 mg medication on (b) (6) The patient was reported to have palpable tumor in the right breast from an unspecified date in (b) (6) On Extension Day 1406 (b) (6), while receiving siponimod 2 mg/day during the open-label treatment phase of the Extension Study, the patient was diagnosed with breast cancer. The mammography revealed a tumor and biopsy revealed a lobular carcinoma with histology of grade 2 [estrogen receptor positive (>50%),

progesterone receptor positive; human epidermal growth factor receptor 2 score was 1 (clinically negative)]; there was no evidence of metastases. No treatment details were reported for this event. On Extension Day 1413 (b) (6), the treatment with study medication was permanently discontinued due to this event (breast cancer). The event (breast cancer) was ongoing at the time of last reporting. Following discontinuation of study medication, the patient entered the follow-up phase of the study with a final follow-up visit on (b) (6).

120-Day Safety Update

The updated safety database included eight new cases of malignancies. There were four new cases of basal cell carcinoma, three cases of breast cancer, and 1 case of Bowen's disease. Two patients who had been randomized to siponimod in the controlled trial but who did not elect to continue in the open-label extension trial were diagnosed with malignant melanoma 147 and 609 days after discontinuing siponimod treatment. Even with the inclusion of all skin cancer cases, the IR for cutaneous malignancy did not change from the prior safety report summary.

The additional breast cancer cases yield a frequency of 0.3% (6/1737 patients) and an estimated IR of 0.1 per 100 PY. In a large summary review of cancer rates in patients with MS, the estimated incidence rate of breast cancer was 1.64% (95% confidence interval: 0.98-2.3%).[25] That published estimate would place the observed rate of breast cancer in the siponimod MS program as well below the expected population incidence rate. The lower incidence rate observed during the controlled trial phase lend further support to the breast cancer risk being lower than expected and not increased by siponimod therapy.

> *Reviewer Comment: While the nonclinical and clinical studies' findings failed to identify the increased risk of cutaneous malignancy noted with fingolimod, the malignancy risk associated with the approved S1P modulator, fingolimod, was not fully elucidated until postmarketing experience. Longitudinal experience will demonstrate whether siponimod shares this increased risk for cutaneous malignancies but given the similarity of siponimod to fingolimod there is* a priori *reason to expect that siponimod will be associated with a similar risk of skin malignancy to that observed in association with longitudinal fingolimod therapy. Labeling should provide this risk as a class-related effect and supplement this warning with data based on postmarketing reporting acquired via enhanced pharmacovigilance. Seminoma and testicular cancer should be monitored as specific events of concern.*

8.8.2. Human Reproduction and Pregnancy

The siponimod development program included a small number of pregnancies with few adverse outcomes. The data from the clinical program are insufficient to support conclusions about the effects of siponimod on human reproduction and pregnancy.

Background

The receptor sphingosine-1-phosphate receptor that siponimod interacts with is known to be involved in vascular formation during embryogenesis in rodents. Reproductive and developmental studies in pregnant rats and rabbits demonstrated siponimod-induced embryotoxicity and fetotoxicity in both species and teratogenicity in rats.

Therefore, in trials with siponimod, protocols mandated reliable contraception measures during treatment. A negative pregnancy test was required prior to start of therapy, and pregnancy testing was performed routinely during study visits throughout the trial. Patients who became pregnant during the study were required to discontinue treatment.

Pregnancies

MS Trials
The applicant reports a total of 15 known pregnancies in 12 female patients participating in siponimod clinical trials in MS. In pregnancies with siponimod exposure, post-conception exposure to siponimod was estimated between 22-78 days.

Other Trials
There were no pregnancies reported in other clinical trials with siponimod.

Pregnancies with Live Births
Of the 15 pregnancies reported in Controlled and Long-term Safety Pools, 8 pregnancies resulted in full-term deliveries without maternal or neonatal complications. An analysis of adverse events in those patients with post-conception exposure revealed seven total AEs, all unique, as follows: congenital anomaly of external ear, chloasma, congenital melanocytic nevus, hydrocele, hypertrophic cardiomyopathy, ichthyosis, and omphalitis.

