

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209899Orig1s000

CLINICAL REVIEW(S)

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

CLINICAL REVIEW

Application Type	505(b)(1) NDA
Application Number(s)	209899
Priority or Standard	Standard
Submit Date(s)	3/25/2019
Received Date(s)	3/25/2019
PDUFA Goal Date	3/25/2020
Division/Office	Division of Neurology 2
Reviewer Name(s)	David E. Jones, M.D.
Review Completion Date	3/20/2020
Established/Proper Name	Ozanimod
(Proposed) Trade Name	Zeposia
Applicant	Celgene
Dosage Form(s)	0.25 mg, 0.50 mg, and 1.0 mg capsules
Applicant Proposed Dosing Regimen(s)	After titration, 1 mg by mouth daily
Applicant Proposed Indication(s)/Population(s)	Relapsing multiple sclerosis
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

Table of Contents

Glossary.....	8
1. Executive Summary	10
1.1. Product Introduction.....	10
1.2. Conclusions on the Substantial Evidence of Effectiveness	10
1.3. Benefit-Risk Assessment	11
1.4. Patient Experience Data.....	15
2. Therapeutic Context	15
2.1. Analysis of Condition.....	15
2.2. Analysis of Current Treatment Options	16
3. Regulatory Background	18
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	18
4.1. Office of Scientific Investigations (OSI)	18
4.2. Product Quality	18
4.3. Clinical Microbiology	18
4.4. Nonclinical Pharmacology/Toxicology	18
4.5. Clinical Pharmacology	19
4.6. Devices and Companion Diagnostic Issues	19
4.7. Consumer Study Reviews.....	19
5. Sources of Clinical Data and Review Strategy	20
6. Review of Relevant Individual Trials Used to Support Efficacy	20
7. Integrated Review of Effectiveness.....	20
8. Review of Safety	20
8.1. Safety Review Approach	20
8.2. Review of the Safety Database	25
8.2.1. Overall Exposure	25
8.2.2. Relevant characteristics of the RMS safety population:.....	27
CDER Clinical Review Template	2
<i>Version date: September 6, 2017 for all NDAs and BLAs</i>	

8.2.3. Adequacy of the safety database:	30
8.3. Adequacy of Applicant’s Clinical Safety Assessments.....	31
8.3.1. Issues Regarding Data Integrity and Submission Quality	31
8.3.2. Categorization of Adverse Events	31
8.3.3. Routine Clinical Tests	33
8.4. Safety Results	36
8.4.1. Deaths	36
8.4.2. Serious Adverse Events.....	40
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects	53
8.4.4. Significant Adverse Events	70
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions	73
8.4.6. Laboratory Findings	92
8.4.7. Vital Signs	107
8.4.8. Electrocardiograms (ECGs).....	116
8.4.9. QT	121
8.4.10. Pulmonary Function Tests	122
8.4.11. Immunogenicity.....	126
8.5. Analysis of Submission-Specific Safety Issues	126
8.5.1. Lymphopenia / Serious Infections	126
8.5.2. Liver Injury / Increased Hepatic Transaminases	128
8.5.3. Malignancy.....	130
8.5.4. Bradyarrhythmia and Atrioventricular Block.....	131
8.5.5. Hypertension.....	132
8.5.6. Macular Edema	133
8.5.7. Seizure.....	134
8.5.8. Pulmonary Effects	134
8.6. Safety Analyses by Demographic Subgroups	136
8.7. Specific Safety Studies/Clinical Trials	140
8.8. Additional Safety Explorations	140
8.8.1. Human Carcinogenicity or Tumor Development	140
8.8.2. Human Reproduction and Pregnancy.....	140

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

8.8.3. Pediatrics and Assessment of Effects on Growth	143
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound	143
8.9. Safety in the Postmarket Setting.....	144
8.9.1. Safety Concerns Identified Through Postmarket Experience	144
8.9.2. Expectations on Safety in the Postmarket Setting	144
8.9.3. Additional Safety Issues From Other Disciplines	144
8.10. Integrated Assessment of Safety.....	144
9. Advisory Committee Meeting and Other External Consultations.....	146
10. Labeling Recommendations	146
10.1. Prescription Drug Labeling	146
The labeling has not been finalized at the time of this review.	146
10.2. Nonprescription Drug Labeling.....	146
11. Risk Evaluation and Mitigation Strategies (REMS)	146
12. Postmarketing Requirements and Commitments.....	147
13. Appendices	148
13.1. References	148

Table of Tables

Table 1. Reviewer Table. FDA-approved treatments for relapsing multiple sclerosis	17
Table 2. Reviewer Table. Studies of ozanimod submitted with this NDA	21
Table 3. Reviewer Table. Distribution and biological activity of S1P receptors	24
Table 4. Reviewer Table. Extent of Exposure in controlled RMS Trials (Pool A)	26
Table 5. Applicant Table. Extent of Exposure Pool B, Safety Population	27
Table 6. Reviewer Table. Demographic Data for the controlled RMS population (Pool A)	28
Table 7. Reviewer Table. Disease Characteristics of the controlled RMS population (Pool A)	30
Table 8. Reviewer Table. SAEs occurring more than once in controlled RMS population (Pool A)	41
Table 9. Reviewer Table. SAEs occurring more than once with ozanimod in RPC01-3001.....	45
Table 10. SAEs occurring more than once with ozanimod in the IBD safety population (Pool C)	50
Table 11. Reviewer Table. AE’s leading to study discontinuation in the controlled RMS population (Pool A)	53
Table 12. Reviewer Table. AEs leading to study discontinuation in the IBD population (Pool C)	61
Table 13. Reviewer Table. AEs leading to study drug withdrawal in the controlled RMS population (Pool A)	62
Table 14. Reviewer Table. AEs leading to study drug withdrawal in Study RPC01-3001.....	63
Table 15. Reviewer Table. AEs leading to study drug withdrawal in the IBD population (Pool C)	67
Table 16. Reviewer Table. AE’s leading to treatment interruption in the controlled RMS population (Pool A)	67
Table 17. Reviewer Table. AEs leading to treatment interruption in Study RPC01-3001	68
Table 18. Reviewer Table. AEs leading to treatment interruption in IBD population (Pool C)	69
Table 19. Reviewer Table. TEAE classified as severe in the controlled RMS population (Pool A)	70
Table 20. Reviewer Table. TEAE classified as severe in Study RPC01-3001	71
Table 21. Reviewer Table. TEAE classified as severe in the IBD population (Pool C)	72
Table 22. Reviewer Table. Subjects with TEAE, Controlled RMS population (Pool A)	73
Table 23. Reviewer Table. TEAEs stratified by SOC in the Controlled RMS population (Pool A) .	74
Table 24. Reviewer Table. TEAE by PT reported 20 or more times by ozanimod-treated subjects, controlled RMS population (Pool A)	76
Table 25. Reviewer Table. ODE-1 analysis of TEAE by assigned treatment, Pool A	78
Table 26. Reviewer Table. Summary of Subjects with TEAE in Study RPC01-3001	81
Table 27. Reviewer Table. TEAEs stratified by SOC in Study RPC01-3001.....	81
Table 28. Reviewer Table. TEAEs PT reported 25 or more times by ozanimod-treated subjects, in Study RPC01-3001.....	83
Table 29. Reviewer Table. ODE-1 analysis of TEAE in RPC01-3001	84
Table 30. Reviewer Table. Summary of Subjects with TEAE in IBD population (Pool C)	86
Table 31. Reviewer Table. TEAEs stratified by primary SOC in the IBD population (Pool C).....	86
Table 32. Reviewer Table. TEAEs PT reported 15 or more times in the IBD population (Pool C)	87
Table 33. Reviewer Table. ODE-1 analysis of TEAE by assigned treatment, Pool C	88
Table 34. Reviewer Table. Summary of Healthy Volunteers Experiencing TEAE (Pool E)	89

Table 35. Reviewer Table. TEAEs stratified by primary SOC in healthy volunteers (Pool E)	90
Table 36. Reviewer Table. TEAEs PT reported 10 or more times by healthy volunteers (Pool E) 91	
Table 37. Reviewer Table. ODE-1 analysis of TEAE in healthy volunteers, Pool E.....	91
Table 38. Reviewer Table. Hepatobiliary Labs, controlled RRMS population (Pool A)	93
Table 39. Reviewer Table. Hepatobiliary Labs, RMS Study RPC01-3001.....	94
Table 40. Reviewer Table. Pancreatic Labs, controlled RRMS population (Pool A)	99
Table 41. Reviewer Table. LDL, controlled RRMS population (Pool A).....	100
Table 42. Reviewer Table. Electrolytes, controlled RRMS population (Pool A).....	100
Table 43. Reviewer Table. Renal Labs, controlled RRMS population (Pool A)	102
Table 44. Reviewer Table. Binary Urine Protein in the controlled RRMS population (Pool A) ..	104
Table 45. Reviewer Table. Hematology Labs, controlled RRMS population (Pool A).....	105
Table 46. Reviewer Table. Sitting Heart Rate (HR) in controlled RMS population (Pool A)	107
Table 47. Reviewer Table. First Dose Sitting HR in controlled RMS population (Pool A).....	109
Table 48. Reviewer Table. Sitting SBP in controlled RMS population (Pool A)	111
Table 49. Reviewer Table. First Dose Sitting SBP in controlled RMS population (Pool A)	113
Table 50. Reviewer Table. Reviewer Table. Sitting DBP in controlled RMS population (Pool A)	114
Table 51. Reviewer Table., PR interval in controlled RRMS population (Pool A)	117
Table 52. Reviewer Table. QTcF in controlled RRMS population (Pool A)	118
Table 53. Reviewer Table. ECG abnormalities in controlled RMS population (Pool A).....	120
Table 54. Reviewer Table. FEV1 in the controlled RMS population (Pool A)	122
Table 55. Reviewer Table. FEV1 in Study RPC01-3001	123
Table 56. Reviewer Table. FVC in the controlled RMS population (Pool A)	124
Table 57. Reviewer Table. FVC in Study RPC01-3001	125
Table 58. Reviewer Table. DLCO in controlled RRMS population (Pool A).....	125
Table 59. Reviewer Table. Infections in the controlled RMS population (Pool A)	127
Table 60. Reviewer Table. Malignancies in the controlled RMS population (Pool A)	130
Table 61. Reviewer Table. TEAEs of hypertension in the controlled RMS population (Pool A) .	133
Table 62. Reviewer Table. TEAEs of seizure in the controlled RMS population (Pool A).....	134
Table 63. Reviewer Table. Dyspnea and abnormal PFTs in the controlled RMS population (Pool A).....	134
Table 64. Reviewer Table. SAEs stratified by gender in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A).....	136
Table 65. Reviewer Table. Common TEAEs stratified by gender in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A).....	136
Table 66. Reviewer Table. Lymphocyte counts stratified by gender in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A).....	138
Table 67. Reviewer Table. SAEs stratified by age in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A)	138
Table 68. Reviewer Table. Common TEAEs stratified by age in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A).....	139
Table 69. Pregnancies in Ozanimod RMS development program	141

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

Table of Figures

Figure 1. Applicant Figure. Pooling Strategy for Ozanimod Studies.....	23
Figure 2. Sponsor Figure. Exposure to Ozanimod in Pools A1, A, B, C, D, E	26
Figure 3. Sponsor Table. Urine Protein by Visit, Pool A1.....	103
Figure 4. Reviewer Figure. Mean lymphocyte counts over time with ozanimod 1 mg.....	106

Glossary

ALC	absolute lymphocyte count
ANC	absolute neutrophil count
AC	advisory committee
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
ARR	annualized relapse rate
AST	aspartate aminotransferase
BMI	body mass index
BRF	Benefit Risk Framework
CD	Crohn's disease
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	Central Nervous System
CRO	contract research organization
CSR	clinical study report
CSS	Controlled Substance Staff
DILI	drug-induced liver injury
DLCO	diffusion capacity of the lungs for carbon monoxide
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
EDSS	Expanded Disability Status Scale
FDA	Food and Drug Administration
FEV1	forced expiratory volume at one second
FVC	forced vital capacity
GGT	gamma glutamyl transferase
IBD	inflammatory bowel disease
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IR	information request
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

ITT	intent to treat
LDL	low density lipoprotein
LFT	liver function test
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MERP	macular edema review panel
MRI	magnetic resonance imaging
MS	multiple sclerosis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OCT	optical coherence tomography
OLE	open label extension
OLP	open label phase
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PML	progressive multifocal leukoencephalopathy
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
PT	preferred term
REMS	risk evaluation and mitigation strategy
RMS	relapsing multiple sclerosis
S1P	sphingosine-1-phosphate
SAE	serious adverse event
SOC	system organ class
TB	total bilirubin
TEAE	treatment emergent adverse event
UC	ulcerative colitis
ULN	upper limit of normal
VZV	varicella zoster virus
WBC	white blood cell

1. Executive Summary

1.1. Product Introduction

Ozanimod (RPC1063, Zeposia) is a sphingosine-1-phosphate (S1P) receptor modulator that is purportedly selective for S1P1 and S1P5 with little activity at S1P2, S1P3, and S1P4. Ozanimod is considered a New Molecule Entity (NME), for which the Applicant (Celgene Corporation) has submitted a New Drug Application (NDA) with a proposed indication of relapsing multiple sclerosis (RMS). The proposed maintenance dose of ozanimod is 1 mg per day after an eight-day dose escalation (0.25 mg per day on days 1 to 4, 0.5 mg per day on days 5 to 7, 1.0 mg on days 8 and beyond).

There are currently two other S1P receptor modulators approved for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. These are fingolimod (Gilenya), a relatively non-selective S1P receptor modulator, and siponimod (Mayzent), which is purportedly also selective for S1P1 and S1P5.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Please refer to Dr. Larry Rodichok's Review of Clinical Efficacy for this NME. In brief, there is substantial evidence from two large Phase 3 trials that used an active comparator (interferon β -1a) that ozanimod has a statistically significant treatment effect on annualized relapse rate (ARR). In addition to support from a smaller, six-month, placebo-controlled Phase 2 trial that met its primary MRI endpoint, this effect on ARR is also supported by ozanimod's statistically significant treatment effect on several magnetic resonance imaging (MRI) metrics in its Phase 3 trials; however, these trials do not suggest that ozanimod has a treatment effect on disability as measured by Kurtzke's Expanded Disability Status Scale (EDSS).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

As noted in Dr. Larry Rodichok's review of ozanimod's efficacy, two adequate and well-controlled randomized Phase 3 clinical trials provide substantial evidence that ozanimod offers a beneficial treatment effect on relapses in subjects with relapsing multiple sclerosis (RMS) compared with interferon β -1a, and this benefit is supported by a similar effect on various MRI metrics. Conversely, these Phase 3 clinical trials do not suggest that ozanimod has a treatment effect on 3-month or 6-month confirmed disability progression as measured by Kurtzke's Expanded Disability Status Scale (EDSS).

Although the relative paucity of adverse events (AEs) in all arms of the ozanimod clinical trials suggests that there may be an issue with AE under-reporting, the risks identified with ozanimod appear very similar to that of other S1P receptor modulators and include infections, lymphopenia, bradyarrhythmia, atrioventricular block (although all were first degree after implementation of an initial dose escalation), hepatic transaminase elevations suggestive of liver injury, hypertension, and mild respiratory effects. A few subjects in the ozanimod development program developed malignancies but many of these appear to have predated the initiation of the study drug; however, ozanimod does appear to share an increased risk of cutaneous malignancies with other S1P receptor modulators. There were also a few cases of macular edema, but some had confounding factors, suggesting that the risk of macular edema may be less with ozanimod than with other S1P receptor modulators.

As is typical in clinical trials for RMS, the inclusion / exclusion criteria for the ozanimod clinical trials selected a relatively healthy population; further, this population was mostly from Eastern Europe and almost exclusively Caucasian, so the generalizability of this safety analysis to the overall RMS population may be somewhat limited. Further, one of ozanimod's long-lasting, active metabolites (RP112273) is a monoamine oxidase-B (MAO-B) inhibitor, potentially limiting the population to whom ozanimod can be safely administered.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The pathophysiology of RMS consists of a clear inflammatory component (i.e., disease relapses and new MRI lesions) and a poorly understood “degenerative” (i.e., disease progression) component. Overall, it appears that MS becomes less “inflammatory” and more “degenerative” over time; however, both processes contribute to increasing disability. Worsening disability from “inflammatory” disease is due to incomplete recovery from inflammatory events; conversely, disability progression from “degenerative” disease is insidious but of unclear etiology. With current metrics, distinguishing disability progression due to “degeneration” from disability worsening from “inflammation” is difficult.	Reducing the inflammatory component of RMS with a S1P receptor modulator like ozanimod appears beneficial in that it may spare individuals with RMS from relapses; however, the effect of doing so on long term disability and the transition from RMS into more “degenerative” disease is less clear.
Current Treatment Options	There are over a dozen agents approved for relapsing forms of MS. Data for these agents strongly suggest that they reduce both relapse rates and MRI activity; however, the efficacy of some of these agents in reducing disability progression at 12 or 24 weeks is questionable given less robust results and conflicting results among trials.	The RMS clinical trials demonstrate that ozanimod has a treatment effect on relapses and MRI metrics but not on disability worsening or progression.
Benefit	Please refer to the review of efficacy by Dr. Larry Rodichok.	
Risk and Risk Management	<u>Safety Database</u> The ozanimod safety database contains data from two Phase 3 active-controlled (interferon β-1a) and one Phase 2, placebo-controlled clinical trials in adults with relapsing multiple sclerosis. These data are supported by placebo-controlled studies in adults with inflammatory bowel disease (IBD) and clinical pharmacology studies in healthy adult volunteers.	The degree of drug exposure to the proposed dose of ozanimod is adequate, and the demographics of the study subjects adequately reflects the intended population for use, although over 90% of the study population is from Eastern Europe.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p><u>Safety Concerns</u></p> <ul style="list-style-type: none"> • The most common AEs in subjects 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%). • Eight deaths (0.3%) occurred in ozanimod-treated adults with RMS, including two from cancer (pancreatic with liver metastases and disseminated cancer with unknown primary), two from 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). Three deaths (0.8%) occurred in ozanimod treated adults with IBD, including worsening Crohn’s disease, “influenza-related” pneumonia, and adenocarcinoma of gastric, pancreatic, biliary, or endometrial origin. • Ozanimod was associated with lymphopenia and an increased risk of infection, potentially more so in individuals exposed to previous immunosuppressants. • 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 	<p>Due to its risk of lymphopenia and infections, ozanimod’s labeling should include a Warning for an increased risk of infections, including herpes infections and potentially progressive multifocal leukoencephalopathy, cryptococcal meningitis, and other opportunistic infections.</p> <p>Given the established relationship between initiation of other S1P receptor modulators and bradyarrhythmia, the studies of ozanimod excluded subjects with many pre-existing cardiac conditions and utilized an 8-day dose escalation. Ozanimod’s labeling should recommend a baseline electrocardiogram, include a Warning for the potential risk of bradycardia/bradyarrhythmia, and note which cardiac conditions were not studied in the ozanimod clinical trials.</p> <p>The labeling for ozanimod should also include Warnings established for other S1P modulators, including liver injury, macular edema, hypertension, respiratory effects, PRES, severe exacerbations in multiple sclerosis after discontinuation, and unintended immunosuppressive effects.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>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.</p> <ul style="list-style-type: none"> • In addition to infections and bradyarrhythmia, ozanimod was also associated with hepatic transaminase elevations, hypertension, respiratory effects, macular edema, posterior reversible encephalopathy syndrome (PRES), and probably cutaneous malignancies. These AEs are known to be associated with other approved S1P receptor modulators and likely represent drug class effects. <p><u>Safety in the post-marketing setting</u> It is unclear if the risk of serious infections and malignancies will be increased with prolonged use of ozanimod in the post-marketing setting.</p> <p><u>Risk management</u> Labeled Warnings and a Medication Guide regarding the risks of infections, bradyarrhythmia, liver injury, hypertension, respiratory effects, macular edema, and PRES may mitigate the risks of serious outcomes from these events. The initial ozanimod dose escalation may further mitigate the risks of bradycardia and AV block in individuals without significant cardiac comorbidity.</p> <p>The risks of exposure to ozanimod during pregnancy, childhood, and adolescence is unclear.</p>	<p>The risk of malignancy, especially cutaneous malignancy, may rise in the postmarket setting as it did with another S1P receptor modulator for MS. In addition to requested pharmacovigilance to further define the magnitude of this risk, malignancies should be included in Section 6 (Adverse Reactions) of the labeling for ozanimod.</p> <p>Since ozanimod will be administered to women of childbearing potential even though its risk of adverse outcomes in pregnancy has not been characterized fully, there are postmarketing requirements for a pregnancy registry and a pregnancy outcomes study as well as requested pharmacovigilance for congenital renal abnormalities with prenatal exposure.</p> <p>There should also be postmarketing requirements under the Pediatric Research Equity Act (PREA) to perform pediatric and supportive nonclinical juvenile animal studies to establish the safety of ozanimod in children and adolescents with relapsing forms of multiple sclerosis.</p>

1.4. Patient Experience Data

Please refer to the review of efficacy by Dr. Larry Rodichok.

2. Therapeutic Context

2.1. Analysis of Condition

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system (CNS) that likely occurs when a genetically susceptible individual is exposed to an environmental trigger. MS is one of the most common causes of non-traumatic neurologic disability in young adults, and recent estimates suggest that almost one million people in the United States have the disease; therefore, the economic impact of MS (estimated at \$10 billion annually in the US in 2013) is huge (Wallin et al., 2019; Reich et al., 2018). Approximately 50% of people with untreated MS have severe ambulatory limitations within 20 years of disease onset, and MS reduces life-expectancy by 5-10 years (Confavreux and Vukusic, 2006).

The International MS Genetics Consortium (IMSGC) has identified approximately 230 genetic loci that contribute to the risk of developing MS, and most of these are associated with the function of the immune system. The environmental triggers for MS are less well defined, although vitamin D deficiency and delayed exposure to the Epstein-Barr Virus (EBV) are considered to be risk factors for MS. The pathophysiology of MS includes a well-described inflammatory (or immune-mediated) component, which seems predominant earlier in the disease, and what is termed a “degenerative” component, which is less well understood but is felt to predominate later in the disease (Compston and Coles, 2008; Reich et al., 2018). The currently recognized clinical phenotypes of the disease include relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and primary progressive multiple sclerosis (PPMS); the modifier “active” is used to indicate either relapses or MRI activity, and the modifier “progression” indicates disability progression not attributable to relapses. Conversely, the term “worsening” should be used for disability progression attributable to relapses (Lublin et al. 2014).

About 85% of people who develop MS begin with RRMS, which has a predilection for women and an average age of diagnosis of approximately 30 years (Weinshenker et al., 1989). RRMS is characterized by recurrent inflammatory episodes, termed “relapses,” in which auto-reactive lymphocytes marginate across the blood-brain barrier (BBB) and enter the CNS, leading to acute injury to myelin, oligodendrocytes, and axons and potentially causing new or worsening neurologic deficits. Potential targets of acute inflammatory injury include the subcortical white matter, brainstem, optic nerve, and spinal cord; however, recent data suggests that the grey

matter and neurons can also be a target of this inflammatory attack and that these cortical lesions may correlate better with disability (Compston and Coles, 2008; Reich et al., 2018). The diagnostic criteria for RRMS require clinical or imaging evidence of dissemination of clinical events “in time and space,” suggesting that a patient must experience at least two clinically or radiologically distinct episodes to be diagnosed with RRMS; however, after one clinical event, the most current iteration of the McDonald diagnostic criteria allow the coexistence of asymptomatic enhancing and nonenhancing lesions or intrathecal immunoglobulin synthesis to support dissemination in time (Polman et al., 2011; Thompson et al., 2018). Although early relapses may be followed by complete recovery, over time, relapses are associated with an accumulation of residual deficits and increasing disability (Confavreux et al., 1980; Weinshenker et al., 1989).

