CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209899Orig1s000

SUMMARY REVIEW

Summary Review

Date	March 25, 2020
From	Paul Lee, MD, PhD, CDTL, Division of Neurology 2 (DN2) Nick Kozauer, MD, Acting Director, DN2 Billy Dunn, MD, Director, Office of Neuroscience
Subject	Cross-Discipline Team Leader Summary Review
NDA#	209889
Applicant	Celgene Corporation
Date of Submission	March 25, 2019
PDUFA Goal Date	March 25, 2020
Proprietary Name	Zeposia
Established or Proper Name	ozanimod
Dosage Form(s)	0.23 mg, 0.46 mg, 0.92 mg immediate release capsules
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with relapsing forms of multiple sclerosis
Applicant Proposed Dosing Regimen(s)	0.92 mg orally once daily, following an initial 7-day dose escalation schedule (consisting of 0.23 mg for the first 4 days, followed by 0.46 mg for the next 3 days)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
Recommended Dosing Regimen(s) (if applicable)	0.92 mg orally once daily, following an initial 7-day dose escalation schedule (consisting of 0.23 mg for the first 4 days, followed by 0.46 mg for the next 3 days)

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Ozanimod 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 relapsing forms of multiple sclerosis (MS). There are two other S1P modulators approved for the treatment of relapsing forms of MS. Fingolimod is an S1P receptor modulator not selective for specific S1P receptors, and siponimod is selective for the S1P1 and S1P5 receptors. Therapies which modulate S1P receptor modulators, including ozanimod, siponimod, and fingolimod, reduce peripheral lymphocyte counts by preventing lymphocyte egress from lymph nodes.

Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (secondary progressive MS with relapses), are phenotypes of the chronic and potentially disabling central nervous system disease of apparent autoimmune etiology termed "multiple sclerosis." In the relapsing forms of MS, patients experience episodes of focal neurological deficits and disseminated lesions of demyelination within the brain. Symptoms of relapsing forms of MS commonly include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. Over time, many, but not all, patients with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. Over fifteen therapies have been approved for the treatment of relapsing forms of MS, and all these approved therapies share a basic common feature of modifying the immune response. Ozanimod would represent the third in the class of S1P modulator therapies. The other approved S1P modulators (fingolimod and siponimod) approved for the treatment of relapsing forms of MS have been shown to be effective in significantly reducing the frequency of patients' relapses and in reducing accumulation of irreversible disability.

The applicant presents the results from two adequate and well-controlled clinical trials (RPC01-201B and RPC01-301) as the basis of support for the effectiveness of ozanimod for the treatment of relapsing forms of MS. Both trials were randomized, double-blind, double-dummy, active-controlled, parallel group studies that compared 0.5 mg and 1 mg doses of ozanimod with interferon (IFN) β-1a (Avonex, 30 µg given intramuscularly weekly). The two studies were designed similarly with a same set of the primary and key secondary endpoints. The primary efficacy endpoint of the two studies was the annualized relapse rate (ARR) derived from the incidence of protocol defined clinical relapses. Secondary endpoints included number of new or enlarging T2 lesions, number of gadolinium-enhancing lesions, and time to disability progression confirmed at 3 months. The analysis of disability progression was based on the pooled disability data from the two studies.

In both studies, treatment with ozanimod at 1 mg and 0.5 mg doses resulted in statistically significant reductions in ARR compared to treatment with IFN β-1a. A dose-dependent effect was observed favoring the treatment effect of the 1 mg dose over the 0.5 mg dose of ozanimod in both studies. In Study RPC01-301, the reduction in ARR at the end of the treatment period was approximately 48% with ozanimod 1 mg and 31% with ozanimod 0.5 mg compared to IFN β-1a. The reduction in ARR at Month 24 in Study RPC01-201B was approximately 38% with ozanimod

1 mg and 21% with ozanimod 0.5 mg. The pooled analysis of disability progression did not show a statistically significant treatment difference between either of the ozanimod dose groups and the IFN β-1a treatment group indicating ozanimod was not superior to the active comparator in reducing acquired long-term disability.

S1P modulators have known risks for causing 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 activity at the other S1P receptor subtypes. More selective S1P modulators that bind more selectively to S1P1 but not all S1P receptor subtypes are intended to have a lower incidence of cardiovascular effects without impacting effects on lymphocyte sequestration that presumably underlie the proposed mechanism of S1P modulators' effectiveness in treating relapsing forms of MS.

The safety profile of ozanimod appears largely similar to that of the S1P modulator fingolimod, with the exceptions of milder, but not absent, cardiac effects, and the presence of intermediate metabolites that act as monoamine oxidase inhibitors. As is the case with other S1P modulators, ozanimod can cause bradycardia and atrioventricular conduction delays; ozanimod should be titrated to its maintenance dose. However, ozanimod's maximum cardiac effect is mild and observed at the end of its seven-day titration; therefore, unlike fingolimod and siponimod, first dose monitoring with initiation of ozanimod is not needed for any patients. Additionally, the clinical trial population of ozanimod included patients with mild conduction delays and these patients tolerated ozanimod without worsening of their underlying cardiac conduction abnormalities. Patients with a history of serious bradycardia or severe AV conduction delay would be expected to be at higher risk of experiencing an adverse event related to cardiac toxicity than patients without such histories and should discuss the cardiac risks of ozanimod with a cardiologist before initiating treatment. Patients treated with ozanimod are also at risk for infections, macular edema, liver injury, hypertension, posterior reversible encephalopathy syndrome, and respiratory effects consistent with a restrictive airway disease. Progressive multifocal leukoencephalopathy and severe exacerbations after discontinuation are assumed risks associated with the S1P class of therapies, even though these adverse events were not observed in ozanimod's clinical trials.

The overall benefit-risk profile of ozanimod appears similar to that of the other two S1P modulator therapies approved for the treatment of relapsing forms of MS, and supports approval for the treatment of relapsing forms of MS. Ozanimod appears to be well-tolerated by patients with the mildest forms of AV block. While there are some aspects of ozanimod's safety profile that differ from other approved S1P modulators, such as potential risk of serotonin syndrome with co-administration with monoamine oxidase inhibitors or dietary tyramine, these safety concerns can be mitigated by labeling warnings.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (SPMS with relapses), are phenotypes of the chronic and potentially disabling central nervous system disease multiple sclerosis, a disease of apparent autoimmune etiology which in its relapsing form is characterized by episodes of worsening focal neurological deficits and disseminated lesions representing demyelination. • The usual age of onset of relapsing forms of MS is 20 to 50 years. Symptoms commonly include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. Over time, many, but not all, patients with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. 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 biomarkers or predictors of outcome.	Relapsing forms of MS are serious and disabling. The defining symptom of relapsing forms of MS are paroxysms of focal neurological deficits termed "relapses" which can be temporarily disabling and reduce quality of life.
Current Treatment Options	• There are seventeen therapies approved to treat relapsing forms of MS. All of these therapies reduce patient relapse rates, 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. • Sphingosine-1-phosphate (S1P) modulators reduce peripheral serum lymphocyte counts by preventing lymphocyte egress from lymph nodes, a process that is mediated by S1P receptors	All therapies approved for the treatment of relapsing forms of MS reduce the frequency of relapses and some of these therapies also reduce accumulation of disability. Although S1P receptor subtype 1 modulation appears to mediate lymphocyte sequestration, some of the most significant cardiac and vascular

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and is presumed to be related to the therapy's mechanism of action. In 2010, fingolimod was the first S1P receptor modulator approved for the treatment of relapsing forms of MS. In 2019, siponimod became the second S1P receptor modulator approved for the treatment of relapsing forms of MS. Fingolimod is a nonselective modulator of S1P receptors; siponimod is selective for S1P receptor subtypes 1 and 5. Ozanimod is selective for S1P receptor subtypes 1 and 4.	effects of fingolimod are attributed to binding at other S1P receptor subtypes. A more selective modulator that binds to fewer S1P receptor subtypes would be predicted to reduce the likelihood of some cardiovascular effects without impacting effects on lymphocyte sequestration.
Benefit	• Based on the results of Study RPC01-201B, the absolute reduction in relapse rate for the ozanimod 1 mg treatment group was 0.104 (0.276 for IFN β-1a vs. 0.172 for ozanimod). • Based on the results of Study RPC01-301, the absolute reduction in relapse rate for the ozanimod 1 mg treatment group was 0.17 (0.35 for IFN β-1a vs. 0.18 for ozanimod). • The overall average reduction in relapses estimated for patients with relapsing forms of MS based on these trials would be 0.14 fewer relapses per year, or a 45% relative reduction in relapse risk as compared to patients treated with IFN β-1a. Based on this mean treatment effect size, one would need to treat 7 patients with ozanimod 1 mg per year to prevent one relapse. • Neither Study RPC01-201B nor Study RPC01-301 achieved a significant treatment effect on 3-month or 6-month confirmed disability when compared to IFN β-1a.	Two adequate and well-controlled trials in patients with relapsing forms of MS independently demonstrated approximately 50% relative reductions in MS relapses for the 1 mg dose of ozanimod relative to patients treated with IFN β-1a, another approved treatment for relapsing forms of MS. Ozanimod was not superior to an active comparator in preventing confirmed longitudinal disability.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Ozanimod, a selective S1P receptor modulator, has a safety profile largely similar to other approved S1P modulator therapies. • The most common adverse events in patients randomized to ozanimod in the active-controlled Phase 3 studies were upper respiratory infection (26.2%), hepatic transaminase elevations (10.2%), headache (8.8%), influenza-like illness (5.0%), orthostatic hypotension (4.3%), urinary tract infection (4.1%), back pain (4.0%), and hypertension (3.4%). • Severe adverse events associated with treatment were rare, occurring in less than 2% of patients treated with ozanimod as compared to 1.1% of patients treated with placebo and 0.5% treated with interferon. • Nine deaths (0.3%) occurred in ozanimod-treated adults with MS, including two due to cancer (two pancreatic carcinoma cases and one disseminated cancer with unknown primary), two due to accidents (train and motorcycle), and single cases of drowning, pulmonary embolism after orthopedic surgery, bilateral pneumonia, and chronic kidney failure (in a woman with posterior reversible encephalopathy syndrome and flaccid paralysis). • There was a low frequency of adverse events reported with ozanimod treatment that led to treatment discontinuation. In the controlled trials in patients with relapsing forms of MS, 2.4% of patients discontinued ozanimod for an adverse event, most often	Ozanimod can cause infections, macular edema, bradycardia, atrioventricular conduction delays, liver injury, hypertension, posterior reversible encephalopathy syndrome, and respiratory effects. Progressive multifocal leukoencephalopathy and severe exacerbation after discontinuation, and are assumed risks associated with this class of therapies, even if they were not observed in trials with ozanimod. These significant concerns warrant inclusion in labeling. Most adverse events associated with ozanimod were treatable, not medically serious, or reversible upon discontinuation. The patient deaths in the ozanimod development program do not suggest a clear association with treatment. Patients should have an electrocardiogram, complete blood count, ophthalmic examination, and liver function tests prior to initiation of ozanimod. Ozanimod is initiated as a seven-day titration to reduce the risk of bradyarrhythmias. Patients with histories of significant bradyarrhythmias should

