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*APPLICATION NUMBER:*

**209884Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date:</b>	March 26, 2019
<b>From:</b>	Paul Lee, MD, PhD, CDTL, DNP Eric Bastings, MD, Deputy Director, DNP Billy Dunn, MD, Director, DNP Ellis Unger, MD, Director, ODE-I
<b>Subject:</b>	Summary Memorandum
<b>NDA#:</b>	209884
<b>Applicant:</b>	Novartis Pharmaceuticals Corporation
<b>Date of Submission:</b>	June 28, 2018
<b>PDUFA Goal Date:</b>	March 26, 2019
<b>Proprietary Name:</b>	Mayzent
<b>Established or Proper Name:</b>	Siponimod
<b>Dosage Form(s):</b>	0.25 mg and 2 mg
<b>Applicant Proposed Indication(s)/Population(s):</b>	Treatment of adult patients with secondary progressive multiple sclerosis
<b>Action or Recommended Action:</b>	Approval
<b>Approved/Recommended Indication(s)/Population(s) (if applicable):</b>	Treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	David Jones Paul Lee (Team Lead)
Biometrics Review	Xiang Ling Kun Jin (Team Lead)
Pharmacology Toxicology Review	Richard Siarey Lois Freed (Team Lead)
OPQ Review	Rajan Pragani Suong Tran Mariappan Chelliah Xueli Zhu Nallaperumal Chidambaram Joan Zhao Ta-Chen Wu

<b>Material Reviewed/Consulted</b> OND Action Package, including:	<b>Names of discipline reviewers</b>
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OPDP	Domenic D'Alessandro
OSI	Cheryl Grandinetti Kassa Ayalew (Team Lead)
CDTL Review	Paul Lee
Microbiology	Not applicable
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OSE/DMEPA	Chad Morris Lolita White (Team Lead)
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DTOP	Wiley Chambers (Team Lead)
OMP	Christine Bradshaw Aline Moukhtara (Team Lead)
IRT/QT	Hongshan Li Moh Jee Ng (Team Lead)

DNP=Division of Neurology Products  
 ODE-I=Office of Drug Evaluation-I  
 OND=Office of New Drugs  
 OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management  
 DPARP=Division of Pulmonary, Allergy, and Rheumatology Products  
 DTOP=Division of Transplant and Ophthalmology Products  
 IRT/QT=Interdisciplinary Review Team for QT studies

## 1. Benefit-Risk Assessment

### Benefit-Risk Integrated Assessment

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator that binds selectively to the S1P1 and S1P5 receptors, proposed by the applicant for the treatment of secondary progressive multiple sclerosis (MS). Another S1P receptor modulator not selective for specific S1P receptor subtypes, fingolimod, is approved for the treatment of relapsing forms of MS. S1P receptor modulators, including siponimod and fingolimod, reduce lymphocyte counts by preventing lymphocyte egress from lymph nodes. Fingolimod has a known risk for bradyarrhythmia and atrioventricular (AV) conduction block. While the S1P receptor subtype 1 appears to mediate lymphocyte sequestration, some of the cardiac and vascular effects of S1P modulators are attributed to the S1P receptor subtype 3. A more selective modulator that binds to receptor subtype 1, but not subtype 3, such as siponimod, would be expected to have a lower incidence of cardiovascular effects, without impacting effects on lymphocyte sequestration.

Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (secondary progressive MS with relapses), are a group of chronic and potentially disabling MS phenotypes of apparent autoimmune etiology characterized by episodes of worsening focal neurological deficits and disseminated lesions of demyelination. Symptoms include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. Over several years, many, but not all, patients with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. In some patients, disability may accrue progressively in the absence of obvious relapse events, a process termed secondary progressive disease. Secondary progressive disease that occurs with continued relapses is described as active secondary progressive disease, with the relapses being the clinical manifestation, in part, of an inflammatory demyelination that is presumed to be distinct from the pathogenesis of the progressive component of the disease. In the active secondary progressive phase of the disease, patients can accrue disability both from acute relapses and from the progressive component of the disease. Active secondary progressive disease and relapsing-remitting disease overlap in evolution. Categorization as secondary progressive disease is based on clinical judgment; there are no clinical findings or biomarkers that meaningfully define or predict the phenotypes of relapsing forms of MS. A continued progression of disability with no concurrent inflammatory activity and no clinical relapses is described as non-active secondary progressive MS. Importantly, to support an indication for the treatment of secondary progressive MS (as distinct from active secondary progressive MS), it is critical that efficacy be established in patients who have non-active secondary progressive MS (SPMS), and that the drug effect be clearly distinguished from an effect on inflammatory demyelination and clinical relapses that are present in patients with active SPMS (a relapsing form of MS). Multiple drugs have been approved for the treatment of relapsing forms of MS. Conversely, there is a significant unmet medical need for the treatment of non-active SPMS.

The applicant presents the results from one adequate and well-controlled clinical trial (Study CBAF312A2304; A2304 in this review) as the primary basis of support for the effectiveness of siponimod for the treatment of SPMS. The applicant provides additional supportive data from a double-blind, placebo-controlled, Phase 2 safety and efficacy dose-ranging study (Study CBAF312A2201; A2201 in this review) in patients with relapsing-remitting multiple sclerosis (RRMS).

Study A2304 provides substantial evidence of efficacy. Analysis of the primary efficacy endpoint, 3-month confirmed disability progression, show a 21% relative risk reduction compared to placebo, a finding that is highly significant ( $p < 0.0134$ ), and supported by a number of sensitivity analyses. A total of 26.3% of patients with SPMS taking siponimod experienced progression of their disability, as compared to 31.7% of patients taking placebo, over a median duration of 17.8 months.

There was no significant benefit over placebo for the first key secondary endpoint, the time to 20% worsening on the Timed 25 Foot Walk (T25FW) test. With a sequential testing strategy, there is no basis for formal hypothesis testing in subsequent analyses. Nevertheless, the effect sizes and extremely low nominal  $p$ -values ( $p < 0.0001$ ) for the annualized relapse rate (55% reduction) and T2 lesion volume change, endpoints that are typically assessed in MS trials and represent distinct domains from the primary endpoint, lend additional persuasiveness to the evidence of efficacy. In totality, the results from Study A2304 provide substantial evidence of effectiveness of siponimod.

Study A2201 provides additional supportive data, demonstrating that the 2-mg siponimod dose achieves near-maximal reduction of combined unique active lesions (CUAL) on MRI during 3 months of treatment, with a nominally significant 66% reduction in the annualized relapse rate.

The results, however, do not support the indication sought by the applicant, as insufficient evidence of a treatment benefit has been provided for patients with non-active (non-relapsing) secondary progressive disease, as described in greater detail in this memo. Patients in Study A2304 who benefitted from the drug do fit the clinical phenotype of patients with active SPMS. It is noteworthy that 36% of patients in Study A2304 had one or more relapses in the 2 years prior to study entry, and that 22% of patients with available imaging had one or more gadolinium-enhancing lesions on their baseline MRI scan, indicating active disease. The application also provides evidence of a siponimod effect on the inflammatory aspects of multiple sclerosis. The indication supported by the submitted data is therefore for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. It must be emphasized that thirteen different therapies have been approved to treat relapsing forms of multiple sclerosis, and that the population for which siponimod will be indicated is the same as for those drugs. The siponimod labeling will be the first explicitly describing that relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, but all sponsors of the drugs approved for the treatment of relapsing forms of multiple sclerosis will be requested to update their indication statements to conform with this contemporary nomenclature.

The safety profile of siponimod was largely similar to that of fingolimod, with the exception of apparently milder, but not absent, cardiac effects. As fingolimod, siponimod can cause bradycardia and atrioventricular conduction delays, and the treatment should be titrated to the maintenance dose. Patients with a history of bradycardia or atrioventricular conduction delay are at higher risk of experiencing an adverse event related to cardiac toxicity than patients without such history. Patients treated with siponimod are also at risk for infections, macular edema, liver injury, hypertension, and respiratory effects consistent with a restrictive airway disease. Progressive multifocal leukoencephalopathy, severe exacerbations after discontinuation, and posterior reversible encephalopathy syndrome are assumed risks associated with this class of therapies, even though they were not observed in siponimod clinical trials.

Based on the results of Study A2304, for every 100 patients with active SPMS taking siponimod instead of placebo over a period of ~18 months, progression of disability would be prevented in (mean) 5.4 patients and approximately one patient would be expected to experience a severe or life-threatening adverse reaction, without a change in mortality.

The overall benefit-risk profile is very similar to that of fingolimod, and siponimod will be approved for the same indication.

#### Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (SPMS with relapses), are a group of chronic and potentially disabling MS phenotypes of apparent autoimmune etiology characterized by episodes of worsening focal neurological deficits and disseminated lesions of demyelination. The usual age of onset of relapsing forms of MS is 20 to 50 years. Symptoms include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. Over several years, many, but not all, patients with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. In some patients, disability may accrue progressively in the apparent absence of relapse events, a process termed secondary progressive disease. Secondary progressive disease that occurs with continued relapses is</li> </ul>	<p>Relapsing forms of MS are serious and disabling. There is clinical and pathological evidence that the disease processes promoting relapsing forms of the disease are distinct from those in progressive forms of MS.</p> <p>Patients with an initial diagnosis of relapsing-remitting MS can acquire what appears to be a parallel, progressive disabling disease process. Clinically, the addition of a progressive disability independent of relapses is termed "secondary progressive" disease. Some</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>described as active secondary progressive disease, with the relapses being the clinical manifestation, in part, of an inflammatory demyelination that is presumed to be distinct from the pathogenesis of the progressive component of the disease. The clinical course of relapsing forms of MS varies widely. Some patients may have a relatively benign manifestation with few discrete relapse events; others may become severely disabled after only a few years. There are no reliable predictors of outcome. Active secondary progressive disease and relapsing-remitting disease overlap in evolution. Assignment of a secondary progressive disease diagnosis is based on clinical judgment; there are no clinical findings or biomarkers that meaningfully define or predict the phenotypes of relapsing forms of MS.</p> <ul style="list-style-type: none"> <li>Progressive forms of MS, which include primary progressive and SPMS without relapses, are characterized by a steady accumulation of disability without relapses. There are many clinical and pathological studies that suggest different disease processes in relapsing and progressive forms of MS. It is suggested that progressive disease is a neurodegenerative process; however, there is not a clearly defined pathophysiology or mechanism that explains the development of disability in patients with progressive forms of MS who are not experiencing relapses.</li> </ul>	<p>patients with secondary disease will continue to have frequent or infrequent relapses, which define active secondary progressive disease. Patients with secondary progressive disease who experience progressive accumulation of disability with cessation of relapses would be described as having non-active secondary disease.</p> <p>The transition of a patient from a relapsing-remitting to an active secondary progressive disease is only evident in hindsight after sufficient disability has accumulated without confirmed coincident relapses to provide a basis for the clinical judgment. There is no accepted examination finding or clinical test that can identify progressive disease with certainty.</p>
<p><b>Current Treatment Options</b></p>	<ul style="list-style-type: none"> <li>Thirteen different therapies are approved to treat relapsing forms of MS. All of these therapies reduce the relapse rate, and many include disability progression outcomes in their labeling. All except glatiramer acetate and mitoxantrone include at least one trial that showed a statistically significant treatment effect for a disability progression outcome.</li> </ul>	<p>Multiple drugs are approved for the treatment of relapsing forms of multiple sclerosis. A single drug, mitoxantrone, is approved for the treatment of secondary progressive and "progressive relapsing multiple sclerosis," an older term synonymous with active secondary</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>Fingolimod was the first sphingosine-1-phosphate (S1P) receptor modulator approved for the treatment of relapsing forms of multiple sclerosis in patients aged 10 years and older. Fingolimod reduces lymphocyte counts by preventing lymphocyte egress from lymph nodes, a process that is mediated by sphingosine-1-phosphate receptors. Fingolimod is a nonselective modulator of sphingosine-1-phosphate receptors; siponimod is selective for sphingosine-1-phosphate receptor subtypes 1 and 5. Siponimod's development program was informed by fingolimod's clinical programs and post-marketing experience.</li> <li>Mitoxantrone is approved for the treatment of secondary progressive and "progressive relapsing multiple sclerosis," an older term synonymous with active secondary progressive disease. Mitoxantrone is an anti-neoplastic therapy with significant risks. Mitoxantrone is rarely used in the treatment of multiple sclerosis because of cardiac toxicity and the lifetime risk of secondary leukemia, which are exposure-dependent and therefore limit the duration of administration.</li> </ul>	<p>progressive disease. There is an unmet medical need for a therapy that has less toxicity than mitoxantrone for the treatment of patients with secondary progressive multiple sclerosis.</p> <p>Fingolimod, a drug exerting non-specific sphingosine-1-phosphate (S1P) receptor modulation, is an effective therapy for relapsing forms of multiple sclerosis, with a well-established safety profile. Therapies binding to S1P receptors can cause life-threatening bradyarrhythmias and atrioventricular conduction delays. Chronic administration of S1P modulators is associated with an increased risk for serious infections, macular edema, liver injury, hypertension, cutaneous malignancies, respiratory effects, and severe increases in disability after discontinuation.</p> <p>Although S1P receptor subtype 1 modulation appears to mediate lymphocyte sequestration, some of the cardiac and vascular effects of fingolimod are attributed to S1P receptor subtype 3. A more selective modulator that binds to receptor subtype 1, but not subtype 3, would be predicted to reduce the likelihood of some cardiovascular effects without impacting effects on</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		lymphocyte sequestration.
<b>Benefit</b>	<ul style="list-style-type: none"> <li>Over a median 18 months of observation, 26.3% of patients in the siponimod group experienced confirmed progression in disability, compared to 31.7% of patients in the placebo group. Thus, the absolute reduction in risk of progression was 5.4%, and the relative risk reduction was 21% (hazard ratio = 0.79, <math>p = 0.0134</math>). Based on the mean effect size in this study, one would need to treat 19 patients for 18 months in order to prevent one confirmed progression, i.e., the number needed to treat (NNT) over 18 months is 19. Calculation of a NNT over one year is problematic, because disability does not progress at a constant rate with respect to time.</li> <li>Patients in the siponimod and placebo groups had estimated annual relapse rates of 0.071 and 0.16, respectively, a difference that was nominally statistically significant (<math>p &lt; 0.0001</math>). Thus, the absolute reduction in relapse rate was 0.089 relapses/year (a relative reduction of 55.5%). Based on the mean treatment effect size, one would need to treat 11 patients with siponimod for 1 year to prevent 1 relapse.</li> </ul>	<p>A pivotal trial in patients with SPMS, with and without recent documented relapses, showed a treatment-related reduction in confirmed disability progression (confirmation through a 3-month period). The benefit was only established in patients with recent MS relapses (i.e., active disease).</p> <p>The pivotal trial results provide insufficient evidence to support a claim that siponimod is effective in patients with SMPS who are not continuing to have relapses, i.e., in patients with non-active SMPS.</p> <p>The data from siponimod clinical trials support that siponimod reduces the frequency of MS relapses.</p>
<b>Risk and Risk Management</b>	<ul style="list-style-type: none"> <li>Siponimod, a selective sphingosine-1-phosphate receptor modulator, has a safety profile similar to the approved non-selective sphingosine-1-phosphate receptor modulator, fingolimod.</li> <li>The most common adverse events in the safety data from the controlled study portion of the pivotal trial in MS (at least 5% and at least as frequent as placebo) were: headaches (14.5%), falls (11.6%), hypertension (10.5%), upper respiratory tract infections (8.3%), dizziness (6.8%), nausea (6.7%), diarrhea (6.4%), AST increased (5.9%),</li> </ul>	<p>Siponimod can cause infections, macular edema, bradycardia, atrioventricular conduction delays, liver injury, hypertension, and respiratory effects. Progressive multifocal leukoencephalopathy, severe exacerbation after discontinuation, and posterior reversible encephalopathy syndrome are assumed risks associated with this class of therapies, even if they were not</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>and pain in extremities (5.5%).</p> <ul style="list-style-type: none"> <li>• There was a 1.4% difference between siponimod (12.6%) and placebo (11.2%) treatment groups in the frequency of adverse events reported as grade 3 or grade 4 (i.e., severe or medically significant but not immediately life-threatening, or life-threatening) during the controlled study in patients with SPMS. In the same study, the frequency of death was 0.46% in patients treated with siponimod, versus 0.73% of patients on placebo.</li> <li>• There was a low frequency of adverse events reported with siponimod treatment that led to treatment discontinuation. In the controlled trial in patients with SPMS, 8.2% of patients discontinued siponimod due to an adverse event, most commonly bradyarrhythmia (1.2%), versus 4.9% of patients on placebo (most often because of fatigue, a reason for discontinuation in 0.7% of patients on placebo).</li> <li>• The frequency of adverse events requiring treatment was about the same in patients treated with siponimod than in those on placebo (~69% in both).</li> <li>• Siponimod can cause bradycardia and atrioventricular conduction delays at the time of treatment initiation. Siponimod dosing is initiated at a low starting dose, with titration to the maintenance dose. Patients with a history of bradycardia or atrioventricular conduction delay are at higher risk of experiencing an adverse event related to cardiac toxicity than patients without such history. Patients taking drugs that reduce heart rate and slow atrioventricular conduction are also at greater risk.</li> <li>• Siponimod increases the risk of certain infections. A higher frequency of</li> </ul>	<p>observed in trials with siponimod. These significant concerns warrant inclusion in labeling.</p> <p>Most adverse events associated with siponimod therapy were not medically serious, and were treatable, or reversible upon discontinuation.</p> <p>Patients should have an electrocardiogram, complete blood count, ophthalmic examination, CYP2C9 genotyping, and liver function tests prior to initiation of siponimod.</p> <p>(b) (4)</p> <p>Patients with histories of bradycardia or bradyarrhythmias require first-dose monitoring in a medical setting. The drug is contraindicated in patients with significant heart disease.</p> <p>The maintenance dose is determined by genotype. Less extensive metabolizers should receive a maintenance dose of 1 mg instead of 2 mg. Siponimod is contraindicated in patients with the CYP2C9 *3/*3 genotype.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>herpetic infections was observed in patients in the siponimod treatment arms of placebo-controlled trials.</p> <ul style="list-style-type: none"> <li>Siponimod is mainly metabolized via CYP2C9. Analysis of patients with CYP2C9 polymorphisms revealed that patients with *1/*3 and *2/*3 genotypes had reduced metabolism of siponimod (by more than 50%) and that patients with *3/*3 genotype had essentially no metabolism of siponimod.</li> <li>Labeling can sufficiently mitigate the identified safety risks.</li> </ul>	<p>A Risk Evaluation and Management Strategy is not necessary to ensure that the benefits of siponimod outweigh the risks of cardiac conduction abnormalities, infections, and other adverse events.</p>

## 2. Background

This application contains data in support of the safety and effectiveness of siponimod, a sphingosine-1-phosphate (S1P) receptor modulator selective for the S1P1 and S1P5 receptor subtypes, administered daily as an oral tablet, proposed by the applicant for the treatment of secondary progressive multiple sclerosis (SPMS). Siponimod is a new molecular entity (NME) that has not been approved for any indication and has not previously been the subject of any marketing application.

Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease (RRMS), and active secondary progressive disease (SPMS with relapses), are a group of chronic and potentially disabling MS phenotypes of apparent autoimmune etiology characterized by episodes of worsening focal neurological deficits and disseminated lesions of demyelination. The usual age of onset of relapsing forms of MS is 20 to 50 years. Symptoms include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. Over the years, many, but not all, patients with relapsing-remitting disease experience some degree of persistent disability that may gradually worsen over years, as a result of incomplete recovery of the disability that resulted from MS relapses. In some patients, disability may accrue progressively independent of relapse events, a process termed secondary progressive disease. There are many clinical and pathological studies that suggest that the disease processes in relapsing and progressive forms of multiple sclerosis are different. It has been suggested that progressive disease is a neurodegenerative process; however, there is not a clearly defined pathophysiology or mechanism that explains the development of disability in patients with progressive forms of MS who are not experiencing relapses.

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 (in particular in the early phase of SPMS) and worsening of disability can occur in RRMS. The duration of the transition from RRMS to SPMS is unknown but thought to last a few years. The distinction between RRMS and SPMS may be even more difficult in patients who are taking a medication for MS. To distinguish a drug 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), patients included in a trial should, by history, have a sufficiently long relapse-free period prior to the trial to make it as likely as possible that they will not experience relapse during the study. There is, at this time, not an accepted period of time without relapses that defines the onset of non-relapsing SPMS, although some experts have suggested a 36-month period. As noted below, the division has suggested a 2-year period as possibly sufficient, although a longer period may be needed.