Over time, a slow, insidious progression of disability--that appears to be independent of the occurrence of relapses--is seen in many patients with RRMS (Weinshenker et al., 1989; Confavreux et al., 2000; Tremlett et al., 2009). On average, transition into this phase of the disease, termed SPMS, occurs ~15 years after the diagnosis of RRMS, although frequent relapses soon after diagnosis (and incomplete recovery from early relapses) appears to hasten this transition (Confavreux 2003; Paz Soldan 2015). The progression of disability in SPMS is felt to be driven by the poorly understood “degenerative” aspect of the disease. Hypotheses regarding the pathophysiology of this “degenerative process” in SPMS include a bioenergetic deficit from mitochondrial dysfunction, compartmentalized inflammation behind an intact blood-brain barrier, increased free radicals, or simply “neurodegeneration” (Mahad et al, 2015). Relapses and new MRI lesions can still occur in SPMS but are less frequent, especially later in this phase of the disease (Correale et al, 2017).

2.2. Analysis of Current Treatment Options

There are over a dozen MS drugs that are FDA-approved to treat relapsing MS, including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and active SPMS. Therapies for RMS reduce the annualized relapse rate in patients with RMS by approximately 30 to 70% but unfortunately achieve inconsistent results on disability progression, which is not surprising because of the different aspects of the pathophysiology of MS and the incomplete effect of relapses on disability progression. Even though meta-analyses of clinical trials in RMS (Sormani et al, 2009; Sormani and Bruzzi, 2013) suggest that the development of new MRI lesions may be a surrogate for relapses, the well-described “clinical-radiologic paradox” and the relatively weak correlation between MRI activity and disability suggest that MRI is not a good measure of how a patient functions, feels, or survives, thus lessening the importance of this endpoint from a regulatory point of view (Barkhof 1999, Sormani et al 2010). See Table 1 for a list of currently approved MS medications.

Table 1. Reviewer Table. FDA-approved treatments for relapsing multiple sclerosis

Approved Drug	Product Name	Relevant Indication	Year Approved	Route & Frequency	Efficacy Information	Major Safety Concerns
Beta interferon 1b	Betaseron (Betaferon in EU)	Relapsing forms of MS	1993	subcutaneous every other day	32% reduction in ARR	Hepatotoxicity, depression
Beta interferon 1a	Avonex	Relapsing forms of MS	1996	IM weekly	37% reduction in disability progression	Hepatotoxicity, depression
Glatiramer acetate ¹	Copaxone	Relapsing forms of MS	1996	subcutaneous daily ²	29% reduction in ARR	None
Mitoxantrone	Novantrone	Relapsing forms of MS	2000	IV every 3 months	60% reduction in ARR; 64% reduction in disability progression	Cardiotoxicity, leukemia
Beta interferon 1a	Rebif	Relapsing forms of MS	2002	subcutaneous 3 times weekly	32% reduction in ARR	Hepatotoxicity, depression
Natalizumab	Tysabri	Relapsing forms of MS	2004	IV every 4 weeks	61% reduction in ARR	Progressive Multifocal Leukoencephalopathy,
Beta interferon 1b	Extavia	Relapsing forms of MS	2009	subcutaneous every other day	32% reduction in ARR	Hepatotoxicity, depression
Fingolimod ³	Gilenya	Relapsing forms of MS	2010	orally once daily	55% reduction in ARR	1 st dose bradycardia, macular edema, fetal risk
Teriflunomide	Aubagio	Relapsing forms of MS	2012	orally once daily	31% reduction in ARR	Boxed warnings for hepatotoxicity and teratogenicity
Dimethyl fumarate	Tecfidera	Relapsing forms of MS	2013	orally twice daily	44-53% reduction in ARR	Lymphopenia, PML
PEGylated Interferon Beta	Plegridy	Relapsing forms of MS	2014	subcutaneous every 2 weeks	36% reduction in ARR	Hepatotoxicity, depression
Alemtuzumab ⁴	Lemtrada	Relapsing forms of MS after inadequate response to ≥ 2 MS treatments	2015	2 intravenous courses 12 months apart	49% reduction in ARR ⁵	Boxed warnings for serious/fatal autoimmune conditions; serious and life-threatening infusion reactions, stroke, and increased risk of malignancies
Ocrelizumab	Ocrevus	Relapsing forms of MS and Primary Progressive MS (PPMS)	2016	IV every 2 weeks x 2 then IV x1 every 6 months	46% reduction in ARR (RMS) ⁵ ; 24% reduction in disability progression (PPMS)	Infusion reactions, increased risk of breast cancer
Monomethyl fumarate ^{6,7}	Bafiertam	Relapsing forms of MS	2018	Oral twice daily	44-53% reduction in ARR	Lymphopenia, PML
Siponimod	Mayzent	Relapsing forms of MS	2019	Oral once daily	55% reduction in ARR	1 st dose bradycardia, macular edema, fetal risk

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

Approved Drug	Product Name	Relevant Indication	Year Approved	Route & Frequency	Efficacy Information	Major Safety Concerns
Cladribine	Mavenclad	Relapsing forms of MS	2019	2 oral courses, one year apart	58% reduction in ARR	Malignancy, teratogenicity, infections, lymphopenia, liver injury
Diroximel fumarate ⁷	Vumerity	Relapsing forms of MS	2019	orally twice daily	44-53% reduction in ARR	Lymphopenia, PML

¹ Glatopa and other generic versions of the glatiramer acetate are now available.

² Daily and 3 times weekly formulations of glatiramer acetate are now available.

³ Indicated for ≥ 10 years old

⁴ Not indicated for use in patients less than 18 years of age due to safety concerns

⁵ Compared to an active comparator (subcutaneous interferon β-1a).

⁶ Tentatively approved pending patent expirations

⁷ Utilized the 505(b)(2) regulatory pathway and relied on Tecfidera as the referenced product.

3. Regulatory Background

Please refer to the review of efficacy by Dr. Larry Rodichok. Of note, the initial submission of this NDA resulted in a Refuse to File action on 2/23/2018 because a major active metabolite (RP112273) had not been adequately characterized.

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

4.1. Office of Scientific Investigations (OSI)

Please refer to the OSI review by OSI.

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Control (CMC) review.

4.3. Clinical Microbiology

Please refer to the CMC/microbiology review.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical pharmacology / toxicology review.

4.5. Clinical Pharmacology

Please refer to the clinical pharmacology review, from which this reviewer highlights the following points:

- “Ozanimod is a sphingosine 1-phosphate (S1P) receptor agonist, which binds selectively to S1P subtypes 1 (S1P1) and 5 (S1P5). Ozanimod causes internalization of S1P1 and retention of lymphocytes in the lymphoid tissues ... The mechanism by which ozanimod exerts therapeutic effects in relapsing multiple sclerosis (RMS) may involve reduction of lymphocyte migration into the central nervous system.”
- “Ozanimod is extensively metabolized in humans to several circulating active metabolites, including two major active metabolites, CC112273 and CC1084037, with similar activity and selectivity for S1P1 and S1P5 to the parent drug ... The half-life ($t_{1/2}$) of ozanimod is approximately 20 hours, while the $t_{1/2}$ of CC112273 and CC1084037 is about 280 hours, leading to accumulation of these active metabolites (relative to the parent) after multiple dosing.”
- “Ozanimod is not recommended in patients with hepatic impairment ... The [single dose] dedicated hepatic impairment study was not designed to evaluate the effect of hepatic impairment on the PK of ozanimod’s major metabolites RP112273 and CC1084037. In addition, there are no safety and efficacy data in this patient population as subjects with hepatic impairment, including mild, were excluded from the phase 2/3 trials.”
- Ozanimod is “Contraindicated with MAO inhibitors e.g., phenelzine, isocarboxazid, linezolid, safinamide, selegiline, rasagiline, etc.”
- “Co-administration of ozanimod with the following is not recommended: strong CYP2C8 inhibitors (gemfibrozil), strong CYP inducers (rifampin), BCRP Inhibitors (cyclosporine, eltrombopag, curcumin).”

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

5. Sources of Clinical Data and Review Strategy

Please refer to the review of efficacy by Dr. Larry Rodichok. This reviewer's approach to the Review of Safety is described in Section 8 below.

6. Review of Relevant Individual Trials Used to Support Efficacy

Please refer to the review of efficacy by Dr. Larry Rodichok.

7. Integrated Review of Effectiveness

Please refer to the review of efficacy by Dr. Larry Rodichok.

8. Review of Safety

8.1. Safety Review Approach

The Applicant submitted data from 21 clinical trials of ozanimod in this NDA, including 14 Phase 1 studies of ozanimod (mostly in healthy volunteers) and seven later-stage studies in individuals with RMS and inflammatory bowel disease (IBD), specifically ulcerative colitis (UC) and Crohn's disease (CD). A study assessing the effect of a single dose of pseudoephedrine on systolic blood pressure in subjects taking ozanimod and a drug interaction study between ozanimod and CYP2C8 and CYP3A4 modulators were initiated after the data cut-off date for this submission. Subjects completing later-stage studies in RMS and UC had the option to roll over into open label extension (OLE) studies. As per Table 2, the largest clinical trials of ozanimod were performed in subjects with RMS, and those of ozanimod in subjects with IBD were relatively small. Because this NDA was submitted with a proposed indication of RMS, this review will primarily focus on the RMS population but will present data from the clinical studies of subjects with IBD and the clinical pharmacology studies in healthy volunteers when needed to support the RMS safety data.

Table 2. Reviewer Table. Studies of ozanimod submitted with this NDA

Protocol #	Design	Exposure (n)
Phase 1 Studies		
RPCS 001	Single / multiple ascending dose study of ozanimod in healthy volunteers	Ozanimod: 68 Placebo: 24
RPC01-102	Thorough QT/QTc study of ozanimod in healthy adults	Ozanimod: 62 Placebo: 62
RPC01-1901	Fed and fasted PK study of ozanimod in healthy adults	Ozanimod 1 mg: 24
RPC01-1902	Drug-drug interaction study of itraconazole, rifampin, and ozanimod in healthy adults	Ozanimod 0.25 mg: 18 Ozanimod 1 mg: 18
RPC01-1903	Drug-drug interaction study of cyclosporine and ozanimod in healthy adults	Ozanimod 0.25 mg: 18
RPC01-1904	Study of ozanimod in subjects with hepatic impairment	Ozanimod 0.25 mg: 31
RPC01-1905	Study of ozanimod in healthy Japanese and Caucasian adults	Ozanimod 0.25 mg: 28 Ozanimod 0.5 mg: 29 Ozanimod 1 mg: 18 Placebo: 16
RPC01-1906	Study of ozanimod in subjects in subjects with end stage renal disease	Ozanimod 0.25 mg: 16
RPC01-1907	Drug-drug interaction study of ethinyl estradiol, norethindrone, and ozanimod in healthy women	Ozanimod 1 mg: 21
RPC01-1908	Drug-drug interaction study of ozanimod and diltiazem or propranolol in healthy adults	Ozanimod 0.25 mg: 36
RPC01-1909	Mass balance study in healthy adult men	[¹⁴ C]-ozanimod: 6
RPC01-1910	Study to characterize the cardiac effect of ozanimod re-initiation after different drug washout intervals	Ozanimod titration: 56 Placebo: 18
RPC01-1911	Study to compare the PK/PD of ozanimod in healthy Caucasian and Japanese adults	Caucasian: 42 Japanese: 39
Clinical Trials in Subjects with Ulcerative Colitis (UC)		

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

Protocol #	Design	Exposure (n)
RPC01-202	Phase 2, randomized, double-blind, placebo-controlled, 9-week study	Ozanimod 0.5 mg: 65 Ozanimod 1 mg: 67 Placebo: 65
RPC01-3102	Open-label extension of Phase 3, double-blind, placebo-controlled, 52-week study	Ozanimod 1 mg: 398 ¹
Clinical Trials in Subjects with Crohn's Disease (CD)		
RPC01-2201	Phase 2, open-label study with 12-week indication and 148 week extension	Ozanimod 1 mg: 69 ¹
Clinical Trials in Subjects with Relapsing MS (RMS)		
RPC01-1001	Phase 1, open-label, PK/PD, 12 -week study	Ozanimod 0.25mg: 24 Ozanimod 0.5 mg: 24 Ozanimod 1 mg: 11
RPC01-201A	Phase 2, randomized, double-blind, placebo controlled, 24-week study with blinded extension	Ozanimod 0.5 mg: 87 Ozanimod 1 mg: 83 Interferon β -1a 30 mcg: 88
RPC01-201B	Phase 2/3. randomized, double-blind, active comparator, 24-month study	Ozanimod 0.5 mg: 439 Ozanimod 1 mg: 434 Interferon β -1a 30 mcg: 440
RPC01-301	Phase 3, randomized, double-blind, active comparator, 12-month study	Ozanimod 0.5 mg: 453 Ozanimod 1mg: 448 Interferon β -1a 30mcg: 445
RMS Extension Study		
RPC01-3001	Single-arm, open-label extension of 1001, 201A, 201B, and 301 studies	Ozanimod 1 mg: 2485 ¹

¹As of data cutoff date (30Jun2018)

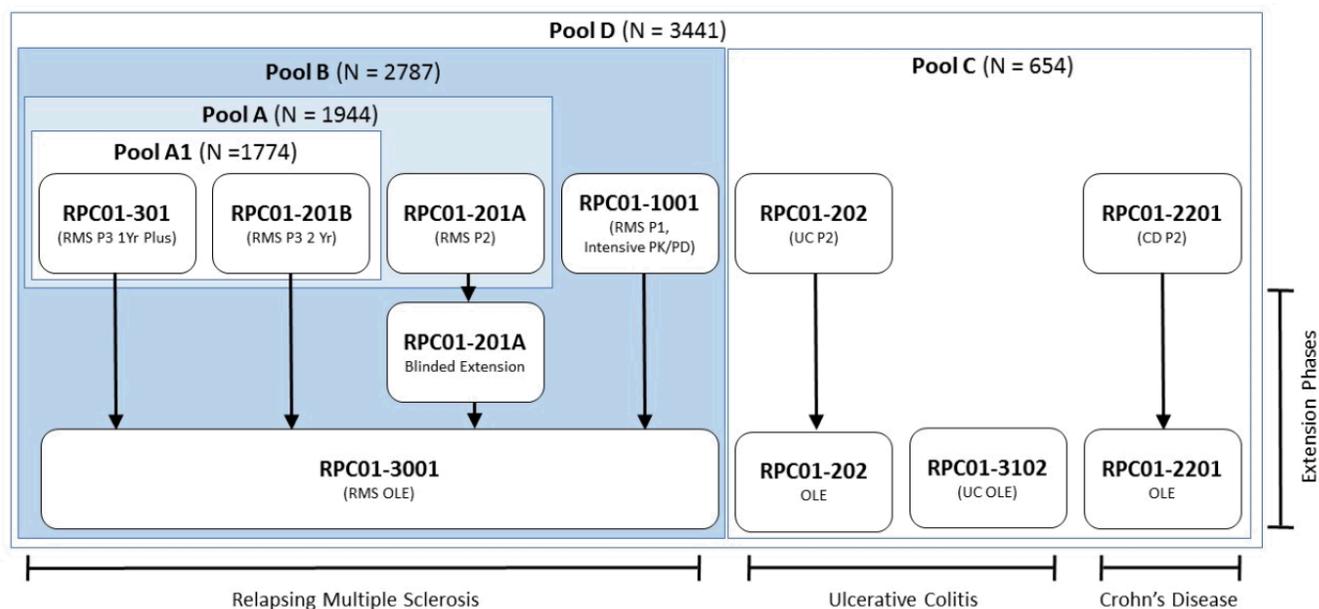
As noted in Table 2, the Applicant seeks approval of ozanimod 1 mg (after an initial eight day dose escalation) for the treatment of adults with RMS based on the results of a placebo-controlled study (with a blinded extension), two studies using an active comparator (intramuscular interferon β -1a), and an open-label extension of these studies.

The Applicant pooled safety data from these clinical trials for analysis. The six safety data pools are summarized below and in Figure 1.

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

- Pool A consists of subjects who participated in one of the three controlled RMS studies. Subpool A1 consists of those subjects from the two pivotal RMS studies that utilized an active-comparator (intramuscular interferon β -1a).
- Pool B consists of the subjects who received ozanimod in one of five RMS studies, including the open label extension for the studies in Pool A and an intensive PK/PD Phase 1 study in subjects with RMS.
- Pool C consists of subjects in the UC/CD studies of ozanimod.
- Pool D consists of subjects in the studies of ozanimod in subjects with RMS, UC, and CD.
- Pool E consists of the healthy volunteers (and subjects with hepatic or renal impairment) who participated in one of the 11 Phase 1 studies of ozanimod.

Figure 1. Applicant Figure. Pooling Strategy for Ozanimod Studies



CD = Crohn's disease, OLE = open label extension, PK/PD = pharmacokinetic/pharmacodynamic, RMS = relapsing multiple sclerosis, UC = ulcerative colitis. Note: N is given for the number of ozanimod-treated subjects in each pool. Pool B includes subjects who were treated with placebo or IFN β -1a and were re-randomized to receive ozanimod in an extension phase. Pool E (Clinical Pharmacology Studies) not shown. Study RPC01-3101 (parent study to RPC01-3102) is an ongoing blinded study not included in Pool C. Study RPC01-2201 is an open-label study.

Pool A will be the most relevant dataset for the review of this NDA, but data from all of the pools will be considered. Information will be gleaned from the provided study datasets, the Clinical Study Reports (CSRs), the Summary of Clinical Safety (SCS), the Integrated Summary of Safety (ISS), Safety Updates, and the Applicant's responses to formal Information Requests (IR). The quality and "fitness" of the study datasets were assessed by the Office of Computational Science (OCS) Jumpstart team, and this reviewer used the JMP application to analyze the

provided datasets. This review will focus on the proposed marketed dose of ozanimod (1 mg).

Ozanimod is a S1P receptor modulator that is purportedly selective for two (S1P1 > S1P5) of the five known S1P receptors. As per Table 3, S1P receptors have protean functions and are relatively ubiquitous in the human body. The relevant mechanism of S1P modulators in RMS is likely the sequestration of circulating lymphocytes in secondary lymphoid structures by limiting their S1P1-mediated egress from these tissues.

Table 3. Reviewer Table. Distribution and biological activity of S1P receptors

Subtype	Locations	Proposed Effects
S1P ₁	Lymphocytes Thymocytes Mast cells Eosinophils Vascular smooth muscle Endothelial cells Atrial myocytes Gastric smooth muscle Neurons Astrocytes Oligodendrocytes	Regulate lymphocyte egress from lymphoid tissue Regulate thymocyte egress from thymus Modulate vasomotor tone Increased endothelial permeability Cardiac conduction ¹ Neurogenesis Astrocyte migration Oligodendrocyte progenitor differentiation / survival
S1P ₂	Vascular smooth muscle Gastric smooth muscle Neurons	Modulate vasomotor tone Gastric smooth muscle contraction Neuronal excitability
S1P ₃	Endothelial cells Vascular smooth muscle Atrial myocytes Neurons Astrocytes	Increased endothelial permeability Vasomotor tone regulation Cardiac conduction
S1P ₄	Lymphocytes	Cell shape and motility
S1P ₅	Oligodendrocytes	Oligodendrocyte progenitor differentiation / migration

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

There are currently two S1P receptor modulators that are approved for use in subjects with RMS, to include clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), and active secondary progressive multiple sclerosis (SPMS). One (fingolimod) is relatively non-selective and interacts with S1P1, S1P3, S1P4, and S1P5, while the other (siponimod) is purportedly selective for S1P1 and S1P5; despite this, the safety profiles for these two S1P receptor modulators are remarkably similar. Identified safety issues with this class of medications include bradyarrhythmia and atrioventricular blocks, lymphopenia, infections (including progressive multifocal leukoencephalopathy [PML] and cryptococcal meningitis),

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

macular edema, posterior reversible leukoencephalopathy syndrome (PRES), respiratory effects (including reductions in forced vital capacity [FVC], forced expiratory volume in one second [FEV1], and diffusion capacity of the lung for carbon monoxide [DLCO]), liver injury, fetal risk, severe increase in disability (and immune system effects) after cessation of the drug, increased blood pressure, malignancies (including cutaneous malignancies and lymphoma), and hypersensitivity reactions. These safety signals may partially inform the safety review of ozanimod; however, vigilance for other potential safety signals with this NME was maintained.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Per the ISS, the pooled Safety Population consisted of “all subjects who were randomized and received ≥ 1 dose of study drug.” Subjects randomized to ozanimod in the Phase 2/3 RMS and IBD studies began the study drug with an initial dose escalation (0.25 mg on Days 1 to 4, 0.5 mg on Days 5 to 7) before starting the maintenance dose (0.5 or 1 mg) of the drug on day 8.

There were 2917 subjects in Pool A of the Safety Population, which consists of all subjects who participated in the controlled studies of ozanimod for RMS. There were 2782 subjects who received ozanimod in any of the RMS Studies (Pool B of the Safety Population), most of whom received at least one dose of ozanimod 1 mg. The overall ozanimod Safety Population also included studies in subjects with UC/CD (n=380) and healthy volunteers. Per the CSR, the clinical pharmacology studies of ozanimod in healthy volunteers (Pool E) included “371 subjects in the Pool E Safety Population, of which 151 subjects received ≥ 1 dose of < 0.5 mg ozanimod, 15 subjects received 0.5 mg ozanimod, 116 received 1 mg ozanimod, and 89 subjects received > 1 mg ozanimod.” See Figure 2, which suggest that the total exposure to ozanimod for all indications was 4861.4 patient years of exposure (PYE).

Figure 2. Sponsor Figure. Exposure to Ozanimod in Pools A1, A, B, C, D, E

Pool D (All Indications) Pool B + Pool C			
Group	N	Duration	PYE
Ozanimod 1 mg	2996	13.1 (11.5)	3233.2
Ozanimod 0.5 mg	1095	18.0 (7.5)	1620.2
Total ozanimod	3162	18.7 (12.0)	4861.4

Pool B (RMS) Pool A + RPC01-1001 RPC01-201A (EXT) RPC01-3001			
Group	N	Duration	PYE
Ozanimod 1 mg	2625	12.7 (11.1)	2779.1
Ozanimod 0.5 mg	1930	18.8 (7.0)	1601.6
Total ozanimod	2782	19.0 (11.6)	4380.6

Pool A (RMS) Pool A1 + RPC01-201A			
Group	N	Duration	PYE
Ozanimod 1 mg	965	17.0 (6.6)	1362.2
Ozanimod 0.5 mg	979	16.7 (6.6)	1358.0
IFN β-1a	885	17.8 (6.2)	1304.8
Placebo	88	6.0 (0.6)	40.5
Total	2917	16.8 (6.7)	4065.4

Pool A1 (RMS) RPC01-301 RPC01-201B			
Group	N	Duration	PYE
Ozanimod 1 mg	882	18.1 (6.0)	1323.3
Ozanimod 0.5 mg	892	17.8 (6.0)	1318.0
IFN β-1a	885	17.3 (6.2)	1304.8
Total	2559	17.9 (6.0)	3946.1

Pool C (IBD) RPC01-202 RPC01-3101* RPC01-2201 RPC01-3102			
Group	N	Duration	PYE
Ozanimod 1 mg	371	16.0 (14.0)	454.2
Ozanimod 0.5 mg	65	5.3 (3.0)	26.6
Total ozanimod	380	16.5 (14.6)	480.8

Pool E (Healthy Subjects) RPC01-102, RPC01-1901, RPC01-1902, RPC01-1903, RPC01-1904, RPC01-1905, RPC01-1906, RPC01-1907, RPC01-1908, RPC01-1909, and RPCS 001			
Group	N	Duration	PYE
Ozanimod > 1 mg	89	11.9 (6.2)	2.89
Ozanimod 1 mg	116	7.0 (7.0)	2.22
Ozanimod 0.5 mg	15	1.7 (1.8)	0.07
Ozanimod < 0.5 mg	151	2.8 (5.3)	1.16
Total	371	6.2 (7.0)	6.34

Reviewer Comment: Most of the ozanimod Safety Population had RMS, the indication for which this NDA is being submitted, and many of the subjects received the proposed marketing dose of 1 mg.

Table 4 and Table 5 summarizes the duration of exposure to ozanimod in subjects who participated in the controlled RMS trials (Pool A) and their extensions, respectively.