> *Reviewer Comment: Based on the nonclinical data, the predicted impact of siponimod on fetal development would be potential cardiac, renal, or vascular malformations. The observed fetal AEs are heterogeneous and only one was cardiac-related. Labeling should contraindicated siponimod use during pregnancy.*

Pregnancies without Live Births
There were 7 pregnancies with in Controlled and Long-term Safety Pools that did not result in a live birth, 5 patients had elective abortions, and 2 patients had spontaneous abortions. The elective abortions were in response to undesired pregnancy. The applicant confirmed in a January 20, 2019, response to an Information Request that there were no reports of *in utero* or *ex utero* malformations in any of the aborted fetuses.

120-day Safety Update

The 120-day Safety Update added 3 pregnancies to the prior 15 for a total of 18 known pregnancies in the Siponimod development program. There were 4 new AEs in the reporting period related to reproductive toxicity as follows: 11-beta hydroxylase deficiency, atrial septal defect, hydrocele, and mitochondrial encephalomyopathy.

Reviewer Comment: Atrial septal defect is a common congenital abnormality but is concerning to find in a siponimod exposed patient because such a defect would be predicted in association with siponimod exposure based on nonclinical findings.

Lactation

The applicant reports that siponimod is excreted into milk in the lactating rat (with a 2-fold lower exposure in milk compared to plasma). The applicant has not performed measurements of siponimod in human breast milk. The applicant reports there are no data available on the effects of siponimod on the breastfed child or the effects of siponimod on milk production.

Reviewer Comment: The applicant recommends labeling state that (b) (4) *I concur with the applicant's proposal. The small number of events precludes definitive statements regarding risk. Nevertheless, the nonclinical data are compelling, and labeling for siponimod should reflect a significant potential risk of malformation and fetal death and should advise against use of siponimod while pregnant* (b) (4) *For further information regarding the nonclinical studies' findings related to pregnancy, please refer to the Nonclinical review.*

8.8.3. Pediatrics and Assessment of Effects on Growth

Patients < 18 years old were not exposed to siponimod because of the age exclusions of protocols in the siponimod development program. There were no clinical data submitted derived from pediatric patients. The indication statement for labeling will only refer to an indicated use in adult patients.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

The applicant reports that healthy subjects received siponimod as single doses (0.1 to 75 mg) or as multiple non-titrated doses (0.25 to 20 mg). The single maximum tolerated dose was determined to be 25 mg based upon the occurrence of symptomatic bradycardia after single doses of 75 mg. The highest investigated multiple dose of 20 mg over 28 days was well

tolerated (9 subjects receiving 100 mg on the last day of dosing and 5 subjects receiving up to 200 mg daily for a duration of 3-4 days). Some of the 9 subjects had asymptomatic mild to moderate transient elevations of liver function tests.

The applicant reported that a patient in Study A2201 attempted suicide by taking 41 siponimod 2 mg tablets. The patient survived and experienced transient, asymptomatic, mild elevation in liver transaminases. There were no other AEs reported with this overdose. There were no other suicide attempts attempted by overdose in clinical trials.

Of note, there is presently no specific antidote for siponimod overdose. Dialysis and plasma exchange would not eliminate siponimod from a patient's body to yield a clinically meaningful change.

Abuse Potential

The applicant states that "chemistry, nonclinical and clinical data with siponimod do not indicate any signals of abuse, misuse, or dependence potential in animals or humans, nor do the data demonstrate any potential pharmacological similarities to existing drugs of abuse or psychoactive effects that may be of interest for drug abuse, such as reinforcing, mood-elevating, sedative, stimulant, hallucinogenic or acute cognitive effects." The applicant adds, "[t]hese data are consistent with postmarket data for the pharmacologically similar drug fingolimod, which has not shown any signs of abuse, misuse, diversion, or dependence in the community. Therefore, it can be concluded that siponimod has no abuse or dependence potential and is not expected to be subject to abuse, misuse or diversion in the community, or result in harm to public health because of abuse, misuse or dependence."