In the current nomenclature, patients with early secondary progressive disease who continue to experience relapses, i.e., continue to have a relapsing form of the disease, are described as having “active” secondary progressive disease. Here, the term “active” reflects the inflammatory demyelination that is still present (and presumed to be distinct from the pathogenesis of the progressive component of the disease), and the resulting continuation of clinical relapses. It is important to note that drugs approved for “relapsing forms of MS” are approved to treat patients with active SPMS (also described as relapsing SPMS). Patients who later transition to progressive disease with no inflammatory demyelination and no clinical relapses, are described in the current nomenclature as having “non-active” SPMS.

To support an indication for the treatment of SPMS, it is critical that efficacy be established in patients who have “non-active” SPMS, and that the drug effect be clearly distinguished from an effect on a relapsing form of MS (which includes active SPMS), for which multiple drugs have been approved.

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator described as selective for the S1P1 and S1P5 receptor subtypes. Fingolimod was the first sphingosine-1-phosphate (S1P) receptor modulator approved by FDA. Fingolimod’s indication is for the treatment of relapsing forms of MS in patients aged 10 years and older. Fingolimod administration reduces lymphocyte counts by preventing lymphocyte egress from lymph nodes, a process that is mediated by sphingosine-1-phosphate subtype 1 receptors. Fingolimod is a nonselective modulator of sphingosine-1-phosphate receptors; siponimod is selective for sphingosine-1-phosphate receptor subtypes 1 and 5. Siponimod’s development program was informed by fingolimod’s clinical programs and postmarketing experience.

Siponimod binds preferentially to the S1P1 and S1P5 receptors, causing initial agonism and ultimately internalization of these receptor subtypes. The S1P1 receptor is used by lymphocytes to egress from lymph nodes. Loss of surface S1P1 receptors yields an increase in lymphocytes remaining in the lymph node. This sequestration of lymphocytes yields a reduction in serum lymphocytes and is presumed to be the basis of the clinical treatment effects of siponimod.

The applicant presents the results from one adequate and well-controlled clinical trial as the primary basis of support for the effectiveness of siponimod for the treatment of SPMS. This was a double-blind, placebo-controlled, Phase 3 safety and efficacy study (Study A2304) in patients with SPMS. The applicant provides additional supportive data from a double-blind, placebo-controlled, Phase 2 safety and efficacy dose-ranging study (Study A2201) in patients with RRMS. Although both studies used a placebo control, they had different designs, used different oral doses of siponimod, and used different outcome measures to assess treatment effects in patient populations with relapsing-remitting and SPMS.

## Regulatory History

The early regulatory history of siponimod development focused on meetings related to nonclinical data and safety. The IND was placed on partial clinical hold in March 2009, because of a lack of nonclinical data to support the proposed Phase 2 dose-ranging trial (A2201). Additional nonclinical studies led to removal of the hold in May 2009.

[REDACTED] (b) (4)  
In November 2011, the applicant submitted two Phase 3 protocols for clinical trials in patients with relapsing forms of MS and requested a Special Protocol Assessment (SPA) of these protocols. The Agency issued a no agreement letter for these SPAs in January 2012.

In April 2012, the applicant submitted the protocol for Study A2304 with a request for a SPA. SPA agreement was reached in August 2012. A Fast Track application for the indication of the treatment of SPMS was granted in September 2012, [REDACTED] (b) (4)

There were two proposed amendments to the SPA agreement; the Agency only reached agreement with the applicant on the first amendment, which reduced the cardiac monitoring for patients with no history of cardiac issues and altered the trial epochs.

[REDACTED] (b) (4)

In September 2017, the applicant requested a Type C meeting to discuss whether the data from Studies A2304 and A2201 would be adequate to support a filing for the proposed indication of SPMS. The written response stated that for Study A2304, “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.”

In a pre-NDA meeting held in October 2017, the Agency stated that an application with a proposed indication for SPMS would not be a refuse to file issue and that the indication statement would be determined after completion of the review. After a rolling review was granted in January 2018, the submission of New Drug Application #209884 was complete on June 28, 2018.

### 3. Product Quality

The technical lead on the Office of Product Quality review was Dr. Wendy Wilson-Lee (Dr. Wilson Lee’s review lists the entire OPQ team involved with the review of this application). OPQ recommends approval of this application.

The OPQ review notes that siponimod is a film-coated, immediate-release tablet for oral administration manufactured in two strengths, 0.25 mg and 2 mg, based on the siponimod active moiety.

The OPQ review concludes that a (b) (4) retest date is acceptable for the drug substance when stored at temperatures up to (b) (4) C. Based on extrapolation of the long-

term stability data, a shelf life of 18 months may be granted for the 0.25 mg and 2 mg tablets packaged in HDPE bottles when stored at 2°C - 8°C (36°F - 46°F). The tablets may be stored at 20°C - 25°C (68°F to 77°F) for up to 1 month after dispensing.

The OPQ review agrees with the applicant's proposal that a shelf life of 9 months may be granted for the 0.25 mg tablets packaged in (b) (4) blisters (titration pack) when stored at 2°C - 8°C (36°F - 46°F). The tablets may be stored at 20°C - 25°C (68°F to 77°F) for up to 1 week after dispensing.

All manufacturing facilities were evaluated and deemed acceptable.

## 4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Richard Siarey. Dr. Lois Freed provided a supervisory review. Dr. Siarey recommends approval, and Dr. Freed concurs. The principal conclusions from Dr. Siarey's and Dr. Freed's reviews are as follows:

- In safety pharmacology studies, siponimod had cardiac and respiratory effects. Oral siponimod acutely decreased heart rate in rats, guinea pigs, rabbits, and monkeys. Other cardiovascular observations included decreased blood pressure in guinea pigs and second-degree block in guinea pigs and monkeys. Effects of siponimod on respiratory function included an increase in tidal volume and a decrease in respiration rate in rats.
- In mouse, rat, and monkey repeat-dose toxicology studies, there were deaths and early sacrifices due to breathing difficulties and convulsions in mice, breathing difficulties in rats, and deteriorating physical condition and convulsions in monkeys. All species at all doses had greatly reduced circulating white blood cells with accompanying lymphoid tissue depletion, consistent with the pharmacological action of siponimod. Toxicity noted in other target organs included the kidney (nephrotoxicity), lungs (fibrin/hyaline material, fibrosis, and smooth muscle hyperplasia), liver (hypertrophy), and thyroid gland (hypertrophy) in mice, lungs (alveolar macrophages and inflammation), liver (hypertrophy), and uterus in rats, and GI tract (inflammation, crypt hyperplasia, and mucosal erosion) and skeletal muscle (myofiber necrosis) in monkeys. The findings were largely dose-dependent in all species, and, in most cases, a no adverse effect level (NOAEL) could not be determined. Dr. Freed notes a lack of toxicokinetic data at the lowest doses tested in the pivotal trials, but given the adverse effects noted at other doses, does not see a need for additional studies.

- Oral bioavailability of siponimod was high in all species. Siponimod distributed to most tissues in rodents, and was detected in the brain and CSF, with the highest exposure observed in white matter.
- In genetic toxicology studies, siponimod did not demonstrate mutagenic potential in the Ames assay, human peripheral lymphocytes, or TK6 assay. Siponimod did not demonstrate clastogenic potential in the *in vivo* mouse and rat micronucleus clastogenicity assays.
- The carcinogenicity study in mouse was positive for malignant lymphoma in female mice at all doses and for hemangiosarcoma and combined hemangioma and hemangiosarcoma in both male and female mice at all doses. There is uncertainty about the applicability of the hemangiosarcoma finding to humans. The carcinogenicity study in rat was positive for thyroid follicular cell adenoma and combined follicular cell adenoma and carcinoma in male rats.
- In a standard battery of reproductive and development studies, oral siponimod was teratogenic in rats and lethal to fetuses in both rats and rabbits. Siponimod and metabolites were measured in rat milk up to 72 hours post-dose, suggesting that nursing pups would be exposed to siponimod. Placental transfer of siponimod and metabolites occurred in rabbits.
- A post-marketing requirement for a juvenile animal toxicology study is recommended to support clinical development of siponimod in the pediatric population under the Pediatric Research Equity Act (PREA).

## 5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Drs. Dawei Li (the primary reviewer), Angela Men (the clinical pharmacology team lead), Manuela Grimstein, Xinyuan Zhang, Simbarashe Zvada, Kevin Krudys, Jeffrey Kraft, and Christian Grimstein. The final signatory for the OCP review was Dr. Mehul Mehta. OCP concludes the application is approvable from a clinical pharmacology standpoint.

Table 1 summarizes the conclusions of the OCP review with respect to the pharmacologic and clinical pharmacokinetic properties of siponimod.

**Table 1: Summary of OCP Review Findings**

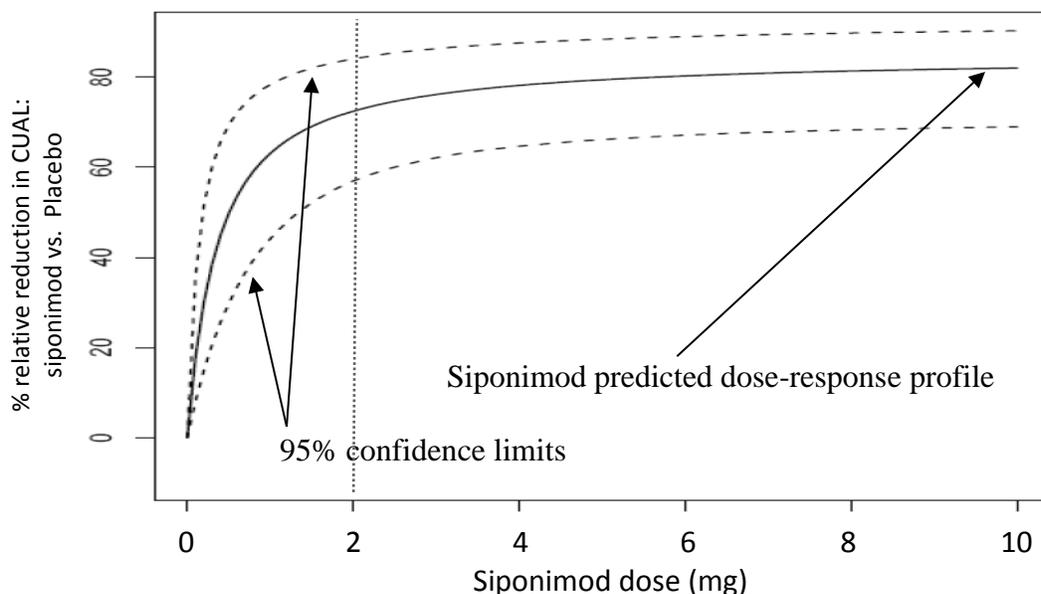
<b>Pharmacology</b>	
<b>Mechanism of action</b>	Siponimod promotes internalization and degradation of S1P1 receptors, thereby acting as a functional antagonist on S1P1. This antagonism is proposed to reduce the recirculation of T-cells into the central nervous system (CNS) to limit central inflammation.
<b>Active moieties</b>	Siponimod is the active moiety circulating in plasma, accounting for 57% of total radioactivity in a mass-balance study.
<b>QT prolongation</b>	Siponimod increased the mean placebo-corrected baseline-adjusted mean QTcF ( $\Delta\Delta\text{QTcF}$ ) by more than 5 milliseconds, with a maximum mean effect of 7.8 milliseconds (2 mg, therapeutic dose) at 3 hours post-dose. The upper bound of the one-sided 95% CI for the $\Delta\Delta\text{QTcF}$ at all time points remained below 10 milliseconds. The study did not suggest an arrhythmogenic potential related to QT prolongation.
<b>General Information</b>	
<b>Drug exposure at steady-state following the therapeutic dosing regimen</b>	In patients with SPMS receiving siponimod 2 mg daily, the geometric trough concentrations were 23.2 ng/mL and 28.9 ng/mL on day 28 and month 24, respectively, in Study A2304.
<b>Dose-proportionality</b>	Siponimod exposure increases in an apparent dose-proportional manner over the multiple-dose range of 0.3 to 20 mg/day in healthy subjects.
<b>Accumulation</b>	A mean accumulation ratio of 1.88 to 2.72 was observed at steady-state.
<b>Absorption</b>	
<b>Bioavailability (oral)</b>	Absolute bioavailability is approximately 84%.
<b>T<sub>max</sub> (oral)</b>	The median siponimod T <sub>max</sub> ranged from 3 - 8 hours.