Table 4. Reviewer Table. Extent of Exposure in controlled RMS Trials (Pool A)

Exposure	Placebo N=88	IFN β-1a 30 mcg N=885	Ozanimod 0.5mg N=979	Ozanimod 1 mg n=965
≥ 6 months	79 (89.8%)	849 (95.9%)	939 (95.9%)	932 (96.6%)
≥ 12 months	-	804 (90.8%)	820 (83.8%)	818 (84.8%)
≥ 18 months	-	408 (46.1%)	407 (41.6%)	416 (43.1%)
≥ 24 months	-	310 (35.0%)	291 (29.7%)	299 (31.0%)

Source: ADEX where SAF CFL and POOL1FL='Y' where PARAMCD=TRTDURM ≥ {6,12,18, or 24} by TRT01A

Reviewer Comment: Part A of Study RPC01-201 was a 24 week study, while Part B was a 24-month study. The drop-off in exposure noted after 12 months is not surprising since RPC01-301 continued until the last enrolled subject had been treated for 12 months.

Pool B of the ozanimod safety population consisted of 2782 subjects, of whom 1030 received at least one dose of ozanimod 0.5 mg and 2625 received at least one dose of ozanimod 1 mg. The duration of exposure is delineated in the following table from the Integrated Summary of Safety.

Table 5. Applicant Table. Extent of Exposure Pool B, Safety Population

Exposure Interval	Ozanimod 0.5 mg (N = 1030) n (%)	Ozanimod 1 mg (N = 2625) n (%)	Total Ozanimod (0.5 and/or 1 mg)^a (N = 2782) n (%)
≥ 6 months	985 (95.4)	2565 (97.5)	2701 (96.9)
≥ 12 months	938 (90.8)	2491 (94.7)	2619 (94.0)
≥ 18 months	521 (50.4)	2141 (81.4)	2387 (85.6)
≥ 24 months	395 (38.2)	1069 (40.6)	1809 (64.9)
≥ 30 months	58 (5.6)	852 (32.4)	1690 (60.6)
≥ 36 months	0	521 (19.8)	1018 (36.5)
≥ 42 months	0	307 (11.7)	597 (21.4)
≥ 48 months	0	154 (5.9)	295 (10.6)
≥ 54 months	0	77 (2.9)	144 (5.2)
≥ 60 months	0	20 (0.8)	32 (1.1)

N = number randomized to treatment, n = number receiving treatment for exposure interval.

Reviewer Comment: The exposure to ozanimod 1 mg in the RMS development program studies exceeds the ICH guidelines for chronically administered medications (i.e., n=1,500 exposed, n=300-600 for 6 months, n=100 for 1 year).

8.2.2. Relevant characteristics of the RMS safety population:

There is a well-recognized geographical distribution of RMS in which the prevalence of RMS increases with greater distance from the equator. This distribution may relate to vitamin D, since vitamin D is more easily synthesized closer to the equator and since there is an inverse correlation between vitamin D levels and the risk of RMS activity;

indeed, there are some subpopulations who prefer a diet high in Vitamin D (e.g., Alaskan Inuits) that have a much lower risk of RMS than expected given where they live. RMS is more common in women than in men (approximately 3:1) and in people of Northern European, Caucasian descent, although a recent study from Southern California suggests an increasing incidence in people of African descent. The prevalence of RMS is quite low in childhood, increases during adolescence, and is highest between 20-40 years of age. The classic epidemiologic characteristics of an individual diagnosed with MS is a 30yo post-partum woman (Compston and Coles, 2008, Reich et al, 2018, Ascherio and Munger, 2016).

Although the Integrated Summary of Safety (ISS) assesses the demographics of the disease characteristics of Pool A1 (Studies RPC01-201B and RPC01-301, which compare two doses of ozanimod to an active comparator, intramuscular interferon β -1a), it seems more appropriate to focus on Pool A, which includes subjects from Pool A1 and the smaller, placebo-controlled Study RPC01-201A. Although the Applicant is correct in noting that Study RPC01-201A was of shorter duration (24 weeks) than the other studies, the inclusion of additional safety data (and a small placebo arm) may enhance the safety analysis of ozanimod somewhat.

The RMS safety population was identified by querying for subjects in Pool A of the ISS ADSL dataset for whom the POOL1FL and SAF CFL flags were 'Y'. This query yielded 2917 subjects, whose demographics are delineated in Table 6 below; in brief, the RMS safety population had an average age of 36 years, was 67% women, and was almost entirely white (99%) and from Eastern Europe (90%).

Table 6. Reviewer Table. Demographic Data for the controlled RMS population (Pool A)

Demographic Parameters	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965
Age (years)				
Mean (SD)	35.6 (9.1)	38.9 (8.7)	35.9 (9.2)	35.6 (9.2)
Median	35	39	36	35
Min, Max	18, 55	19, 54	18, 55	18, 55
<40 years	582 (66%)	45 (51%)	638 (65%)	621 (64%)
\geq 40 years	303 (34%)	43 (49%)	341 (35%)	344 (36%)
Sex				
Female	602 (68%)	62 (70%)	658 (67%)	635 (66%)
Male	283 (32%)	26 (30%)	321 (33%)	330 (34%)
Race				
White	875 (99%)	87 (99%)	964 (98%)	959 (99%)

Demographic Parameters	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965
Black or African	7 (1%)	1 (1%)	10 (1%)	5 (1%)
Other	3 (0%)	0	5 (1%)	1 (0%)
Ethnicity				
Not Hispanic or Latino	879 (99%)	88 (100%)	969 (99%)	947 (98%)
Hispanic or Latino	6 (1%)	0	10 (1%)	18 (2%)
Region				
Eastern Europe	795 (90%)	78 (89%)	878 (90%)	866 (90%)
Western Europe	55 (6%)	6 (7%)	61 (6%)	57 (6%)
North America	27 (3%)	4 (5%)	33 (3%)	32 (3%)
Rest of World	8 (1%)	0	7 (1%)	10 (1%)

Source: ADSL where SAF CFL='Y' and POOL1FL='Y' by TRT01A

Reviewer Comment: Overall, the demographics of the safety population appear comparable among the treatment arms and are generally representative of what would be expected for a typical RMS population. With that caveat, this reviewer notes that the safety population is almost entirely white and worries that this may limit the generalizability of the results: although many people with RMS are of Caucasian descent, it does appear that people of African descent are at risk of worse outcomes from RMS. Further, 90% of the safety population is from Eastern Europe, leading this reviewer to worry about the generalizability of the results, especially given the seemingly low rates of adverse event reporting in this and other applications with study populations predominantly from this region.

As is common in clinical trials of RMS, subjects with “clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, renal, or other major systemic disease,” including specific cardiac conditions, poorly controlled diabetes mellitus type 2, and a history of uveitis, were excluded from participating in the clinical trials of ozanimod in subjects with RMS.

Reviewer Comment: Although the aforementioned exclusions are appropriate to enhance the safety of subjects participating in clinical trials, it should be recognized that these safety analyses may underestimate the risk of using ozanimod in the overall MS population, so this reviewer recommends that the characteristics of the population enrolled in the ozanimod RMS studies be described in the labeling for ozanimod.

The disease characteristics of this RMS safety population follow in Table 7 below.

Table 7. Reviewer Table. Disease Characteristics of the controlled RMS population (Pool A)

Disease Characteristics	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965
Baseline EDSS				
Mean (SD)	2.6 (1.2)	2.9 (1.3)	2.6 (1.2)	2.6 (1.2)
Median	2.5	3	2.5	2.5
<4 (%)	743 (84%)	63 (72%)	789 (81%)	791 (82%)
\geq 4 (%)	142 (16%)	25 (28%)	190 (19%)	174 (18%)
Years since MS Diagnosis (years)				
Mean (SD)	3.7 (4.5)	4.6 (5.1)	3.5 (4.4)	3.8 (4.7)
Median	1.8	3.0	1.6	1.9
Min, max	0, 28	0, 20	0, 33	0, 31
Prior MS Medications				
0	55 (6%)	3 (3%)	75 (8%)	63 (7%)
1	553 (62%)	55 (63%)	616 (63%)	624 (65%)
>1	277 (31%)	30 (34%)	288 (30%)	278 (29%)
Relapses in last 12 months				
Mean (SD)	1.3 (0.6)	1.3 (0.6)	1.3 (0.7)	1.3 (0.6)
Median	1	1	1	1
Min, max	0, 4	0, 3	0, 8	0, 4
Baseline GdE lesions				
Mean (SD)	1.8 (3.4)	1.4 (3.4)	1.6 (3.2)	1.7 (3.5)
Median	0	0	0	0
Min, max	0, 22	0, 19	0, 26	0, 53

Source: ADSL where SAFEFL='Y' and POOL1FL='Y' by TRT01A

Reviewer Comment: Subjects in this population appears to have early, inflammatory disease, which is appropriate for a study in subjects with RMS. The disease characteristics appear comparable among these four treatment arms.

8.2.3. Adequacy of the safety database:

The ozanimod safety database contains a sufficient number of RMS subjects treated for an adequate duration to allow a satisfactory safety review capable of reaching meaningful conclusions about the safety of ozanimod in an RMS indication. The demographics and disease characteristics of the ozanimod RMS Safety Population are similar to that of a typical RMS population, although it would have been preferable if more non-white subjects and more subjects from areas outside of Eastern Europe had

been enrolled. As is commonly done in RMS trials, the ozanimod RMS Safety Population does not include subjects with significant concomitant disease, limiting the generalizability of this safety data to the overall RMS population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The safety data provided by the Applicant are of sufficient quality to permit their review. A data fitness assessment by the Agency's Office of Computational Science (OCS) concluded that the datasets submitted for review were substantially complete and found few examples of duplicated, inconsistent, or missing data. The Applicant responded appropriately to all queries about their submitted data with timely responses to the Division's Information Requests (IRs).

This reviewer was able to replicate the key findings of the safety summaries provided by the Applicant. Comparing subject-level data across sources did not uncover gross discrepancies between datasets, narratives, supplied CRFs, listings, or summary tables.

8.3.2. Categorization of Adverse Events

The Applicant definition of an adverse events (AE) was reasonable and consistent with typical definitions of AEs:

"An AE is any untoward medical occurrence that does not necessarily have a causal relationship with the investigational medicinal product. An AE can therefore be any unfavorable or unintended sign, including an abnormal laboratory finding, symptom or disease temporally associated with the use of an investigational medicinal product whether or not considered related to the investigational medicinal product."

Unless they were atypical in severity or some other characteristic, MS relapses and disability progression were not considered to be AEs. Investigators' verbatim terms for AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Reviewer Comment: The Applicant's definition of AEs and process to code these AEs appear adequate to allow for reasonably accurate estimates of event risks by preferred term (PT) and System Organ Class (SOC).

During the studies of ozanimod, Investigators monitored subjects for the occurrence of AEs, which were recorded on electronic Case Report Forms (eCRFs). In addition to reviewing abnormal findings on physical examinations, laboratory results, and other

testing for clinically significant changes, Investigators solicited AEs by questioning subjects at each study visit, although subjects could also volunteer AEs between visits. Abnormal laboratory values or test results constituted AEs only if they induced clinical signs or symptoms, were considered clinically significant, or required therapy. Any adverse event that occurred (or worsened in severity) between the administration of the first dose of the study medication and 28 days after the last dose of the study medication was considered to be a treatment emergent adverse event (TEAE).

All AEs were to be included in the eCRF regardless of the Investigator's impression regarding the relatedness of an AE to the study medication. In addition to a description of the event, the Investigator was to record the severity of the AE. Instead of using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), the severity of AEs was graded using the following definitions:

- “Mild: an AE usually transient in nature and generally not interfering with normal activities;
- Moderate: an AE that is sufficiently discomforting to interfere with normal activities;
- Severe: an AE that is incapacitating and prevents normal activities.”

The protocols state that Investigators were to follow all AEs until resolution “unless the event is considered by the Investigator to be unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow up.” Other information collected about AEs on the eCRF included the time of occurrence, duration, action taken (treatment and/or follow-up tests), and outcome (recovered/resolved, recovering/resolving, received/resolved with sequelae, not recovered/not resolved, fatal, or unknown). Although of limited utility, the Investigator's assessment of the relationship (unrelated, unlikely related, possibly related, probably related, related) of the AE to the study medication was also recorded on the eCRF.

Reviewer Comment: The methods to ascertain AEs and the information collected on the eCRF appears reasonable and appropriate.

The Applicant defined a serious adverse event (SAE) as “any untoward medical occurrence or effect that fulfills the following criteria:

- Results in death
- Is life-threatening (NOTE: the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires hospitalization or prolongation of an existing inpatient hospitalization
- Results in persistent or significant disability or incapacity

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

- Is a congenital abnormality / birth defect
- Important medical events not captured by the above but which may, for example, require medical intervention to prevent one of the outcomes above.”

In addition to deaths and SAEs, TEAEs leading to study withdrawal, study drug discontinuation, or treatment interruption are of special interest, as are those whose severity was graded as severe. The Applicant defined the following to be adverse events of special interest (AESIs):

- Serious and opportunistic infections
- Malignancy
- Cardiac events
- Pulmonary events
- Macular edema
- Hepatic events
- Lymphopenia

Reviewer Comment: The definition of SAEs is reasonable and appropriate, as is the Applicant’s choice of AESIs, especially given the safety profiles of other S1P receptor modulators.

8.3.3. Routine Clinical Tests

Serologies

Testing for viral serologies and syphilis was performed at screening, and the study exclusions included evidence of recurrent or chronic infection with HIV, syphilis, tuberculosis, or hepatitis A, B, or C. In addition, subjects had to demonstrate evidence of IgG antibodies to the varicella zoster virus (VZV) to participate in the study, although VZV seronegative subjects could be rescreened 30 days after VZV vaccination.

First Dose Cardiac Monitoring

Presumably because of the known risks of bradyarrhythmia and atrioventricular (AV) block with the administration of the first dose of other S1P receptor modulators (and two cases of second degree AV block in the Phase I development of ozanimod), an 8-day dose escalation was implemented in the Phase 2/3 clinical trials in an attempt to mitigate this risk. In addition to a resting heart rate less than 55 beats per minute (bpm) at screening, the exclusion criteria for the Phase 2/3 ozanimod clinical trials included the following cardiac conditions:

- “Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring

hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea

- Prolonged QTcF interval (QTcF >450 msec males, >470 msec females), or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome, concurrent therapy with QT-prolonging drugs)
- Patients with other pre-existing stable cardiac conditions who have not been cleared for the study by an appropriate cardiac evaluation by a cardiologist
- Other clinically significant conduction abnormalities or any other significant cardiac condition that could jeopardize a patient's health or put them at significant safety risk during the course of the study in the opinion of treating investigator"

After the first dose of ozanimod was administered, subjects were closely monitored for cardiac AEs at a site capable of managing symptomatic bradycardia. Although this cardiac monitoring included the use of a Holter monitor early in the ozanimod development program, all subjects were to have baseline and hourly vital signs, including orthostatics, for 6 hours after the first dose of ozanimod was administered. ECGs were also performed at baseline and six hours after the first dose of ozanimod. Additional monitoring was required until resolution of the following situations:

- "The heart rate 6 hours post-dose is < 45 bpm
- The heart rate 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum PD effect on the heart may not have occurred)
- The ECG 6 hours post-dose shows new onset second degree or higher AV block
- The ECG 6 hours post-dose shows a prolonged QTcF interval (>450 msec males, >470 msec females)."

Subjects requiring pharmacologic intervention for symptomatic bradycardia were to have continuous ECG monitoring in a medical facility and to have repeat cardiac monitoring with the administration of the study medication on Study Day 2 (and Study Day 5 and 8 if cardiac safety issues were noted during the previous cardiac monitoring).

Reviewer Comment: The methodology for cardiac monitoring after administration of the first dose of ozanimod appears reasonable and appropriate.

Vital Signs

In addition to the aforementioned first dose cardiac monitoring, vital signs were taken routinely at each study visit. In the Phase 2/3 studies of ozanimod, these included body temperature, weight, heart rate, and systolic and diastolic blood pressure in the supine, sitting, and standing position. The height of subjects was collected at baseline, allowing the calculation of a body mass index (BMI).

Laboratories

Hematology laboratory parameters (including white blood cell, lymphocyte, and platelet counts, hemoglobin, and hematocrit) were checked at baseline and periodically during the study so that changes could be analyzed. The exclusion criteria for the Phase 2/3 studies included an absolute white blood cell count (WBC) < 3500/uL, an absolute lymphocyte count (ALC) < 800/uL, and an absolute neutrophil count (ANC) < 1500/uL.

Since S1P receptor modulators such as ozanimod can affect immune function by sequestering circulating lymphocytes in secondary lymphoid tissue, the following laboratory abnormalities were identified as being of special interest:

- “ALC: < 800 cells/μL, < 500 cells/μL, < 200 cells/μL, and < LLN
- ANC: < 500 cells/μL and < 1000 cells/μL
- Total WBC: > 20,000 cells/μL, < 3000 cells/μL, < 2000 cells/μL, and < 1000 cells/μL”

Numerous serum chemistries were also checked at baseline and periodically during the study. Given the occurrence of transaminase elevations suggestive of liver injury with other S1P receptor modulators, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and total bilirubin (TB) were of special interest and were managed as follows.

- “If patients have elevations in the LFTs (ALT or/and AST) greater than 3 times the ULN, a retest must be performed within 14 days. Upon confirmation of the abnormality, retests should be performed weekly until the elevated LFT decreases to below 3 times the ULN. If the LFT increase is confirmed to be above 5 times the ULN the study medication must be permanently discontinued.”

Urinalyses and coagulation studies were checked at baseline and periodically during the study to assess for abnormalities and changes from baseline.

Pulmonary Monitoring

Pulmonary function tests, including a forced vital capacity (FVC), a forced expiratory volume in one second (FEV1), and when available, a diffusion capacity of the lungs for carbon monoxide (DLCO), were assessed at baseline and periodically during the study. Subjects with a baseline FEV1 or FVC < 70% of predicted were excluded from participating in the Phase 2/3 studies.

Ophthalmology Monitoring

Given the association of macular edema with other S1P receptor modulators, risk factors for macular edema, including a history of uveitis, diabetes mellitus type 1, and

uncontrolled diabetes mellitus type 2, were among the exclusion criteria for the ozanimod studies, and optical coherence tomography (OCT) was performed at baseline and periodically during the study. Symptoms or OCT changes suggestive of macular edema required referral to an ophthalmologist:

- “Study drug must be discontinued in any patient who has a diagnosis of macular edema that is of new onset or worsened since baseline. Patients with a diagnosis of macular edema must be followed up monthly and more frequently if needed based on the ophthalmologist’s judgment. Further ophthalmological evaluations will be conducted until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than 3 months). If the patient does not show definite signs of improvement on examination 6 to 8 weeks after discontinuation of study drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated.”

Dermatology monitoring

As cutaneous malignancies have been reported with other S1P receptor modulators, a history of cancer (except excised and resolved basal cell carcinoma or squamous cell carcinoma of the skin) was among the exclusion criteria for the ozanimod clinical trials. Treating Investigators were to perform dermatologic examination on subjects at baseline, at months 6, 12, and 24 (if applicable), and at the end of treatment /study. A dermatologist was to be consulted to evaluate and treat any suspicious skin findings.

Suicidality

Previous suicide attempts and current signs of major depressive disorders were exclusionary for the ozanimod clinical trials. The Columbia Suicide Severity Rating Scale (C-SSRS) was assessed at baseline and periodically throughout the study.

8.4. Safety Results

8.4.1. Deaths

Per the ISS, a total of six deaths occurred in the clinical development program for ozanimod as of 30Jun2018, although this does not include one death from metastatic pancreatic carcinoma that occurred more than 28 days after discontinuation from Study RPC01-3001. Five of these seven deaths occurred in subjects with RMS, two during the active-controlled studies and three during (or after) their open-label extension (Study RPC01-3001).

- A 29yo female subject (b) (6) who was randomized to ozanimod 0.5 mg died on Day 637 of Study RPC01-201B from an accidental drowning in a river during a family holiday.

Reportedly, the subject did not have a personal or family history of depression or suicidal behavior.

Reviewer Comment: Review of the C-SSRS evaluations is also unrevealing for suicidal ideation or behavior, so it does not appear that ozanimod played a role in this event.

- A 21yo female subject (b) (6) who received ozanimod 1 mg for approximately 11 months was hospitalized for abdominal pain, urinary retention, and acute pyelonephritis after treatment for an MS relapse. She was subsequently readmitted to the hospital for visual loss, generalized weakness, and tonic-clonic seizures. An EEG showed “diffuse changes in electrical activity,” and an MRI showed “large lesions suggestive of viral (herpetic) leptomeningoencephalitis and gadolinium-enhanced lesions typical of MS.” Reportedly, the subject’s condition improved after acyclovir was initiated, but testing for herpes simplex virus (HSV) and the JC virus (JCV) was negative. Although the radiologist interpreted her MRI findings as Posterior Reversible Encephalopathy Syndrome (PRES), she was transferred to an infectious disease hospital, presumably for viral encephalitis. Seemingly because she had flaccid tetraparesis, hyporeflexia, severe muscle pain, labile blood pressure, and respiratory failure, her diagnosis was revised to acute inflammatory demyelinating polyneuropathy (Guillain Barre Syndrome), although her CSF did not show albuminocytologic dissociation. An electromyogram (EMG) was reportedly not performed. The subject had a long and complicated medical course (including ventilatory dependent respiratory failure, pneumothorax, gastrointestinal bleeding, thrombocytopenic purpura), and she died about ten months after the beginning of this event (and stopping the study medication) as a result of chronic kidney failure.

Reviewer Comment: This case is very confusing. The initial presentation of visual loss, seizures, and “large lesions” on MRI sounds reminiscent of PRES, perhaps precipitated by hypertension in response to urinary retention, especially since PRES has been reported in individuals taking an S1P receptor modulator. It appears from the narrative that another early diagnostic impression was viral meningoencephalitis, and the subject reportedly initially improved after acyclovir was started. She then was noted to have a flaccid tetraparesis, for which a diagnosis of Guillain Barre Syndrome (GBS) was posited; however, without albuminocytologic dissociation (and with “large lesions” on MRI), the diagnosis of GBS seems unlikely, and an electromyogram was not performed. A flaccid encephalomyelitis, as has been reported with West Nile Virus and members of the enterovirus family, may be a reasonable alternative unifying diagnosis, as is acute intermittent porphyria, which was suggested by a neurologist external to the study. Given the diagnostic ambiguity with this case, it is difficult to

postulate a role for ozanimod in its occurrence.

- A 27yo female subject (b) (6) who received ozanimod 0.5 mg for approximately 12 months and ozanimod 1 mg for 2 months died from injuries related to a train accident, the details of which are not provided. Although the event was initially suspected to be a suicide, the Investigator removed suicide as a reported term because the subject reportedly did not have a history of depression, and there was no evidence of suicidal intent.

Reviewer Comment: Review of the C-SSRS evaluations from Study RPC-301 is also unrevealing for suicidal ideation or behavior, but this does not negate the possibility that this event was a suicide. The lack of information regarding this case makes the potential role of ozanimod ambiguous.

- A 48yo male subject (b) (6) who received ozanimod for approximately 25 months died on Study Day 404 of Study RPC01-3001 due to a pulmonary embolism after a 38-day hospitalization for a surgical repair of a lower limb fracture sustained when he was hit by an automobile.

Reviewer Comment: Immobilization after an orthopedic event increases the risk of thromboembolism. There is no obvious link between ozanimod and this event, although a possible contribution of ozanimod cannot be excluded

- A 42yo female subject (b) (6) who received ozanimod 0.5 mg for approximately 33 months and ozanimod 1 mg for 1.5 months died from to a pancreatic tumor with multiple metastases to the liver. She initially presented with abdominal pain but reportedly did not have risk factors (tobacco/ alcohol use, obesity, chronic pancreatitis, diabetes mellitus, family history) for pancreatic cancer. The study medication was stopped on Day 137 of Study RPC01-3001, and she died about six weeks after that.

Reviewer Comment: There is no obvious link between ozanimod and this event, although a possible contribution of ozanimod cannot be excluded, especially since malignancy (especially cutaneous malignancy) are noted with other S1P receptor modulators and since decreased tumor surveillance may be expected with the reduction in circulating lymphocytes effected by this class of medication.

Two deaths occurred in the ozanimod IBD development program, one of which occurred in a subject with UC and another in a subject with CD.

- A 43yo female subject (b) (6) with UC who received ozanimod 0.5 mg for approximately 32 weeks and ozanimod 1 mg for 863 days was hospitalized with ascites

on Day 855 of the open label extension and was diagnosed with a mucinous adenocarcinoma of gastric, pancreatic, biliary, or endometrial origin. Despite resection of the omentum, bilateral oophorectomy, and chemotherapy, the subject died on Day 911. She had no history of smoking tobacco.