Based on nonclinical findings showing no evidence of physical dependency, and an Abuse Potential Assessment incorporating data from clinical studies of siponimod that concluded no risk of abuse or dependence, the applicant did not conduct clinical studies of siponimod with the objective to assess withdrawal or rebound effects.

The applicant recommends that because siponimod does not meet any criteria for any of the schedules listed in the US Controlled Substance Act, and that it should not be a scheduled medication.

> *Reviewer Comment: A consultation from the Controlled Substance Staff (CSS) prior to submission requested nonclinical abuse potential studies. The applicant performed the requested studies and after review, CSS concluded that a human abuse potential study was not necessary for submission with the NDA. Please refer to the CSS consultation for further comments about abuse potential.*

Withdrawal and Rebound

While no specific clinical studies of siponimod were conducted to assess withdrawal or rebound effects, in non-clinical studies, oral administration of siponimod to rats in a physical dependency study, and to monkeys in repeat-dose toxicity studies, did not produce withdrawal syndrome following cessation of dosing.

According to the applicant, in Study A2304, approximately 80% of patients had observations of at least 7 days after stopping study drug and 43.9% had 1 month or more of follow-up. The amount of data from longer periods of follow up is limited (18.2% of patients with at least 3 months of follow-up). Information was also collected for patients who discontinued study drug and had a posttreatment follow up visit 3 months after last dose of study drug in Studies A2201 and A2201E1. Analysis of patients who discontinued therapy did not demonstrate findings consistent with a withdrawal syndrome.

Overall, the applicant states that the available data show no evidence of a rebound effect after discontinuing siponimod treatment, defined as higher levels of clinical (relapses, deterioration in EDSS scores) or MRI inflammatory disease activity compared to baseline or to placebo. On review of the follow-up data, newly occurring or worsening AEs that were observed after the discontinuation of siponimod treatment were generally infrequent and did not show any consistent pattern compared to placebo that would be indicative of withdrawal effects. All AEs occurring 1-30 days after study drug discontinuation were also reported as on-treatment AEs. Patients who discontinued and experienced AEs, disability worsening, and new MRI findings did not experience events that met the defined criteria used to identify “severe exacerbations” associated with fingolimod discontinuation.

> *Reviewer Comment: Regarding rebound, the S1P modulator fingolimod has a labeling warning for severe exacerbations in disability and inflammation following discontinuation. These severe exacerbation events were rare and not noted in the development program for fingolimod likely because the number of patients treated was insufficient to observe a rare outcome and because the durations of observation after discontinuation were too short as the effect can occur 3 months or longer after the cessation of S1P modulator treatment. No such events with a marked increase in EDSS score or large number of new enhancing lesions was noted after discontinuation in either Studies A2201 or A2304. Given that siponimod exerts the same basic sequestration effect on lymphocytes as fingolimod, it is still possible the same withdrawal phenomenon will become apparent with siponimod. Siponimod’s relatively shorter half-life should reduce the window of time when severe rebounds may occur after discontinuation, however. Based on the fingolimod data and risk of severe exacerbations being mechanistically intrinsic to all S1P modulator therapies, the applicant has agreed to a labeling risk of severe exacerbation after discontinuation of siponimod as a Warning and Precaution.*

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Siponimod is not approved in any market for use in treating any indication. The safety databases in this submission, along with the 120-day supplement, represent the known safety experience with siponimod.

8.9.2. Expectations on Safety in the Postmarket Setting

Given the similarity of siponimod to the approved S1P modulator, fingolimod, the expectation in the postmarket setting is that the safety issues identified during the siponimod development program will remain prominent in the postmarketing setting. Given the postmarketing experience with fingolimod, it is prudent to anticipate additional concerns for an increase in the frequency and expansion of the types of adverse events related to bradycardia/atrioventricular block, risk of infections (including reactivation of John Cunningham virus causing progressive multifocal leukoencephalopathy and other opportunistic infections), herpetic infections, hypertension, cutaneous malignancies, and severe exacerbations after discontinuation.