<b>Food effect (high-fat)</b>	AUC <sub>inf</sub>	C <sub>max</sub>
<b>Geometric mean ratio (90% confidence interval [CI])</b>	0.96 (0.92-1.00)	0.91 (0.86-0.97)
<b>Distribution</b>		
<b>Volume of distribution</b>	The estimated volume of distribution in healthy volunteers is 124 L.	
<b>Plasma protein binding</b>	> 99.9% (lipoprotein and albumin).	
<b>Elimination</b>		
<b>Mean terminal elimination half-life</b>	Approximately 30 hours.	
<b>Metabolism</b>		
<b>Primary metabolic pathway(s)</b>	Siponimod is extensively metabolized, primarily by CYP2C9 and to a lesser extent CYP3A4. The major circulating metabolites M3 and M17 are inactive.	
<b>Inhibitor/inducer</b>	Siponimod, M3, and M17 are unlikely to inhibit any major CYPs or induce CYP1A2, 2B6, 2C9, and 3A4 at clinically relevant doses.	
<b>Transporter systems</b>	Siponimod is not identified as substrate of P-gp, BCRP, or MRP2 transporters. Siponimod, M3, and M17 are unlikely to inhibit major efflux, uptake, and SLC transporters at clinically relevant doses.	
<b>Excretion</b>		
<b>Primary excretion pathways (% dose) ± SD</b>	Following a single oral dose of <sup>14</sup> C-siponimod at 10 mg, radioactivity was excreted predominantly via the fecal route (87%), only a minor amount of radioactivity was excreted in the urine (<3%).	

The following figure, adapted from the applicant/OCP review, demonstrates the treatment effect of siponimod on combined unique active lesions (CUAL) from magnetic resonance imaging (primary efficacy endpoint) in a Phase 2 dose-finding study (Study CBAF312A2201, A2201 hereafter). Five siponimod doses were examined

(0.25, 0.5, 1.25, 2, and 10 mg) for treatment effects on CUAL in patients with RRMS. The 2-mg dose achieved a near-maximal effect on CUAL reduction. The higher (10-mg) dose was associated with a higher frequency of adverse events. Thus, 2 mg was chosen as the dose for the pivotal trial.

**Figure 1: Combined Unique Active Lesions\* at Month 3 as a Function of Dose, Estimated by Bayesian Longitudinal Analysis (Applicant's analysis)**



\*Combined unique active lesions are defined as new Gd-enhanced T1 lesions or new or enlarging T2 lesions.

The OCP review expresses concerns that the sponimod 2-mg dose chosen for the Phase 3 trial and for marketing might not achieve near-maximal efficacy in patients with SPMS, the applicant's proposed indicated population, because, in addition to the significant inherent differences between the relapsing and progressive forms of disease, the primary endpoint in the pivotal trial, 3-month confirmed disability progression, was not the same endpoint used in dose-finding trial (CUAL).

The OCP review finds that alternative dosing regimens are required based on CYP2C9 genotype because of the significant effects of genotype on the  $AUC_{inf}$  of sponimod in the subpopulation of patients with the CYP2C9 \*1/\*3, \*2/\*3, and \*3/\*3 genotypes. The maintenance dose in patients with the \*1/\*3 or \*2/\*3 genotypes should be reduced from 2 to 1 mg/day and use of sponimod in patients with the \*3/\*3 genotype should be contraindicated.

The OCP review finds that other intrinsic factors such as age, gender, body weight, race, and renal or hepatic impairment, do not significantly impact the systemic exposures of siponimod, and dose adjustments for these factors are not necessary.

The OCP review notes that food decreased the  $C_{max}$  and AUC of siponimod by 10% and 4%, respectively, but these changes are not considered clinically relevant, and the review concludes that siponimod may be administered without regard to food.

The OCP team notes that the siponimod AUC is likely to increase 2- to 4-fold in the presence of a dual inhibitor of CYP3A4 and CYP2C9, such as fluconazole, and to decrease approximately 60 to 80% in the presence of a strong CYP3A4 and moderate CYP2C9 inducer, such as rifampicin. Concomitant administration of a moderate CYP3A4 inducer, such as efavirenz, resulted in an approximately 50% decrease in siponimod AUC in patients with CYP2C9 \*1/\*3 or \*2/\*3 genotypes.

To simplify the dosing regimen with concomitant medication use and to keep the recommendations consistent when the drug is co-administrated with an inducer and an inhibitor, the OCP review team makes the following dosing recommendations:

- Taking a moderate CYP2C9/3A4 dual inhibitor (e.g., fluconazole) or a moderate CYP2C9 inhibitor concomitantly with a strong or moderate CYP3A4 inhibitor is not recommended, regardless of genotype.
- Concomitant use of strong CYP3A4/moderate CYP2C9 inducers (e.g., rifampicin or carbamazepine) is not recommended for all patients regardless of genotype. Caution should be exercised for concomitant use of moderate CYP2C9 inhibitors.
- Concomitant use of moderate CYP3A4 inducer with siponimod is not recommended for patients with CYP2C9 \*1/\*3 or \*2/\*3 genotypes.

With the addition of the recommendations above, the OCP review otherwise finds the applicant's proposed dosing regimen acceptable.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical-Efficacy**

Dr. David Jones was the clinical reviewer for this application, and Dr. Paul Lee was the clinical team lead. Dr. Xiang Ling was the biometrics reviewer, and Dr. Kun Jin was the biometrics team lead. Dr. Jones finds that the application provides substantial evidence

of efficacy for the treatment of patients with relapsing forms of multiple sclerosis, but not for the applicant's proposed indication, the treatment of patients with SPMS. The rationale for the final indication is provided in this section.

The applicant submitted data from one pivotal efficacy Phase 3 clinical trial, Study CBAF312A2304 (A2304 hereafter). This single study is supported by findings from a smaller, dose finding Phase 2 trial, CBAF312A2201 (A2201 hereafter).

### **Study A2304**

Study A2304 was a multi-national, multi-center, randomized, double blind, placebo-controlled study, intended to evaluate the safety and efficacy of siponimod in patients with protocol-defined SPMS. Study A2304 utilized a 6-day titration schedule to achieve an oral maintenance dose of 2 mg daily. The treatment duration in Study A2304 was variable (up to 37 months) because the trial was event-driven.

Dr. Jones indicates in his review (on page 38) that there exists no biomarker to distinguish relapsing and progressive forms of multiple sclerosis, nor is there a broadly accepted definition of SPMS. Thus, enrollment criteria for Study A2304 were unique and defined a diagnosis of SPMS as follows:

- a progressive increase in disability (of at least 6 months duration) in the absence of, or independent of, relapses
  - Written investigator attestation that the disease had entered the progressive stage (according to the study definition) at least 6 months prior to enrollment
- Disability as assessed by a screening Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5 (inclusive).
- Documented EDSS progression of  $\geq 1$  point in the 2 years prior to study for subjects with EDSS  $< 6.0$  at screening, and  $\geq 0.5$  point for patients with EDSS  $\geq 6.0$  at screening.
- For patients without documented EDSS scores, a written summary of the clinical evidence of disability progression in the previous 2 years was required to be submitted for central review.

The primary efficacy endpoint of Study A2304 was the time to 3-month confirmed disability progression, as measured by the EDSS. The study defined 3-month disability progression as a 1.0-point increase in EDSS from baseline for subjects with baseline EDSS between 3.0 and 5.0 (or 0.5-point increase for subjects with a baseline EDSS of 5.5 to 6.5) that persisted until a scheduled visit three months after the initial disability progression. The outcome measure was expressed as a hazard ratio, analyzed by a Cox proportional hazards model with treatment, country, baseline EDSS, and SPMS subgroup (subjects with or without superimposed relapses) as covariates. The protocol

also specified that imputation was not performed for subjects who dropped out of the study before having a CDP event. Subjects who did not experience a 3-month CDP event during the study were censored on the date of the last EDSS assessment.

The secondary efficacy endpoints were, in sequential order, time to 20% worsening on the Timed 25 Foot Walk (T25FW) test and change from baseline in T2 lesion volume (as measured on magnetic resonance imaging). Analysis of the T25FW endpoint utilized a Cox proportional hazards model with treatment, country, baseline EDSS, and SPMS subgroup as covariates. Analysis of the change in T2 lesion volume from baseline endpoint used a mixed model for repeated measures with visit as a categorical variable and an unstructured covariance matrix.

The primary and secondary efficacy endpoints were analyzed in hierarchical fashion. Annualized relapse rate (ARR) was a secondary endpoint but was not included in the pre-specified hierarchical analysis. The analysis population was all patients randomized who received at least one dose of study drug.

There were 1651 patients randomized in a 2:1 ratio as follows: 1105 patients were randomized to siponimod, and 546 patients were randomized to placebo.