- A 30yo female subject (b) (6) who received ozanimod 1 mg for approximately 11 months died from complications of worsening Crohn's disease (duodenal fistula, sepsis).

Reviewer Comment: Although the labeled warnings for malignancy and infection with other S1P receptor modulators may suggest a role for ozanimod in these cases, UC is known to increase the risk of adenocarcinoma, and a duodenal fistula from CD would increase the risk of infection / sepsis.

The 120-day safety update includes information on four additional deaths that occurred in the ozanimod development program.

- At screening, Subject (b) (6) was a 46yo woman who was randomized to ozanimod 1 mg in Study RPC01-201A in (b) (6) and continued ozanimod 1 mg in the RPC01-201A and the RPC01-3001 extension studies. On Day 977 of Study RPC01-3001, she was hospitalized for bilateral pneumonia, leukopenia (WBC 3.62 Tsd/ μ L), and thrombocytopenia. She was started on antibiotics but continued to worsen, so she was intubated. Reportedly, her absolute lymphocyte count was 440/mL, and a bronchial aspirate showed *Streptococcus viridans*, *Neisseria*, and *Haemophilus parainfluenzae*. A second bronchial aspirate showed *Stenotrophomonas maltophilia*. She continued to worsen and died on Study Day 988.
- A 64yo man (Subject (b) (6)) with a history of ulcerative colitis was randomized to ozanimod 1 mg in Study RPC01-3101 but stopped taking the study medication on Day 40 due to fatigue and bloody stool. Despite a reportedly normal ALC, he was admitted to the intensive care unit of Day 45 due to acute respiratory failure and "influenza-related pneumonia." He died of cardiac arrest on Day 59.

Reviewer Comment: As an increased risk of infection has been demonstrated with ozanimod and other S1P receptor modulators, a contribution of ozanimod to these two deaths is at least possible.

- A 48yo woman (Subject (b) (6)) was randomized to interferon β -1a in RPC01-201B and subsequently transitioned to ozanimod 1 mg in Study RPC01-3001. On Day 506 of Study RPC01-3001 Day 506, she was hospitalized for severe symptoms of trigeminal neuralgia and was found to have "disseminated cancer with unknown primary focus," with evidence of metastases to her brain, C3-vertebral body, right lung, liver, kidneys,

right adrenal gland, and pelvis. She discontinued the study medication on Day 513 of Study RPC01-3001. Her hospital course was complicated by pneumonia on Day 524 and a generalized tonic-clonic seizure on Day 525. She was discharged from the hospital with Hospice services on Day 530 and died on Day 531.

Reviewer Comment: Since an increased risk of malignancy (especially cutaneous malignancies) has been reported with other S1P receptor modulators, a contribution of ozanimod to this case is possible.

- A 22yo woman (Subject (b) (6)) was randomized to ozanimod 0.5mg in Study RPC01-201B and subsequently transitioned to ozanimod 1 mg in Study RPC01-3001. On Day 837 of Study RPC01-3001, she died in a motorcycle accident.

Reviewer Comment: Data are not presented to suggest a possible role of ozanimod in this death from a motorcycle accident.

Although there were not many deaths in the ozanimod development program, there is an imbalance with deaths in the ozanimod arms of the trials. Although infections and malignancies are common causes of death overall, this analysis (and the reported risk of infections and malignancies with other S1P receptor modulators) suggest that infections and malignancies should be foci of this review and are discussed further in Sections 8.5.1 and 8.5.3.

8.4.2. Serious Adverse Events

Serious adverse events (SAE) are flagged in the ADAE datasets (AESER='Y') and are defined as "any untoward medical occurrence" that

- "Results in death
- Is life-threatening
- Requires hospitalization or prolongation of an existing inpatient hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality / birth defect
- Important medical events not captured by the above but which may, for example, require medical intervention to prevent one of the outcomes above."

SAE, controlled RMS Studies (Pool A)

This reviewer's analysis of the ISS ADAE dataset suggests that there were only 144 SAEs reported in the overall Safety Population of Pool A, and most of these only occurred in one subject. Although most of the subjects in the RMS Safety Population were in studies that utilized an active comparator, it is somewhat surprising that this analysis did not reveal any

SAEs in the 88 subjects who were randomized to placebo in Study RPC01-201A. The SAEs that occurred more than once in the RMS Safety Population (Pool A) are delineated in Table 8.

Table 8. Reviewer Table. SAEs occurring more than once in controlled RMS population (Pool A)

AEDECOD	IFN β -1a 30 mcg n=885	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Appendicitis	2	1	3	4
Ankle fracture	0	2	0	2
Atrial fibrillation	0	2	0	2
Cervical radiculopathy	0	2	0	2
Epilepsy	1	1	1	2
Hemorrhoids	0	2	0	2
Intervertebral disc disorder	1	0	2	2
Invasive breast carcinoma	0	1	1	2
Ovarian cyst	0	0	2	2
Renal colic	1	1	1	2
Sinus tachycardia	0	2	0	2
Syncope	0	1	1	2

Source: ISS ADAE where AESER='Y' and TREMFL1='Y' by AEDECOD and TRT01A.

Reviewer Comment: Percentages are not calculated in Table 8 because of the very low incidence of SAEs in the controlled RMS population, which is reassuring but complicates the identification of clear safety signals from background rates. The rates of appendicitis above are not clearly different between interferon β -1a and ozanimod, although the rates of this infection are noted to be somewhat higher with the S1P receptor modulators in the reviews of fingolimod and siponimod. Given the targets for (and the experience with) S1P receptor modulators, syncope, invasive breast carcinoma, and epilepsy from the list of SAEs in Table 8 are of interest.

Syncope

Since bradyarrhythmia are known to be associated with the initiation of S1P receptor modulators, the two cases of syncope are of interest, even though the Investigators deemed these events to be unrelated to the study medication.

- A 37yo female subject ((b) (6)) was randomized to ozanimod 1 mg daily and was hospitalized for syncope (“fainting”) on Study Day 260. According to the CSR, although this event was included within the category Cardiac: Bradycardia, the “sponsor determined that this case of syncope was not associated with

bradycardia.” No cause of this event was determined, and no treatment was given for it.

- A 49yo female subject ((b) (6)) was randomized to ozanimod 0.5mg daily and was hospitalized on Study Day 468 for syncope that was described as an “episode of fainting related to dehydration while gardening during hot weather.”

Reviewer Comment: Bradyarrhythmia associated with S1P receptor modulators are felt to occur soon after the initiation of the drug, making these cases less likely to be related to ozanimod. The second case has the additional confounder of dehydration.

Invasive Breast Carcinoma

Even though MS has a strong predilection for women, the two cases of invasive breast cancer are of interest because cutaneous malignancies and lymphoma have been noted with other S1P receptor modulators.

- Subject (b) (6) is a 51yo woman who was diagnosed with “invasive breast carcinoma” on Day 400 of Study RPC01-201B, in which she was randomized to ozanimod 1 mg daily. Her risk factors for breast cancer include a 32 year smoking history and one year of hormone replacement therapy; furthermore, her father had a history of esophageal cancer. She was initially treated with cyclophosphamide, doxorubicin, and dexamethasone and later had a radical modified mastectomy of her right breast.
- Subject (b) (6) is a 46yo woman who was diagnosed with “invasive breast cancer” on Day 469 of Study RPC01-301, in which she was randomized to ozanimod 0.5 mg daily. She did not have clear risk factors for breast cancer, and she completed the study on Day 490. She subsequently had a left mastectomy with axillary node dissection that did not show evidence of lymph node involvement, so she was started on tamoxifen.

Reviewer Comment: Although the Investigators considered the relationship of these events to the study drug to be unrelated and unlikely related, respectively, the role of siponimod cannot be ruled out in these cases, especially given the association of cutaneous malignancies and lymphoma with other S1P receptor modulators and the second subject’s lack of known risk factors for breast cancer.

Epilepsy

The two cases of epilepsy noted in subjects randomized to ozanimod in Table 8 are not surprising, as the risk of seizures is known to be elevated in people with MS.

- Subject (b) (6) was a 38yo gentleman with a history of epilepsy and affective disorder who was hospitalized with an epileptic seizure on Study Day 4. The seizure was described as tonic-clonic in semiology and associated with post-ictal weakness. Reportedly, there was no clear provoking factors for the seizure. The semiology of his prior seizures (including the occurrence of Todd's paralysis) was not included in the CSR.

Reviewer Comment: The role of ozanimod in this SAE is not clear, since this subject had a reported history of epilepsy; however, the close proximity of this AE to initiation of the study medication is notable and may suggest a role of the study drug.

- A 23yo man (Subject (b) (6)) who was randomized to ozanimod 1.0 mg daily was hospitalized for an epileptic seizure on Study Day 321. With the seizure, he had "loss of consciousness," head deviation, and convulsion of the whole body including the extremities. Reportedly, he did not have a history of seizure, and there were "no risk factors for seizures, such as trauma, alcohol, drugs or toxins, or metabolic disturbances." He was treated with midazolam, diazepam, ceftriaxone, and diclofenac. The subject was intubated for 20 hours, seemingly due to respiratory depression from the benzodiazepines. He was started on valproic acid and discharged from the hospital on Study day 321.

Reviewer Comment: The role of ozanimod in this seizure is not clear, since the risk of seizure in people with MS is greater than that in the general population and may be as high as 3-5%. The reported head deviation may suggest a structural lesion serving as an epileptic focus, and being treated with ceftriaxone may suggest an underlying infection that could lower his seizure threshold.

With the caveat that little can be gleaned from single events, this reviewer perused Pool A for any SAEs that occurred just once with ozanimod but were of interest. This revealed single reports of the following SAEs in subjects randomized to ozanimod: acute hepatitis B, basal cell carcinoma, breast cancer, cerebral infarction, fetal growth restriction, generalized tonic-clonic seizure, Guillain-Barre Syndrome, keratoacanthoma, malignant melanoma, medulloblastoma, pulmonary embolism, seizure, sinus bradycardia, spontaneous abortion, subdural hematoma, supraventricular tachycardia, and testicular seminoma. With the possible exceptions of seizure and malignancies, the coding of these SAE's does not suggest significant splitting into separate coding baskets or an obvious safety signal.

Seizure

- At screening, subject (b) (6) was a 44yo man who was randomized to ozanimod

0.5mg in Study RPC01-201B. On Study Day 198, he was hospitalized with a generalized tonic-clonic seizure of unknown duration. The narrative suggests that he had “moderate hydrocephalia,” choroid plexus cysts, and a “conditionally epileptic EEG” and that he was treated with carbamazepine and valproic acid.

- At screening, subject (b) (6) was a 23yo man with a history of epilepsy who was randomized to ozanimod 0.5mg in Study RPC01-201B. On Study Day 716, he was hospitalized for a seizure and “post-ictal pyrexia” and was treated with ceftriaxone. Reportedly, he failed to renew his prescription for valproate two days before this AE.

Reviewer Comment: The imaging results for subject (b) (6) suggest that a structural focus may have increased his risk of seizure, and the history of epilepsy and medication non-adherence (and possibly infection) confound interpretation of the role of ozanimod in the seizure experienced by subject (b) (6).

Malignancy

- At screening, subject (b) (6) was a 33yo woman who was randomized to ozanimod 0.5mg in Study RPC01-201B. On Study Day 365, she was hospitalized with an abnormal MRI showing a mass in the right cerebellar hemisphere that was eventually diagnosed as medulloblastoma. Upon review, the radiologist deemed that this mass was evident (but misconstrued as a demyelinating lesion) on an MRI that predated initiation of the study drug.
- At screening, subject (b) (6) was a 34yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-201B. On Study Day 225, she was diagnosed with malignant melanoma in situ on her left ankle. The narrative of this case suggest that a mole was present on her left ankle before randomization but that consultation with a surgical oncologist was not requested until after it was observed that the mole had increased in size. Histopathology of this lesion confirmed malignant melanoma in situ. Reportedly, the subject did not have any known risk factors for skin cancer.
- At screening, subject (b) (6) was a 31yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-301 and was diagnosed with a basal cell carcinoma (BCC) on her right upper back on Study Day 150. Reportedly, the subject “believed that the growth started as a raised itchy bump which appeared around the same time she started the study medication.”

Reviewer Comment: There is evidence to suggest that the onset of these three malignancies predated the initiation of ozanimod, minimizing the chances that the study drug played a causative role in the development of these events.

- At screening, subject (b) (6) was a 39yo man who was randomized to ozanimod 1 mg in Study RPC01-301. On Study Day 51, the subject was hospitalized with a right testicular tumor, the pathology of which revealed testicular seminoma (pure) stage I. Since the surgical margins were without neoplastic foci, the event was considered resolved without chemotherapy or radiation.

Reviewer Comment: Given the brief duration that the subject was on ozanimod before being diagnosed with testicular seminoma, it seems highly likely that this tumor preceded the initiation of the study drug. This reviewer notes that testicular cancer is the most common type of solid cancer in 15-44yo men and that testicular seminoma is the most common subtype of testicular cancer in the US (Trabert et al, 2015).

- At screening, subject (b) (6) was a 46yo woman who was randomized to ozanimod 1 mg in Study RPC01-201B. On Study Day 425, she was diagnosed with a tumor in the atrium of her left nasal cavity, for which the “microscopic picture may have been consistent with a keratocanthoma type lesion.”

Reviewer Comment: The seeming ambiguity of the pathology of this skin lesion limits its interpretability, although other epithelial malignancies (especially cutaneous malignancies) have been reported with other S1P receptor modulators.

SAE, uncontrolled RMS population (Study RPC01-3001)

Since Pool B contains events that occurred in both the controlled and uncontrolled RMS population, this reviewer chose to assess those events that occurred in the large uncontrolled study of ozanimod in RMS (RPC01-3001). Although the utility of a safety analysis of an uncontrolled population is obviously inferior to that of a controlled population, this analysis offers value in that it may inform subsequent analyses, including potential risks that become more apparent with an increased duration of exposure. This analysis yields 177 SAEs: Table 9 includes those SAEs that occurred more than once in Study RPC01-3001.

Table 9. Reviewer Table. SAEs occurring more than once with ozanimod in RPC01-3001

AEDECOD	Ozanimod 1 mg n=2494
Pyelonephritis acute	5 (0.2%)
Uterine leiomyoma	5 (0.2%)
Appendicitis	4 (0.2%)
Lower limb fracture	3 (0.1%)

AEDECOD	Ozanimod 1 mg n=2494
Pneumonia	3 (0.1%)
Abdominal hernia	2 (0.1%)
Bronchitis	2 (0.1%)
Cervical dysplasia	2 (0.1%)
Craniocerebral injury	2 (0.1%)
Epilepsy	2 (0.1%)
Hemarthrosis	2 (0.1%)
Headache	2 (0.1%)
Intentional overdose	2 (0.1%)
Lumbar spinal stenosis	2 (0.1%)
Lumbar vertebral fracture	2 (0.1%)
Lyme disease	2 (0.1%)
Lymphadenitis	2 (0.1%)
Melanocytic nevus	2 (0.1%)
Menometrorrhagia	2 (0.1%)
Pleurisy	2 (0.1%)
Seizure	2 (0.1%)
Spinal osteoarthritis	2 (0.1%)
Type 2 diabetes mellitus	2 (0.1%)
Uterine hemorrhage	2 (0.1%)
Vaginal hemorrhage	2 (0.1%)
Varicose vein	2 (0.1%)
Visual impairment	2 (0.1%)

Source: ISS ADAE where STUDY='RECRPC013001,' AESER='Y,' and TREMFL3='Y' by AEDECOD and TRTA.

Reviewer Comment: The incidence of SAEs is again very low in the open-label extension of the ozanimod RMS studies, but the list is highlighted by several types of infection, including pyelonephritis, appendicitis, pneumonia, and bronchitis. Given the presumed mechanism of action of ozanimod (sequestration of circulating lymphocytes in secondary lymphoid tissue) and the experience with other S1P receptor modulators, infections are not unexpected and are an adverse event of special interest (AESI) with ozanimod. Little information is provided in the narratives for the cases of uterine and vaginal bleeding, except that the SAE in Subject (b) (6) occurred after removal of an intrauterine device (IUD).

Of the remaining SAEs, the four seizure / epilepsy events (in three subjects) are of interest, especially given the number of similar SAEs in the controlled ozanimod RMS population and the experience with other S1P receptor modulators.

Seizure / Epilepsy

Four SAEs of seizure or epilepsy were reported in three subjects in Study RPC01-3001.

- A 39yo woman (Subject (b) (6)) developed a high fever from bronchitis and was hospitalized on Day 531 of Study RPC01-3001 with “epilepsy.” Reportedly, an electroencephalogram (EEG) showed “frequent bursts of sharpened alpha and theta rhythm and frequent complexes acute-slow waves.” The subject was treated with diazepam and valproate.
- Another 39yo woman (Subject (b) (6)) developed a “series of epileptic seizures” on Study Day 164 of the ozanimod open-label extension (RPC01-3001). Reportedly, there were no triggering factors for this event. She was treated with diazepam, and an EEG on Study Day 167 was reportedly normal.
- A 51yo woman (Subject (b) (6)) experienced a seizure on Day 568 of Study RPC01-3001 in the setting of severe hypertension (224/105 mm Hg) and a urinary tract infection. She was treated with midazolam and levetiracetam. It seems that she did not continue levetiracetam after this hospitalization, and she had a 2nd seizure on Study Day 592.

Reviewer Comment: The role of ozanimod in these epilepsy / seizure SAEs is not clear, since the risk of seizure in people with MS is greater than the general population and may be as high as 3-5%. Two of these cases had features (high fever, accelerated hypertension) that could lower the seizure threshold.

Similar to what was done with Pool A, this reviewer perused RPC01-3001 for other notable SAEs in the RPC3001 extension study. Single SAEs of interest include myocardial ischemia, breast cancer, cerebrovascular accident, cholecystitis (one acute and one chronic), clear cell renal carcinoma, hemorrhagic cystitis, gastrointestinal hemorrhage, glioblastoma, ischemic stroke, malignant melanoma, metastasis, pancreatic carcinoma, acute pancreatitis, papillary thyroid cancer, pulmonary embolism, pyelonephritis, status epilepticus, and thrombocytopenia. The case of status epilepticus occurred in a subject with epilepsy in the setting of missed anticonvulsant doses and fasting.

Reviewer Comment: Although it is difficult to make conclusions from uncontrolled data, there does not appear to be an obvious safety signal or excessive “splitting” of the SAEs in this analysis. Although the cases of hemorrhagic cystitis and gastrointestinal hemorrhage may appear to be related, the former was likely in the setting of a UTI (treated with ceftriaxone, norfloxacin, and tamsulosin), and the later was in a subject with gastroesophageal reflux who was taking ibuprofen and had recently received methylprednisolone for an MS relapse. The case of thrombocytopenia (platelet count of

10, units not provided) did not recur with resuming ozanimod, making the relationship of this SAE to the study medication unlikely. The SAEs for thromboembolic disease and several different types of cancer noted in this population are of interest and are explored below.

Thromboembolic disease

The pulmonary embolism SAE occurred after surgical intervention for a leg fracture that was sustained when Subject (b) (6) was hit with a car; since this case was fatal, it is described in Section 8.4.1 but was not deemed to be related to the study medication. The other three thromboembolic SAEs reported in Study RPC01-3001 follow below:

- At screening, Subject (b) (6) was a 45yo woman with a history of hypertension and use of an oral contraceptive who was randomized to interferon β -1a in Study RPC01-301 and transitioned to ozanimod 1mg in the RPC01-3001 open label extension. On Day 106 of Study RPC01-3001, she was hospitalized for myocardial ischemia and diagnosed with ischemic heart disease, coronary atherosclerosis, and grade 2 hypertension. She was treated with aspirin, clopidogrel, metoprolol, enalapril, spironolactone, and simvastatin. The study medication was continued.
- At screening, Subject (b) (6) was a 55yo woman with a history of hypertension and a “lupus-like syndrome” who was randomized to interferon β -1a in Study RPC01-301 and transitioned to ozanimod 1 mg in the RPC01-3001 open label extension. On Day 337 of Study RPC01-3001, she was hospitalized for an ischemic stroke. Her exam was consistent with bilateral upper motor neuron lesions. A head CT showed “hypodense foci in the white matter of both cerebral hemispheres considered to have occurred at various time points and to be angiogenic,” and a brain MRI showed “demyelinating lesions with no signs of disease activity, some more foci than in the previous scan, with suspected overlapping of individual acute angiogenic lesions.”
- At screening, subject (b) (6) was a 44yo woman who was randomized to ozanimod 1 mg in Study RPC01-201B and remained on this dose in the RPC01-3001 open label extension. On Day 425 of Study RPC01-3001, she was hospitalized for acute right hemiparesis, speech disturbance, and a blood pressure of 170/90 mmHg. She was diagnosed with an ischemic stroke, although her MRI “showed absence of any acute lesion with related to MS.” The study medication was stopped, and she started aspirin and enalapril.

Reviewer Comment: All three of these thromboembolic events appear to have at least hypertension as a preceding risk factor. The narrative for Subject (b) (6)

is not convincing for an acute stroke, and the narratives for Subjects (b) (6) and (b) (6) do not describe MRI findings to support a diagnosis of stroke.

Malignancy

The subjects with metastasis (Subject (b) (6)) and pancreatic carcinoma (Subject (b) (6)) were fatal and are described in Section 8.4.1. Details of the other cases of malignancy in Study RPC01-3001 follow:

- At screening, Subject (b) (6) was a 42yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-201B and transitioned to ozanimod 1 mg in the RPC01-3001 open label extension. On Day 200 of Study RPC01-3001, she was hospitalized with cancer of the left breast (infiltrative moderately differentiated breast cancer without lymphoid infiltration). The subject discontinued the study and started chemotherapy. Although the narrative does not discuss the subject's risk factors for breast cancer, the study datasets suggest that she was a nonsmoker but was taking an oral contraceptive.
- At screening, Subject (b) (6) was a 46yo woman who was randomized to ozanimod 0.5mg in Study RPC01-201A but transitioned to ozanimod 1 mg in the RPC01-3001 open-label extension. Soon after transitioning to Study RPC01-3001, she was hospitalized with renal clear cell carcinoma, for which the left kidney was removed with clear surgical margins and chemotherapy was planned. Reportedly, the subject did not have a family history of malignancy or a personal history of radiation exposure, sun exposure, or pre-malignant lesions.
- At screening, Subject (b) (6) was a 54yo woman who was randomized to ozanimod 1mg in Study RPC01-201B and remained on ozanimod 1mg in the RPC01-3001 open-label extension. On Day 126 of Study RPC01-3001, she was hospitalized with a tumor of the left temporal lobe that was diagnosed as a glioblastoma, which was treated with surgical resection, radiation, and temozolomide. The study medication was stopped. Reportedly, the subject's mother had a history of breast cancer.
- At screening, Subject (b) (6) was a 51yo man who was randomized to ozanimod 1 mg in Study RPC01-201B and remained on this dose in the RPC01-3001 open-label extension. On Day 520 of Study RPC01-3001, he was diagnosed with a melanocytic nevus on his right trunk. Histopathology was consistent with malignant melanoma, which was treated with surgery. Reportedly, the subject did not have risk factors for skin cancer.

- At screening, Subject (b) (6) was a 40yo woman with an approximately five year history of thyroid nodules and hypothyroidism who was randomized to ozanimod 1mg in Study RPC01-201A and remained on this dose of ozanimod in the 201A blinded extension and the RPC01-3001 open label extension. On Day 242 of Study RPC01-3001, she had a biopsy of her thyroid gland that revealed papillary thyroid carcinoma of her right thyroid lobe, which was subsequently surgically resected (with the isthmus). The study medication was temporarily held, and the Investigator considered this event to be unrelated to ozanimod.

Reviewer Comment: Although malignancies (especially cutaneous malignancies) have been reported with other S1P receptor modulators, there is not a clear pattern to the malignancies reported in Study RPC01-3001.

There was also an extension to the placebo-controlled RPC01-201A study, although some of these subjects subsequently rolled into the larger RPC01-3001 extension study. This blinded extension study had 249 subjects, and the analysis of its ADAE dataset (where APERIODC='Extension') reveals 22 SAEs (AESER='Y'). SAEs of interest in this analysis include single reports of anterior communicating artery aneurysm (reported twice by the same subject), acute myocardial infarction in a 43yo woman with a history of hypertension, rheumatoid arthritis in a 46yo man with a history of rheumatoid arthritis, mild pancytopenia in a 43yo woman with borderline vitamin B12 deficiency, and a 39yo woman (Subject (b) (6), described elsewhere in this review) who developed "hepatitis," seemingly autoimmune, after exposure to numerous bee stings.