8.9.3. Additional Safety Issues from Other Disciplines

At the time of this review, I am unaware of any safety issues from other disciplines. Please refer to other disciplines' reviews for additional discipline-specific safety concerns.

8.10. Integrated Assessment of Safety

1. Infections

Infections are a well-established adverse event associated the approved S1P modulator, fingolimod, and it appears that siponimod has a similar association. In controlled trials of MS, the percentage of patients exposed to siponimod experienced infection AEs at a nearly identical frequency of patients treated with placebo. Siponimod exposure was associated with similar risk of upper and lower respiratory tract infections and urinary tract infections as placebo-treated patients. However, siponimod treatment was associated with higher rates of herpes infections and herpetic recrudescence (*i.e.,* varicella zoster). Most of the infections reported during siponimod therapy were grades 1 or 2 in severity. In controlled phases of MS trials, in patients administered siponimod, there were infections reported as serious adverse events, but the number of total events was small. Pneumonia and upper respiratory tract SAEs were more common in siponimod-treated patients. Urinary tract infections occurred at high frequencies in both the siponimod and placebo treatment groups in Study A2304, but urinary tract infections were not a frequent in Study A2201, which argues against a generalized higher risk of urinary tract infections in all patients with MS and instead reflects the increased frequency of the urinary dysfunction that occurs in patients with SPMS. There were more cases of varicella reactivation in siponimod-treated

patients, and one SAE of varicella meningitis in a siponimod-treated patient. There were no opportunistic infections reported in controlled phases of MS trials, but there is a recently reported initial case of cryptococcal meningitis in a patient treated with 2 mg siponimod in the extension trial. There were two deaths due to sepsis and one death due to severe pneumonia. The contribution of siponimod to these deaths could be a result of immune suppression caused by sequestration of lymphocytes, though the exact role of siponimod in these deaths is unclear due to mitigating circumstances as discussed in Section 8.4.1.

Infection risk and the risk of opportunistic infections such as progressive multifocal leukoencephalopathy and cryptococcal meningitis should be described in a Warnings and Precautions statement on labeling of siponimod, and the applicant has proposed language appropriate for such a statement.

2. Lymphopenia

Administration of siponimod yields a reduction in serum lymphocytes, predominantly CD4+ and CD8+ subtypes, with relative sparing of neutrophils. Lymphopenia and related treatment emergent AEs occurred more frequently in siponimod treatment groups than in placebo treatment groups. Lymphopenia requiring discontinuation of treatment occurred in approximately 0.2% of patients and only occurred in siponimod treatment groups.

(b) (4)

3. Macular Edema

Macular edema was *a priori* expected to be a treatment-related adverse event due to siponimod's effects on vascular permeability and prior experience with S1P modulators. Macular edema was reported in approximately 2% of patients exposed to siponimod. The frequency of macular edema associated with siponimod exposure is identical to the frequency observed with the approved S1P modulator, fingolimod.

The applicant has proposed a Warnings and Precautions statement for macular edema, and this reviewer agrees with including macular edema among Warnings and Precautions. This reviewer further agrees with the applicant's proposed labeling identifying an increased frequency of macular edema observed in patients with histories of uveitis and diabetes mellitus as is the case with labeling for the approved S1P modulator, fingolimod.

4. Bradycardia/Arrhythmia

Initiation of siponimod requires a 6-day titration to maintenance dose. The dose titration used to initiate siponimod is associated with a reduced rate of cardiac TEAEs as compared to dose initiation without titration. For patients without known cardiac histories, the titration was well-tolerated and adverse events requiring treatment discontinuation were

rare. All but a few obvious symptomatic adverse events in this group rectified without treatment.

In order to determine whether a patient has an occult arrhythmia or to confirm an ongoing issue, all patients should have an ECG prior to initiation of siponimod.