Patients were enrolled from 294 sites in 31 countries worldwide. Approximately 9.5% of the patients were from the United States.

Five patients did not receive a dose of study treatment; all five were assigned to the siponimod treatment arm and excluded from the primary analysis. Discontinuations were 10.1% and 13.4% in the siponimod and placebo groups, respectively. There were 66.7% of patients in the siponimod treatment arm and 59.0% of patients in the placebo treatment arm who remained on their respective treatments for their entire treatment epoch in the controlled trial.

Demographic and baseline disease-related characteristics of the randomized patients were well-matched between the treatment arms. As is typical for trials in patients with MS, over 60% of patients were white women, and the mean age was approximately 48 years in both treatment arms.

The review team was able to confirm the results for the primary efficacy outcome as provided by the applicant:

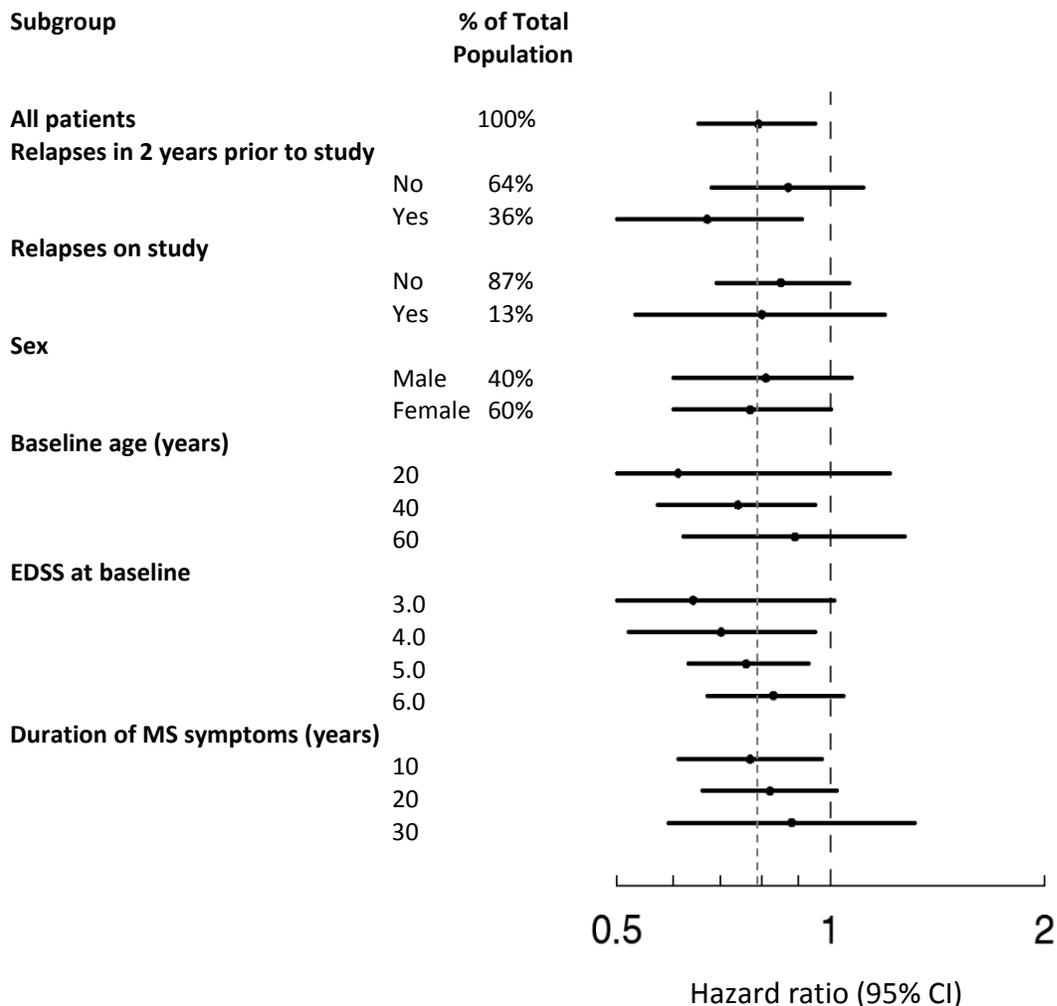
**Table 2: Study A2304: Primary Analysis of Time to Confirmed Disability Progression**

Treatment	n/N (%)	Relative risk reduction	Absolute risk reduction	Hazard ratio (95% CI)	p-value
Siponimod (N=1099)	288/1096 (26.3)	21.2%	5.4%	0.79 (0.65; 0.95)	0.0134
Placebo (N=546)	173/545 (31.7)				

n/N: n = number of subjects with events/N = number of subjects included in the analysis (those with non-missing covariates)

Dr. Ling (on pages 8-19 of the biometrics review) conducted or confirmed multiple sensitivity and subgroup analyses to account for impact on treatment effect of relapses influencing disability, study/treatment discontinuation, gender, race, age, and other factors. The results of these analyses were generally consistent with the primary analysis.

**Figure 2: Subgroup Analyses on the Primary Endpoint, Time to Confirmed Disability Progression (adapted from Applicant’s figure)**



Drs. Jones and Ling evaluated a number of subgroup analyses, some of which are displayed in Figure 2, adapted from the Applicant’s figure. Of note, patients who had experienced relapses during the 2 years prior to enrollment (36% of study participants) had a mean relative risk reduction of 33%, whereas patients who had not experienced a relapse in the 2 years prior to enrollment (64% of the study population) had only a 13% relative risk reduction. Thus, patients with more active disease, although in the minority, drove the overall treatment effect. Findings were similar in subgroups of patients with other attributes consistent with the relapsing form of MS: patients with younger age, shorter disease duration, relapses during the study, and baseline gadolinium-enhancing lesions. These subgroups were all more responsive to siponimod, showing greater benefit.

The results for the secondary efficacy outcomes, T25FW test and change from baseline in T2 lesion volume, assessed in hierarchical fashion, presented by the applicant and confirmed by the review team, are shown in Tables 3 and 4, respectively.

**Table 3: Study A2304: Time to 3-month Confirmed Worsening in T25FW**

Treatment	n/N	(%)	Hazard ratio (95% CI)	p-value
Siponimod (N=1099)	432/1087	(39.7)	0.94 (0.80; 1.10)	0.44
Placebo (N=546)	225/543	(41.4)		

n/N: n = number of subjects with events/N = number of subjects included in the analysis (those with non-missing covariates). “Worsening” is defined as a  $\geq 20\%$  worsening in the timed 25-foot walk.

Dr. Ling indicates (on page 20 of the biometrics review) that because the first key secondary endpoint failed to show statistical significance, the testing procedure stopped. Analysis of the second key secondary endpoint, change from baseline in T2 lesion volume, therefore is considered descriptive.

**Table 4: Study A2304: Change from Baseline in T2 Lesion Volume**

Treatment	N	LSmeans (SE)	Difference (95% CI)	Nominal p-value
Siponimod (N=1099)	995	183.9 (66.3)	-695.3 (-877.3; -513.3)	<0.0001
Placebo (N=546)	495	879.2 (85.4)		

N = number of subjects included in the analysis (i.e. With post-baseline MRI scan and non-missing covariates). Obtained from a repeated measures model.

Dr. Ling confirmed the results of an analysis of the non-hierarchical secondary endpoint, ARR. This analysis is not corrected for multiple comparisons.

**Table 5: Study A2304: ARR for Confirmed Relapses**

Treatment	Estimated ARR (95% CI)	ARR ratio (95% CI)	Δ ARR (relapses/year)	Nominal p-value
Siponimod (N=1099)	0.071 (0.055; 0.092)	0.445 (0.337; 0.587)	0.089	<0.0001
Placebo (N=546)	0.160 (0.123; 0.207)			

Obtained from a negative binomial regression model adjusted for treatment, country/region, baseline EDSS, baseline number of T1 Gd-enhancing lesions, and SPMS group.

Although the relative reduction in relapse rate (ARR ratio) is important, the net reduction (i.e., absolute treatment effect) was 0.089 relapses/year.

Dr. Ling notes that this robust (55%) reduction in ARR obligates further exploration of whether there is an impact on disability separate from the treatment effect on relapses. Dr. Ling performed these analyses and states (on page 16 of the biometrics review) that these additional analyses were statistically inconclusive for a treatment effect independent of relapses. Dr. Jones suggests that this exploratory finding clearly supports the assertion that benefit of siponimod is limited to the subgroup of patients experiencing relapses. He notes that the ARR finding in Study A2304 is strengthened by the exploratory but also nominally significant reduction in ARR noted in the A2201 trial for the same dose of siponimod (2 mg).

#### Potential Impact of Unblinding in Study 2304

To reduce the potential for unblinding due to heart rate reductions after the initial dose, the Applicant utilized a first-dose team and a first-dose database that was separate from other databases. During the review, the applicant disclosed that study personnel at 62 clinical sites had access to this first-dose database that, if viewed by investigators, could be used to unblind study personnel who should have been blinded.

The Office of Scientific Investigations (OSI) inspected the applicant and identified this as a significant data reliability concern. The inspectional findings demonstrate that the blinding for Study A2304 was not adequately maintained as specified in the protocol throughout the course of the trial at these 62 (21%) of 294 sites. Study personnel were given inappropriate access to the first-dose and main databases, affecting 285 (17%) out of 1651 total study subjects. Unfortunately, data from audit trails were limited; there was difficulty determining whether and when particular users accessed the databases, and what data were viewed. On further review of the types of access granted, and of the data available in the databases at the time of users' inappropriate dual database access, it was determined that 32 users of the main database had access to potentially unblinding data in the first-dose database, affecting 101 of 1651 total study subjects (6.1%).

OSI concluded that they could not attest to the reliability of these study data, and recommended a sensitivity analysis of the primary endpoint, excluding these 101 subjects because of the possibility of bias.

Dr. Ling confirmed the sensitivity analysis performed by the applicant on the primary efficacy endpoint of Study A2304, removing these 101 subjects. The results of this sensitivity analysis and simulation are as follows:

**Table 6: Study A2304: Sensitivity Analysis of Time to CDP After Removing 101 Subjects with Potential Unblinding of Investigators**

Treatment	n/N (%)	Relative risk reduction	Hazard Ratio (95% CI)	Chi-Square/ <i>p</i> -value
Siponimod	274/1031 (26.6)	17%	0.83 (0.68; 1.01)	3.4825/0.062
Placebo	157/509 (30.8)			

n/N: n=number of subjects with events/N=number of subjects included in the analysis (with non-missing covariates).