SAE, IBD Population (Pool C)

Although the demographics and characteristics of a population with IBD will be quite different from those in an RMS population, a similar analysis of SAEs is performed in the 654 subjects (645 of whom received at least one dose of ozanimod 1 mg) in the population with inflammatory bowel disease (Pool C), especially because the number of SAEs was notably low in the RMS population. This analysis yielded 97 SAEs, and those occurring more than once in the IBD ozanimod safety population are shown in Table 10.

Table 10. SAEs occurring more than once with ozanimod in the IBD safety population (Pool C)

AEDECOD	Overall Ozanimod N=654
Colitis ulcerative	15 (2.3%)
Crohn's disease	6 (0.9%)
Intestinal obstruction	6 (0.9%)
Anemia	4 (0.6%)

AEDECOD	Overall Ozanimod N=654
Colitis	4 (0.6%)
Dehydration	3 (0.5%)
Abdominal abscess	2 (0.3%)
Colon adenoma	2 (0.3%)
Parkinsonism	2 (0.3%)
Pulmonary bulla	2 (0.3%)
Small intestinal obstruction	2 (0.3%)

Source: ISS ADAE where 'AESER='Y' and TREMFL4='Y' by AEDECOD and TRTA.

Perusal of interesting SAEs reported only once in Pool C revealed single reports of fatal adenocarcinoma (Subject (b) (6) described above), pancreatic adenocarcinoma, prostate carcinoma, rectal cancer, and basal cell carcinoma. Single reports of acute coronary syndrome, ischemic stroke, and pulmonary microemboli are also noted. There was also one SAE of abnormal LFTs.

Reviewer Comment: Although this reviewer is not an expert in inflammatory bowel disease, many of the SAEs in the analysis from which Table 10 is generated appear more attributable to the disease process than ozanimod. Single cases of several different malignancies are noted in this analysis, although it should be recognized that UC can increase the risk of adenocarcinoma. There was one SAE of rheumatoid arthritis, but the limited narrative for this SAE suggests worsening of a pre-existing condition. The SAEs of thromboembolism and that of abnormal LFTs of interest.

Thromboembolism:

- At screening, Subject (b) (6) was a 54yo man with a history of hypertension and ulcerative colitis who was randomized to placebo in the Induction Period of Study RPC01-202 and transitioned to ozanimod 1mg in the open-label phase (OLP) of the study. On Day 193 of the OLP, he developed chest pain and was hospitalized for acute coronary syndrome and was found to have an occluded left anterior descending (LAD) artery, for which he had angioplasty and deployment of a drug-eluting stent. The Investigator considered the relationship of this event to the study medication to be unlikely.
- At screening, Subject (b) (6) was a 63yo woman with a history of hypertension, chronic obstructive pulmonary disease (COPD), and ulcerative colitis who was randomized to ozanimod 0.5 mg in the Induction Period of Study RPC01-202 and transitioned to ozanimod 1 mg in the OLP of the study. On OLP Day 648, she was hospitalized for evaluation of bowel disease and elevations of blood urea nitrogen

(BUN) and serum creatinine. On Study Day 655, she developed “severe hypotension,” oligoanuria, and an elevated temperature after a colonoscopy and endoscopy. Her D-dimer was elevated at 630 (reference range < 255), and a scintigraphic lung evaluation showed multiple subsegmental avascular alterations suggestive of pulmonary microemboli. Treatments included dopamine, ceftriaxone, nadroparin, heparin, furosemide, and metronidazole. The Investigator considered this event to be unrelated to the study drug.

- At screening, Subject (b) (6) was a 48yo woman with a history of ulcerative colitis who was randomized to ozanimod 0.5 mg in the Induction Period of Study RPC01-202 and transitioned to ozanimod 1mg in the OLP of the study. On OLP Day 1308, she was hospitalized with an ischemic stroke, the details of which are not provided in the narrative. The Investigator considered this event to be unrelated to the study medication.

Reviewer Comment: The history of hypertension and the relatively short duration of exposure to ozanimod before the onset of symptoms from an occluded LAD coronary artery suggest that the first subject had pre-existing coronary artery disease, and the temporal correlation of the pulmonary microemboli with a prolonged hospitalization suggest an alternative explanation for the microemboli. Although the long duration of exposure to ozanimod before the ischemic stroke may suggest a possible association between the event and the study drug, the absence of details regarding this event limit analysis of this SAE.

Abnormal LFTs:

- At screening, Subject (b) (6) was a 30yo woman with a history of ulcerative colitis who was randomized to ozanimod 1mg in Study RPC01-3102. On Study Day 101, she developed elevated LFTs. Since her LFTs continued to increase (ALT 218 U/L, AST 300 U/L, ALP 254 U/L, and GGT 275 U/L), she was hospitalized on Study Day 135. Of note, she had worsening ulcerative colitis during this time; however, her LFTs improved with cessation of the study medication.

Reviewer Comment: This reviewer agrees with the Investigator that the relationship of this event to the study medication seems probable, although the concomitant worsening of her UC is confounding.

Healthy Volunteers (Pool E)

Two SAEs were reported by the 496 healthy volunteers in the safety population of the clinical pharmacology studies (Pool E). One of these was a food allergy, and the other was a bronchioalveolar carcinoma that was deemed to be pre-existing at screening; neither appears to be related to the study drug.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

If subjects wished to discontinue the study medication, they were encouraged to continue to be followed in the study but obviously were free to discontinue from the study as well.

Investigators could withdraw subjects from the protocol for several reasons, including an opinion that it was not safe for the subject to continue the study medication, poor subject adherence, the development of an intercurrent illness, or for special events (confirmed AST or ALT > 5x ULN, macular edema, FEV1 or FVC < 50% of predicted, pregnancy).

AEs leading to study discontinuation, controlled RMS studies (Pool A)

This reviewer’s analysis of the ISS ADAE dataset only revealed 100 events that lead to study discontinuation in the controlled RMS Safety Population (Pool A), and most of these only occurred in one subject. Only two AEs leading to discontinuation (anxiety disorder, blood cholesterol increased) occurred in the interferon β-1a arm, and only one (weight increased) occurred in a subject randomized to placebo. Some of these AEs leading to study discontinuation are also noted in the section on SAEs. Table 11 delineates those adverse events leading to discontinuation that occurred more than once with ozanimod.

Table 11. Reviewer Table. AE’s leading to study discontinuation in the controlled RMS population (Pool A)

AEDECOD	IFN β-1a 30 mcg n=885	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
ALT increased	0	2	3	5
AST increased	0	1	3	4
GGT increased	0	1	3	4
Liver function test abnormal	0	2	1	3
Urticaria	0	1	2	3
Back pain	0	0	2	2
Blood bilirubin increased	0	1	1	2
Bradycardia	0	2	0	2
Cystoid macular edema	0	2	0	2
Headache	0	0	2	2
Insomnia	0	2	0	2
Macular edema	0	1	1	2
Supraventricular tachycardia	0	0	2	2

Source: ISS ADAE where AESTFL='Y' and TREMFL1='Y' by AEDECOD and TRT01A.

Overall, the rate of AEs leading to study discontinuation in Pool A of the ozanimod development program appears very low, complicating the identification of clear safety

signals. Although the overall incidence of transaminase elevation is low, the splitting of this AE into different codes minimizes the impact of this potential signal, which occurred in 14 subjects. Given the experience with other S1P receptor modulators, bradycardia and macular edema are of interest and are also described below.

Transaminase Elevations

- At screening, Subject (b) (6) was a 28yo woman at screening who was randomized to ozanimod 0.5 mg in Study RPC01-201B despite an elevated total bilirubin of 27.2 umol/L at screening. On Study Day 187, she experienced asymptomatic elevations of ALT (179 U/L), AST (81 U/L), and TB (30.1 umol/L), so the study medication was stopped on Study Day 194. On Study Day 197, her ALT and TB were even higher at 223 U/L and 42.8 umol/L. Her history was unrevealing for exposures that might explain these transaminase elevations, and her abdominal ultrasound was likewise unrevealing. Her transaminase elevations improved, and the event was considered resolved on Study Day 278. As her total bilirubin was elevated at baseline, an external expert hepatic panel judged that this AE does not represent a Hy's law case.
- At screening, Subject (b) (6) was a 43yo man who was randomized to ozanimod 1 mg in Study RPC01-301 despite having a mild elevation in total bilirubin (20.9 umol/L) at screening. After a mild ALT elevation (48 U/L) and a further increase in his total bilirubin (26.3 umol/L), the study medication was discontinued.
- At screening, Subject (b) (6) was a 35yo woman who was randomized to ozanimod 1mg in Study RPC01-201B despite an elevated total bilirubin (26.5 umol/L) at screening. On Study Day 551, she developed a mild elevation in her total (20.2 umol/L) and direct (11.3 umol/L) bilirubin and moderate elevations in her ALT (7x ULN at 249 U/L) and AST (2x ULN at 97 U/L). The subject was unaware of exposures that might have caused these asymptomatic laboratory changes. The study medication was discontinued on Study Day 553, and the transaminase elevations rapidly improved and were considered resolved on Study Day 561. The Investigator considered the relationship of the event to the study medication probable.

Reviewer Comment: As these cases had total bilirubin elevations at baseline, this reviewer agrees that they do not represent Hy's law cases of drug-induced-liver-injury (DILI).

- At screening, subject (b) (6) was a 52yo woman who was randomized to ozanimod 1 mg in Study RPC01-201B. On Study Day 639, she was noted to have laboratory evidence of an asymptomatic liver injury, including an ALT of 303 U/L, an AST of 181 U/L, and an ALP of 217 U/L; even more concerning was a total bilirubin

elevation of 62.1 umol/L. On Study Day 658, her AST and ALT peaked to 482 U/L and 376 U/L, respectively. Testing for autoantibodies and hepatitis and CMV serologies was unrevealing, but an ultrasound was reportedly not performed. The study medication was not stopped until Study Day 662, after which her laboratory abnormalities quickly normalized (TB 9.1 umol/L on Study Day 662, AST 20 U/L on Study Day 667, AST 58 U/L on Study Day 667 and 30 U/L on Study Day 700). In part because of the rapid improvement in AST, ALT, and TB elevations with cessation of the study medication and the concomitant ALP elevation, an external panel considered these abnormalities in the case to be more likely reflective of biliary pathology than DILI.

Reviewer Comment: This reviewer agrees that the abnormalities in this case are suggestive of biliary pathology and less likely to represent a Hy's law case of DILI.

- At screening, subject (b) (6) was a 43yo man who was randomized to ozanimod in Study RPC01-201B and experienced transaminase elevations (ALT >3x ULN at 150 U/L with minor AST [98 U/L], ALP [134 U/L], and GGT [111 U/L] increases) on Study Day 92; however, his total bilirubin remained normal. As his transaminases remained elevated on Study Day 106, the study medication was discontinued even though he was asymptomatic and had a normal liver ultrasound. The transaminase elevations were much improved on Study Day 133 and resolved on Study Day 174.
- At screening, subject (b) (6) was a 53yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-201B (despite having an GGT elevation of 3x ULN) and was noted to have mild elevations in ALT and ALP but a higher GGT elevation (11x ULN) on Study Day 96. The study medication was stopped on Study Day 140, when she was noted to have an ALT elevation of 3x ULN but a normal total bilirubin. Her ALT normalized, and her GGT was improved on Study Day 160.
- At screening, subject (b) (6) was a 21yo man who was randomized to ozanimod 1 mg in Study RPC01-301 but developed an asymptomatic increase in ALT (>3x ULN at 128 U/L) and AST (49 U/L) on Study Day 272. Although his total bilirubin remained normal, his transaminases increased to 174 U/L and 65 U/L, respectively, so the study medication was stopped on Study Day 333 after which his transaminase elevations improved and were considered resolved on Study Day 351. He denied obvious exposures to explain his transaminase elevations, and liver imaging was not performed.
- At screening, subject (b) (6) was a 31yo man who was randomized to ozanimod 1 mg in Study RPC01-201B despite a mildly elevated ALT (49 U/L) at screening but not baseline. On Study Day 105, the subject experienced asymptomatic ALT (>5x ULN at

305 U/L), AST (94 U/L), and GGT (>3x ULN at 216 U/L) elevations, but his total bilirubin remained normal. His liver ultrasound were normal, and hepatitis B and C serologies were negative. The study medication was discontinued on Study Day 113, and the event was considered resolved on Study Day 280.

- At screening, subject (b) (6) was a 28yo man who was randomized to ozanimod 1 mg in Study RPC01-201B despite having an elevated AST at baseline (>3x ULN at 195 U/L). His ALT was higher on Study Day 4 (252 U/L), and the study medication was stopped on Study Day 8. His total bilirubin remained normal.
- At screening, subject (b) (6) was a 34yo woman who was randomized to ozanimod 1mg in Study RPC01-201B but was noted to have an elevated GGT (>6x ULN at 193 U/L) on Study Day 183. Her GGT remained elevated, but her other hepatic transaminases were essentially normal until Study Day 457, when she was noted to have mild ALT (2x ULN at 85 U/L) and AST (41 U/L) elevations. The study medication was stopped on Study Day 460, and the event was considered resolved on Study Day 501. The subject denied recent exposures that would explain her transaminase elevation.
- At screening, Subject (b) (6) was a 54yo woman who was randomized to ozanimod 1 mg in Study RPC01-301. On Study Day 140, although she was asymptomatic, she was deemed to have “toxic hepatitis” based on an ALT of 314 U/L., and AST of 92 U/L, and a GGT 627 U/L. Her total bilirubin remain normal. Of note, she was treated with methylprednisolone for an MS relapse on Study Day 120. Hepatitis C serologies were negative. An abdominal ultrasound showed that her gallbladder had a deformed body neck, a thickened wall, and biliary sediment; further, her liver was increased in size with increased echogenicity, reportedly consistent with fatty hepatosis. The study medication was eventually stopped, and the subject later disclosed the use of two prohibited medications (an herbal extract with phenobarbital and ketorolac).
- At screening, subject (b) (6) was a 37yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-301. On Study Day 91, she was noted to have moderate transaminase elevations (ALT 490 U/L, AST 250 U/L, GGT 227 U/L), so the study medication was discontinued. Her total bilirubin remain normal during this event. The work-up of this AE, including screening for exposures that could precipitate this event, an abdominal ultrasound, and serologies (hepatitis and HIV), was unremarkable. The event was considered recovered, albeit with persistent mild transaminase elevations, on Study Day 120, and the Investigator deemed that the relationship of this event to the study medication was probable.

Clinical Review

David E. Jones, M.D.

NDA 209899

Zeposia (ozanimod)

- At screening, subject (b) (6) was a 25yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-201B. After several self-limited episodes of mild LFT (primarily GGT) abnormalities, she was found to have an ALT >3x ULN (124 U/L), an elevated AST (71 U/L), and a peak GGT of 588 U/L (>12x ULN). Her AST peaked at 300 U/L and AST at 141 U/L on Study Day 567, but her total bilirubin remained normal. The subject denied exposures to explain these transaminase elevations, and an ultrasound revealed no abnormalities. The study medication was discontinued on Study Day 569, and her ALT and AST rapidly improved. The Investigator considered the relationship of this event to the study medication possible.
- At screening, subject (b) (6) was a 29yo man who was randomized to ozanimod 1mg in Study RPC01-301 and developed asymptomatic abnormal liver function tests (ALT >3x ULN at 130 U/L, AST elevated at 62 U/L) on Study Day 15. His ALT and AST peaked at 203 and 87 U/L, respectively on Study Day 27, so the study medication was discontinued on Study Day 43. His total bilirubin remained normal throughout the Study, and his transaminases were noted to have normalized on Study Day 118.

Reviewer Comment: Although there does not appear to be any Hy's law cases suggestive of DILI in these 14 cases, it appears that ozanimod, like other S1P receptor modulators, can be associated with transaminase elevations suggestive of mild to moderate but seemingly reversible hepatic injury.

Bradycardia

Two subjects stopped the study medication after experiencing bradycardia soon after beginning ozanimod.

- A 24yo woman (Subject (b) (6)) was randomized to ozanimod 0.5 mg in Study RPC01-201B. She was admitted for extended cardiac monitoring on Day 1 of the study since her heart rate six hours post dose was lower than her baseline. Reportedly, she had bradycardia again on Study Day 5 (58 bpm) and Study Day 8 (heart rate not reported), so she discontinued the study medication. Of note, she reportedly had a HR of 53 on Study Day 71, over 2 months after stopping the study medication.
- A 29yo man (Subject (b) (6)) with a reported history of atrial fibrillation was randomized to ozanimod 0.5 mg and developed bradycardia on Day 1 of Study RPC01-301. As his heart rate at Hour 6 was lower than his baseline (64 bpm), he was admitted for extended cardiac monitoring. His heart rate nadir (53 bpm) occurred seven hours after he received his first dose of ozanimod (0.25 mg), and his ECG demonstrated a short PR interval (<120 msec). Although these events were asymptomatic, he dropped out of the study due to this AE.

Reviewer Comment: As subject (b) (6) had bradycardia two months after stopping the study medication, it is difficult to fully attribute her bradycardia to ozanimod. As his baseline heart rate was 64 bpm, it is not entirely clear to this reviewer why Subject (b) (6) dropped out of Study RPC01-301 with a heart rate of 53 bpm after taking the first dose of ozanimod. Neither of these cases is particularly concerning for a serious bradycardia signal with ozanimod.

Macular Edema

Four subjects stopped the study medication after developing macular edema while taking ozanimod.

- A 38yo man (Subject (b) (6)) with a history of myopia was randomized to ozanimod 0.5mg in Study RPC01-201B and was found to have macular edema and central serous choroidopathy in his left eye on Study Day 366. Reportedly, the subject was initially asymptomatic, but his visual acuity and optical coherence tomography (OCT) results were abnormal. He was treated with “vitrealent plus and methylethylpiridinol,” but he developed visual symptoms, and his OCT remained abnormal with evidence of macular edema in his left eye. Per the narrative, the “Macular Edema Review Panel evaluated the OCT findings as consistent with a central serous choroidopathy, which is an independent mechanism for macular edema but has not been associated with S1P agents.”
- A 37yo woman (Subject (b) (6)) with a reported history of visual disturbance, cataracts, and macular edema was randomized to ozanimod 0.5 mg in Study RPC01-201B and was diagnosed with cystoid macular edema of the left eye on Study Day 211. Reportedly, she was asymptomatic at the time, so the diagnosis was made after she was found to have abnormal visual acuity (and an abnormal OCT) during a regular visit. There was no evidence of central serous chorioretinopathy. The study medication was discontinued on Day 212, and reportedly subsequent OCT findings were improved. The Macular Edema Review Panel (MERP) noted that her screening evaluation revealed a left epiretinal membrane, suggestive of a history of macular edema and increasing her risk of cystoid macular edema.
- A 41yo woman (Subject (b) (6)) with a history of optic neuritis and retinal fibrosis was randomized to ozanimod 1 mg in Study RPC01-301 and was diagnosed with macular edema of the right eye on Day 183 of the study. Reportedly, she was asymptomatic and did not have a history of diabetes mellitus or uveitis. The MERP concurred with the diagnosis of macular edema but noted posterior synechiae and epiretinal membrane changes suggestive of

prior ocular inflammation, which may have increased her risk for developing macular edema.

- A 50yo woman (Subject (b) (6)) who was randomized to ozanimod 0.5mg in Study RPC01-301 injured her left eye (traumatic contusion, hyphema, and lens subluxation) with a piece of coat zipper on Day 22 of the study. She was subsequently diagnosed with cystic macular edema of the left eye on Study Day 182. The MERP concurred with the diagnosis of macular edema and felt that this was likely attributable to the prior eye trauma but could not rule out an effect of the study drug.

Reviewer Comment: All four of these cases of macular edema may have potentially confounding factors, especially the cases with a history of macular edema, a probable history of uveitis, and a history of eye trauma. With that caveat, macular edema is a known complication of other S1P receptor modulators.

AEs leading to study discontinuation, uncontrolled RMS population (Study RPC01-3001)

Although an analysis of an uncontrolled OLE population is of less utility than one of a controlled population, this reviewer's analysis of the ADAE dataset suggests that the only AE leading to study termination (AESTFL='Y') occurring more than once in Study RPC01-3001 was macular edema, which was reported twice. As before, cases of macular edema are of interest and are explored further in Section 8.5.

- A 32yo man (Subject (b) (6)) was randomized to interferon β -1a in Study RPC01-301 and transitioned to ozanimod 1 mg in Study RPC01-3001. Although his ophthalmological screening examinations were reportedly normal, the subject experienced decreased vision of the left eye on Day 15 of Study RPC01-3001, and a diagnosis of macular edema was made based on abnormalities of his visual acuity assessment and OCT. The study medication was discontinued on Day 20, and the event was considered recovered / resolved on Day 84. The Macular Edema Review Panel (MERP) concurred with the diagnosis of cystic macular edema but noted evidence of a pre-existing uveitis (cells in the vitreous) on his screening OCT.
- At screening, Subject (b) (6) was a 29yo woman who was randomized to interferon β -1a in Study RPC01-301 and transitioned to ozanimod 1 mg in Study RPC01-3001. At screening, she had abnormal (increased) central foveal thickness bilaterally without evidence of macular edema; however, she was noted to have bilateral macular edema on Day 279 of Study RPC01-3001. Even though she was asymptomatic, the study medication was stopped on Study Day 301 and this AE eventually was classified as recovered / resolved on Study RPC01-3001 Day 365. The

MERP opined that the right eye was normal and that the subject was predisposed to cystic macular edema of the left eye by a previously noted epiretinal membrane.

Reviewer Comment: Both of these cases of macular edema have features that may confound the relationship with ozanimod, including pre-existing uveitis and a pre-existing epiretinal membrane, respectively.

Additional study discontinuations of interest in Study RPC01-3001 that have not previously been discussed include the following:

Malignancy

- At screening, Subject (b) (6) was a 42yo woman with a strong family history of cancer (father died of stomach cancer, sister had endometrial cancer, and brother had renal cell carcinoma) who was randomized to interferon β -1a in Study RPC01-301 and transitioned to ozanimod 1 mg in the RPC01-3001 OLE. On Day 772 of Study RPC01-3001, she was hospitalized due to a pulmonary and a renal mass. Since she withdrew consent and refused further contact on Day 777, further information about this case is unavailable.
- At screening, Subject (b) (6) was a 51yo man who was randomized to ozanimod 1 mg in Study RPC01-201B and remained on ozanimod 1 mg in the RPC01-3001 OLE. On Study Day 520, he was hospitalized for a melanocytic nevus on his right trunk; because histopathology showed evidence of lymph node metastasis, he was diagnosed with malignant melanoma. Reportedly, the subject did not have risk factors for melanoma. He was withdrawn from Study RPC-3001 on Day 655.
- At screening, Subject (b) (6) was a 55yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-201B and transitioned to ozanimod 1 mg in the RPC01-3001 open label extension. On Day 756 of Study RPC01-3001, she was diagnosed with a left breast neoplasm, of which a core needle biopsy showed invasive breast cancer. The subject was withdrawn from the study on Day 814.

Reviewer Comment: The woman was pulmonary and renal masses had a strong family history of malignancy, but the other two cases of malignancy may be related to the use of ozanimod.

Macular edema

- At screening, Subject (b) (6) was a 42yo woman who was randomized to ozanimod 1 mg in Study RPC01-201A. She remained on ozanimod 1 mg in the RPC01-201A and then the RPC01-3001 open label extension. On Day 719 of Study RPC01-3001, she was found to have “macular pigment.” She was diagnosed with

macular edema in her left eye on Day 813 given abnormal visual acuity testing and an abnormal OCT showing increased foveal thickness in that eye. She withdrew from Study RPC01-3001 on Day 902. The Macular Edema Review Panel deemed that she likely had choroid serous retinopathy and not macular edema.

Study Discontinuation, IBD Population (Pool C)

This reviewer identified forty-seven AEs leading to study discontinuation that occurred in the IBD population (Pool C), some of which are also noted as SAEs. Those AEs leading to study discontinuation and occurring more than once are delineated in Table 12.