Patients with risk of cardiac adverse events, specifically patients with a current or history of bradycardia or arrhythmias, had new ECG persistent findings and more serious adverse events. These higher risk patients require a pre- and post-dose ECG evaluation on Day 1 of treatment in a monitored setting for safe initiation of siponimod.

Labeling should define the high-risk cardiac group and provide appropriate recommended monitoring after initial dose of not less than 6 hours of observation for high risk patients, and instructions regarding further care if serious adverse events are noted in any patient. Patients in the high-risk cardiac group should have first dose monitoring to include a pre- and a post-dose ECG with 6 hours of in-house physician monitoring. Siponimod should be contraindicated for patients with significant cardiac disease such as heart failure, myocarditis, cardiomyopathy, angina pectoris or myocardial infarction (within 6 months), unstable angina. Siponimod should be contraindicated for patients with significant cardiac conduction disorders such as left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz Type II second degree AV-block or higher-grade AV-block, unless patient has a functioning pacemaker.

5. Malignancy

Siponimod may be associated with increased risk of malignancies. Due to protocol-mandated dermatology evaluations, there was a high frequency of cutaneous malignancies reported in the controlled and long-term safety patient pools. There was not a clear increased risk of all skin malignancies associated with siponimod therapy, but there were cases of malignant melanoma and squamous cell carcinoma reported in the siponimod treatment group in controlled trials without any cases identified in the placebo treatment group despite the same monitoring. The increased attention for skin malignancies was driven by the increased frequency of skin malignancies noted in the postmarketing longitudinal experience with the approved S1P modulator, fingolimod. Siponimod and fingolimod have similar treatment effects on circulating lymphocyte numbers and in many key respects have nearly identical treatment outcomes. Therefore, it is reasonable that the increased risk of skin malignancies associated with fingolimod therapy will be observed with siponimod. Labeling should provide data regarding melanoma risk appearing increased with siponimod and otherwise reference fingolimod's Warning and Precautions regarding cutaneous malignancies as a risk of S1P modulator therapy. The applicant should collect postmarketing reports of serious skin malignancies and provide them to the Division in a timely fashion as part of enhanced pharmacovigilance for skin malignancies.

Other malignancies appeared at similar frequencies between siponimod and placebo treatment groups, apart from seminomas. There is no specific mechanism to explain why S1P modulation would be a risk factor for seminoma. The most plausible mechanism of this increased risk would be a loss of circulating lymphocytes and reduced immune surveillance, but this broadly applicable mechanism would result in an increased frequency in all malignancies. This mechanism does not explain why an increased risk of seminoma was not seen with a less selective S1P modulator, fingolimod, unless siponimod's selectivity reduces a very specific lymphocyte pool used for this surveillance that was not appreciated in the data from the completed clinical trials.

This reviewer recommends increased pharmacovigilance for all malignancies with timely reporting of malignancies and annual summaries.

6. Seizures

The SAE rate of 1.7% (odds ratio=3.4) for seizures and related events is not unexpected given the expected observation of seizure events one would anticipate in the patient population with MS who are at significantly higher risk of developing seizures than the general population. However, the relative absence of SAEs related to seizure in the placebo treatment group, who presumably are also at the same high risk of seizures due to MS, suggests that siponimod therapy may be associated with higher risk than the expected population risk of seizures, even if the observed frequency of 1.7% is well below the rate one expected to see based on natural history studies of epilepsy in patients with MS. I therefore agree with the applicant's proposed labeling that will report the controlled population data and the observed frequency of seizures in siponimod 2 mg and placebo-treated patients in Section 6 to provide prescribers and patients with notice of the possible association.

7. Respiratory Effects

As with other S1P modulators, siponimod was associated with a reduction in FEV1, FVC, and DLCO. While treatment emergent respiratory disorders adverse events such as dyspnea, cough, and airway restriction occurred in less than 5% of patients taking siponimod, respiratory events such as cough and dyspnea were more frequently reported in siponimod-treated patients, and there was a serious adverse event and a treatment discontinuation due to dyspnea in the siponimod treatment group and none in the placebo treated group.