Dr. Ling concludes that removal of these 101 patients (only 6.1% of the total study population) decreased the relative risk reduction from 21% to 17%, with the *p*-value changing from 0.0134 to 0.062. Note that the rates of progression in these 101 subjects were 14/65 (21.5%) in subjects in the siponimod group, and 16/36 (44.4%) in subjects in the placebo group. *Thus, the relative risk reduction in these 101 subjects was greater than 50% – far greater than the 17% relative risk reduction in the remainder of the subjects.*

A critical question was whether results were biased in favor of siponimod in this group of 101 subjects, i.e., the probability that the extremely favorable results observed in these 101 subjects were a chance finding.

One way to consider whether the results were biased in this 101-subject sample was to consider the study results after removing other randomly selected groups of 101 subjects. If there was unblinding in these 101 subjects that led to bias, then removal of randomly selected groups of 101 subjects would not be expected to have as marked an impact on the study results. Conversely, if there was no bias, then removal of any group of 101 randomly selected subjects would be expected to have a similar effect on the study results.

To address the possibility that removal of any 101 patients would significantly alter the primary outcome measure result, Dr. Ling performed a “bootstrap” simulation, removing randomly selected groups of 101 subjects from the overall population 5000 times, each time with analysis of the primary endpoint.

Based on the empirical distributions of the chi-square test statistic from 5000 repeats, Dr. Ling calculated the probability of observing a more extreme test statistic, that is, comparing the test statistic with omission of these 101 subjects to test statistics generated after removing randomly selected groups of 101 subjects. The probability of observing a test statistic as extreme as observed when randomly removing 101 subjects from the original analysis data set was 0.028.

Based on the chi-square finding, Dr. Ling expressed concern that the smaller treatment effect after removing the potentially unblinded subjects may be unlikely to occur by chance.

Dr. Jones acknowledges the applicant's sensitivity analyses showing continued significance of the ARR despite removal of the 101 patients affected by the database issue and further acknowledges the sensitivity analysis on MRI findings, though not necessary because MRI data were not compromised in this database issue.

Dr. Jones shares Dr. Ling's concern with respect to the finding from the "bootstrap" analysis, that removal of the 101 patients affected by the dual database issue has significantly greater impact on the 3 month-CDP finding than removal of 101 random patients.

### **Study A2201**

Study A2201 was a double-blind, randomized, placebo-controlled, multi-center, adaptive dose-ranging, parallel-group Phase 2 study conducted in patients with RRMS. Study A2201 has limited interpretability because of its small size and short duration.

The primary efficacy endpoint of this trial was the dose-response relationship among five doses of siponimod and placebo during three months of treatment in patients with RRMS. The dose-response was determined based on the monthly number of combined unique active magnetic resonance imaging (MRI) lesions (CUAL) during three months of treatment. CUAL were defined as new gadolinium [Gd]-enhanced lesions on T1-weighted MRI scans or new or enlarging lesions on T2-weighted MRI scans, without double-counting of lesions.

Secondary endpoints included MRI variables (number of monthly new Gd-enhanced T1 lesions, number of all monthly Gd-enhanced T1 lesions, number of monthly new or enlarging T2 lesions, number of new T1 hypointense lesions from baseline to end of treatment, proportion of patients without any new MRI disease activity) and clinical endpoints: ARR, i.e., all relapses, confirmed and unconfirmed, ARR (confirmed relapses only), proportion of relapse-free patients (confirmed relapses only); and EDSS. All secondary endpoints were considered exploratory, as a testing procedure that controls the overall type-I error rate was not prospectively planned.

A total of 297 patients with relapsing-remitting multiple sclerosis were randomized into an adaptive design trial in which patients were randomized in two separate cohorts in Period 1 and Period 2, respectively, separated by an interim analysis.

In Period 1, patients were randomized in a ratio of 1:1:1:1 to receive siponimod 10, 2, or 0.5 mg/day, or placebo for six months.

50 patients to siponimod 10 mg  
49 patients to siponimod 2 mg  
43 patients to siponimod 0.5 mg  
45 patients to placebo

An unblinded interim analysis was performed when 181 patients randomized in Period 1 had completed 3 months. The purpose of the interim analysis was to decide whether to stop the study or to continue the study, with sample size re-estimation, and to select two additional doses to be investigated in Period 2.

After the interim analysis, patients were randomized in a ratio of 4:4:1 to siponimod 1.25 mg/day, 0.25 mg/day, or placebo for 3 months.

42 patients to siponimod 1.25 mg  
51 patients to siponimod 0.25 mg  
16 patients to placebo

Over half of the patients came from European countries. Approximately 14% of the patients came from the United States.

Overall, 11% of patients discontinued the study, and 21% did not complete the study on their initial randomized treatment.

Other than country of origin, the demographic and other baseline characteristics of patients were well-matched between treatment groups. As is typical for trials of RRMS, most of the patients were Caucasian women in their mid-thirties.

The results for the primary outcome measure in the standard intent-to-treat population (patients who received at least one dose of treatment after randomization), presented by the applicant and confirmed by the review team, are as follows:

**Table 7: Study A2201: Testing Significance of Candidate Dose Response Models at 3 Months**

Candidate Model	T statistic	p-value (one-sided)*
Linear	1.75	0.070
E <sub>max</sub> (with ED <sub>50</sub> =1 mg)	3.93	0.0001
Hill E <sub>max</sub> 1 (with ED <sub>50</sub> =2 mg and h=2)	2.53	0.012
Hill E <sub>max</sub> 2 (with ED <sub>50</sub> =3 mg and h=3)	1.65	0.086
Exponential (with delta=3.633)	1.20	0.182

\* Models with a p-value <0.025 are significantly different from a flat dose-response (i.e., no dose-response) model.

Dr. Jones states that the significant efficacy findings for the 2-mg dose of siponimod suggest significant treatment effects on MRI metrics that could be considered supportive of other observed beneficial effects on accepted clinical endpoints. The results for the secondary outcome measure ARR, though exploratory because of lack of adjustment for multiplicity, presented by the applicant and confirmed by the review team, are as follows:

**Table 8: Analysis of Annualized Relapse Rate for Confirmed Relapses Up to 6 Months**

	Siponimod 10 mg N=50	Siponimod 2 mg N=49	Siponimod 0.5 mg N=43	Placebo N=45
<b>Model-based results</b>				
Group level ARR	0.30	0.20	0.61	0.58
95% CI of ARR	(0.15, 0.61)	(0.08, 0.48)	(0.35, 1.06)	(0.38, 1.00)
ARR ratio to placebo	0.524	0.340	1.051	
95% CI for ARR ratio	(0.22, 1.26)	(0.12, 0.96)	(0.486, 2.27)	
p-value	0.148	0.041	0.899	
% relative reduction	47.6	66.0	-5.1	

It is noteworthy that the 10-mg dose of siponimod provided a ~50% relapse rate reduction, but that effect was not nominally statistically significant, possibly because the study was underpowered for clinical endpoints. The 2-mg dose provided a nominally significant reduction in relapse rate, but, again, this analysis was not corrected for multiple comparisons.

## Efficacy Conclusions

Approval for siponimod for relapsing forms of MS will be based primarily on a single study, Study A2304. As explained in FDA's 1998 Guidance for Industry "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*," there are situations where it can be acceptable to rely on a single study for evidence of effectiveness, generally when "...a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity....". Because disability progression in MS is indicative of irreversible morbidity, the principles enumerated in the Guidance are applicable here.

Study A2304 has many of the characteristics of a single adequate and well-controlled study that make it adequate to support an effectiveness claim:

- Study A2304 was a large multicenter, multinational study. Given that the study enrolled some 1651 subjects, it was substantially larger than most of the studies that have served as the bases for approval of MS drugs. The approval of interferon beta-1a was based on two studies, both with ~600 subjects. Fingolimod's approval was based on two studies, both with ~800 subjects.
- The results of Study A2304 were consistent across important demographic and disease-specific subgroups, except for those with attributes consistent with non-active (not relapsing) progressive disease, as noted above. Treatment effects for the subset of subjects enrolled in the US were consistent with those of the study as a whole. A number of sensitivity analyses conducted by the statistical reviewer support the robustness of the primary outcome findings.
- The study included multiple endpoints involving different facets of the disease. As highlighted in the *Guidance*, the approval of beta-interferon (Betaseron) for prevention of exacerbations in MS was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity – two entirely different, but logically related, endpoints. Study A2304 demonstrated effects on disability progression, exacerbations, and T2 lesion volume.
- Finally, the study had a fairly persuasive  $p$ -value: 0.0134.

There are some weaknesses here, however, that deserve highlighting:

- With respect to the primary endpoint, CDP, the  $p$ -value, though persuasive, was perhaps not as compelling as we typically like to see for a single-study approval. Moreover, as described above in detail, there were 101 subjects, 6.1% of the total number of subjects, for whom treatment assignment was potentially unblinded. The efficacy results in these 101 patients, based on changes in EDSS, were extreme, with a relative risk reduction in CDP on the order of 50%, compared to a relative risk reduction of 17% for the other 93.9% of subjects. Based on the bootstrap analysis conducted by Dr. Ling, the extreme finding in this group of 101 subjects may have been non-random. With the removal of these 101 subjects, the relative reduction in

CDP is reduced from 21% to 17%, and the *p*-value becomes 0.062, which is no longer statistically significant.

- The lack of a positive finding on the timed 25-foot walk is concerning. As noted by Dr. Jones in his review, because the median EDSS in the study was 6 and because EDSS changes between 5 and 8 are entirely dependent on changes in ambulation, the failure to succeed on the T25FW endpoint raises questions about the study's CDP result, although this discrepancy could be explained by hypothesizing that the T25FW is less sensitive to change than the EDSS.

Despite these weaknesses, important aspects of the study argue strongly against a false positive finding. The primary efficacy finding is supported by the secondary MRI endpoint, which should not be susceptible to unblinding, and findings on ARR, which are robust despite removal of the 101 potentially compromised subjects. Although the statistical testing on the secondary endpoints was descriptive because the first secondary endpoint failed to reach statistical significance, and, in the case of ARR, was not controlled for multiple comparisons, the magnitude of the effect sizes and extremely low *p*-values ( $p < 0.0001$ ) for the ARR and the change in T2 lesion volume strengthen the persuasiveness of the primary efficacy results. CDP, ARR, and T2 lesion volume are three endpoints that are typically assessed in MS trials. In totality, the review team agrees that results from Study A2304 provide substantial evidence of siponimod's effectiveness.