Table 12. Reviewer Table. AEs leading to study discontinuation in the IBD population (Pool C)

AEDECOD	Ozanimod 0.5 mg n=65	Ozanimod 1 mg n=645	Overall Ozanimod n=654
Colitis ulcerative	0	9 (1.4%)	9 (1.4%)
Crohn's disease	0	6 (0.9%)	6 (0.9%)
Herpes zoster	0	2 (0.3%)	2 (0.3%)

Source: ISS ADAE where AESTFL='Y' and TREMFL4='Y' by AEDECOD and TRTA.

Single reports of adenocarcinoma, pancreatic cancer, and rectal cancer are noted in this analysis. In addition to the two reports of herpes zoster, single cases of Campylobacter and Staphylococcal infection are also noted. Other single reports of interest include ALT elevation, hyperbilirubinemia, decreased lymphocyte count, first degree AV block, sinus bradycardia, and cystoid macular edema.

Reviewer Comment: Many of the AEs leading to study discontinuation in the IBD study population appear attributable to the underlying disease. Two cases of herpes zoster are noted, and infections are an adverse event of special interest (AESI) with ozanimod. The single AEs leading to study discontinuation that are of interest appear congruent with risks already identified with ozanimod in this review and with other S1P receptor modulators.

Study Discontinuation, Healthy Volunteers (Pool E)

There were four TEAE leading to study discontinuation reported by the 496 healthy volunteers in the clinical pharmacology studies of ozanimod (Pool E). Three of these were hepatic transaminase elevations, of which two were considered mild and one was considered moderate. There was also a case of second degree atrioventricular block:

- As part of a drug interaction study, a reportedly healthy 27yo black woman (Subject (b) (6)) received a 1mg dose of ozanimod after an overnight fast. Her ECGs

between 8 and 17 hours after administration of the study medication “varied between first degree heart block, type 1 second degree heart block, and 2:1 second degree atrioventricular block with junctional escape beats.” Reportedly, her HR nadir was 44 bpm, but she was asymptomatic and hemodynamically stable during this event. The subject remained in the clinical study until Study Day 6 but was not treated with rifampin or a subsequent dose of ozanimod as outlined by the study protocol.

Reviewer Comment: Atrioventricular block is a known potential adverse event with S1P receptor modulators like ozanimod; of note, an ozanimod titration was not utilized in this early clinical pharmacology trial.

Study Drug Discontinuation, Controlled RMS Studies (Pool A)

It is appropriate to encourage subjects who wish to stop the study drug to remain in the study, so in addition to AEs leading to discontinuation from the study, AEs leading to discontinuation of the study treatment are also of interest. Review of the ISS ADAE dataset suggests that not all AEs leading to withdrawal of the study drug (AEACN='DRUG WITHDRAWN') led to discontinuation of the study (AESTFL='Y'), so an analysis of the 90 AEs leading to drug withdrawal (53 in subjects randomized to ozanimod) is shown in Table 13.

Table 13. Reviewer Table. AEs leading to study drug withdrawal in the controlled RMS population (Pool A)

AEDECOD	IFN β-1a 30 mcg n=885	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
ALT increased	3 (0.3%)	1 (0.1%)	4 (0.4%)	5 (0.3%)
GGT increased	0	1 (0.1%)	2 (0.2%)	3 (0.2%)
Liver function test abnormal	2 (0.2%)	2 (0.2%)	1 (0.1%)	3 (0.2%)
Urticaria	0	1 (0.1%)	2 (0.2%)	3 (0.2%)
Back pain	1 (0.1%)	0	2 (0.2%)	2 (0.2%)
Bradycardia	0	2 (0.2%)	0	2 (0.2%)
Cystoid macular edema	0	2 (0.2%)	0	2 (0.2%)
Headache	0	0	2 (0.2%)	2 (0.2%)
Macular edema	3 (0.3%)	1 (0.1%)	1 (0.1%)	2 (0.2%)
Supraventricular tachycardia	0	0	2 (0.2%)	2 (0.2%)

Source: ISS ADAE where AEACN='DRUG WITHDRAWN' and TREMFL1='Y' by AEDECOD and TRT01A.

Reviewer Comment: Elevated hepatic transaminases were the most common reason for withdrawal of the study drug, but the details of many of these were reviewed in the section on AEs leading to study discontinuation. The cases of macular edema with ozanimod are of interest but have already been described in the section on AEs leading

to study discontinuation above; however, the occurrence of macular edema in subjects taking interferon β -1a is somewhat surprising. Similarly, the cases of bradycardia are also of interest but have been previously described. The narratives of the two cases of headache leading to discontinuation of the study drug contain limited information, none suggestive of a worrisome safety signal with the use of ozanimod.

Transaminase Elevation

One of the cases of transaminase elevation leading to study drug discontinuation has not been previously described in this review. Although not coded as a transaminase elevation, a subject who stopped the study drug for acute hepatitis B was also noted to have transaminase elevations.

- At screening, Subject (b) (6) was a 37yo woman who was randomized to ozanimod 1 mg in Study RPC01-201B and who developed a moderate but asymptomatic transaminase elevation (ALT 394 U/L, AST 106 U/L) on Study Day 91. Work-up of this event, including screening for exposures that could precipitate it, an abdominal ultrasound, and testing for hepatitis serologies and autoantibodies, was unremarkable. Her transaminases normalized, and the event was considered recovered / resolved on Study Day 107.
- At screening, Subject (b) (6) was a 24yo man who was randomized to ozanimod 0.5 mg in Study RPC01-201B. On Study Day 92, marked transaminase elevations (ALT 911 U/L, AST 597 U/L) were noted, and an ultrasound showed an enlarged liver. Testing for hepatitis B surface antigen and core IgM were positive, and his ALT and TB peaked at 1214 U/L and 40.4 umol/L, respectively. The study medication was withdrawn.

Study Drug Discontinuation, Uncontrolled RMS population (Study RPC01-3001)

Table 14 delineates that AEs leading to withdrawal of the study drug in more than one subject in Study RPC01-3001. A similar analysis suggests that the study drug was withdrawn from four subjects in the extension of Study PRC01-201A, all for increased ALT or transaminases.

Table 14. Reviewer Table. AEs leading to study drug withdrawal in Study RPC01-3001

AEDECOD	Ozanimod 1 mg n=2494
ALT increased	4 (0.2%)
Lymphocyte count decreased	2 (0.1%)
Macular edema	2 (0.1%)
Pneumonia	2 (0.1%)

Source: ISS ADAE where STUDY='RECRPC013001,' AEACN='DRUG WITHDRAWN' and TREMFL3='Y' by AEDECOD and TRTA.

Reviewer Comment: As with previous analyses, transaminase elevations and macular edema also led to withdrawal of ozanimod in Study RPC01-3001, although the cases of macular edema (and most of the cases of transaminase elevation) have been previously described in this review. The two cases of lymphocyte count decreased (and an additional case coded as lymphopenia) and the case of pneumonia are of interest, as are two cases of malignancy that have not been previously described in this review:

Transaminase Elevations

These two cases of transaminase elevations have not been previously described in this review:

- At screening, Subject (b) (6) was a 38yo woman with a history of autoimmune thyroiditis and psoriasis who was randomized to ozanimod 0.5 mg in Study RPC01-301 and transitioned to ozanimod 1 mg in the RPC01-3001 extension. Of note, her baseline total bilirubin was elevated at 20.2 umol/L. On Day 276 of Study RPC01-3001, the subject experienced asymptomatic ALT/AST (164 and 69 U/L, respectively) and TB (31.8 umol/L) elevations; reportedly, she received high-dose methylprednisolone six weeks (and started an oral contraceptive medication containing estrogen and progesterone three days) before the onset of this AE. Other exposures to explain this AE were not identified, and an abdominal ultrasound and hepatic serologies were unrevealing. As her transaminases continued to increase, the study medication was discontinued on Study Day 290. On Day 323, her ALT peaked at 436 U/L, her AST was 216 U/L, and her TB was 25.5 umol/L. Labs on Study Day 349 included an elevated aPTT of 39.5 seconds (reference range 28.8 – 38.1 seconds) and a PT INR of 1.28 (reference range 0.8 – 1.2). Her antinuclear antibody (ANA) was mildly positive (1:100). Drug-induced hepatitis was suspected, and further testing for autoimmune hepatitis, Wilson’s Disease, and α 1-antitrypsin were recommended; however, the hepatic advisory board deemed that this was not a Hy’s law case due to confounding by Gilbert’s syndrome and the presence of unconjugated hyperbilirubinemia.

Reviewer Comment: This case is also confounded by the other autoimmune comorbidities, the recent exposure to methylprednisolone, and the initiation of an oral contraceptive just before the onset of this case. These confounders lessen the chances that this represents a Hy’s law case of DILI attributable to ozanimod.

- At screening, Subject (b) (6) was 40yo man who was randomized to ozanimod 0.5 mg in Study RPC01-301 and then transitioned to ozanimod 1mg in the RPC01-3001 extension. On Study Day 93 of the OLE, he developed transaminase elevations (ALT >10x ULN at 446 U/L, AST > 5x ULN at 181 U/L, GGT elevated at 88 U/L, TB elevated

at 21.9 umol/L), so the study medication was discontinued. An abdominal ultrasound reportedly revealed no pathologic findings, and the event was considered resolved on Study Day 143.

Reviewer Comment: Although the transaminase and bilirubin elevations are concerning for a Hy's Law case of DILI, the rapid resolution of these laboratory abnormalities with cessation of the study drug is reassuring.

Lymphopenia

The three cases of lymphopenia are of interest:

- At screening, Subject (b) (6) was a 41yo woman who was randomized to ozanimod 0.5mg in Study RPC01-201A (and its extension) and then transitioned to ozanimod 1 mg in Study RPC01-3001. She had a low absolute lymphocyte count (ALC) throughout Study RPC01-201A, and the study medication was withdrawn when it was noted that her absolute lymphocyte count (ALC) was < 200 cells/uL on Day 449 of Study RPC01-3001.
- At screening, Subject (b) (6) was a 50yo woman who was randomized to interferon β -1a in Study RPC01-201B but transitioned to ozanimod 1mg in the RPC01-3001 extension. Due to both an ALT increase (3x ULN at 133 U/L) and an ALC decrease (230 cells/uL), ozanimod was withdrawn on Day 279 of Study RPC01-3001. Her total bilirubin remained normal during the study, and her ALC never dropped below 200 cells/uL.
- At screening, Subject (b) (6) was a 42yo woman who was randomized to ozanimod 0.5mg in Study RPC01-301 and transitioned to ozanimod 1mg in Study RPC01-3001. On Day 274 of Study RPC01-3001, her ALC was noted to be 177 cells/uL. She remained on the study drug until Study Day 563, when she was withdrawn from the study for an ALC of 68 cells/uL and "secondary immunodeficiency." Her ALC improved with cessation of the study drug.

Reviewer Comment: Given the proposed mechanism by which S1P receptor modulators like ozanimod are deemed to benefit subjects with RMS (sequestration of circulating lymphocytes), lymphopenia is not unexpected.

Pneumonia

One of the cases of pneumonia (Subject (b) (6)) occurred in the setting of diffuse metastasis and a seizure and is described in Section 8.4.1 above. Details of the other case of pneumonia follow below:

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

- At screening, Subject (b) (6) was a 43yo woman who was randomized to ozanimod in Study RPC01-301 and remained on this dose of ozanimod in Study RPC01-3001. On Day 197 of Study RPC01-3001, she was hospitalized for “isolated episodes of angina,” dyspnea, thoracic and abdominal pain and was diagnosed with bilateral pneumonia, which was treated with cefazolin, levofloxacin, and metronidazole. The study medication was withdrawn, and the event was considered resolved on Study Day 212.

Malignancy

- At screening, Subject (b) (6) was a 44yo woman who was randomized to ozanimod 1 mg in Study RPC01-201B and remained on this dose of ozanimod in the RPC01-3001 extension. On Day 379 of the OLE extension, she was diagnosed with a rectal adenoma with a medium degree of metaplasia, and the study medication was interrupted but later withdrawn. The outcome of the event is unknown. The Investigator considered this event as unlikely related to ozanimod.
- At screening, Subject (b) (6) was a 36yo woman who was randomized to ozanimod in Study RPC01-201A (and its extension) but transitioned to ozanimod 1 mg in Study RPC01-3001. On Study Day 440 of RPC01-3001, a cervical tumor (invasive tubular non-squamous cancer) was identified. The study medication was stopped, and the subject had extirpation of the uterus and fallopian tubes. She did not have a family history of cancer or a personal history of known exposures than would increase her risk of cancer. The Investigator considered the relationship of this event to the study medication as possible.

Reviewer Comment: The three aforementioned cases of lymphopenia (and likely that of bilateral pneumonia) are at least possibly related to ozanimod. As malignancies have been reported with other S1P receptor modulators, ozanimod may have also played a role in the cases of rectal adenoma and cervical cancer.

Study Drug Discontinuation, IBD Population (Pool C)

As shown in Table 15, there were 50 AEs leading to withdrawal of the study drug in the IBD population (Pool C), although some of these are noted in prior analyses of SAEs and AEs leading to study discontinuation.

Table 15. Reviewer Table. AEs leading to study drug withdrawal in the IBD population (Pool C)

AEDECOD	Ozanimod 0.5 mg n=65	Ozanimod 1 mg n=645	Overall Ozanimod n=654
Colitis ulcerative	1	9	10
Crohn's disease	0	6	6
Lymphocyte count decreased	0	2	2

Source: ISS ADAE where AEACN='DRUG WITHDRAWN' and TREMFL4='Y' by AEDECOD and TRTA.

An addition to two previously reported malignancies (rectal cancer, pancreatic carcinoma), single cases of first degree atrioventricular block, autoimmune hemolytic anemia, Campylobacter infection, cystoid macular edema, erysipelas, hemolytic anemia, herpes zoster, ischemic stroke, and sinus bradycardia are also noted in this analysis.

Reviewer Comment: Other than AEs relating to the underlying IBD, lymphocyte count was the only AEs leading to study drug withdrawal more than once in the IBD population.

Study Drug Discontinuation, Healthy Volunteers (Pool E)

There were nine TEAE leading to study discontinuation reported by the 496 healthy volunteers in the clinical pharmacology studies of ozanimod (Pool E). Three were for transaminase elevations, one of which was deemed moderate and the others mild in severity. Two of the TEAE leading to study discontinuation were second degree atrioventricular block: one (Subject (b) (6)) is described in the section on AEs leading to study discontinuation above, and the other (Subject (b) (6)) occurred in a subject who was on telemetry after receiving a single dose of ozanimod 1.5mg. There were also single cases of ventricular tachycardia, viral infection, urticaria, and eczema leading to study drug discontinuation in Pool E.

Study Drug Interruption, controlled RMS population (Pool A)

In addition to AEs leading to study or study drug discontinuation, the 77 AEs leading to interruption of the study medication in the controlled RMS population (Pool A) are also of interest. AEs that led to study medication interruption and occurred in more than one subject are shown in Table 16.

Table 16. Reviewer Table. AE's leading to treatment interruption in the controlled RMS population (Pool A)

AEDECOD	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
ALT increased	2 (0.2%)	0	1 (0.1%)	4 (0.4%)	5 (0.3%)

AEDECOD	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Vomiting	2 (0.2%)	1 (1.1%)	4 (0.4%)	0	4 (0.2%)
Abdominal pain upper	0	0	2 (0.2%)	0	2 (0.1%)
AST increased	1 (0.1%)	0	0	2 (0.2%)	2 (0.1%)
Cerebral infarction	0	0	2 (0.2%)	0	2 (0.1%)
Headache	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Vertigo	0	0	2 (0.2%)	0	2 (0.1%)

Source: ISS ADAE where AEACN='DRUG INTERRUPTED' and TREMFL1='Y' by AEDECOD and TRT01A.

Reviewer Comment: The number of AEs leading to treatment interruption in Pool A is also quite low and not suggestive of a clear safety signal, although transaminase elevations are a recurring theme in this review. The two AEs for cerebral infarction occurred in the same subject.

Study Drug Interruption, uncontrolled RMS population

Subjects that interrupted the study medication in the uncontrolled RMS population are also of interest. There are 80 such events in the uncontrolled Study RPC01-3001, and events occurring more than once are shown in Table 17. In addition, there were seventeen such events in the extension of Study RPC01-201A: none were transaminase elevations, but the single cases of first degree AV block and herpes zoster are potentially of interest.

Table 17. Reviewer Table. AEs leading to treatment interruption in Study RPC01-3001

AEDECOD	Ozanimod 1 mg n=2494
Lymphopenia	16 (0.6%)
Lymphocyte count decreased	12 (0.5%)
Herpes zoster	3 (0.1%)
ALT increased	2 (0.1%)
AST increased	2 (0.1%)
GGT increased	2 (0.1%)
Seizure	2 (0.1%)
Vomiting	2 (0.1%)

Source: ISS ADAE where STUDY='RECRPC013001,' AEACN='DRUG INTERRUPTED,' and TREMFL3='Y' by AEDECOD and TRTA.

Reviewer Comment: As previously noted, lymphopenia and transaminase elevations are seen relatively frequently in subjects treated with ozanimod. The two seizures occurred in Subject (b) (6), as noted in Section 8.4.2, and the case of papillary thyroid cancer

(Subject (b) (6)) has been previously described. The cases of herpes zoster leading to treatment interruption are of interest.

Herpes Zoster

- At screening, Subject (b) (6) was a 36yo woman who was randomized to ozanimod 0.5mg in Study RPC01-301 and transitioned to ozanimod 1 mg in the RPC01-3001 extension. On Day 430 of Study RPC01-3001, she developed shingles (site not specified), so the study medication was interrupted, and she was treated with valacyclovir and gabapentin. The Investigator consider the relationship between the study medication and this event as probable.
- At screening, Subject (b) (6) was a 48yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-301 and transitioned to ozanimod 1 mg in the RPC01-3001 extension. On Day 368 of Study RPC01-3001, she developed herpes zoster of the left trunk (“7th to 10th thoracic vertebrae”), so the study medication was interrupted and acyclovir was initiated. The Investigator considered the relationship of the event to the study medication as possible.
- Although this reviewer could not locate the narrative for this case, subject (b) (6) was randomized to placebo in Study RPC01-201A and then transitioned to ozanimod 1mg in the RPC01-3001 extension study, in which she developed “herpes dermatitis” which was considered mild in severity and unlikely related to the study medication.

Reviewer Comment: Given the presumed mechanism of action of S1P receptor modulators like ozanimod, there is biologic plausibility that the risk of infections, including herpetic infections, would be increased with the use of these therapies.

Study Drug Interruption, IBD population (Pool C)

An analysis of adverse events leading to treatment interruption was also performed in the IBD population (Pool C). This analysis yielded 56 events, and those events occurring more than once with ozanimod are shown in Table 18.

Table 18. Reviewer Table. AEs leading to treatment interruption in IBD population (Pool C)

AEDECOD	Ozanimod 0.5 mg N=65	Ozanimod 1 mg N=645	Overall Ozanimod N=654
Lymphopenia	0	10 (1.6%)	10 (1.5%)
Lymphocyte count decreased	1 (1.5%)	4 (0.6%)	5 (0.8%)
Herpes zoster	0	3 (0.5%)	3 (0.5%)

AEDECOD	Ozanimod 0.5 mg N=65	Ozanimod 1 mg N=645	Overall Ozanimod N=654
Intestinal obstruction	0	3 (0.5%)	3 (0.5%)
Cytomegalovirus infection	0	2 (0.3%)	2 (0.3%)
Diarrhea	0	2 (0.3%)	2 (0.3%)

Source: ISS ADAE where AEACN='DRUG INTERRUPTED' and TREMFL4='Y' by AEDECOD and TRTA.

Single reports of increased ALT, abnormal LFTs, hyperbilirubinemia are also noted.

Reviewer Comment: Even without splitting lymphopenia into two preferred terms, lymphopenia was the most common AE leading to study drug interruption in the IBD population. Infections, including herpes zoster, and transaminase elevations are also noted as a cause of study drug interruption in this population.

Study Drug Interruption, Healthy Volunteers (Pool E)

A search of the ISS ADAE dataset where AEACN='DRUG INTERRUPTED' and 'TREMFL6='Y' did not yield any rows.

8.4.4. Significant Adverse Events

As per Section 8.3.2, the severity of AEs was graded as mild, moderate, or severe.

Severe TEAE, controlled RMS population (Pool A)

In the ISS ADAE dataset, 374 adverse events were classified as severe (AESEV='SEVERE'), but only 139 of these occurred in the Safety Population of Pool A. See Table 19 for the severe AEs that occurred more than once in the controlled RMS population (Pool A).

Table 19. Reviewer Table. TEAE classified as severe in the controlled RMS population (Pool A)

AEDECOD	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Headache	3 (0.3%)	1 (1.1%)	5 (0.5%)	3 (0.3%)	8 (0.4%)
ALT increased	0	0	2 (0.2%)	1 (0.1%)	3 (0.2%)
Arthralgia	1 (0.1%)	0	3 (0.3%)	0	3 (0.2%)
Hemorrhoids	0	0	3 (0.3%)	0	3 (0.2%)
Abdominal pain upper	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Appendicitis	0	0	0	2 (0.2%)	2 (0.1%)
Asthenia	0	0	0	2 (0.2%)	2 (0.1%)
Bronchitis bacterial	0	0	0	2 (0.2%)	2 (0.1%)
Cervical radiculopathy	0	0	2	0	2 (0.1%)

AEDECOD	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Colitis	0	0	0	2 (0.2%)	2 (0.1%)
GGT increased	0	0	2 (0.2%)	0	2 (0.1%)
Intervertebral disc protrusion	0	0	0	2 (0.2%)	2 (0.1%)
Loss of consciousness	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Pyelonephritis acute	1 (0.1%)	0	0	2 (0.2%)	2 (0.1%)
Pyrexia	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Uterine cervical squamous metaplasia	0	0	2 (0.2%)	0	2 (0.1%)

Source: ISS ADAE where AESEV='SEVERE' and TREMFL1='Y' by AEDECOD and TRT01A.

Reviewer Comment: The results of Table 19 do not show an obvious or concerning signal for AEs graded as severe; headaches are common events (probably more so in individuals with MS), and transaminase elevations have been described with other S1P receptor modulators and are discussed elsewhere in this review, including Section 8.5.1.

Severe TEAE, uncontrolled RMS population

Similarly, 105 adverse events were classified as Severe (AESEV='SEVERE') in RPC01-3001 as per Table 20. Only nine events were classified as 'SEVERE' in the extension of RPC01-201A, and ALT increase is the only one that occurred more than once.

Table 20. Reviewer Table. TEAE classified as severe in Study RPC01-3001

AEDECOD	Ozanimod 1 mg n=2494
Headache	7 (0.3%)
Lymphocyte count decreased	7 (0.3%)
Lymphopenia	6 (0.2%)
Appendicitis	4 (0.2%)
Trigeminal neuralgia	3 (0.1%)
AST increased	2 (0.1%)
Bronchitis	2 (0.1%)
Cranio-cerebral injury	2 (0.1%)
Duodenal perforation	2 (0.1%)
Endometrial hyperplasia	2 (0.1%)
Oropharyngeal pain	2 (0.1%)
Seizure	2 (0.1%)
Tonsillitis	2 (0.1%)

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

AEDECOD	Ozanimod 1 mg n=2494
Upper respiratory tract infection	2 (0.1%)

Source: ISS ADAE where STUDYID=' RECRPC013001,' AESEV='SEVERE,' and TREMFL3='Y' by AEDECOD and TRTA.

Reviewer Comment: The results of Table 20 do not show an obvious or concerning signal for AEs graded as severe; headaches are common events, and transaminase elevations and lymphopenia are AEs for this application. Infections are not unexpected in the setting of lymphopenia with S1P receptor modulators, and trigeminal neuralgia is one of the known complications of MS, estimated to occur in about 5% of individuals with the disease. Seizures are also reported to occur in 3-5% of subjects with MS.

Severe TEAE, IBD population (Pool C)

There were 101 adverse events that were graded as severe in the IBD population (Pool C), and such events occurring more than once are delineated in Table 21.