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	liver transaminase abnormalities (0.8%) versus 1.1% discontinuation rate for placebo treatment. • The frequency of adverse events was higher in ozanimod-treated patients with MS (66.0%) as compared to placebo-treated patients (59.0%) but lower in comparison to patients treated with an approved interferon therapy (79.2%). • An intermediate active metabolite of ozanimod appears to act as a monoamine oxidase inhibitor. • Given the risk of bradycardia and atrioventricular (AV) block with initiating other S1P receptor modulators, ozanimod was initiated with an 8-day dose escalation. Second- or third-degree AV blocks were not reported in the ozanimod active-controlled trials, and the incidence of bradycardia was 0.8% (versus 0.7% with IFN beta-1a) after the first day taking the drug. Since the heart rate nadir occurred on Day 8, the utility of performing first-dose cardiac monitoring after starting ozanimod is unclear. • Ozanimod was associated with lymphopenia and an increased risk of infection, potentially more so in individuals exposed to previous immunosuppressants. • Labeling can sufficiently mitigate the identified safety risks.	consult a cardiologist before initiation of ozanimod. The drug is contraindicated in patients with significant heart disease. Ozanimod should not be taken with other therapies that inhibitor monoamine oxidase and patients should limit dietary tyramine to prevent serotonin syndrome or serious acute hypertension There will be requested pharmacovigilance for malignancies, life-threatening infections, fatal infections, thromboembolic ischemic events, and prenatal exposures associated with renal malformations. A Risk Evaluation and Management Strategy is not necessary to ensure that the benefits of ozanimod outweigh the risks of cardiac conduction abnormalities, infections, and other adverse events.

2. Background

This application contains data in support of the safety and effectiveness of ozanimod, 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 relapsing forms of multiple sclerosis. Ozanimod is a new molecular entity (NME) that has not been approved for any indication. The Division refused to file a previous application for this product because of inadequate characterization of intermediate active metabolites of ozanimod (see Clinical Pharmacology).

Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and secondary progressive multiple sclerosis with relapses (active secondary progressive disease), are related phenotypes of a chronic and potentially disabling central nervous system disease of apparent autoimmune etiology characterized by episodes of worsening focal neurological deficits and disseminated lesions of demyelination. Patients diagnosed with relapsing forms of MS are typically White women between 20 to 50 years of age. Symptoms commonly include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. As disease duration increases, many, but not all, patients with relapsing 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 with clear independence from acutely disabling relapse events, a process termed secondary progressive disease.

There is no widely accepted biomarker to assess disease status in patients with relapsing forms of MS. The diagnosis of relapsing forms of MS relies on clinical criteria, and the ongoing evaluation of patients with multiple sclerosis is reliant on clinical investigation. To support an indication for the treatment of relapsing forms of multiple sclerosis, clinical trials should demonstrate that a therapy is associated with a significant, clinically meaningful decrease in the frequency of MS-associated relapses, typically measured as an annual relapse rate (ARR). Some therapies approved for the treatment of relapsing forms of multiple sclerosis, including other S1P modulators, have also demonstrated an additional significant reduction of the accrual of disability over three-month or six-month observational periods.

Gilenya (fingolimod) was the first S1P receptor modulator approved by the FDA in 2010, and a second selective S1P modulator, Mayzent (siponimod), was approved in

2019. Fingolimod's indication is for the treatment of relapsing forms of MS in patients aged 10 years and older; siponimod is approved for adults aged 18 and older.

Administration of S1P modulators reduces lymphocyte counts by preventing lymphocyte egress from lymph nodes, a process that is mediated by S1P subtype 1 (S1P1) receptors. Fingolimod is a nonselective modulator of S1P receptors; siponimod is selective for S1P receptor subtypes 1 and 5. Ozanimod 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 ozanimod.

The applicant presents results from two adequate and well-controlled Phase 3 clinical trials as the primary basis of support for the effectiveness of ozanimod for the treatment of relapsing forms of multiple sclerosis. These two safety and efficacy studies, Study RPC01-201B and Study RPC01-301, were both randomized, double-blind, double-dummy, active-controlled, parallel-group studies comparing 0.5 mg and 1 mg doses of ozanimod with IFN β-1a (30 µg intramuscularly given weekly) in adult patients with relapsing forms of MS. These studies used different durations of observation but shared the same set of primary (ARR) and key secondary endpoints (new or enlarging T2 lesions, number of gadolinium-enhancing T1 lesions, and time to disability progression confirmed at 3 months).

Regulatory History

The Division issued a Study May Proceed letter (b) (4) on January 17, 2011. A partial clinical hold was imposed on (b) (4) April 7, 2011, because of 3 subjects who experienced cardiac adverse events in the initial Phase 1 trial. This partial clinical hold was removed after review of further clinical information on April 27, 2011. An End of Phase 1 meeting was held on May 1, 2012. The key topic of this meeting was cardiac monitoring for bradycardia; the Division provided agreement that the applicant's proposed cardiac monitoring strategy was acceptable.

The applicant sought and received agreement to a Special Protocol Assessment (SPA) on February 28, 2013, for the protocol for Study PC01-201. This SPA was modified with agreements by the Division on December 3, 2013, January 5, 2015, and September 8, 2015.

The applicant similarly sought a SPA with agreement on February 28, 2013, for the protocol for Study RPC01-301. This SPA was modified with the Division's agreement on October 16, 2014, and September 8, 2015.

The applicant and the Division met for a pre-NDA meeting on November 27, 2017.

The applicant submitted NDA 209899 on December 22, 2017. On February 23, 2018, the Division issued a Refuse to File (RTF) letter regarding this submission under 21 CFR 314.101(d) because the application was insufficiently complete to permit a substantive review. The clinical pharmacokinetic and potential toxicity of RP112273, a recently identified predominant and active metabolite of ozanimod, had not yet been established in the application. This lack of characterization of a key active metabolite was the basis of the RTF decision. The RTF letter stated as follows:

> "The long-term stability of RP112273, a recently identified predominant and active metabolite of ozanimod, has not yet been established. Retained plasma samples were used to quantify RP112273 in studies RPC01-201 (Part A and B), RPC01-301, RPC01-1904, RPC01-1906 and for most of subjects in study RPC01-1001. The samples were analyzed outside of the long-term stability window (136 days) for RP112273, and more than one year after collection for some of the samples. Long-term stability evaluations for RP112273 are ongoing. Per the Guidance for Industry on Bioanalytical Method Validation (2013), 'Assays of all samples of an analyte in a biological matrix should be completed within the time period for which stability has been demonstrated'. Because of the above issue, the clinical pharmacokinetics of RP112273 have not been adequately characterized. The results of the pharmacokinetic analyses for RP112273 will inform critical assessments related to Zeposia dosing, e.g., the need for dosing adjustments for intrinsic or extrinsic factors that might affect the pharmacokinetic or pharmacodynamics of ozanimod. Without such information, labeling cannot be written to inform drug use in specific populations or patients taking concomitant medications."

The nonclinical team also contributed the following issues to the RTF letter:

> "RP112273, an active metabolite with potency at the S1P1 and 5 receptors similar to that of the parent compound, accounts for the majority ((b) (4)%) of drug-related material in circulation in humans. Therefore, you will need to demonstrate that RP112273 has been assessed in a standard battery of nonclinical studies. To bridge to the existing nonclinical data, you would need to demonstrate adequate plasma RP112273 exposures in males and females,

using the same dosing regimens used in the pivotal studies, in all species tested. Based on a preliminary examination, the available TK data are insufficient to allow a determination of the adequacy of the safety assessment for RP112273. While the issues below are not related to the refusal to file decision for this application, you should address them if the application is resubmitted."

The applicant requested a Type C meeting to discuss its proposed studies and plans for remediation of the issues that led to the RTF decision. The meeting was granted as a written response only format with a response issued on November 9, 2018. A second Type C meeting discussed final plans for the NDA's resubmission format and final questions about the re-submission. The applicant submitted an initial pediatric study plan (iPSP) with agreement on February 28, 2019.

The applicant re-submitted NDA 209899 on March 25, 2019.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) 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 ozanimod is an immediate release drug product provided in strengths of 0.23 mg, 0.46 mg, and 0.92 mg of ozanimod (0.25 mg, 0.5 mg and 1.0 mg of ozanimod hydrochloride).

The OPQ team found no significant issues with the three manufacturing processes for the drug product and substance. The applicant's approach to impurity control was deemed acceptable.

The OPQ review agrees that that the drug product can be stored at room temperature and that applicant's proposed 24-month shelf life for the 0.23 mg drug product and 36-month shelf life for the 0.46 mg and 0.92 mg drug products are likewise acceptable.

All inspected manufacturing facilities and suppliers were deemed acceptable.