Although the applicant sought an indication for treatment of "adult patients with secondary progressive multiple sclerosis," the biometrics and clinical reviewers describe numerous credible reasons for why this patient population should not be the indicated treatment population. Patients in the pivotal trial with established treatment benefit do fit the clinical phenotype of patients with active secondary progressive disease. An unqualified indication for the treatment of secondary progressive multiple sclerosis does include a claim of effective use for patients with non-active (not relapsing) progressive disease, a population for which efficacy has not been established. The indication supported by the submitted data is for the treatment of adult patients with relapsing forms of multiple sclerosis, with elaboration "to include clinically isolated syndrome, relapsing-remitting MS, and active secondary progressive disease."

## 8. Safety

Dr. Paul Lee reviewed this submission as primary reviewer and as team lead. Dr. Wiley Chambers from the Division of Transplant and Ophthalmology Products conducted a consultative safety review regarding ophthalmological findings related to macular edema. Dr. Rekha Jhamnani from the Division of Pulmonary, Allergy, and Rheumatology Products provided a consultative safety review of lung function test findings.

The following table, copied from Dr. Lee’s review, summarizes the extent of exposure to siponimod in the applicant’s development program:

**Table 9: Siponimod Safety Population: Duration of Exposure**

Dosage	Number of patients with MS exposed to siponimod					
	≥ 1 dose	≥ 1 month	≥ 3 months	≥ 12 months	≥ 24 months	≥ 36 months
<b>0.25 mg</b>	N=51	N=50	N=0	N=0	N=0	N=0
<b>0.5 mg</b>	N=43	N=42	N=39	N=0	N=0	N=0
<b>1.25 mg</b>	N=42	N=42	N=32	N=0	N=0	N=0
<b>2 mg</b>	N=1148	N=1117	N=1083	N=865	N=277	N=81
<b>10 mg</b>	N=50	N=42	N=38	N=0	N=0	N=0
<b>2-10 mg*</b>	N=1737	N=1692	N=1648	N=1449	N=1024	N=776

\*includes all exposures of at least 1 dose in all trials of siponimod

The safety database is adequate because it contains more than one thousand patients exposed to any dose of siponimod for more than 365 days, and therefore exceeds by more than ten-fold the International Council on Harmonization recommendations for chronically-administered medications (i.e., 100 patients exposed for one year). Most of the patients in the database are Caucasian women less than 45 years old, which is to be expected for a study of multiple sclerosis because of the disease’s typical demographics.

### Deaths

The applicant reported 20 deaths in patients exposed to either placebo or siponimod, and these deaths occurred exclusively in the patients with multiple sclerosis treated in Studies A2201, A2201 extension, A2304, and 2304 Extension. 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,” (defined as currently enrolled in trial and receiving blinded or open-label treatment with siponimod as of last study visit) at the time of their deaths. Two of the deaths in siponimod-treated patients could be attributed to advancement of multiple sclerosis. Causes of death in the siponimod development program otherwise were largely heterogeneous and confounded by factors outside of treatment.

There appeared to be an imbalance in deaths associated with vascular events (two cases of myocardial infarction, two cases of pulmonary embolism) in the siponimod treatment group. Further analysis of all vascular events in the trials revealed little difference in the overall frequency of events (3.0% versus 2.5%) and an odds ratio of 1.0 between siponimod and placebo for vascular events.

### Serious Adverse Events

Approximately 17% of patients exposed to siponimod 2 mg experienced a serious adverse event, versus approximately 13% of patients on placebo. The most common

serious adverse events in siponimod treatment groups were seizures, urinary tract infections, and increased hepatic transaminases.

The applicant suggested labeling language to describe the observed frequency of seizures. The review team agrees that the higher frequency of seizures in siponimod-treated patients should be noted in labeling, but also concluded that the published high prevalence and incidence of epilepsy and seizures in the worldwide population of patients with multiple sclerosis were not recapitulated in either the placebo or siponimod treatment groups, making interpretation of an association between seizures and siponimod difficult.

#### Interruptions and Discontinuations

During controlled trials, approximately 7% of patients treated with siponimod had a treatment interruption, as compared to approximately 3% of patients on placebo. The most common adverse events leading to treatment interruption were macular edema, herpes zoster, elevated alanine aminotransferase, carbon monoxide diffusing capacity reduced, and vomiting. Except for vomiting, these adverse events were expected treatment-related adverse events identified during development and postmarketing experience of the non-specific sphingosine-1-phosphate receptor modulator fingolimod.

During controlled trials, approximately 8% of patients treated with siponimod, and approximately 5% of patients on placebo discontinued treatment due to an adverse event. The most common adverse events leading to study drug discontinuation were bradycardia, bradyarrhythmias, and macular edema. Bradycardia and atrioventricular conduction disorders are a known consequence of sphingosine-1-phosphate receptor modulation, and the protocols for clinical trials stipulated monitoring and discontinuation criteria for these known cardiac conduction effects.

#### Treatment-Emergent Adverse Events

The following table, reproduced from the clinical safety review, summarizes the most common treatment-emergent adverse events (TEAEs) that occurred in Studies A2304 and A2201:

**Table 10: Adverse Events Reported in ≥5% of Patients Taking Siponimod 2 mg, and with an Incidence At Least 1% Greater for Siponimod than for Placebo, Using Customized Pooled Preferred Terms**

	<b>Siponimod 2 mg (N=1148) %</b>	<b>Placebo (N=607) %</b>
Falls and Balance Disturbances <sup>1</sup>	19.6%	17.1%
Headaches	17.3%	14.3%
Hypertension <sup>2</sup>	12.5%	8.7%
Falls	11.5%	10.5%
Elevated Liver Transaminases <sup>3</sup>	10.5%	2.8%
Nausea and Vomiting	8.4%	4.9%
Arrhythmia <sup>4</sup>	7.9%	6.1%
Dizziness <sup>5</sup>	7.0%	5.4%
Edema <sup>6</sup>	6.9%	3.6%
Diarrhea	6.3%	4.3%
Bradycardia	6.2%	3.3%

<sup>1</sup> includes falls, dizziness, gait disturbance, balance disturbance, difficulty walking

<sup>2</sup> includes blood pressure increased

<sup>3</sup> includes increased hepatic enzymes, increased AST/ALT/GGT

<sup>4</sup> includes all preferred terms that are cardiac arrhythmias

<sup>5</sup> includes dizziness and light-headedness

<sup>6</sup> includes peripheral and other forms of edema but not angioedema

### **Adverse Events of Special Interest and Special Safety Concerns**

#### *Infections and Lymphopenia*

Siponimod causes an approximate 25% reduction in serum total white blood cell count. Siponimod treatment is associated with lymphopenia in approximately 8% of patients. The non-specific sphingosine-1-phosphosphate modulator fingolimod is associated with increased risk of viral and opportunistic infections. Therefore, increased risk of infections was a primary concern with siponimod throughout its development program. For most infection-related TEAEs in the controlled trials, the frequencies of all infections combined in the siponimod (49.1%) and placebo (49.9%) treatment groups were balanced. The notable exceptions were herpetic infections, which occurred more frequently (4.6%) in siponimod-treated patients than in patients on placebo (3.0%). Varicella virus reactivation, as herpes zoster, was more frequently observed in the siponimod-treated patients (2.9%) than in patients on placebo (0.7%).

As siponimod is associated with serum lymphocyte reduction, the review team recommends a baseline complete blood count and periodic monitoring of the complete blood count for lymphopenia. The team also recommends a description of the risk of

opportunistic infections in the Warnings and Precautions section of the prescribing information, and labeling language noting an increased risk for herpetic infection, including herpetic recrudescence as varicella zoster. The team recommends varicella immunization prior to initiation of siponimod in the absence of verification of adequate varicella immunity.

#### Macular Edema

Macular edema is an anticipated outcome in association with sphingosine-1-phosphate receptor modulation and was reported as an adverse event in approximately 2% of patients exposed to siponimod, versus 0.2% of patients on placebo. Dr. Wiley Chambers from the Division of Transplant and Ophthalmology Products provided a consultative review of the ophthalmological findings associated with siponimod. Dr. Chambers notes that the applicant did not submit the original optical coherence tomography data with the application, and only provided summaries of key findings. He concluded that macular edema was more frequently reported in patients on siponimod treatment, and that the majority of (but not all) cases occurred within the first 1-4 months of therapy. Dr. Chambers recommended a description of the risk of macular edema in the Warnings and Precautions section of labeling, with a recommendation for an ophthalmological examination for any change in vision while patients are taking siponimod.

#### Bradycardia and Atrioventricular Conduction Delays

Sphingosine-1-phosphate (S1P) receptors are expressed in cardiac tissue. Initiation of S1P modulators can cause bradycardia, bradyarrhythmias, and cardiac conduction block. These TEAEs are potentially life-threatening, and fingolimod, the approved non-selective S1P modulator, must be initiated with first-dose monitoring in a medical setting, including pre- and post-dose electrocardiograms. During the development of siponimod, the applicant instituted a titration over 6-days to the maintenance dose, attempting to mitigate the negative chronotropic effects and atrioventricular conduction blocks. On review, the titration was successful at reducing the risk of serious cardiac arrhythmias or bradyarrhythmias in patients with no prior history of significant cardiac disease, as no patient experienced atrioventricular blocks that were persistent, required treatment, or were symptomatic. These patients may initiate siponimod in a non-monitored setting. Conversely, patients with a history of rhythm disturbances or bradycardia remain at risk of significant atrioventricular block. The highest risk for cardiac events appeared to be with initial dosing within six hours of administration on the first day of therapy. Therefore, the review team recommends that patients with sinus bradycardia (HR less than 55 bpm), first- or second-degree (Mobitz type I) AV block, or a history of myocardial infarction or heart failure, receive their first dose of siponimod in a monitored medical setting. All patients should have an electrocardiogram prior to initiation of siponimod to identify cardiac conduction abnormalities that might necessitate first-dose monitoring. Labeling will describe the

risk factors that necessitate first-dose monitoring and provide recommendations regarding how to proceed with initial dosing and restarting treatment after discontinuation.