Table 21. Reviewer Table. TEAE classified as severe in the IBD population (Pool C)

AEDECOD	Ozanimod 0.5 mg N=65	Ozanimod 1 mg N=645	Overall Ozanimod N=654
Colitis ulcerative	0	9 (1.5%)	9 (1.4%)
Crohn's disease	0	8 (1.2%)	8 (1.2%)
Lymphopenia	0	8 (1.2%)	8 (1.2%)
Colitis	0	3 (0.5%)	3 (0.5%)
Intestinal obstruction	0	3 (0.5%)	3 (0.5%)
Abdominal abscess	0	2 (0.3%)	2 (0.3%)
Abdominal pain	0	2 (0.3%)	2 (0.3%)
Anemia	0	2 (0.3%)	2 (0.3%)
Anal abscess	0	2 (0.3%)	2 (0.3%)
Arthralgia	0	2 (0.3%)	2 (0.3%)
Diarrhea	0	2 (0.3%)	2 (0.3%)
Headache	0	2 (0.3%)	2 (0.3%)
Herpes zoster	0	2 (0.3%)	2 (0.3%)
Influenza	0	2 (0.3%)	2 (0.3%)
Sepsis	0	2 (0.3%)	2 (0.3%)
Small intestinal obstruction	0	2 (0.3%)	2 (0.3%)

Source: ISS ADAE where AESEV='SEVERE' and TREMFL4='Y' by AEDECOD and TRTA.

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

Note is again made of single reports of several kinds of malignancies (including adenocarcinoma and pancreatic, prostate, and rectal cancer) and infections (including appendicitis, erysipelas, pneumococcal pneumonia, and staphylococcal infection).

Reviewer Comment: Most of the AEs graded as severe that occurred in Pool C appear related to inflammatory bowel disease, although note is again made of lymphopenia, malignancies, and multiple types of infection, including herpes zoster.

Severe TEAE, Healthy Volunteers (Pool E)

Of the 508 TEAEs reported by healthy volunteers in the ozanimod development program (Pool E), none were classified as severe.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAE, controlled RMS population (Pool A)

The numbers of subjects who were in the controlled RMS population (Pool A) and experienced treatment emergent adverse events (TEAEs), including those leading to study drug discontinuation, those leading to study drug interruption, and those requiring treatment, stratified by treatment group, are shown in Table 22.

Table 22. Reviewer Table. Subjects with TEAE, Controlled RMS population (Pool A)

Subjects experiencing	IFN β -1a 30 mcg n=885	Placebo N=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
TEAE	701 (79.2%)	52 (59.0%)	641 (65.5%)	642 (66.5%)	1283 (66.0%)
TEAE leading to study discontinuation	36 (4.1%)	1 (1.1%)	20 (2.0%)	26 (2.7%)	46 (2.4%)
TEAE leading to study drug discontinuation	34 (3.8%)	1 (1.1%)	21 (2.1%)	26 (2.7%)	47 (2.4%)
TEAE leading to study drug interruption	14 (1.6%)	1 (1.1%)	26 (2.7%)	16 (1.7%)	42 (2.2%)
TEAE requiring concomitant therapy	631 (71.3%)	40 (45.5%)	470 (48.0%)	489 (50.7%)	959 (49.3%)

Source: N Categories (SUBJID) in ISS ADAE where TREMF1='Y' and { ϕ , AESTL='Y,' AEACN='DRUG WITHDRAWN,' AEACN='DRUG INTERRUPTED' or AETRT<>'NONE'} by TRT01A

Reviewer Comment: In the controlled RMS population (Pool A), the overall rate of TEAEs (and the rate of TEAE leading to study drug discontinuation) in the ozanimod groups was lower than that in the interferon β -1a group but somewhat higher than that of the small placebo group. The rates of TEAEs requiring concomitant therapy were much lower in

the ozanimod groups than that of the interferon β-1a group; however, pretreatment is often necessary to manage the flu-like side effects associated with interferon β-1a.

The numbers of subjects who were in the controlled RMS population (Pool A) and experienced treatment emergent adverse events (TEAEs) stratified by primary System Organ Class (SOC) are shown in Table 23.

Table 23. Reviewer Table. TEAEs stratified by SOC in the Controlled RMS population (Pool A)

AEBODSYS	IFN β-1a 30 mcg n=885	Placebo N=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
INFECTIONS AND INFESTATIONS	268 (30.3%)	28 (31.8%)	329 (33.6%)	326 (33.8%)	655 (33.7%)
NERVOUS SYSTEM DISORDERS	112 (12.7%)	21 (23.9%)	170 (17.4%)	153 (15.9%)	323 (16.6%)
INVESTIGATIONS	72 (8.1%)	4 (4.5%)	112 (11.4%)	159 (16.5%)	271 (13.9%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	84 (9.5%)	12 (13.6%)	120 (12.3%)	113 (11.7%)	233 (12.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	430 (48.6%)	5 (5.7%)	111 (11.3%)	119 (12.3%)	230 (11.8%)
GASTROINTESTINAL DISORDERS	81 (9.2%)	8 (9.1%)	107 (10.9%)	106 (11.0%)	213 (11.0%)
VASCULAR DISORDERS	47 (5.3%)	3 (3.4%)	74 (7.6%)	86 (8.9%)	160 (8.2%)
PSYCHIATRIC DISORDERS	62 (7.0%)	5 (5.7%)	76 (7.8%)	77 (8.0%)	153 (7.9%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	49 (5.5%)	4 (4.5%)	63 (6.4%)	57 (5.9%)	120 (6.2%)
EYE DISORDERS	41 (4.6%)	4 (4.5%)	51 (5.2%)	56 (5.8%)	107 (5.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	47 (5.3%)	9 (10.2%)	48 (4.9%)	54 (5.6%)	106 (5.5%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	43 (4.9%)	4 (4.5%)	40 (4.1%)	52 (5.4%)	92 (4.7%)

AEBODSYS	IFN β -1a 30 mcg n=885	Placebo N=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
METABOLISM AND NUTRITION DISORDERS	33 (3.7%)	0	36 (3.7%)	41 (4.2%)	77 (4.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	33 (3.7%)	3 (3.4%)	32 (3.3%)	41 (4.2%)	73 (3.8%)
CARDIAC DISORDERS	20 (2.3%)	1 (1.1%)	34 (3.5%)	30 (3.1%)	64 (3.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	33 (3.7%)	2 (2.3%)	28 (2.9%)	23 (2.4%)	51 (2.6%)
RENAL AND URINARY DISORDERS	17 (1.9%)	2 (2.3%)	26 (2.7%)	17 (1.8%)	43 (2.2%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	19 (2.1%)	0	22 (2.2%)	21 (2.2%)	43 (2.2%)
EAR AND LABYRINTH DISORDERS	16 (1.8%)	1 (1.1%)	16 (1.6%)	20 (2.1%)	36 (1.9%)
HEPATOBIILIARY DISORDERS	7 (0.8%)	0	21 (2.1%)	15 (1.6%)	36 (1.9%)
ENDOCRINE DISORDERS	13 (1.5%)	1 (1.1%)	5 (0.5%)	14 (1.5%)	19 (1.0%)
IMMUNE SYSTEM DISORDERS	3 (0.3%)	1 (1.1%)	6 (0.6%)	6 (0.6%)	12 (0.6%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	3 (0.3%)	4 (0.4%)	7 (0.4%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	1 (0.1%)	3 (0.3%)	4 (0.2%)
SOCIAL CIRCUMSTANCES	4 (0.5%)	0	3 (0.3%)	0	3 (0.2%)
SURGICAL AND MEDICAL PROCEDURES	1 (0.1%)	0	2 (0.2%)	1 (0.1%)	3 (0.2%)

Source: ISS ADAE where TREMFL1='Y' and SAFEFL='Y' by AEBODSYS by TRT01A by USUBJID.

Reviewer Comment: The highest percentages of TEAEs in the controlled RMS population randomized to ozanimod are for the Infections and Infestations, Nervous System Disorders, and Investigations SOCs. Since the form of interferon β -1a used in the ozanimod development program is intramuscular, it is not surprising that the percentage of General Disorders and Administration Site Conditions TEAEs is much higher for subjects randomized to interferon β -1a. Although first dose bradyarrhythmia /

atrioventricular blocks, macular edema, and respiratory effects have been associated with the use of S1P receptor modulators, the percentages of TEAEs in the Cardiac Disorders, Eye Disorders, and Respiratory, Thoracic, and Mediastinal SOCs are only slightly higher in the ozanimod arms of this analysis. This reviewer is somewhat surprised that the percentages of TEAEs in the Vascular Disorders and Musculoskeletal and Connective Tissue Disorders SOCs are greater in the ozanimod arms of this analysis and will be vigilant for these potential signals going forward in this review.

There were over 3200 different verbatim (reported) terms used by subjects in the ISS controlled RMS population (Pool A) to describe TEAEs, but these were coded into 935 preferred terms (PTs) to facilitate the analysis of this dataset. Overall, the coding of these verbatim terms into PTs appears to be reasonably accurate. Table 24 contains the TEAEs that occurred in the controlled RMS population (Pool A), but it should be noted that the same TEAE could occur more than once in the same subject and that similar TEAEs could be split between different codes, e.g., ALT increased, AST increased, liver function test abnormal, hepatic enzyme increased, etc. Given the number of reported TEAEs, Table 24 is limited to TEAEs occurring 20 or more times in the ozanimod arms of the controlled RMS studies.

Table 24. Reviewer Table. TEAE PTs reported 20 or more times by ozanimod-treated subjects, controlled RMS population (Pool A)

AEDECOD	IFN β -1a 30 mcg n=885	Placebo N=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Headache	140	8	191	237	428
Nasopharyngitis	99	15	176	153	329
Upper respiratory infection	72	4	91	67	158
Influenza like illness	1062	0	58	64	122
ALT increased	21	0	54	65	119
Urinary tract infection	26	3	46	52	98
GGT increased	8	0	35	56	91
Back pain	27	7	40	42	82
Orthostatic hypotension	27	1	38	44	82
Pharyngitis	20	4	45	35	80
Dysmenorrhea	13	3	37	41	78
Hypertension	18	1	33	33	66
Abdominal pain upper	8	0	24	30	54
Arthralgia	19	0	29	23	52
Depression	20	0	26	25	51
Bronchitis	13	0	24	26	50
Fatigue	13	1	23	27	50

AEDECOD	IFN β -1a 30 mcg n=885	Placebo N=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Insomnia	18	4	26	24	50
Pain in extremity	19	1	25	22	47
Pyrexia	485	1	26	18	44
Rhinitis	10	3	25	19	44
Respiratory tract infection viral	10	0	18	24	42
Respiratory tract infection	24	1	17	23	40
Anxiety	12	0	18	20	38
AST increased	10	0	17	18	35
Diarrhea	12	2	21	13	34
Hypercholesterolemia	17	0	15	17	32
Nausea	11	3	13	17	30
Paresthesia	14	2	16	14	30
Sinusitis	19	1	16	14	30
Cough	19	1	18	10	28
Influenza	15	0	18	10	28
Anemia	19	0	17	10	27
Asthenia	10	0	13	14	27
Oral herpes	12	2	18	8	26
Vertigo	7	1	11	15	26
Dizziness	8	1	13	12	25
Muscle spasms	10	1	11	14	25
Toothache	11	2	9	16	25
Alopecia	4	1	14	9	23
Tonsillitis	10	0	12	10	22
Hypoesthesia	15	2	11	10	21
Liver function test abnormal	0	0	13	8	21
Hepatic enzyme increased	5	0	5	15	20

Source: ISS ADAE where TREMFL1='Y' and SAF CFL='Y' by AEDECOD and TRT01A

Reviewer Comment: Since TEAEs could be reported more than once by the same subject, Table 24 does not contain percentages of subjects experiencing a TEAE, although it should be remembered that the number of subjects who received ozanimod is over twice that who received interferon β -1a in the controlled RMS population. Furthermore, it is apparent that there is some splitting of TEAEs into different PTs. Despite these caveats, it is clear that headaches, infections, and transaminase elevations were the most commonly reported TEAEs by subjects randomized to ozanimod in the controlled RMS population. Since blood pressures and heart rates were checked in the supine, sitting,

and standing position, the incidence of orthostatic hypotension noted in Pool A is not surprising. Dysmenorrhea, hypertension, abdominal pain, and fatigue also occurred somewhat more frequently in subjects who received ozanimod in Pool A; hypertension has been noted to be associated with the use of other S1P receptor modulators.

A TEAE summary in which a particular TEAE is only counted once per subject and in which related TEAEs are grouped together may give a clearer picture of the safety of a medication, so the results of the Office of Drug Evaluation-1 (ODE-1) safety analysis tool for TEAE reported by 20 or more subjects follow in Table 25.

Table 25. Reviewer Table. ODE-1 analysis of TEAE by assigned treatment, Pool A

AEDECOD	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
infection, all	479 (54.1%)	27 (30.7%)	350 (35.8%)	343 (35.5%)	693 (35.6%)
URI, cold, rhinitis, upper resp tract infection, flu-like illness	441 (49.8%)	22 (25.0%)	279 (28.5%)	261 (27.0%)	540 (27.8%)
Headache	69 (7.8%)	10 (11.4%)	94 (9.6%)	91 (9.4%)	185 (9.5%)
GOT, GPT, GGTP, LFTs	35 (4.0%)	0	76 (7.8%)	107 (11.1%)	183 (9.4%)
infection, viral	49 (5.5%)	2 (2.3%)	59 (6.0%)	57 (5.9%)	116 (6.0%)
UTI	30 (3.4%)	2 (2.3%)	46 (4.7%)	52 (5.4%)	98 (5.0%)
Orthostasis	25 (2.8%)	1 (1.1%)	38 (3.9%)	41 (4.2%)	79 (4.1%)
asthenia, fatigue, malaise, weakness, narcolepsy	24 (2.7%)	1 (1.1%)	39 (4.0%)	39 (4.0%)	78 (4.0%)
hypertension, BP increased	17 (1.9%)	2 (2.3%)	33 (3.4%)	42 (4.4%)	75 (3.9%)
dyspepsia, N, V, indigestion, epigastric pain, gastritis	25 (2.8%)	2 (2.3%)	33 (3.4%)	38 (3.9%)	71 (3.7%)
abdominal pain, distension, bloating, spasm, IBS, megacolon	24 (2.7%)	1 (1.1%)	30 (3.1%)	35 (3.6%)	65 (3.3%)
bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	18 (2.0%)	0	25 (2.6%)	35 (3.6%)	60 (3.1%)

AEDECOD	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Depression	22 (2.5%)	0	33 (3.4%)	26 (2.7%)	59 (3.0%)
somnolence, fatigue, sedation	14 (1.6%)	2 (2.3%)	32 (3.3%)	26 (2.7%)	58 (3.0%)
insomnia, sleep disturbance, abnormal dreams	20 (2.3%)	4 (4.5%)	26 (2.7%)	29 (3.0%)	55 (2.8%)
diarrhea, colitis, enteritis, proctitis, gastroenteritis, C- diff	17 (1.9%)	2 (2.3%)	30 (3.1%)	25 (2.6%)	55 (2.8%)
arthralgia, arthritis, arthrosis	18 (2.0%)	0	31 (3.2%)	23 (2.4%)	54 (2.8%)
eye other	23 (2.6%)	1 (1.1%)	24 (2.5%)	25 (2.6%)	49 (2.5%)
Insomnia	18 (2.0%)	4 (4.5%)	23 (2.3%)	24 (2.5%)	47 (2.4%)
Anemia	29 (3.3%)	1 (1.1%)	26 (2.7%)	20 (2.1%)	46 (2.4%)
Arrhythmia	15 (1.7%)	0	23 (2.3%)	20 (2.1%)	43 (2.2%)
anxiety, nervousness, panic attacks	18 (2.0%)	1 (1.1%)	19 (1.9%)	23 (2.4%)	42 (2.2%)
fall, dizziness, balance disorder	9 (1.0%)	3 (3.4%)	20 (2.0%)	18 (1.9%)	38 (2.0%)
fall, dizziness, balance disorder, gait disturbance, difficulty walking	9 (1.0%)	3 (3.4%)	20 (2.0%)	18 (1.9%)	38 (2.0%)
Nausea, vomiting	12 (1.4%)	2 (2.3%)	19 (1.9%)	18 (1.9%)	37 (1.9%)
fever, rigors	49 (5.5%)	1 (1.1%)	18 (1.8%)	16 (1.7%)	34 (1.7%)
neuralgia, neuritis, neuropathy	10 (1.1%)	1 (1.1%)	13 (1.3%)	16 (1.7%)	29 (1.5%)
Bleeding	4 (0.5%)	1 (1.1%)	13 (1.3%)	16 (1.7%)	29 (1.5%)
Influenza	13 (1.5%)	0	18 (1.8%)	10 (1.0%)	28 (1.4%)
Cough	16 (1.8%)	1 (1.1%)	17 (1.7%)	11 (1.1%)	28 (1.4%)

AEDECOD	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Hyperbilirubinemia, alk phos, jaundice	1 (0.1%)	1 (1.1%)	14 (1.4%)	14 (1.5%)	28 (1.4%)
vertigo; vestibular dysfunction	9 (1.0%)	1 (1.1%)	12 (1.2%)	16 (1.7%)	28 (1.4%)
herpes virus	16 (1.8%)	2 (2.3%)	13 (1.3%)	14 (1.5%)	27 (1.4%)
paresthesia, hypoaesthesia	10 (1.1%)	2 (2.3%)	14 (1.4%)	12 (1.2%)	26 (1.3%)
solid neoplasia, ALL (benign, malignant, unknown)	16 (1.8%)	0	11 (1.1%)	13 (1.3%)	24 (1.2%)
dizziness, light-headedness	8 (0.9%)	1 (1.1%)	13 (1.3%)	11 (1.1%)	24 (1.2%)
visual disturbance	11 (1.2%)	0	14 (1.4%)	10 (1.0%)	24 (1.2%)
Bradycardia	5 (0.6%)	0	10 (1.0%)	13 (1.3%)	23 (1.2%)
infection, fungal	19 (2.1%)	2 (2.3%)	12 (1.2%)	10 (1.0%)	22 (1.1%)
dysfunctional uterine bleeding, menometrorrhagia	8 (0.9%)	0	11 (1.1%)	11 (1.1%)	22 (1.1%)
hyper/hypo thyroid, thyroiditis, goiter	15 (1.7%)	1 (1.1%)	7 (0.7%)	14 (1.5%)	21 (1.1%)
allergic RXN, hypersensitivity	9 (1.0%)	1 (1.1%)	12 (1.2%)	8 (0.8%)	20 (1.0%)
Fracture	7 (0.8%)	1 (1.1%)	12 (1.2%)	8 (0.8%)	20 (1.0%)

Reviewer Comment: The TEAEs reported by the highest percentage of subjects randomized to ozanimod in the controlled RMS population are infections, headaches, and transaminase elevations. Although the percentages for all infections and upper respiratory infections (including flu-like symptoms) are higher in the interferon β -1a arm, post-injection flu-like adverse reactions are very common in those taking an interferon. Infections involving the urinary, bronchial, and gastrointestinal tracts were reported more frequently in subjects randomized to ozanimod; however, this reviewer is surprised that herpetic infections were reported by a slightly higher percentage of subjects randomized to interferon β -1a, especially given the potential signal for herpes zoster noted with ozanimod throughout Section 8.4.4.

Severe TEAE, uncontrolled RMS population (Study RPC01-3001)

Although OLEs are uncontrolled and have more variability in the duration of exposure to the study drug, safety analysis of these studies offer some information about the longer term safety of a drug; therefore, similar analyses to those performed in Table 22 through Table 25 are performed in an uncontrolled RMS population (Study RPC01-3001).

The number of subjects who experienced TEAEs leading to study drug discontinuation, leading to study drug interruption, and requiring treatment in Study RPC01-3001 are shown in Table 26.

Table 26. Reviewer Table. Summary of Subjects with TEAE in Study RPC01-3001

Subjects experiencing	Ozanimod 1 mg n=2494
TEAE	1702 (61.2%)
TEAE leading to study discontinuation	29 (1.0%)
TEAE leading to study drug discontinuation	30 (1.1%)
TEAE leading to study drug interruption	67 (2.4%)
TEAE requiring concomitant therapy	1311 (47.1%)

Source: N Categories of SUBJID of ISS ADAE where STUDYID=' RECRPC013001,' TREMFL3='Y,' and {φ, AESTFL='Y,' AEACN='DRUG WITHDRAWN,' AEACN='DRUG INTERRUPTED,' or AETRT<>'NONE'}.

Reviewer Comment: The percentages of subjects with TEAEs, TEAEs leading to study discontinuation or drug interruption, and TEAEs requiring concomitant therapy in the uncontrolled RMS population are somewhat lower than those in subjects randomized to ozanimod in Pool A (Table 22). This suggests that the incidence of TEAEs (or intolerance to the drug) may not increase with longer exposures to ozanimod.

The numbers (and percentages) of subjects who were in Study RPC01-3001 (an uncontrolled ozanimod open-label extension) and experienced treatment emergent adverse events (TEAEs) stratified by primary System Organ Class (SOC) are shown in Table 27.

Table 27. Reviewer Table. TEAEs stratified by SOC in Study RPC01-3001

AEBODSYS	Ozanimod 1 mg n=2494
INFECTIONS AND INFESTATIONS	926 (37.1%)
INVESTIGATIONS	391 (15.7%)
NERVOUS SYSTEM DISORDERS	377 (15.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	306 (12.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	284 (11.4%)
GASTROINTESTINAL DISORDERS	228 (9.1%)

AEBODSYS	Ozanimod 1 mg n=2494
PSYCHIATRIC DISORDERS	177 (7.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	128 (5.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	121 (4.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	117 (4.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	115 (4.6%)
VASCULAR DISORDERS	109 (4.4%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	105 (4.2%)
EYE DISORDERS	104 (4.2%)
METABOLISM AND NUTRITION DISORDERS	73 (2.9%)
RENAL AND URINARY DISORDERS	72 (2.9%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	70 (2.8%)
HEPATOBIILIARY DISORDERS	49 (2.0%)
CARDIAC DISORDERS	32 (1.3%)
EAR AND LABYRINTH DISORDERS	27 (1.1%)
ENDOCRINE DISORDERS	22 (0.9%)
IMMUNE SYSTEM DISORDERS	17 (0.7%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	10 (0.4%)
SOCIAL CIRCUMSTANCES	7 (0.3%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	3 (0.1%)

Source: N Categories of SUBJID of ISS ADAE where STUDYID=' RECRPC013001' and TREMF3='Y' by AEBODSYS.

Reviewer Comment: Other than a notable increase in the percentage of subjects reporting TEAEs in the Blood and Lymphatic System Disorders SOC (which will be explored further in this review), the percentages of subjects reporting TEAEs in other SOCs in this analysis appear equivalent (or less than) those in the Pool A analysis.

Similar to Table 24, Table 28 below delineates the TEAE PTs that were reported 25 or more times of the 2494 RMS subjects in the safety population of the large open label study of ozanimod in subjects with RMS (RPC01-3001).

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

Table 28. Reviewer Table. TEAE PTs reported 25 or more times by ozanimod-treated subjects, in Study RPC01-3001

AEDECOD	Ozanimod 1 mg n=2494
Nasopharyngitis	394
Headache	363
Lymphopenia	239
Upper respiratory tract infection	210
Lymphocyte count decreased	189
Gamma-glutamyl transferase increased	119
Respiratory tract infection	113
Back pain	112
Urinary tract infection	101
Hypertension	95
Respiratory tract infection viral	83
Bronchitis	77
Alanine aminotransferase increased	68
Influenza	65
Arthralgia	63
Depression	60
Anemia	57
Pain in extremity	55
Sinusitis	53
Pharyngitis	50
Leukopenia	42
Cystitis	41
Diarrhea	41
Insomnia	41
Rhinitis	40
Hypercholesterolemia	37
Oral herpes	37
Toothache	37
Cough	34
Fatigue	33
Oropharyngeal pain	33
C-reactive protein increased	31
Anxiety	30
Abdominal pain upper	26
Aspartate aminotransferase increased	25

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

Source: ISS ADAE where STUDYID=' RECRPC013001' and TREMFL3='Y' by AEDECOD

Reviewer Comment: Similar to Table 24, Table 28 does not contain percentages of subjects experiencing a TEAE because TEAEs could be reported more than once by the same subject. Infections, headaches, and transaminase elevations are again the most commonly reported TEAEs; however, it is noted that lymphopenia is reported more frequently in this analysis than in the similar analysis of TEAE in the controlled RMS population. Given the presumed biologic mechanism of S1P modulators, lymphopenia would be expected in subjects exposed to ozanimod, so this reviewer will explore whether lymphopenia increases with duration of exposure in Section 8.4.6. Hypertension is also noted in Table 28 (and with other S1P receptor modulators), so this potential signal will be further explored in subsequent analyses in the section reviewing vital sign changes with ozanimod.