4. Nonclinical Pharmacology/Toxicology

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

- The applicant provided data that demonstrated the ability of ozanimod and its metabolites to reduce circulating CD4+, CD8+, and B220+ lymphocyte subtypes in Sprague Dawley rats. Ozanimod was also able to reduce circulating lymphocytes in C57Bl/6 mice, beagle dogs, and cynomolgus monkeys. The ozanimod-related decrease in circulating leukocytes was associated with a reversible decrease in lymphoid cellularity of the spleen and an alteration in thymic differentiation in rats and monkey. In the rat and monkey studies, lymphoid depletion in the spleen was evident at all doses tested in the pivotal general toxicology studies. In all species tested, the reduction in circulating lymphocytes was reversible upon cessation of treatment. Decreased peripheral lymphocyte counts led to diminished immune system function in immunotoxicity studies conducted in adult and juvenile rats. These findings are consistent with the known effects of agonism at S1P receptors in animals and in humans.

- The applicant provided data from a cardiovascular safety study in cynomolgus monkeys that demonstrated dose-dependent cardiovascular effects of ozanimod. Heart rate decreased by 20% and the R-R interval increased by 37% at the highest dose given and persisted for 24 hours after dosing. Diastolic blood pressure was decreased by 20% at the highest dose given relative to pretest values and normalized 2-3 hours after dosing. Reduction in heart rate and increased blood pressure are seen in patients treated with ozanimod.

- The lung was a prominent target of ozanimod in rat and monkey. In rats, the medium and highest doses of ozanimod tested demonstrated consistent, dose-dependent increased respiratory rates and decreased tidal volumes. Increased lung weight and pulmonary macrophage infiltration were the most common ozanimod-related findings in the respiratory system of rats and monkeys. Pulmonary edema was reported in rats but not in monkeys.

- Ozanimod significantly attenuated the disease score in the mouse (C57BL/6) experimental autoimmune encephalomyelitis model relative to control and reduced the rate of demyelination compared to an appropriate control

condition in the mouse model of cuprizone-induced demyelination model. These results support potential efficacy in the treatment of relapsing forms of MS in humans.

- The applicant provided genotoxicity data (bacterial reverse mutation and in vitro chromosomal aberration assays) for ozanimod and three major metabolites (CC112273, CC1084037, and RP101124). Except for metabolite CC1084037, which was positive in the in vitro chromosomal aberration assay, the in vitro genotoxicity assessment of ozanimod and its metabolites was negative. The applicant performed follow-up genotoxicity testing (in vivo micronucleus and Comet assay) of CC1084037; results of these two tests were negative. Dr. Toscano concluded that there was adequate characterization of ozanimod and all assessed metabolites.

- The applicant provided data from a two-year carcinogenicity study in rats which was negative for drug-induced neoplasia. However, the exposures achieved for the metabolites CC112273 and CC1084037 were not higher than the maximum recommended human dose. A 6-month transgenic mouse study that exceeded the maximum human dose exposure for CC112273 and CC1084037 showed a drug-related increase in the incidences of hemangiomas and hemangiosarcomas in both male and female rats.

- Dr. Toscano and Dr. Freed agreed that the applicant had conducted an adequately designed battery of studies to assess the reproductive and developmental effects of ozanimod. Embryolethality and developmental effects were observed in rat and rabbit fetuses exposed to ozanimod and its metabolites in utero. In the pivotal fertility study conducted in rat, there were no drug-related effects observed up to the highest administered dose which exceeded the clinical exposure at the maximum recommended human dose by 2550-fold for ozanimod, 14-fold for CC112273, and 3-fold for CC1084037. Overall, ozanimod-related findings in these embryolethality and developmental studies conducted in rat and rabbit occurred at exposures to the major human metabolites CC112273 and CC1084037 that would be expected to occur at the maximum recommended human dose.

- In the pre- and postnatal development (PPND) study conducted in rat, hyperactivity (manifesting as increased motor activity in the open field assessment) and increased sensitivity to touch in the F1 generation were the only drug-related findings. Dr. Toscano noted several deficiencies in the PPND conducted by the applicant, specifically, the PPND lacked a complex

learning and memory task assessment, and the exposures to metabolites CC112273 and CC1084037 were lower than those in humans at the maximum recommended human dose. Dr. Toscano therefore recommended a postmarketing requirement (PMR) to conduct a PPND study in rats to address these gaps in the data. Dr. Freed agreed that the metabolite exposures were lower but noted the applicant had tried administering doses of CC112273 that were orders of magnitude higher than the maximum recommended human dose but could not achieve higher systemic exposures. She concluded that the data provided by the applicant had demonstrated ozanimod had clear, significant adverse effects on prenatal development that would discourage use during pregnancy and that another prenatal exposure study was not necessary.

- Dr. Freed found the applicant's two juvenile animal toxicology studies performed in rats were not adequate. In a 10-week study, the neurobehavioral evaluation did not include a complex task (e.g., Morris or Cincinnati water maze) and was assessed in too few animals, and there was no indication that an expanded neurohistopathological evaluation was conducted. The lack of neuropathological assessment is a significant gap for a therapy with activity at S1P5 receptors because the S1P5 receptor is expressed in brain and has a role in neurodevelopment. In a second juvenile toxicology study in rats, ozanimod administration at all doses reduced white blood cell counts and attenuated several antibody responses, but the applicant did not assess reversibility of these findings. Dr. Freed therefore recommends a juvenile toxicology study to assess the effects of ozanimod in the rat as a PMR. She notes that an adequate juvenile toxicology study is not required for safe use of ozanimod in adult patients but would be required to support potential future trials in pediatric patients.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) Review was written by Drs. Hristina Dimova (primary reviewer), Angela Men (the clinical pharmacology team lead), Raman Baweja, and Atul Bhattaram. The final signatory for the OCP review was Dr. Mehul Mehta. OCP recommends approval.

The OCP review provides an assessment of the applicant's response to the Refuse to File decision issued on February 23, 2018. The major basis of the Refuse to File decision for the initial NDA submission was the inadequate characterization of the clinical pharmacokinetics of the predominant, and active, metabolite of ozanimod,

CC112273 (also called RP112273), and another active disproportionate metabolite (CC1084037) which had been identified late in the development program. To address the deficiencies that led to the Refuse to File decision, the applicant provided PK data for CC112273 and CC1084037 using retained plasma samples from 17 Phase 1 clinical pharmacology studies as well as available data from three Phase 2 and 3 studies. The applicant also performed a revised population PK (popPK) analysis and conducted several new phase 1 studies as follows: Phase 1 drug-drug interaction (DDI) studies RPC01-1912 (DDI with CYP2C8 and/or CYP3A modulators) and Study RPC01-1914 (DDI with pseudoephedrine) assessing the single-dose and multiple-dose PK parameters for ozanimod and metabolites, including RP112273 and CC1084037. The OCP team found the findings from these studies addressed the prior submission's deficiencies and allowed for the resubmitted NDA's filing and substantive review.

Table 1, adapted from the OCP review, summarizes the conclusions of the OCP team with respect to the pharmacologic and clinical pharmacokinetic properties of ozanimod.

Table 1 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	Ozanimod and its active metabolites are S1P1 and S1P5 agonists. Ozanimod causes retention of lymphocytes in the lymphoid tissues and a dose-dependent reduction in peripheral lymphocyte count. The mechanism by which ozanimod exerts therapeutic effects in MS may involve reduction of lymphocyte migration into the central nervous system.
Active moieties	Major active moieties: ozanimod, CC112273, and CC1084037. Ozanimod, CC112273, and CC1084037 are approximately 6%, 73%, and 15% of circulating total active drug exposure, respectively. Several other active metabolites together contribute to the remaining 6% of circulating total active drug exposure.
QT prolongation	No relevant QTc prolongation effect of ozanimod's major metabolite, CC112273, was detected in the Thorough QTc study.
General Information	
Drug exposure at steady-state following the therapeutic dosing regimen	The mean exposures ($AUC_{0-\tau}$) at the steady state (Day 85) following ozanimod 1 mg daily in patients with relapsing forms of MS were 4.5 ng*h/mL for ozanimod and 143.8 ng*h/mL for RP112273.
Dose-proportionality	Exposure of ozanimod and CC112273 increased dose-proportionally in the dose range of 0.5 mg to 1 mg.

Accumulation	Steady-state concentrations of ozanimod are reached within 5 to 7 days of QD dosing with approximately 2-fold drug accumulation at steady state. The mean time to steady state for CC112273 is approximately 45 days with an estimated mean accumulation ratio of approximately 16. Time to steady state and accumulation ratio for CC1084037 are expected to be similar to CC112273 since both metabolites have a similar t1/2 and their exposure are highly correlated.	
Variability	In relapsing MS patients, the inter-subject variability (%CV) was estimated for ozanimod CL/F as 23.5% and for CC112273 CL/F, Vc/F and formation rate constant as 74.5%, 25.9%, and 37.2%, respectively.	
Absorption		
Bioavailability (oral)	Co-administration with a high-fat meal showed no significant effect on the rate and the extent of absorption.	
T_{max} (oral)	The Tmax of ozanimod is approximately 6-8 hours. Tmax for the major active metabolite RP112273 is variable with median values between 6 and 10 hours.	
Food effect (high-fat) Geometric mean ratio (90% confidence interval [CI])	AUC_{inf} 1.10 (1.05-1.15)	C_{max} 1.06 (1.02-1.14)
Distribution		
Volume of distribution	The mean apparent volume of distribution of ozanimod (Vz/F) is 5590 L.	
Plasma protein binding	Plasma protein binding of ozanimod, CC112273, and CC1084037 is 98.2%, 99.8%, and 99.3%, respectively.	
Elimination		