Labeling should indicate in a Warnings and Precautions statement about the respiratory effects of siponimod.

Due to the uncertainty about the persistence and long-term consequences of reduced lung functional measures in a patient population with a progressive neurological disease that can

compromise respiratory function, we are requiring the applicant to conduct a postmarketing study of lung function measures (FEV1, FVC, and DLCO) and respiratory-related adverse events in patients who initiate siponimod (b) (4)

8. Embolic and Thrombotic Events

A disproportionate number of strokes and myocardial infarctions were reported in siponimod-treated patients in controlled trials. Analysis of these cases confirmed the presence of concurrent risk factors, but confounding factors alone did not fully explain the larger number of cases in the siponimod treatment group. The difference between the placebo and siponimod treatment groups was small. Further data supplied by the long-term safety pool did not show an augmentation of the potential safety signal.

Language in Section 6 describing the frequency of thromboembolic events in clinical trials appears adequate and is how similar risk was described for fingolimod.

9. Liver Injury

Siponimod causes persistent elevations in AST, ALT, and GGT. These elevations are not associated with fulminant hepatic failure. The increased transaminase levels in serum reached by most patients were not associated with any symptoms. Discontinuation of siponimod leads to reversal of observed changes. A baseline evaluation of hepatic enzymes and monitoring during treatment can mitigate potential risks of liver injury.

Labeling should provide appropriate instructions regarding monitoring and symptoms concerning for liver injury in a Warnings and Precautions statement.

10. Elevated total cholesterol

Siponimod therapy was associated with a small increase in serum total cholesterol that was sustained throughout the entire duration of treatment. Hypercholesterolemia adverse events were reported more frequently in siponimod treatment groups than in placebo treatment groups in controlled trials.

The absolute increase in total cholesterol was less than 1 mmol/L and had high variability. The difference in adverse events between the siponimod and placebo treatment groups was small, was certainly multifactorial, and of unclear clinical significance because they were not associated with an increase in adverse events such as increased low-density lipoprotein or diminished high density lipoprotein. The evidence does not appear to support a significant risk that merits attention in labeling. The increased risk of vascular events in siponimod trials was not due to cholesterol effects because the association between high

cholesterol, specifically elevated low-density lipoprotein, requires decades to manifest.

11. Genotype
There are differences in enzymatic activity for the CYP2C9 enzyme that processes siponimod, and there were some differences in frequencies of reported adverse events with clear association to siponimod therapy such as macular edema between patients with the high and low CYP2C9 enzymatic activities. The applicant has proposed to continue a genotype-based dosing of siponimod that was based on pharmacokinetics and pharmacodynamic testing to ensure that patients have the same approximate serum exposure regardless of their genotype and relative enzyme function. Labeling should recommend that patients with the highest metabolism (*1/*1, *1/*2, and *2/*2) should use a maintenance dose of 2 mg and that patients with reduced metabolism (*1/*3 and *2/*3) should use a maintenance dose of 1 mg. Labeling should indicate that patients with the *3/*3 genotype will be contraindicated from treatment with siponimod. (b) (4) Additionally, because genotyping of CYP2C9 is required before initiation of siponimod to determine dosing/eligibility, the applicant will be required to validate a commercial genotype assay for this purpose. The existing commercial assays for assessment of CYP2C9 for warfarin dose adjustment can be used "off label" until an assay is validated for siponimod specifically.

12. Falls and Dizziness
In controlled MS trials, there were more SAEs of falls accompanied by traumatic injuries such as lacerations, concussions, and fractures in the siponimod treatment groups than in placebo treatment groups. The overall frequencies of falls, however, were less than 1% different between treatment groups, 11.1% versus 10.2% for siponimod and placebo, respectively. Falls and trauma are common in MS, and there was an absence of a clear difference in the frequency and nature of the falls described in the siponimod group to suggest a treatment effect. While the mismatch in falls was not compelling, dizziness was more frequent in siponimod, 7.0% versus 5.3%. Dizziness should be included in Section 6 of labeling as a difference noted between siponimod and placebo.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Finalized prescription labeling is not available at the time of this review's completion. Labeling negotiations with the applicant are ongoing.