### Respiratory Effects

Prior experience with 51P receptor modulation suggested that patients exposed to siponimod might experience symptoms consistent with restrictive airway disease and persistent changes in forced-expiratory volume over one second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO). A review by Dr. Rekha Jhamnani, from the Division of Pulmonary, Allergy, and Rheumatology Products, summarized the applicant's findings related to pulmonary changes in the exposed population. Overall, the review concluded that chronic treatment with siponimod was associated with a dose-dependent reduction in FEV1 that began at three months of therapy (-0.03 liter), appeared to peak at six months (approximately -0.1 liter) and persisted through the two-year period of available observation data. The applicant was unable to provide longitudinal data from the extension trial to describe the long-term persistence of effects over multiple years of exposure and did not have data regarding persistence of the diminished FEV1 after discontinuation of therapy. There was no change in DLCO associated with siponimod therapy. In the controlled trial, there were respiratory-related TEAEs, the most common of which were asthma, reported in 0.4% of siponimod-treated patients versus 0.2% of patients on placebo, and nasal congestion, reported in 0.4% of siponimod-treated patients versus 0.2% of patients on placebo. There were no serious respiratory adverse events, and no respiratory adverse events that were a cause of death. Study drug discontinuation was required in patients who had reductions in FEV1, FVC, or corrected DLCO below 60% of pre-treatment value at any visit, and those patients were to be referred to a pulmonary specialist. Five patients discontinued siponimod treatment due to respiratory function testing changes meeting these requirements, whereas no patient on placebo discontinued the study due to respiratory testing changes. The consultant review concluded that labeling should describe the FEV1 reduction. Considering the paucity of long-term exposure beyond two years and lack of data with respect to the persistence of FEV1 reduction after discontinuation, the review team recommends a postmarketing requirement for a study to examine the persistence of the FEV1 reduction during treatment with siponimod and after discontinuation of siponimod.

### Liver Injury

Siponimod is metabolized extensively by hepatic enzymes CYP2C9 and CYP3A4. The review team noted that siponimod is associated with increased serum levels of liver transaminases. In the controlled pivotal study, adverse events related to increased liver transaminases were among the most common treatment-emergent adverse events (10% in siponimod-treated patients versus 3% in patients on placebo), serious adverse events (1.3% in siponimod-treated patients versus 0.3% on placebo), adverse events leading to treatment discontinuation (0.9% in siponimod-treated patients versus no case in

patients on placebo), and adverse events leading to drug interruption (0.3% in siponimod-treated patients versus no case in patients on placebo). There were cases of alanine aminotransferase or aspartate aminotransferase levels eight (0.5%) or ten (0.2%) times the upper limit of normal range in the siponimod treatment group (versus no patient on placebo with values > three times the upper limit of normal range), but there were no cases meeting Hy's law criteria, and no reported cases of fulminant liver failure. The safety review concludes that the risk of liver injury should be described in the Warnings and Precautions section of labeling, and that a baseline evaluation of liver transaminases should be obtained in all patients before initiation of siponimod.

#### Increased Blood Pressure

Siponimod was associated with a mean increase of 3 mmHg systolic and 1 mmHg diastolic blood pressure during chronic treatment. These mean increases are similar to those noted in clinical trials with fingolimod, a nonselective sphingosine-1-phosphate receptor modulator that carries a Warnings and Precautions statement for "Increased Blood Pressure." In the controlled study, hypertension and related treatment-emergent adverse events were reported in approximately 13% of patients treated with siponimod, versus approximately 9% of patients on placebo. The safety review concludes that hypertension should be described in the Warning and Precautions section of labeling, with a recommendation to monitor blood pressure in patients on siponimod.

#### Safety Conclusions

Siponimod is associated with adverse reactions, some serious, but the risks of most treatment-emergent events can be reduced through minimally invasive screening and mitigated by discontinuation of therapy. The identified risks are consistent with what is known regarding the safety profile of fingolimod, a non-specific S1P modulator. With established efficacy for the treatment of relapsing forms of multiple sclerosis, siponimod's safety profile certainly does not preclude approval.

While there is no need for a postmarketing risk management and mitigation strategy, there are safety issues that require monitoring and some that would benefit from further clarity. The Warnings and Precautions section of the prescribing information will need to provide detailed descriptions and monitoring recommendations related to the risk of infections, the need for first-dose monitoring, cardiac effects, risk of macular edema, risk of hepatic injury, reduced expiratory volume, and elevated blood pressure. A postmarketing requirement for a longitudinal respiratory study has been communicated to the applicant, to assess the chronicity of the respiratory effects of siponimod.

## **9. Advisory Committee Meeting**

This application was not referred to an Advisory Committee for review because this drug is not the first in its class, the safety profile is similar to that of other drugs

approved for this indication, the clinical trial design was acceptable, the efficacy findings were clear, and the safety profile was acceptable in light of the serious nature of the disease being treated. Labeling will make prescribers fully aware of the risks, allowing them to inform patients and decide whether to use the drug.

## **10. Pediatrics**

No clinical pediatric data are provided. An initial Pediatric Study Plan to study siponimod in patients ages 10-18 years old with relapsing forms of multiple sclerosis that was proposed by the applicant was deemed acceptable. The postmarketing requirement for a pediatric study is described in Section 13.

## **11. Other Relevant Regulatory Issues**

### **Office of Scientific Investigations review**

The Office of Scientific Investigations (OSI) reviewer for this application was Dr. Cheryl Grandinetti. The OSI review team inspected three clinical sites (Drs. Hodgkinson [Australia], Maida [Austria], and Mao-Draayer [United States]) and the applicant, Novartis Pharmaceuticals Corporation (United States), during the review of this application. The final classifications of the inspections of Drs. Hodgkinson and Mao-Draayer were “No Action Indicated (NAI).” The final classification of the inspection of Dr. Maida was “Voluntary Action Indicated (VAI),” because of a failure to report a protocol violation to the FDA and failure to maintain source records, specifically protocol-mandated attestation statements that patients had SPMS, for the 42 patients enrolled at the site. Dr. Jones identified no other Good Clinical Practice (GCP) issues in his clinical review. Dr. Jones concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

### **Controlled Substance Staff review**

The Controlled Substance Staff (CSS) reviewer for this application was Dr. Jovita Randall-Thompson. Based on the pharmacology of siponimod, the lack of evidence of abuse in nonclinical abuse and dependence studies, and the absence of abuse-related adverse events in clinical trials, Dr. Randall-Thompson concluded that siponimod has no abuse potential.

### **Division of Chemistry and Toxicology Devices (DCTD)/Office of In Vitro Diagnostics (OID) review**

The Division of Chemistry and Toxicology Devices (DCTD)/Office of In Vitro Diagnostics (OID) provided a consultation. The reviewing consultant for this

application was Dr. Jeffrey Kraft. Because siponimod maintenance dose and contraindication is determined by CYP2C9 genotype, DCTD was consulted regarding the need for a companion diagnostic test to identify patient CYP2C9 genotype. The consultation review had the following conclusions and recommendations:

- Currently, all legally marketed *in vitro* diagnostic (IVD) devices for CYP2C9 genotyping are intended as an aid in the identification of patients at risk for increased warfarin sensitivity. The applicant will therefore need to validate an IVD device or identify a device manufacturer (e.g., a manufacturer of a currently legally marketed CYP2C9 genotyping IVD device) to validate an IVD device for an intended use for the identification of patients in the population who should not receive siponimod (i.e., patients with the CYP2C9\*3/\*3 genotype) and to provide the validation data to the Agency to support the new intended use.
- A companion diagnostic should be developed and approved or cleared contemporaneously as the novel therapeutic product, so that it will be available for use when the therapeutic product is approved. However, given the stage of review of the application, the validation of an IVD companion diagnostic will be requested in the postmarketing phase.

## 12. Labeling

See the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

## 13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary for siponimod.

- Other Postmarketing Requirements and Commitments

The following are postmarketing requirements:

- Conduct a juvenile rat toxicology study to evaluate effects of siponimod on growth, reproductive development, and neurological and neurobehavioral development.

Draft Protocol Submission:	07/2018
Final Protocol Submission:	04/2019
Study/Trial Completion:	08/2019

Final Report Submission: 02/2020

- Conduct a two-part study of siponimod in pediatric patients with relapsing forms of multiple sclerosis (RMS) at least 10 years and less than 18 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of siponimod in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine titration and maintenance doses of siponimod that will result in PK and PD effects that are comparable to those of the 5-day titration and the 1 or 2 mg genotype-based maintenance doses administered to adult patients. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of siponimod compared to an appropriate control.

Draft Protocol Submission: 03/2020  
Final Protocol Submission: 09/2020  
Study/Trial Completion: 09/2025  
Final Report Submission: 03/2026

- A prospective, parallel cohort study in patients with relapsing forms of multiple sclerosis to assess the potentially serious risk of pulmonary toxicity. The two cohorts should consist of patients newly prescribed siponimod and patients receiving another drug used to treat relapsing forms of multiple sclerosis. The study design should minimize differences between the cohorts by defining the populations in both cohorts so that they will be similar, by ensuring that both cohorts have similar clinical assessments (specifically FEV1, FVC, and DLCO), and by ensuring that patients who discontinue treatment have continued follow-up. In addition, the study protocol should account for duration of exposure, treatment changes, and loss to follow-up. Sample size should be supported by estimates of the rates of the events of interest.

Draft Protocol Submission: 06/2020  
Final Protocol Submission: 12/2020  
Study Completion: 12/2026  
Final Report Submission: 12/2027

- Conduct prospective pregnancy exposure registry cohort analyses in the United States that 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. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Draft Protocol Submission:	03/2020
Final Protocol Submission:	09/2020
Annual Interim Report Submissions:	09/2021
	09/2022
	09/2023
	09/2024
	09/2025
	09/2026
	09/2027
	09/2028
	09/2029
	09/2030
Study Completion:	09/2031
Final Report Submission:	09/2032

- Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3591-4 (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 Mayzent during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	03/2020
Final Protocol Submission:	09/2020
Annual Interim Report Submissions:	05/2021
	05/2022
	05/2023
	05/2024
	05/2025
	05/2026
	05/2027
	05/2028
	05/2029
	05/2030
	05/2031
Study Completion:	09/2031
Final Report Submission:	09/2032

The following is a postmarketing commitment:

- Establish an in-vitro diagnostic device to guide the use of siponimod in patients with relapsing forms of multiple sclerosis. The device should detect, at a minimum, the presence of the \*2 and \*3 alleles in cytochrome P450 2C9 (CYP2C9). The device should detect patients homozygous for the CYP2C9 \*3/\*3 genotype with statistical confidence.

Draft Protocol Submission:	12/2020
Final Protocol Submission:	12/2021
Study/Trial Completion:	12/2022
Final Report Submission:	12/2023

#### **14. Recommended Comments to the Applicant**

The approval letter will instruct the applicant to conduct enhanced pharmacovigilance for the safety concerns identified in the safety review, including expedited reporting of specified summary information in periodic reports.

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**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.**  
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/s/  
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PAUL R LEE  
03/26/2019 05:46:16 PM

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