Mean terminal elimination half-life	The half-life (t½) of ozanimod is approximately 20 hours; t½ of RP112273 and CC1084037 is about 280 hours.
Metabolism	
Primary metabolic pathway(s)	Ozanimod is extensively metabolized in humans with over 13 metabolites identified in plasma, urine, and feces, including the active metabolites CC112273 [also referred to as RP112273], CC1084037 [also referred to as RP100798], RP101988, RP101075, RP112289, RP101442) and one circulating inactive metabolite RP101124. Ozanimod and the active metabolites have similar activity and selectivity for S1P1 and S1P5. Following multiple dose administration of ozanimod in healthy subjects, ozanimod, CC112273, and CC1084037 each represents approximately 6%, 73%, and 15% of circulating total active drug exposure, respectively. Multiple enzyme systems play a role in the metabolism of ozanimod. The oxidative pathway to form metabolite RP101988 is mediated by ALDH/ADH. Formation of RP101075 by dealkylation is predominantly mediated by CYP3A4. RP101075 is N-acetylated by NAT-2 to form RP101442 or deaminated by monoamine oxidase B (MAO-B) to form the major metabolite CC112273. CC112273 is either reduced to form CC1084037 or undergoes CYP2C8-mediated oxidation to form RP101509. CC1084037 is oxidized to form CC112273 by AKR 1C1/1C2, and/or 3β- and 11β-HSD and undergoes reversible metabolism to CC112273.
Inhibitor/inducer	Ozanimod and major metabolites CC112273 and CC1084037 have no inhibitory effect on CYPs 1A2, 2B6, 2C19, 2C8, 2C9, 2D6, and 3A and no induction effect on CYPs 1A2, 2B6, and 3A. CC112273 and CC1084037 are MAO-B inhibitors.
Transporter systems	Ozanimod, CC112273, CC1084037 and other metabolites have no inhibitory effect on P-gp, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, and MATE2-K. CC112273 and

	CC1084037 inhibit BCRP with an IC50 values of 25.2 nM and 22.8 nM, respectively. At clinically relevant concentrations of CC112273 and CC1084037, inhibition of BCRP is not expected.
Excretion	
Primary excretion pathways (% dose) ± SD	After oral administration of a single oral dose of [14C]-ozanimod HCl, the total mean recovery of the administered radioactivity was 63%, with 26% recovered from urine and 37% recovered from feces. The low recovery of total radioactivity is due to the long t½ of total radioactivity of 99 hours. Ozanimod, CC112273, and CC1084037 concentrations in urine were negligible, indicating that renal clearance is not an important excretion pathway for ozanimod, CC112273, and CC1084037.

The OCP review agrees that the dose escalation over seven days proposed by the applicant mitigates most of the heart rate change associated with the full treatment dose (1 mg) observed when the 1 mg dose was administered to ozanimod naïve patients.

Because the human mass-balance study showed only partial recovery (63%) of radiolabeled ozanimod, there was a need to assess the impact of hepatic and renal impairments on the pharmacokinetics of ozanimod and its metabolites.

Study RPC01-1904 examined the effect of hepatic impairment on ozanimod and its metabolites following a single dose of 0.25 mg of ozanimod in subjects with mild (Child-Pugh Grade A), and moderate (Child-Pugh Grade B) hepatic impairment as compared with subjects with normal hepatic function. Following a single oral dose administration of ozanimod 0.25 mg, total (bound + unbound) systemic exposures (i.e., $AUC_{0\text{-last}}$) for ozanimod and CC112273 in subjects with mild hepatic impairment were approximately 11% lower and 31% lower, respectively, compared to subjects with normal hepatic function. Total systemic exposures (i.e., $AUC_{0\text{-last}}$) for ozanimod and CC112273 in subjects with moderate hepatic impairment were approximately 27% higher and 33% lower, respectively, compared to subjects with normal hepatic function. The applicant concluded that (b) (4)

(b) (4) the differences in systemic exposures were not clinically meaningful.

The OCP review differed with the applicant's conclusion for two reasons, inadequacy of the hepatic impairment study's data, and an absence of safety data in the indicated population at steady state. Study RPC01-1904 used a single dose of ozanimod, but the OCP review noted that active metabolites, such as CC112273, would be expected to accumulate in the setting of hepatic impairment and therefore would circulate at higher, potentially clinically significant, concentrations in individuals with hepatic impairment at steady state. To address this important consideration would require a study with serial dose administration to achieve steady state. As evidence of the importance of a steady state trial, the OCP review cited data from Study RPC01-1912 which showed that a three-day course of a strong inhibitor of a key hepatic enzyme for processing ozanimod (which approximates hepatic impairment) followed by 14 days of ozanimod administration led to circulating CC112273 levels increasing by 47% in healthy volunteers. Secondly, there are no safety data available in any individuals with hepatic impairment who received more than a single dose of ozanimod. The study protocols for the Phase 2 and 3 trials excluded patients with mild or worse hepatic impairment from the trials. Thus, the only safety data in any patients with hepatic impairment in the entire development program were obtained in Study RPC01-1904, which only exposed patients to a single dose of ozanimod. Therefore, the OCP review concluded that ozanimod should not be recommended for use in patients with hepatic impairment because there are neither PK nor safety data at steady state to support safe use of ozanimod as a chronic treatment for MS in such patients. The OCP review recommends a post-marketing requirement (PMR) to assess the effect of hepatic impairment on ozanimod and its major metabolites' pharmacokinetics when ozanimod is dosed until steady state is reached for CC112273.

With respect to drug-drug interactions, ozanimod's major metabolite CC112273 is formed via MAO-B; in addition, the ozanimod metabolites RP112273 and CC1084037 are MAO-B inhibitors in vitro. Monoamine oxidase inhibition can lead to peripheral and central neurotransmitter accumulation, and MAO inhibitors, when taken in combination with vasoconstrictors such as pseudoephedrine or dietary tyramine can cause hypertensive crises. To address a potential impact of MAO inhibition in vivo, the applicant conducted Study RPC01-1914, a randomized, double-blind, placebo-controlled study to assess the potential of ozanimod to enhance pressor responses to pseudoephedrine in healthy subjects, and Study RPC01-1913, a double-blind, placebo- and positive-controlled study of pressor response when ozanimod was co-administered with oral tyramine. Co-administration of ozanimod with

pseudoephedrine increased the pseudoephedrine-induced heart rate response by approximately 3 beats per minute, which was not deemed to be clinically significant by the clinical review team. In Study RPC01-1913, the placebo-treated subjects had the highest sensitivity to tyramine-induced blood pressure elevation, a result that was unexpected and paradoxical because placebo treatment typically establishes a physiological baseline for tyramine sensitivity and should not represent a maximum response. Thus, the results of Study RPC01-1913 were ultimately not interpretable. The applicant provided data showing no inhibition of MAO-B activity in platelets and in vitro data from a serotonergic mouse model study showing no evidence of serotonin syndrome with CC112273 exposure and suggested (b) (4) (b) (4) ozanimod had no potential risk for serotonin syndrome or hypertensive crisis with concomitant use of antidepressants or MAO inhibitors. The OCP review team did not agree that these nonclinical data were sufficient to overcome possible clinical concerns with the possibility of serotonin syndrome. (b) (4) (b) (4) (b) (4) The clinical review agreed with OCP that ozanimod's (b) (4) needed to reflect the potential risks of serotonin syndrome and hypertensive crisis. The OCP team additionally recommends a new tyramine challenge study with additional design considerations to improve interpretability as a PMR. Until there are adequate data to support an assertion that co-administration of ozanimod and MAO inhibitors or tyramine is safe, the OCP team concluded that co-administration of MAO inhibitors (e.g., phenelzine, isocarboxazid, linezolid, rasagiline, safinamide, selegiline) as well as tyramine-containing foods with ozanimod is contraindicated.

(b) (4) (b) (4). The OCP team explained that co-administration of ozanimod with strong inhibitors of CYP2C8 could not be recommended because the exposures (AUC_{last}) of the active metabolites of ozanimod (CC112273, CC1084037, and RP101988) were all increased by 47-69%. In addition, the increase in AUC_{inf} of these metabolites could not be determined due to the metabolites' long half-lives (indicating potentially even more increase in AUC_{inf} than in AUC_{last}). (b) (4) (b) (4). Rifampin co-administered with ozanimod significantly reduced the exposure of ozanimod major metabolites CC112273 and CC1084037. Otherwise, the OCP team concurred with the applicant that co-administration of inhibitors of BCRP (e.g., cyclosporine, eltrombopag) would not be recommended.

With respect to intrinsic factors, the OCP review agreed with the applicant's conclusions that renal impairment, race/ethnicity, biological sex, body weight, and fed status appeared to have no relevant effects on the pharmacokinetics of ozanimod and its metabolites. PK and pharmacodynamic data suggested that smokers had lower exposures to the major active metabolite CC112273 and experienced a reduced effect on absolute lymphocyte counts which could impact the clinical efficacy of ozanimod in smokers. However, upon detailed review, the exposure to CC112273 and the lymphocyte counts overlapped within the 95% confidence intervals for non-smokers, and, most significantly, smokers administered the 1 mg dose of ozanimod had on average a lower ARR than nonsmokers, suggesting a lack of effect of smoking on the primary clinical efficacy outcome measure of the pivotal trials at the dose proposed for marketing.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Larry Rodichok was the clinical efficacy reviewer for this application. Dr. Sharon Yan was the biometrics reviewer, and Dr. Kun Jin was the biometrics team lead. Dr. Rodichok finds that the application provides substantial evidence of efficacy for ozanimod in the treatment of patients with relapsing forms of MS. Drs. Yan and Kun agree that the application provides adequate statistically significant evidence of efficacy for both the 0.5 mg and 1 mg doses of ozanimod in the prevention of clinical relapses. The clinical and biometrics reviewers agree there is no significant evidence at any dose of ozanimod to establish the superiority of ozanimod when compared to IFN β-1a in preventing disability progression.

The applicant submitted data from two adequate and well-controlled efficacy studies, Study RPC01-201B (hereafter "Study 201B"), and Study RPC01-301 (hereafter "Study 301"). Study 201B was a Phase 3, two-year, randomized, double-blind, double-dummy, active-controlled, parallel-group study. Study 301 was a Phase 3, one-year, randomized, double-blind, double-dummy, active-controlled, parallel group study. Both of these studies evaluated the efficacy of ozanimod at dose levels of 0.5 mg and 1 mg daily (expressed as ozanimod hydrochloride) compared to IFN β-1a intramuscular injection weekly.