10.2. Nonprescription Drug Labeling

Not applicable. Siponimod will be available by prescription only in the U.S.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS does not appear to be necessary for the safe use of siponimod in the indicated population. Please refer to the review conducted by the DRISK review team for further details of recommendations regarding risk evaluation.

12. Postmarketing Requirements and Commitments

At the time of completion of this review, it appears there will be five postmarketing studies requested of the applicant, two related to pregnancy, one related to pulmonary function test changes, a pediatric study, and juvenile toxicology studies to support a pediatric study requirement. There is a postmarketing commitment to develop a genotype assay for CYP2C9.

The first study, a postmarketing requirement, will be a prospective pregnancy exposure registry cohort analyses in the United States that will compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to siponimod during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to siponimod before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small for gestational-age births, and any other adverse outcomes, including postnatal growth and development. The applicant should assess outcomes throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, should be assessed through at least the first year of life.

The second requested study, a postmarketing requirement, will be a pregnancy outcomes study using a different study design than provided for the prospective pregnancy exposure study (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to siponimod during pregnancy compared

to an unexposed control population.

The third study, a postmarketing requirement, requested of the applicant will be a prospective study of the respiratory effects, specifically, the changes in FEV1, FVC, and DLCO associated with siponimod, (b) (4)
Patients will be followed after discontinuation (b) (4)

The fourth study, a postmarketing requirement, will be a juvenile rat toxicology study to evaluate effects of siponimod on growth, reproductive development, and neurological and neurobehavioral development. This study is necessary to support the proposed pediatric study commitment.

The fifth study, a postmarketing requirement, is a study to be conducted in patients with relapsing forms of MS ages 10-17. This study would be conducted in two parts. The first part will be a PK and PD assessment of the genotyped based dosing in pediatric patients to confirm that systemic exposures at these does are similar to those of adult patients with those genotypes. In part two, the applicant should conduct a controlled, blinded trial with an appropriate comparator to satisfy this requirement.

The applicant will need to validate an assay for the CYP2C9 genotyping that is required to determine genotyping for maintenance dose and contraindication. This will be a postmarketing commitment. Presently, the applicant can rely on the CYP2C9 genotype assay currently marketed for determining genotype of CYP2C9 to determine appropriate warfarin therapy dose, but such use will be considered "off label" until the applicant can validate a commercially available assay for genotype in the context of siponimod therapy.

13. Appendices

13.1. References

1. 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.
2. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. *Brain.* 1989;112 (Pt 6):1419-1428.
3. Confavreux C, Vukusic S. The clinical course of multiple sclerosis. *Handb Clin Neurol.* 2014;122:343-369.

4. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014;83(3):278-286.
5. Ascherio A, Munger KL. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention-An Update. *Seminars in neurology.* 2016;36(2):103-114.
6. Tutuncu M, Tang J, Zeid NA, et al. Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. *Mult Scler.* 2013;19(2):188-198.
7. Turner AP, Alschuler KN, Hughes AJ, et al. Mental Health Comorbidity in MS: Depression, Anxiety, and Bipolar Disorder. *Current neurology and neuroscience reports.* 2016;16(12):106.
8. Vodusek DB. Urogenital dysfunction in patients with multiple sclerosis. *Acta neuropsychiatrica.* 2009;21 Suppl 2:22-27.
9. Gasparini S, Ferlazzo E, Ascoli M, et al. Risk factors for unprovoked epileptic seizures in multiple sclerosis: a systematic review and meta-analysis. *Neurol Sci.* 2017;38(3):399-406.
10. Cameron MH, Nilsagard Y. Balance, gait, and falls in multiple sclerosis. *Handb Clin Neurol.* 2018;159:237-250.
11. Ferrari A, Spaccapelo L, Gallesi D, Sternieri E. Focus on headache as an adverse reaction to drugs. *The journal of headache and pain.* 2009;10(4):235-239.
12. Coote S, Finlayson M, Sosnoff JJ. Level of mobility limitations and falls status in persons with multiple sclerosis. *Archives of physical medicine and rehabilitation.* 2014;95(5):862-866.
13. Tseng CH, Huang WS, Lin CL, Chang YJ. Increased risk of ischaemic stroke among patients with multiple sclerosis. *European journal of neurology.* 2015;22(3):500-506.
14. Chou IJ, Kuo CF, Tanasescu R, et al. Epilepsy and associated mortality in patients with multiple sclerosis. *European journal of neurology.* 2019;26(2):342-e323.
15. Burman J, Zelano J. Epilepsy in multiple sclerosis: A nationwide population-based register study. *Neurology.* 2017;89(24):2462-2468.
16. Gao F, Gao Y, Meng F, Yang C, Fu J, Li Y. The Sphingosine 1-Phosphate Analogue FTY720 Alleviates Seizure-induced Overexpression of P-Glycoprotein in Rat Hippocampus. *Basic & clinical pharmacology & toxicology.* 2018;123(1):14-20.
17. Gao F, Liu Y, Li X, Wang Y, Wei D, Jiang W. Fingolimod (FTY720) inhibits neuroinflammation and attenuates spontaneous convulsions in lithium-pilocarpine induced status epilepticus in rat model. *Pharmacology, biochemistry, and behavior.* 2012;103(2):187-196.
18. Feinstein A, Pavisian B. Multiple sclerosis and suicide. *Multiple Sclerosis Journal.* 2017;23(7):923-927.
19. Tauil CB, Grippe TC, Dias RM, et al. Suicidal ideation, anxiety, and depression in patients with multiple sclerosis. *Arq Neuropsiquiatr.* 2018;76(5):296-301.
20. Tremlett H, Zhao Y, Devonshire V. Natural history comparisons of primary and secondary progressive multiple sclerosis reveals differences and similarities. *J Neurol.* 2009;256(3):374-381.

21. Albor C, du Sautoy T, Kali Vanan N, Turner BP, Boomla K, Schmierer K. Ethnicity and prevalence of multiple sclerosis in east London. *Mult Scler.* 2017;23(1):36-42.
22. Murtonen A, Kurki S, Hanninen K, Soilu-Hanninen M, Sumelahti ML. Common comorbidities and survival in MS: Risk for stroke, type 1 diabetes and infections. *Multiple sclerosis and related disorders.* 2018;19:109-114.
23. McGlynn KA, Trabert B. Adolescent and adult risk factors for testicular cancer. *Nature reviews Urology.* 2012;9(6):339-349.
24. Shanmugalingam T, Soultati A, Chowdhury S, Rudman S, Van Hemelrijck M. Global incidence and outcome of testicular cancer. *Clinical epidemiology.* 2013;5:417-427.
25. Marrie RA, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of cancer in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2015;21(3):294-304.

13.2. Financial Disclosure

Covered Clinical Studies (Name and/or Number): CSIPONIMODA2304, CSIPONIMODA2201, CSIPONIMODA2201E1

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: • Study A2304: 852 U.S., 3632 non-U.S. • Study A2201: 85 U.S., 559 non-U.S. • Study A2201E1: 107 U.S., 574 non-U.S.		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0 (all studies)		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): • Study A2304: 20 • Study 2201: 5 • Study A2201E1: 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

<table>
<tr><td colspan="3">influenced by the outcome of the study: 0

Significant payments of other sorts:

• Study A2304: 20
• Study 2201: 5
• Study A2201E1: 5

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in applicant of covered study: 0</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements?</td><td>Yes ☒</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided?</td><td>Yes ☒</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A</td></tr>
<tr><td>Is an attachment provided with the reason?</td><td>Yes ☒</td><td>No ☐ (Request explanation from Applicant)</td></tr>
</table>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL R LEE
03/26/2019 11:38:53 AM