Study 201B

Study 201B was a Phase 2B, multi-national, randomized, double-blind, double-dummy, active controlled trial intended to evaluate the safety and efficacy of ozanimod in patients with relapsing forms of MS. Study 201B randomized patients 1:1:1 into three treatment arms as follows: ozanimod 0.5 mg daily, ozanimod 1 mg daily, and intramuscular IFN β-1a administered weekly. Enrollment criteria stipulated enrollment of patients who met the 2010 McDonald diagnostic criteria for relapsing MS with at least one documented relapse within the 12 months prior to enrollment plus evidence of at least 1 gadolinium-enhancing lesion on brain magnetic resonance imaging within the 12 months prior to randomization. In addition to the double-dummy design to preserve patient blinding to treatment, the clinical raters who conducted key assessments of patients were blinded to patient treatment status as well, but there was not an independent body that adjudicated in-trial relapses. The trial duration was fixed at 24 months. The study utilized a seven-day titration to maximum treatment dose. This study was conducted using a protocol with an agreed-upon SPA.

The primary efficacy endpoint of Study 201B was the ARR after 24 months of treatment.

Secondary endpoints were ranked and analyzed in closed sequential hierarchical order as follows:

1. The number of new or enlarging hyperintense T2-weighted brain magnetic resonance imaging (MRI) lesions over 24 months
2. The number of T1 gadolinium-enhancing brain MRI lesions at Month 24
3. Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months

There were 1320 patients randomized into Study 201B as follows: 443 ozanimod 0.5 mg, 434 ozanimod 1 mg, and 443 IFN β-1a. Patients were enrolled at 299 sites in 21 countries worldwide. Most (86.1%) of the enrolled patients came from Eastern Europe, primarily (28.4%) from Poland. Approximately 3.5% of the patients were from the United States.

The intent-to-treat population for the primary efficacy analysis was defined as all randomized patients who received at least one dose of study medication. There were seven randomized patients who were not treated with assignments as follows: four in the ozanimod 0.5 mg treatment arm, one in the ozanimod 1.0 mg treatment arm, and two who had been randomized to IFN β-1a. Of these seven randomized but

untreated patients, three were not treated because of baseline electrocardiogram findings that rendered them ineligible for receiving treatment, one voluntarily withdrew, and three were "randomized in error" because they were found to have met exclusion criteria that should have excluded them from trial enrollment. The rate of completion of treatment in randomized assignment was 84.4% for the ozanimod 0.5 mg treatment group, 89.4% for the 1 mg ozanimod treatment group, and 84.9% for the IFN β-1a treatment group, respectively. The most common reason for trial discontinuation in all treatment arms was "withdrawal by subject."

Demographic and baseline disease-related characteristics of the randomized patients were well-matched between the three treatment arms. As is typical for clinical trials in patients with relapsing forms of MS, the majority of the patients were women (67.2%), less than forty years old (66.5%), and virtually all were White (98.3%).

The biometrics review team confirmed the results for the primary efficacy outcome as provided by the applicant:

Table 2: Study 201B: Primary Analysis of Annualized Relapse Rate

	Ozanimod 0.5 mg n=439	Ozanimod 1 mg n=433	IFN β-1a 30 μg n=441
Patients with Relapses n (%)	121 (27.6)	102 (23.6)	149 (33.8)
0	318 (72.4)	331 (76.4)	292 (66.2)
1	76 (17.3)	75 (17.3)	92 (20.9)
2	32 (7.3)	17 (3.9)	39 (8.8)
3	8 (1.8)	6 (1.4)	12 (2.7)
≥ 4	5 (1.1)	4 (0.9)	6 (1.4)
Primary Analysis: Poisson Model			0.276 (0.234, 0.324)
Adjusted ARR (95% CI)	0.218 (0.183, 0.259)	0.172 (0.142, 0.208)	
Rate Ratio Ozanimod/IFN β (95% CI)	0.791 (0.652, 0.958)	0.623 (0.506, 0.768)	
Percent Reduction	78.9%	37.7%	
p-value	0.0167	<0.0001	
Rate Ratio Ozanimod 1mg/0.5mg (95% CI)		0.789 (0.634, 0.981)	
Percent Reduction		21.1%	
p-value		0.0331	
Sensitivity Analysis: Negative Binomial Model			
Adjusted ARR (95% CI)	0.226 (0.176, 0.291)	0.178 (0.137, 0.233)	0.288 (0.226, 0.366)
Rate Ratio Ozanimod/IFN β (95% CI)	0.786 (0.611, 1.010)	0.620 (0.477, 0.806)	
Percent Reduction	21.4%	38.0%	
p-value	0.0593	0.0004	
Rate Ratio Ozanimod 1mg/0.5mg (95% CI)		0.789 (0.602, 1.034)	
Percent Reduction		21.1%	
p-value		0.086	

Patients with Confirmed + Unconfirmed Relapses, n (%)	129 (29.4)	108 (24.9)	155 (35.1)
Adjusted ARR (95% CI) (Poisson)	0.252 (0.215, 297)	0.191 (0.159, 0.228)	0.308 (0.264, 0.358)
Rate Ratio Oz/IFN β (95% CI)	0.820 (0.682, 0.987)	0.620 (0.506, 0.759)	
Percent Reduction	18.0%	38.0%	
p-value	0.0354	<0.0001	

Source: Biometrics Review

In her review, Dr. Yan states that the prespecified primary analysis was to compare the ARRs in each of the ozanimod dose groups to the IFN β-1a group using a Poisson regression model at the alpha = 0.025 level. She agrees with the findings from the analysis provided by the applicant that treatment with ozanimod resulted in a statistically significant reduction in ARR compared to IFN β-1a with an adjusted ARR of 0.172 for the ozanimod 1 mg group and 0.218 for the ozanimod 0.5 mg group, compared to 0.276 for the IFN β-1a group. The biometrics review notes that the corresponding reduction in ARR versus IFN β-1a was 37.66% (p<0.0001) for ozanimod 1 mg group and 20.95% (p=0.0167) for ozanimod 0.5 mg group. The review further concludes that the reduction in ARR was more pronounced in the ozanimod 1 mg group than in the ozanimod 0.5 mg group, indicating a dose-response relationship.

There were three key secondary efficacy outcomes to be assessed in a hierarchical fashion: new or enlarging T2 lesions at Month 24, T1 gadolinium-enhancing lesions at Month 24, and time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months.

New or Enlarging T2 Lesions

The biometrics review states that, at Month 24, the adjusted mean for the cumulative number of new or enlarging T2 lesions per scan was 1.84 for ozanimod 1 mg group and 2.09 for ozanimod 0.5 mg group, compared to 3.18 for the IFN β-1a group. A statistically significant treatment difference was achieved in both ozanimod dose groups as compared to IFN β-1a group with a p-value of < 0.0001. Dr. Yan however notes a problem with interpretation of this analysis is that there were a large number of patients with missing scans (110 in the ozanimod 0.5 mg group, 106 in the ozanimod 1 mg group, and 105 in the IFN β-1a group) which introduces a potential bias into the analysis because the primary analysis only represented patients who had a Month 24 scan. The imputation methodologies in two of the sensitivity analyses

provided by the applicant relied on a potentially flawed methodology that allowed a patient who dropped out of the study early to have a lesion number value imputed as the average lesion number of the patients who had completed a longer duration of the study. Dr. Yan raises the concern that the apparent reductions in lesion numbers in both ozanimod treatment groups relative to the IFN β-1a treatment group are not reflective of the whole intention-to-treat population because of the quantity of missing data and the fact that two of the applicant's three imputation methods utilized the mean findings from a potentially biased subset of patients who had a Month 12 or 24 scan, that is, patients who remained in the trial for longer durations and thus likely had greater cumulative treatment effects than the patients who were earlier drop-outs.

T1 Gadolinium-Enhancing Lesions

As with new or enlarging T2 lesions, the primary analysis of the number of gadolinium-enhancing lesions was based on patients who had a Month 24 MRI scan. At Month 24, the estimated mean T1 gadolinium enhancing lesion number was 0.18 for the ozanimod 1 mg group and 0.20 for the ozanimod 0.5 mg group as compared to 0.37 for the IFN β-1a group. These values represented a reduction in lesion numbers of 53% and 47% for the ozanimod 1 mg group (p=0.0006) and the 0.5 mg group (p=0.0030), respectively, as compared with the lesions in the IFN β-1a group. Dr. Yan reiterates the potential bias associated with a large number of patients with missing Month 24 scans and again questions whether the T1 lesion estimates are truly accurate because of these missing data.

3-month and 6-month Confirmed Disability Progression

The disability findings from Study 201B were pooled for analysis with those of Study 301 and will be discussed with the results of Study 301 below.

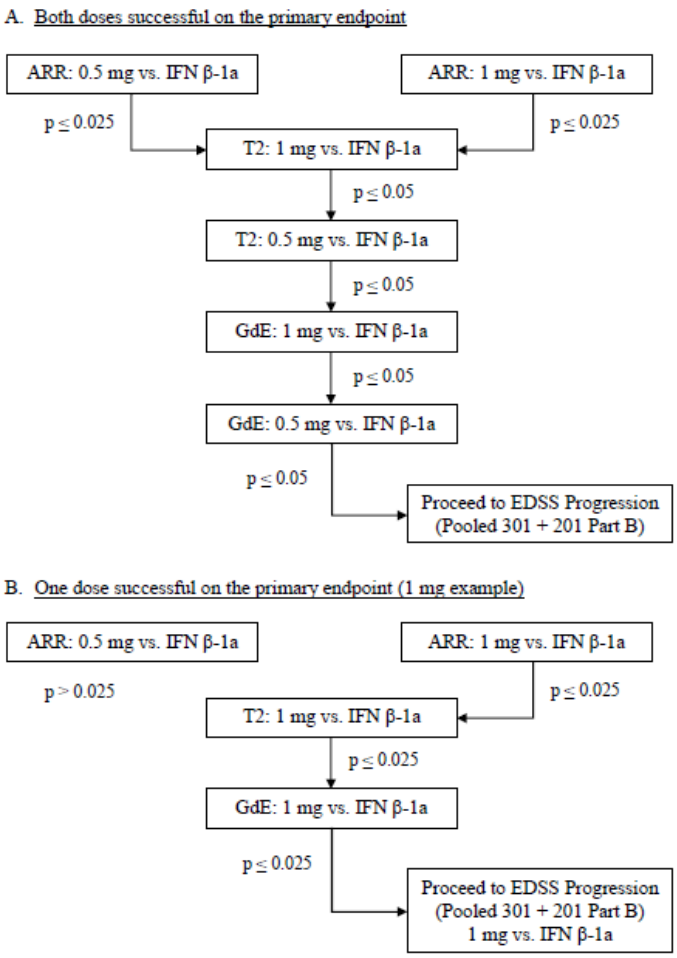
Study 301

Study 301 was a Phase 3, multi-national, randomized, double-blind, double-dummy, active-controlled trial intended to evaluate the safety and efficacy of ozanimod in patients with relapsing forms of MS. Study 301 randomized patients 1:1:1 into three treatment arms as follows: ozanimod 0.5 mg daily, ozanimod 1 mg daily, and intramuscular IFN β-1a administered weekly. Enrollment criteria stipulated enrollment of patients who met the 2010 McDonald diagnostic criteria for relapsing MS with at least one documented relapse within the 12 months prior to enrollment plus evidence of at least 1 gadolinium-enhancing lesion on brain magnetic resonance imaging within the 12 months prior to randomization. In addition to the double-dummy design to preserve patient blinding to treatment, the clinical raters who conducted key assessments of patients were blinded to patient treatment status as well, but there was not an independent body that adjudicated in-trial relapses. The trial duration was variable for patients because the trial was designed to end when the last active enrolled patient completed one year of treatment. The study utilized a seven-day titration to maximum treatment dose. This study was conducted using a protocol with an agreed-upon SPA.

The primary efficacy endpoint of Study 301 was the ARR with an analysis made between each ozanimod dose group and the IFN β-1a group (2 treatment contrasts). To account for multiple comparisons, each of the 2 treatment comparisons with IFN β-1a was to be tested at the α = 0.025 level.

The three key secondary endpoints were to be tested in a sequential, closed hierarchical testing procedure with ozanimod 1 mg dose to be tested before ozanimod 0.5 mg dose for each key secondary endpoint following the given rank order of the key secondary endpoints. If both doses were found to be significant on the primary endpoint, then the first comparison on the key secondary endpoints was to be the number of new or enlarging T2 lesions between the ozanimod 1 mg group and the IFN β-1a group at a 5% level of significance. If that comparison was successful, then the same endpoint was to be tested for the ozanimod 0.5 mg group vs. the IFN β-1a group comparison at the 5% level of significance. This procedure (Figure 1) was to continue down the rank-ordered key secondary endpoint list until a comparison failed to reach statistical significance, after which all subsequent comparisons were to be considered exploratory. If only 1 ozanimod dose was significant on the primary endpoint, then the hierarchical testing procedure was to be employed on the rank-ordered key secondary endpoints for the surviving dose only, at the 2.5% level of significance.

Figure 1: Study 301: Hierarchical Testing Procedure



There were 1346 patients randomized into Study 301 as follows: 447 ozanimod 0.5 mg, 451 ozanimod 1 mg, and 448 IFN β-1a. Patients were enrolled at 224 sites in 25 countries worldwide. Most (92.8%) of the enrolled patients came from Eastern Europe, primarily (28.4%) from the Ukraine. Approximately 2.7% of the patients were from the United States.

The intent-to-treat population for the primary efficacy analysis was defined as all randomized patients who received at least one dose of study medication. All patients who were enrolled and randomized received at least a single dose of study treatment. The rate of completion of treatment in randomized assignment was 94.2% for the ozanimod 0.5 mg treatment group, 93.5% for the 1 mg ozanimod treatment group, and 92.0% for the IFN β-1a treatment group, respectively. The most common reason for trial discontinuation in the ozanimod 0.5 mg treatment arm was voluntary withdrawal (3.1%). The most common reasons for discontinuation in the ozanimod 1 mg treatment group were adverse events (2.9%) and voluntary withdrawal (2.9%).

The most common reason for withdrawal in the IFN β-1a treatment arm was an adverse event (3.6%).

Demographic and baseline disease-related characteristics of the randomized patients were well-matched between the three treatment arms. As is typical for clinical trials in patients with relapsing forms of MS, the majority of the patients were women (67.2%), less than forty years old (65.4%), and virtually all were White (99.6%).

The biometrics review team confirmed the results for the primary efficacy outcome as provided by the applicant:

Table 3: Study 301: Primary Analysis of Annualized Relapse Rate

	Ozanimod 0.5 mg n=451	Ozanimod 1 mg n=447	IFN β– 1a 30 μg n=448
Patients with Confirmed Relapses, n (%)	93 (20.6)	84 (18.8)	132 (29.5)
By Relapse Numbers			
0	358 (79.4)	363 (81.2)	316 (70.5)
1	69 (15.3)	71 (15.9)	92 (20.5)
2	19 (4.2)	13 (2.9)	31 (6.9)
3	2 (0.4)	0	6 (1.3)
≥ 4	3 (0.7)	0	3 (0.7)
Primary Analysis: Poisson Model			
Adjusted Relapse Rate (95% CI)	0.24 (0.188, 0.308)	0.18 (0.140, 0.236)	0.35 (0.279, 0.440)
Rate Ratio	0.688	0.518	
Percent Reduction	31.2%	48.2%	
p-value	0.0013	<0.0001	
Rate Ratio Ozanimod 1mg/0.5mg (95% CI)		0.75 (0.578, 0.982)	
p-value		0.0366	
Sensitivity Analysis: Negative Binomial Model			
Adjusted Relapse Rate (95% CI)	0.24 (0.183, 0.318)	0.18 (0.134, 0.240)	0.35 (0.266, 0.449)
Rate Ratio	0.697	0.520	
Percent Reduction	30.3%	48.0%	
p-value	0.0067	<0.0001	

Rate Ratio Ozanimod 1mg/0.5mg (95% CI) p-value		0.75 (0.555, 1.000) 0.0500	
Patients with Confirmed + Unconfirmed Relapses, n (%) Adjusted Relapse Rate (Poisson) Rate Ratio Percent Reduction p-value	94 (20.8) 0.26 (0.208, 0.331) 0.680 32.0% 0.0008	87 (19.5) 0.21 (0.165, 0.270) 0.547 45.3% <0.0001	136 (30.4) 0.39 (0.311, 0.477)
Rate Ratio Ozanimod 1mg/0.5mg (95% CI) Percent Reduction p-value		0.81 (0.622, 1.041) 19.0% 0.098	

Source: Biometrics Review

In her review, Dr. Yan states that the prespecified primary analysis was to compare the ARRs in each of the ozanimod dose groups to the IFN β-1a group using a Poisson regression model at the alpha = 0.025 level. She agrees with the findings from the analysis provided by the applicant that treatment with ozanimod resulted in a statistically significant reduction in the ARR compared to IFN β-1a with the estimated ARR from the Poisson model being 0.18 for the ozanimod 1 mg group, 0.24 for the ozanimod 0.5 mg group, as compared to 0.35 for the IFN β-1a treatment group. The rate ratio versus the IFN β-1a treatment group was 0.518 (p<0.0001) for ozanimod 1 mg groups and 0.688 (p=0.0013) for ozanimod 0.5 mg groups. Dr. Yan notes that the reduction in ARR was more pronounced in ozanimod 1 mg group than in the ozanimod 0.5 mg group, indicating a dose-response relationship. The ARR rate ratio of ozanimod 1 mg versus ozanimod 0.5 mg was 0.753 (p=0.0366), meaning the 1 mg dose was associated with a further reduction of 25% in the ARR over the reduction observed with 0.5 mg ozanimod. Dr. Yan noted that there were eight relapses not confirmed in the three arms but that a sensitivity analysis that included these relapses did not result in a markedly different outcome in the primary analysis.

In Study 301, there were three key secondary efficacy outcomes to be assessed in a hierarchical fashion: new or enlarging T2 lesions at Month 12, T1 gadolinium-enhancing lesions at Month 12, and time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months.

New or Enlarging T2 Lesions

The cumulative number of new or enlarging T2 lesions was the sum of the lesions on scans at Month 6 and at Month 12. The primary analysis was based on observed cases in which about 87% of the patients had lesion values on both scans. The least square estimated number of lesions per scan (2 scans per patient) was 1.47 for the ozanimod 1 mg group and 2.14 for the ozanimod 0.5 mg group, compared to 2.84 for the IFN β-1a group. The reduction in the number of new or enlarging T2 lesions per scan was 48% ($p<0.0001$) in the ozanimod 1 mg group and 25% ($p=0.0032$) in the ozanimod 0.5 mg group as compared to the IFN β-1a group.

T1 Gadolinium-enhancing Lesions

The primary analysis of the number of gadolinium-enhancing lesions was based on those patients who had a Month 12 scan. At Month 12, the estimated mean lesion number was 0.16 for the ozanimod 1 mg treatment group and 0.29 for the ozanimod 0.5 mg group, compared to 0.43 for IFN β-1a group. This outcome represented reductions in lesion numbers of 63% and 34% for the ozanimod 1 mg ($p<0.0001$) and 0.5 mg groups ($p=0.0182$), respectively, versus the IFN β-1a group. Dr. Yan added that the results from two sensitivity analyses with missing values imputed confirmed the results from the primary analysis.

Confirmed 3-month and 6-month Disability Progression

The analysis of time to onset of disability progression confirmed at 3 months and 6 months was prespecified to be performed on the pooled data of Studies 301 and 201B for the purpose of enhancing the power.

First, the analysis on separate study data was performed by the applicant to examine the appropriateness of the pooling.

For Study 301, the number of patients who had disability progression confirmed at 3 months was 13 for the ozanimod 1 mg group and 17 for ozanimod 0.5 mg group, compared with 19 for the IFN β-1a group. The hazard ratio estimates from the Cox model yielded 0.69 ($p=0.3055$) for the ozanimod 1 mg group and 0.89 ($p=0.7163$) for ozanimod 0.5 mg group, versus IFN β-1a group. Neither of the ozanimod dose groups showed statistically significant treatment difference in 3-month disability progression based on findings in this single study.

For Study 201B, the number of patients who had confirmed 3-month disability progression was 54 for ozanimod 1 mg group and 41 for ozanimod 0.5 mg group, compared with 50 for IFN β-1a group. The percentage of patients who had 3-month disability progression was much higher in this study compared to Study 301, which

may be attributable to the relative differences in durations between the two studies. A higher percentage of patients with 3-month disability progression was observed in ozanimod 1 mg group compared to two other treatment groups. Similarly, more patients treated with ozanimod than patients treated with IFN β-1a had disability progression confirmed at 6 months. Therefore, because of observed differences in the results between the two studies, pooling of the data was not deemed appropriate by the applicant.

Based on the results of 3-month and 6-month disability progression for the two studies, the applicant concluded that no treatment benefit of ozanimod was observed in either the 3-month or 6-month the confirmed disability progression outcomes relative to the active comparator. The biometrics review confirmed the lack of a treatment effect of ozanimod on disability progression relative to the active comparator, including the planned pooled analysis.

Table 4: Study 301 and 201B: 3-month and 6-month Confirmed Disability Analyses

	Ozanimod 0.5 mg	Ozanimod 1 mg	IFN β– 1a 30 μg
Study 301	n=451	n=447	n=448
Number of Patients with 3-month CDP, n (%)	17 (3.8)	13 (2.9)	19 (4.2)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value	0.89 (0.460, 1.705) 0.7162	0.69 (0.340, 1.402) 0.3055	
Number of Patients with 6-month CDP, n (%)	11 (2.4)	9 (2.0)	7 (1.6)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value	1.54 (0.595, 3.963) 0.3755	1.24 (0.460, 3.337) 0.6725	
Study 201B	n=439	n=433	n=441
Number of Patients with 3-month CDP, n (%)	41 (9.3)	54 (12.5)	50 (11.3)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value	0.80 (0.528, 1.206) 0.2849	1.05 (0.711, 1.537) 0.8224	

Number of Patients with 6-month CDP, n (%)	32 (7.3)	42 (9.7)	29 (6.6)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value	1.10 (0.664, 1.815) 0.7154	1.44 (0.893, 2.305) 0.1353	
Pooled Data (Study 201B and Study 301)	N=890	N=880	N=889
Number of Patients with 3-month CDP, n (%)	58 (6.5)	67 (7.6)	69 (7.8)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value	0.86 (0.605, 1.223) 0.4024	1.05 (0.747, 1.463) 0.7959	
Number of Patients with 6-month CDP, n (%)	43 (4.8)	51 (5.8)	36 (4.1)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value	1.19 0.764, 1.852) 0.4434	1.42 (0.927, 2.175) 0.1075	

Source: Biometrics Review

Efficacy Conclusions

Approval for ozanimod for relapsing forms of MS is supported by efficacy findings from two adequate and well-controlled clinical trials, Studies 201B and 301. The finding of a statistically significant and consistent reduction in ARR in two separate trials enrolling over 2500 total patients is strong evidence that ozanimod is an effective treatment for relapsing forms of MS. The absolute magnitude of the reduction in ARR associated with ozanimod treatment, approximately 50%, is comparable to the ARR reduction observed in adequate and well-controlled trials using other S1P modulators.

The disability assessment outcome findings from Studies 201B and 301 do not support a claim that ozanimod is superior to the active comparator (interferon β-1a given as 30µg weekly) on disability progression at either the 3-month or 6-month observation periods.

4. Safety

Dr. David Jones reviewed this application as the primary safety reviewer. Dr. Wiley Chambers from the Division of Ophthalmology conducted a consultative safety review regarding ophthalmological findings related to macular edema. Dr. Natalie Pica 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. Jones's review, summarizes the extent of exposure to ozanimod in the applicant's development program:

Table 5: Ozanimod Safety Population: Duration of Exposure

Exposure	Ozanimod 0.5 mg N=979	Ozanimod 1 mg n=965
≥ 6 months	939 (95.9%)	932 (96.6%)
≥ 12 months	820 (83.8%)	818 (84.8%)
≥ 18 months	407 (41.6%)	416 (43.1%)
≥ 24 months	291 (29.7%)	299 (31.0%)

Source: Clinical Safety Review

The safety database provided by the applicant is adequate because it contains more than one thousand five hundred patients exposed to any dose of ozanimod for more than 365 days. These data exceed 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 relapsing forms of multiple sclerosis because of the disease's typical and well-known demographics.

Deaths

A total of twelve deaths (0.4%, 12/2917 exposed to at least one dose) occurred in the clinical development program for ozanimod. Nine of these deaths occurred in patients with relapsing forms of MS who were on treatment during the active-controlled or open-label extension studies of ozanimod in relapsing forms of MS. One death in a patient with MS from metastatic pancreatic carcinoma occurred more than 28 days after discontinuation from Study RPC01-301. There were two patients who died who were enrolled in the inflammatory bowel disease trials. There were two other deaths due to malignancies (pancreatic and an unknown primary carcinoma).

Two patients (one with Crohn's Disease, one with MS) died from serious infections. Dr. Jones suggests that there could be a role for ozanimod in both the pancreatic cancer cases because reduced circulating lymphocyte numbers presumably impairs immune surveillance for cancer. Both cases had sufficiently long exposures to ozanimod to provide prolonged reductions in lymphocytes and possible reduced cancer surveillance; in one case, the patient had 34.5 months of cumulative exposure to any dose of ozanimod (33 months at 0.5 mg then 1.5 months at 1 mg), and in the other the patient had 3 years of exposure to any dose (863 days at 1 mg, 32 weeks at 0.5 mg). Dr. Jones likewise states that deaths from serious infections are also a potential consequence of ozanimod-induced lymphocyte reduction, and both these cases had exposures that were of sufficient duration (11 months and 40 days) to have reduced lymphocyte counts to the expected treatment nadirs. Finally, Dr. Jones noted that infections and malignancies are known to be associated with treatment using other S1P modulators, and ozanimod therefore should have labeling for these outcomes consistent with other S1P therapies. Otherwise, causes of death in the ozanimod development program were heterogeneous and confounded by factors outside of treatment.

Serious Adverse Events

In the safety data pool containing all treated patients with MS, serious adverse events occurred in 4.6% of ozanimod 1 mg treated patients and 5.3% of ozanimod 0.5 mg treated patients, versus 4.4% of interferon-treated patients. In the longest duration safety database, 8.6% of patients exposed to ozanimod for up to 68 months experienced a serious adverse event. The most common reported serious adverse event in ozanimod treatment groups was appendicitis (which occurred in 0.4% or 4/1944 patients). Most serious adverse events occurred in 1-2 patients and Dr. Jones did not note a consistent pattern to these events indicative of a serious safety signal not otherwise known to this class of therapies.

Interruptions and Discontinuations

During the controlled portions of clinical trials, 2.3% of patients had a treatment interruption in an ozanimod treatment group as compared to 1.6% of interferon-treated patients. The most common adverse event leading to treatment interruption in ozanimod-treated patients (0.3%) was increased alanine aminotransferase.

During the controlled portions of clinical trials, 2.6% of patients treated with any dose of ozanimod experienced an adverse event that led to permanent treatment discontinuation as compared to 3.8% of patients treated with interferon β-1a. The most common adverse events leading to treatment discontinuations in ozanimod treatment were liver transaminase elevations. Liver transaminase elevations are

known to occur with treatment using other S1P modulators and will be described in ozanimod's labeling. Most adverse events leading to interruption or discontinuations of ozanimod treatment were singular events with known associations with the class of therapy and did not indicate a new safety signal of concern.

Treatment-Emergent Adverse Events

The following table summarizes the most common treatment-emergent adverse events that occurred in clinical trial subjects:

Table 6: Treatment-Emergent Adverse Events Reported in ≥5% of Patients in Any Treatment Condition

Preferred Term	Ozanimod 0.5 mg N=892 n (%)	Ozanimod 1 mg N=882 n (%)	Interferon β-1a 30 µg N=885 n (%)
Nasopharyngitis	103 (11.5)	98 (11.1)	84 (9.5)
Headache	82 (9.2)	78 (8.8)	78 (8.8)
Upper respiratory tract infection	67 (7.5)	52 (5.9)	61 (6.9)
Alanine aminotransferase increased	41 (4.6)	47 (5.3)	28 (3.2)
Influenza like illness	44 (4.9)	44 (5.0)	442 (49.9)
Pyrexia	17 (1.9)	16 (1.8)	56 (6.3)

Source: Adapted from Clinical Safety Review

Adverse Events of Special Interest and Special Safety Concerns

Infections and Lymphopenia

Ozanimod causes a reduction in serum total white blood cell count. Ozanimod treatment is associated with lymphopenia in approximately 10% of patients. The S1P modulators' ability to lower serum white count is strongly presumed to be the reason for an associated increased risk of viral and opportunistic infections in patients taking these therapies. Therefore, increased risk of infections was a primary concern with ozanimod throughout its development program. For most infection-related treatment-emergent adverse events in the controlled trials, the frequencies of all infections combined in the ozanimod (33.7%) and interferon (30.3%) treatment groups were balanced. There were no infections distinctly more common in ozanimod-treated patients as compared to interferon-treated patients.

As ozanimod 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, which is considered a risk shared across all S1P modulators even though herpetic infections were not significantly more common in ozanimod-treated patients in the controlled trials. The team recommends varicella immunization prior to initiation of ozanimod in the absence of verification of adequate varicella immunity.

Liver Injury

Ozanimod is metabolized extensively by several enzyme systems within the liver. The review team noted that ozanimod administration is associated with increased serum levels of liver transaminases. In the controlled trials, adverse events related to increased liver transaminases were among the most common treatment-emergent adverse events (9.4% vs 4.0% interferon treated patients), serious adverse events (less than 1%) and adverse events leading to treatment discontinuation (1.2% in 1 mg ozanimod-treated patients versus 0.8% in interferon-treated patients). There were 99 patients (11%) with alanine aminotransferase, aspartate aminotransferase, or bilirubin levels meeting pre-specified criteria for hepatic injury in ozanimod-treated patients versus 53 (5.9%) of patients treated with interferon, 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 ozanimod. Given the paucity of evidence in patients with hepatic impairment (see the Clinical Pharmacology section), and the extensive reliance on hepatic enzymes for metabolism of ozanimod, there will be a PMR for a trial in patients with hepatic impairment in order to determine whether dose adjustment is needed to safely administer ozanimod in the setting of mild liver impairment.

Bradyarrhythmia and Atrioventricular Conduction Delays

S1P receptors are expressed abundantly in cardiac tissue. Initiation of S1P modulators can cause bradycardia, bradyarrhythmias, and cardiac conduction block. These adverse events are potentially life-threatening, and fingolimod, the first 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 ozanimod, when it became evident that ozanimod caused significant bradycardia with initial dosing, the applicant instituted a titration over 7-days to the maintenance dose, attempting to mitigate the negative chronotropic effects and atrioventricular conduction blocks seen with other S1P therapies. 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 or who had first degree atrioventricular block, as no patient experienced cardiac events that were persistent, required treatment, or were symptomatic. The maximum bradycardic effect associated with ozanimod treatment occurs on Day 8, and therefore there does not appear to be a need for first dose monitoring for any patient taking ozanimod. Ozanimod differs from the other S1P modulators because it has several active metabolites with long half-lives capable of S1P1 receptor agonism. Presumably, the presence of these active metabolites, and differences in S1P receptor affinities, explains the overall reduction in severity of bradycardia, and the shift from Day 1 to Day 8 in onset of the maximum bradycardic effect that necessitated first-dose monitoring recommended with fingolimod and siponimod. There were several cases of newly diagnosed first degree heart blocks in patients without prior histories so a Warning and Precaution in labeling for bradyarrhythmia is still warranted.

Macular Edema

Macular edema is an anticipated outcome in association with S1P receptor modulation and was reported as an adverse event in approximately 0.3% of patients exposed to ozanimod, versus 0.3% of patients treated with interferon β-1a. Dr. Wiley Chambers from the Division of Ophthalmology provided a consultative review of the ophthalmological findings associated with ozanimod. He concludes that macular edema is more frequently reported in patients treated with S1P modulators in general and notes there were more total cases reported in patients treated with any dose of ozanimod treatment than were reported with the active comparator. He concludes that, unlike with other S1P modulators in which most cases of macular edema occur within the first 6 months of treatment, there was not a clear window of time when patients appeared at highest risk of developing macular edema after treatment initiation with ozanimod. Without a clear window of time in which a recent baseline macular examination would be prudent, Dr. Chambers concludes a baseline examination is not necessary for most patients who are treated with ozanimod as it is with other approved S1P modulators. Dr. Chambers recommends a description of the risk of macular edema in the Warnings and Precautions section of labeling consistent with other S1P modulator therapies, with a recommendation for an ophthalmological examination for any change in vision while patients are taking ozanimod without an explicit need for a baseline exam. The safety review team agrees with the recommendation of no need for a baseline examination in low risk patients, but since macular edema risk is increased in with diabetes mellitus or a history of uveitis, the safety team recommends a baseline ophthalmological examination in these higher risk patients to ensure patients have an appropriate referential exam should new symptoms arise.

Hypertension

Ozanimod was associated with a mean increase of approximately 5 mmHg systolic and 2 mmHg diastolic blood pressure during chronic treatment. These mean blood pressure increases are similar to those noted in clinical trials with other S1P receptor modulators that have Warnings and Precautions statements for "Increased Blood Pressure." In the controlled trials in this application, hypertension and related treatment-emergent adverse events were reported in approximately 3.9% of patients treated with ozanimod, versus approximately 1.9% of patients treated with interferon β-1a. 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 administered ozanimod. There are also labeling warnings for patients to restrict dietary tyramine and avoid co-administration of ozanimod with monoamine oxidase inhibitors to avoid hypertensive crises (see the Clinical Pharmacology section.)

Respiratory Effects

Prior experience with S1P receptor modulator therapies suggested that patients exposed to ozanimod 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 consult review conducted by Dr. Natalie Pica in the Division of Pulmonary, Allergy, and Rheumatology Products, summarized the applicant's findings related to pulmonary changes in the exposed population. Overall, the consult concluded that respiratory-related adverse events were rare. The effects on FEV1 and DLCO observed in patients with ozanimod were approximate in magnitude and frequency to the effects observed with fingolimod and siponimod. The review concluded that labeling could mitigate the low risk of pulmonary toxicity and that given the two outstanding PMR studies ongoing for fingolimod and siponimod, requiring a third study for ozanimod was unlikely to be of great clinical utility and did not appear necessary.

Safety Conclusions

Ozanimod 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 largely consistent with what is known regarding the safety profile of other S1P modulators, although first dose monitoring for bradycardia and baseline ophthalmological examination of the macula will not be needed for ozanimod, as discussed above. With established efficacy for the treatment of relapsing forms of multiple sclerosis, ozanimod's safety profile does not preclude approval. The Warnings and Precautions section of the prescribing information will provide detailed descriptions and monitoring

recommendations related to the risk of infections, cardiac effects, risk of macular edema, risk of hepatic injury, reduced expiratory volume, and elevated blood pressure. There will be requested pharmacovigilance with expedited reporting for events of particular interest identified in the ozanimod and other S1P development programs that are assumed to be applicable to all drugs within the class; specifically, thromboembolic ischemic events, malignancies (especially cutaneous), and serious or fatal infections. A single case of congenital duplex kidney was observed in the known prenatal exposures to ozanimod in the development program. Though duplex kidney is the most common renal malformation, nonclinical findings suggested potential for renal malformations with ozanimod exposure in utero. Based on these concerns, requested pharmacovigilance will also include cases of prenatal exposure with any congenital renal malformations.

5. 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 the two other drugs in this class approved for this indication, the clinical trial designs were acceptable and performed under agreed SPAs, 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 associated with ozanimod treatment, allowing them to inform patients and decide whether to use the drug.

6. Pediatrics

No clinical pediatric data are provided. An initial Pediatric Study Plan to study ozanimod in patients ages 10-17 years with relapsing forms of multiple sclerosis that was proposed by the applicant, as required by the Pediatric Research Equity Act (PREA), was deemed acceptable. The PMR for a pediatric study is described in Section 9.

7. Other Relevant Regulatory Issues

Office of Scientific Investigations review

The Office of Scientific Investigations (OSI) reviewer for this application was Dr. Jenn Sellers. The OSI team inspected three clinical sites (those of Drs. Dihenia, Likhachev, Nehrych and Zielinskiwhich) that enrolled patients for Study 301. Based on the results of these inspection, the OSI review concluded that Study 301 appears to have

been conducted adequately, and the data generated by these sites and submitted by the applicant appear acceptable in support of an indication to treat relapsing forms of MS. In his review, Dr. Rodichok did not identify any Good Clinical Practice issues in his clinical review. Dr. Rodichok further concluded that the applicant has adequately disclosed the financial interests/arrangements with the clinical investigators who conducted these trials.

Controlled Substance Staff review

The Controlled Substance Staff (CSS) reviewers for this application were Drs. Alicja Lerner and Jovita Randall-Thompson. The CSS review team found that the applicant's description of a "withdrawal evaluation" and the methods used to obtain dependence data did not constitute a valid and acceptable evaluation of abuse, dependence, or withdrawal potential. The CSS review does note that ozanimod is similar to other S1P modulators that are not controlled substances, and that ozanimod will not be a controlled substance if approved because of the *a priori* low suspected potential for abuse and dependency.

8. Labeling

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

9. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS is not necessary for ozanimod.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following are postmarketing requirements:

- Conduct a two-part study of Zeposia (ozanimod) 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 Zeposia (ozanimod) 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 Zeposia (ozanimod)

that will result in PK and PD effects that are comparable to those of the 8-day titration administered to adult patients. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of Zeposia (ozanimod) compared to an appropriate comparator.

Draft Protocol Submission:	03/2022
Final Protocol Submission:	08/2022
Interim/Other (Part A data)	05/2026
Study/Trial Completion:	10/2033
Final Report Submission:	03/2034

- Conduct a 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 Zeposia (ozanimod) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Zeposia (ozanimod) 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:	10/2020
Final Protocol Submission:	06/2021
Annual Interim Report Submissions:	06/2022
	06/2023
	06/2024
	06/2025
	06/2026
	06/2027
	06/2028
	06/2029
	06/2030
	06/2031
Study Completion:	06/2032
Final Report Submission:	06/2033

- Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3809-3 (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Zeposia (ozanimod) during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	10/2020
Final Protocol Submission:	06/2021
Annual Interim Report Submissions:	06/2022
	06/2023
	06/2024
	06/2025
	06/2026
	06/2027
	06/2028
	06/2029
	06/2030
	06/2031
Study Completion:	06/2032
Final Report Submission:	06/2033

- Conduct a randomized, double-blind, placebo-controlled, active-controlled (phenelzine), multiple-dose, parallel-group trial to investigate the pressor effect of oral tyramine during Zeposia (ozanimod) treatment in healthy subjects.

Draft Protocol Submission:	05/2020
Final Protocol Submission:	11/2020
Study/Trial Completion:	02/2022
Final Report Submission:	10/2022

- Conduct a multiple-dose trial to assess the effect of hepatic impairment on the pharmacokinetics (PK) of Zeposia (ozanimod) and its major metabolites and to determine whether a dosing adjustment of Zeposia (ozanimod) is needed in patients with hepatic impairment. The effect of hepatic impairment on the PK of CC112273 and CC1084037 should be assessed after the 1 mg Zeposia (ozanimod) dose administration on Day 8 (following titration from 0.25 mg to 1 mg).

Draft Protocol Submission:	04/2020
Final Protocol Submission:	10/2020
Study/Trial Completion:	02/2022
Final Report Submission:	08/2022

- Conduct a juvenile animal toxicology study of ozanimod in the rat.

Draft Protocol Submission:	06/2020
Final Protocol Submission:	10/2020
Study/Trial Completion:	12/2021
Final Report Submission:	06/2022

10. Recommended Comments to the Applicant

The approval letter will instruct the applicant to conduct requested pharmacovigilance for the safety concerns identified in the safety review, including expedited reporting of malignancies, serious or fatal infections, thromboembolic ischemic events, and pregnancy exposures associated with congenital renal malformations.

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

/s/

PAUL R LEE
03/25/2020 08:58:17 PM

NICHOLAS A KOZAUER
03/25/2020 09:00:22 PM

WILLIAM H Dunn
03/25/2020 09:03:36 PM