As before, a TEAE summary in which a particular TEAE is only counted once per subject and in which related TEAEs are grouped together may give a clearer picture of the safety of a medication. The results of the Office of Drug Evaluation-1 (ODE-1) safety analysis tool for TEAEs reported by more than 25 subjects of the 2494 subjects in the safety population of Study RPC01-3001 follow in Table 29.

Table 29. Reviewer Table. ODE-1 analysis of TEAE in RPC01-3001

AEDECOD	Ozanimod 1mg n=2494
infection, all	1163 (46.6%)
URI, cold, rhinitis, upper resp tract infection, flu-like illness	986 (39.5%)
Headache	249 (10.0%)
GOT, GPT, GGTP, LFTs	210 (8.4%)
infection, viral	166 (6.7%)
Urinary tract infections	126 (5.1%)
asthenia, fatigue, malaise, weakness, narcolepsy	103 (4.1%)
Orthostasis	99 (4.0%)
hypertension, BP increased	94 (3.8%)
dyspepsia, N, V, indigestion, epigastric pain, gastritis	85 (3.4%)
abdominal pain, distension, bloating, spasm, IBS, megacolon	84 (3.4%)
fever, rigors	79 (3.2%)
Anemia	79 (3.2%)
Depression	75 (3.0%)
bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	74 (3.0%)
eye other	74 (3.0%)
arthralgia, arthritis, arthrosis	73 (2.9%)

AEDECOD	Ozanimod 1mg n=2494
somnolence, fatigue, sedation	70 (2.8%)
insomnia, sleep disturbance, abnormal dreams	69 (2.8%)
diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	66 (2.6%)
Insomnia	60 (2.4%)
anxiety, nervousness, panic attacks	59 (2.4%)
Arrhythmia	54 (2.2%)
infection, fungal	46 (1.8%)
fall, dizziness, balance disorder	46 (1.8%)
fall, dizziness, balance disorder, gait disturbance, difficulty walking	46 (1.8%)
herpes virus	45 (1.8%)
Cough	44 (1.8%)
Nausea, vomiting	42 (1.7%)
Influenza	40 (1.6%)
neuralgia, neuritis, neuropathy	39 (1.6%)
vertigo; vestibular dysfunction	39 (1.6%)
Bleeding	38 (1.5%)
hyper/hypo thyroid, thyroiditis, goiter	36 (1.4%)
visual disturbance	35 (1.4%)
solid neoplasia, ALL (benign, malignant, unknown)	34 (1.4%)
paresthesia, hypoaesthesia	34 (1.4%)
Dermatitis	32 (1.3%)
dizziness, light-headedness	31 (1.2%)
dysfunctional uterine bleeding, menometrorrhagia	30 (1.2%)
allergic RXN, hypersensitivity	29 (1.2%)
Fracture	29 (1.2%)
cramps, muscle spasm	28 (1.1%)
Hyperbilirubinemia, alk phos, jaundice	28 (1.1%)
Myalgia, myositis, rhabdomyolysis	27 (1.1%)

Reviewer Comment: As in the controlled RMS population, infections, headaches, and transaminase elevations were among the most commonly reported TEAE in the uncontrolled RMS safety population in Study RPC01-3001. Orthostasis and increased blood pressure are also notable, especially as these adverse events are difficult to attribute to RMS; increased blood pressure has been reported with other S1P receptor modulators.

TEAE, IBD population (Pool C)

The number (and percentage) of subjects in the IBD population (Pool C) who experienced TEAEs leading to study discontinuation, study drug discontinuation, study drug interruption, and requiring treatment are shown in Table 30.

Table 30. Reviewer Table. Summary of Subjects with TEAE in IBD population (Pool C)

	Ozanimod 0.5 mg N=65	Ozanimod 1 mg N=645
TEAE	26 (40.0%)	357 (55.3%)
TEAE leading to study discontinuation	2 (3.1%)	39 (6.0%)
TEAE leading to study drug withdrawal	3 (4.5%)	40 (6.2%)
TEAE leading to study drug interruption	2 (3.1%)	38 (5.9%)
TEAE requiring concomitant therapy	14 (21.5%)	268 (41.6%)

Source: N Categories of SUBJID of ISS ADAE where TREMFL4='Y' and {φ, AESTFL ='Y,' AEACN='DRUG WITHDRAWN,' AEACN='DRUG INTERRUPTED,' or AETRT<>'NONE'} by TRTA.

Reviewer Comment: Although the rates of overall TEAEs and TEAEs requiring additional therapy are somewhat lower in the IBD population (Pool C) compared with the controlled RMS population (Pool A), the rates of TEAEs leading to study discontinuation or drug withdrawal / interruption are somewhat higher in the IBD population.

The numbers (and percentages) of subjects in the IBD population (Pool C) who experienced treatment emergent adverse events (TEAEs), as stratified by primary System Organ Class (SOC), are shown in Table 31.

Table 31. Reviewer Table. TEAEs stratified by primary SOC in the IBD population (Pool C)

AEBODSYS	Ozanimod 0.5 mg n=65	Ozanimod 1 mg n=645
GASTROINTESTINAL DISORDERS	10 (15.4%)	300 (46.5%)
INFECTIONS AND INFESTATIONS	9 (13.8%)	252 (39.1%)
INVESTIGATIONS	4 (6.2%)	204 (31.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4 (6.2%)	129 (20.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (3.1%)	116 (18.0%)
NERVOUS SYSTEM DISORDERS	0	76 (11.8%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (1.5%)	57 (8.8%)
EYE DISORDERS	5 (7.7%)	52 (8.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (3.1%)	50 (7.8%)

AEBODSYS	Ozanimod 0.5 mg n=65	Ozanimod 1 mg n=645
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (3.1%)	44 (6.8%)
METABOLISM AND NUTRITION DISORDERS	0	27 (4.2%)
VASCULAR DISORDERS	3 (4.6%)	27 (4.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.5%)	25 (3.9%)
RENAL AND URINARY DISORDERS	0	22 (3.4%)
PSYCHIATRIC DISORDERS	1 (1.5%)	20 (3.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	16 (2.5%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	16 (2.5%)
CARDIAC DISORDERS	2 (3.1%)	9 (1.4%)
HEPATOBIILIARY DISORDERS	1 (1.5%)	9 (1.4%)
EAR AND LABYRINTH DISORDERS	1 (1.5%)	8 (1.2%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	2 (0.3%)

Source: ISS ADAE where TREMFL4='Y' by AEBODSYS by TRTA by USUBJID.

Reviewer Comment: The most commonly reported TEAEs by the IBD population are in the Gastrointestinal Disorders SOC, although this may relate to the underlying disease process and not the study medication. Other commonly reported TEAEs are in the Infections and Infestations, Investigations, and Blood and Lymphatic System Disorders SOCs, which is not surprising as infections, transaminase elevations, and lymphopenia are known to occur with other S1P receptor modulators and have already frequently been noted in this review.

Similar to Table 28 above, Table 32 below delineates the TEAE PTs that were reported 15 or more times by subjects in the IBD population (Pool C).

Table 32. Reviewer Table. TEAE PTs reported 15 or more times in the IBD population (Pool C)

AEDECOD	Ozanimod 0.5 mg n=65	Ozanimod 1 mg n=645
Lymphopenia	0	47
Anemia	4	42
Arthralgia	1	42
Nasopharyngitis	3	38

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

AEDECOD	Ozanimod 0.5 mg n=65	Ozanimod 1 mg n=645
Lymphocyte count decreased	0	33
Upper respiratory tract infection	0	33
Alanine aminotransferase increased	1	32
Headache	0	32
Crohn's disease	0	30
Nausea	1	30
Diarrhea	0	29
Abdominal pain	1	28
Gamma-glutamyl transferase increased	0	27
Colitis ulcerative	2	25
Aspartate aminotransferase increased	1	19
Back pain	1	18
Hypertension	1	18
C-reactive protein increased	0	17
Pyrexia	1	16
Vomiting	0	16

Source: ISS ADAE where TREMFL4='Y' by AEDECOD and TRTA.

Reviewer Comment: Similar to Table 28, Table 32 does not contain percentages of subjects experiencing a TEAE because TEAEs could be reported more than once by the same subject. In addition to TEAEs that may relate to the underlying IBD, lymphopenia, infections, hepatic transaminase elevations, headaches, and hypertension are again noted to be commonly reported TEAEs in this population.

As before, a TEAE summary in which a particular TEAE is only counted once per subject and in which related TEAEs are grouped together may give a clearer picture of the safety of a medication; the results of the Office of Drug Evaluation-1 (ODE-1) safety analysis tool for TEAEs reported by 10 or more of the 654 subjects in the IBD safety population follows in Table 33.

Table 33. Reviewer Table. ODE-1 analysis of TEAE by assigned treatment, Pool C

AEDECOD	Overall ozanimod n=654
infection, all	148 (22.6%)
URI, cold, rhinitis, upper resp tract infection, flu-like illness	89 (13.6%)
diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	76 (11.6%)
leukopenia (neutropenia and/or lymphopenia)	73 (11.2%)
Lymphopenia	65 (9.9%)
GOT, GPT, GGTP, LFTs	55 (8.4%)

AEDECOD	Overall ozanimod n=654
Anemia	48 (7.3%)
abdominal pain, distension, bloating, spasm, IBS, megacolon	44 (6.7%)
arthralgia, arthritis, arthrosis	37 (5.7%)
dyspepsia, N, V, indigestion, epigastric pain, gastritis	37 (5.7%)
infection, viral	30 (4.6%)
Headache	30 (4.6%)
Nausea, vomiting	30 (4.6%)
eye other	22 (3.4%)
hypertension, BP increased	19 (2.9%)
fever, rigors	18 (2.8%)
rash, eruption, dermatitis	17 (2.6%)
abscess, boil, furuncle	16 (2.4%)
bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	15 (2.3%)
visual disturbance	14 (2.1%)
UTI	13 (2.0%)
infection, bacterial	11 (1.7%)
herpes virus	11 (1.7%)
solid neoplasia, ALL (benign, malignant, unknown)	11 (1.7%)
asthenia, fatigue, malaise, weakness, narcolepsy	11 (1.7%)
Hyperbilirubinemia, alk phos, jaundice	11 (1.7%)
Cough	10 (1.5%)

Reviewer Comment: Although some of the more common TEAEs in Pool C may relate to the underlying IBD, infections, lymphopenia, transaminase elevation, anemia, headache, and increased blood pressure are again seen as common adverse events in this analysis.

TEAE, Healthy Volunteers (Pool E)

The number (and percentage) of subjects in healthy volunteers (Pool E) who experienced TEAEs leading to study discontinuation, study drug discontinuation, study drug interruption, and requiring treatment are shown in Table 34.

Table 34. Reviewer Table. Summary of Healthy Volunteers Experiencing TEAE (Pool E)

	Overall Ozanimod n=496
TEAE	251 (50.6%)
TEAE leading to study discontinuation	4 (0.8%)
TEAE leading to study drug withdrawal	9 (1.8%)

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

	Overall Ozanimod n=496
TEAE leading to study drug interruption	0
TEAE requiring concomitant therapy	71 (14.3%)

Source: N Categories of SUBJID of ISS ADAE where TREMFL6='Y' and {φ, AESTFL='Y,' AEACN='DRUG WITHDRAWN,' AEACN='DRUG INTERRUPTED,' or AETRT<>'NONE'} by TRTA.

Reviewer Comment: Not surprisingly, the rates of TEAE (including those leading to study discontinuation or study drug withdrawal / interruption and those requiring concomitant therapy) are lower in the shorter clinical pharmacology studies in healthy volunteers than in those studies in subjects with RMS or IBD.

The numbers (and percentages) of healthy volunteers (Pool E) who experienced treatment emergent adverse events (TEAEs), as stratified by primary System Organ Class (SOC), are shown in Table 35.

Table 35. Reviewer Table. TEAEs stratified by primary SOC in healthy volunteers (Pool E)

AEBODSYS	Overall Ozanimod n=496
GASTROINTESTINAL DISORDERS	99 (20.0%)
NERVOUS SYSTEM DISORDERS	94 (19.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	84 (16.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	69 (13.9%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	30 (6.0%)
INFECTIONS AND INFESTATIONS	22 (4.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	20 (4.0%)
CARDIAC DISORDERS	15 (3.0%)
INVESTIGATIONS	13 (2.6%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11 (2.2%)
PSYCHIATRIC DISORDERS	11 (2.2%)
VASCULAR DISORDERS	10 (2.0%)
EYE DISORDERS	8 (1.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	5 (1.0%)

Clinical Review
 David E. Jones, M.D.
 NDA 209899
 Zeposia (ozanimod)

AEBOBSYS	Overall Ozanimod n=496
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	5 (1.0%)

Source: ISS ADAE where TREMFL6='Y' by AEBOBSYS.

Table 36 below delineates the TEAE PTs that were reported 10 or more times by healthy volunteers in Pool E.

Table 36. Reviewer Table. TEAE PTs reported 10 or more times by healthy volunteers (Pool E)

AEDECOD	Overall Ozanimod n=496
Headache	63
Dermatitis contact	44
Administration site reaction	39
Constipation	24
Nausea	20
Dizziness	17
Diarrhea	11
Medical device site irritation	10

Source: ISS ADAE where TREMFL6='Y' by AEDECOD.

This analysis also revealed two healthy volunteers who experienced second degree AV block with ozanimod.

Reviewer Comment: Table 35 and Table 36 do not suggest any previously unidentified risks plausibly related to ozanimod. Given the experience with S1P receptor modulators, bradyarrhythmia and atrioventricular block are not unexpected with ozanimod, although it should be noted that the events of second degree AV block occurred before the implementation of an initial dose escalation.

As before, a TEAE summary in which a particular TEAE is only counted once per subject and in which related TEAEs are grouped together may give a clearer picture of the safety of a medication; the results of the Office of Drug Evaluation-1 (ODE-1) safety analysis tool for TEAE reported by 10 or more of the healthy volunteers in Pool E follows in Table 37.

Table 37. Reviewer Table. ODE-1 analysis of TEAE in healthy volunteers, Pool E

AEDECOD	Overall ozanimod n=496
Headache	55 (11.1%)
injection site reaction (all)	40 (8.1%)

AEDECOD	Overall ozanimod n=496
Dermatitis	37 (7.5%)
abdominal pain, distension, bloating, spasm, IBS, megacolon	33 (6.7%)
dyspepsia, N, V, indigestion, epigastric pain, gastritis	25 (5.0%)
Nausea, vomiting	21 (4.2%)
infection, all	20 (4.0%)
Constipation	20 (4.0%)
dizziness, light-headedness	16 (3.2%)
diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	16 (3.2%)
fall, dizziness, balance disorder	16 (3.2%)
fall, dizziness, balance disorder, gait disturbance, difficulty walking	16 (3.2%)
somnolence, fatigue, sedation	12 (2.4%)

Reviewer Comment: This analysis of TEAEs in the studies of ozanimod in healthy volunteers is not revealing for convincing new safety signals that would reasonably be attributable to ozanimod.

8.4.6. Laboratory Findings

It is noted that transaminase elevations and lymphopenia are known issues of interest with other S1P receptor modulators, but care is taken to avoid focusing exclusively on these particular safety issues. In this section, descriptive statistics on laboratory analyses relevant to major organ systems (hepatobiliary, pancreatic, renal, and hematologic) are presented. Narratives of cases identified to be of special interest are reviewed.

Hepatobiliary

Elevated transaminases and hepatic injury are noted in the warnings and precautions section of the labeling for two other S1P receptor modulators and are thus of interest with ozanimod. Descriptive statistics for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), gamma glutamyl transferase (GGT), and alkaline phosphatase (ALP) collected during the controlled treatment phase for the safety population of Pool A are shown in Table 38.

Table 38. Reviewer Table. Hepatobiliary Labs, controlled RRMS population (Pool A)

	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Alanine Aminotransferase (ALT); reference range: 6 – 41 U/L¹					
Mean (std) (IU/L)	22.5 (28.0)	17.7 (8.8)	25.8 (29.7)	29.2 (31.5)	27.5 (30.7)
Median (IU/L)	16	16	19	21	20
Min, max (IU,L)	4, 828	4, 74	3, 1214	4, 1436	3, 1436
# subjects > 5x ULN	10 (1.1%)	0	8 (0.8%)	12 (1.2%)	20 (1.0%)
# subjects > 10x ULN	2 (0.2%)	0	2 (0.2%)	1 (0.1%)	3 (0.2%)
Aspartate Aminotransferase (AST); reference range: 9 – 43 U/L¹					
Mean (std) (IU/L)	19.9 (18.4)	19.2 (5.5)	20.0 (16.1)	21.7 (16.3)	20.9 (16.3)
Median (IU/L)	17	19	17	19	18
Min, max (IU,L)	6, 579	8, 40	6, 778	6, 588	6, 778
# subjects > 5x ULN	7 (0.8%)	0	3 (0.3%)	5 (0.5%)	8 (0.4%)
# subjects > 10x ULN	2 (0.2%)	0	1 (0.1%)	3 (0.3%)	4 (0.2%)
Gamma Glutamyltransferase (GGT); reference range: 5– 52 U/L¹					
Mean (std) (IU/L)	23.0 (27.0)	18.5 (13.3)	31.1 (38.5)	38.8 (44.4)	35.0 (41.7)
Median (IU/L)	16	13	19	24	21
Min, max (IU,L)	3, 1010	5, 78	4, 588	4, 627	4, 627
# subjects > 5x ULN	4 (0.5%)	0	15 (1.5%)	13 (1.3%)	28 (1.4%)
# subjects > 10x ULN	1 (0.1%)	0	2 (0.2%)	1 (0.1%)	3 (0.2%)
Total Bilirubin (TB); reference range: 1.7 – 18.8 umol/L					
Mean (std) (umol/L)	8.4 (4.4)	8.3 (4.6)	9.6 (5.5)	9.8 (6.2)	9.7 (5.9)
Median (umol/L)	7.5	7.2	8.4	8.4	8.4
Min, max (umol/L)	1.7, 42.4	1.9, 45	1.7, 52.5	2.6, 85.2	1.7, 85.2
# subjects > 2x ULN	1 (0.1%)	1 (1.1%)	14 (1.4%)	15 (1.6%)	29 (1.5%)
# subjects > 3x ULN	0	0	0	3 (0.3%)	3 (0.2%)
Alkaline Phosphatase (ALP); reference range: 30-116 U/L¹					
Mean (std) (IU/L)	58.1 (17.1)	65.2 (19.7)	57.5 (20.3)	59.9 (23.6)	58.7 (22.1)
Median (IU/L)	55	61	55	55	55
Min, max (IU,L)	11, 165	29, 143	19, 336	5, 295	5, 336
# subjects > 2x ULN	0	0	4 (0.4%)	2 (0.2%)	6 (0.3%)

Source: ISS ADLBC where POOL1='Y,' SAFCL='Y,' BASETYPE='ACORE', and AVISIT contains 'Month' by TRT01A.

¹ Several normal ranges are given for ALT, AST, and GGT in the ISS ADLBC dataset, so the range specified in this table encompassed the overall range of the given ranges for these three fields.

Reviewer Comment: Although the number of serious laboratory abnormalities appears low in this table, there does appear to be a signal for increased transaminases and liver injury with ozanimod, so this signal will be reviewed further. Because studies RPC01-

201B and RPC01-301 excluded subjects with an AST, ALT, or bilirubin > 1.5x ULN, this reviewer recommends that the labeling for ozanimod reflects both the potential risk of hepatic injury / transaminase elevation with ozanimod and the uncertainty regarding its safety when used in individuals with hepatic impairment.

Although an uncontrolled group is less informative than controlled groups when assessing for the presence of safety signals, a further analysis of the hepatobiliary labs was performed in subjects in Study RPC01-3001 because of the potential seriousness of drug induced liver injury (DILI), the hepatobiliary signal in the controlled RMS population, and the labeled warning for liver injury / transaminase elevations with approved S1P receptor modulators. Table 39 contains descriptive statistics for AST, ALT, GGT, TB, and ALP in the open-label extension (Study RPC01-3001) exploring the continued use of ozanimod 1 mg in subjects with RMS.

Table 39. Reviewer Table. Hepatobiliary Labs, RMS Study RPC01-3001

	Ozanimod 1 mg n=2494
Alanine Aminotransferase (ALT); reference range: 6 – 41 IU/L	
Mean (std) (IU/L)	24.5 (29.2)
Median (IU/L)	18
Min, max (IU,L)	2.9, 2008
# subjects > 5x ULN	4 (0.2%)
# subjects > 10x ULN	4 (0.2%)
Aspartate Aminotransferase (AST); reference range: 9 – 34 IU/L	
Mean (std) (IU/L)	18.7 (18.0)
Median (IU/L)	16
Min, max (IU,L)	6, 1377
# subjects > 5x ULN	6 (0.2%)
# subjects > 10x ULN	2 (0.1%)
Gamma Glutamyltransferase (GGT); reference range: 7 – 52 IU/L¹	
Mean (std) (IU/L)	41.4 (44.3)
Median (IU/L)	26
Min, max (IU,L)	4, 538
# subjects > 5x ULN	37 (1.5%)
# subjects > 10x ULN	2 (0.1%)
Total Bilirubin (TB); reference range: 1.7 – 18.8 umol/L	
Mean (std) (umol/L)	11.0 (5.9)
Median (umol/L)	9.4
Min, max (umol/L)	0, 80.4
# subjects > 2x ULN	50 (2.0%)
# subjects > 3x ULN	5 (0.2%)

	Ozanimod 1 mg n=2494
Alkaline Phosphatase (ALP); reference range: 37-116 IU/L	
Mean (std) (IU/L)	56.9 (22.2)
Median (IU/L)	53
Min, max (IU,L)	9, 1060
# subjects > 2x ULN	3 (0.1%)

¹ Two normal ranges are given for GGT in the ADLB dataset of RPC01-3001: 7- 38 and 11 - 52 U/L

Reviewer Comment: Although this analysis is confounded by an uncontrolled population and a low incidence of significant abnormalities, it does not refute the existence of a signal for transaminase elevations with ozanimod; however, the small numbers suggest that the risk does not increase with longer duration of exposure to this study medication.

The following hepatobiliary cases in subjects randomized to ozanimod were identified to be of interest from the above analyses but have not previously been described. The case narratives are summarized below:

- At screening, Subject (b) (6) was a 39yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-201A (and its extension) but then transitioned to ozanimod 1 mg in Study RPC01-3001. On Study Day 931, she developed fatigue, nausea, and was diagnosed with hepatitis with an ALT of 376 U/L, AST 175 U/L, TB 23.8 umol/L, and GGT 152 U/L. Relevant autoantibodies and serologies were unrevealing, as were an initial screening for risk factors for hepatitis and an abdominal ultrasound. The study medication was permanently discontinued. It was subsequently learned that she experienced about 20 bee stings at the time of this event. Her transaminases improved, but she had a further episode of nausea, right upper quadrant discomfort, and transaminase elevation (AST 1260 U/L, ALT 2008 U/L, TB 43.1 umol/L) after 10 bee stings about two weeks later. She eventually had a liver biopsy, which reportedly was suggestive of autoimmune hepatitis. The narrative suggests that this case of liver injury was most likely due to the bee stings

Reviewer Comment: Although the ALT (>3x ULN) and TB (> 2x ULN) is concerning for a Hy's Law case indicating Drug-Induced Liver Injury (DILI) with ozanimod, the temporal association with both episodes with numerous bee stings suggests that these laboratory abnormalities are likely a result of the bee stings. This reviewer notes that some consider bee venom to be an alternative therapy for MS.

- At screening, Subject (b) (6) was a 43yo woman who was randomized to ozanimod 0.5mg in Study RPC01-201B but transitioned to ozanimod 1 mg in Study RPC01-3001. On Day 546 of Study RPC01-3001, she developed moderate

transaminase elevations (ALT 383 U/L, AST 312 U/L, GGT 285 U/L, ALP 159 U/L). Work-up included an ultrasound that showed calculous cholecystitis, for which she had a laparoscopic cholecystectomy on Study Day 640. She remained on the study medication, and her transaminases normalized.

Reviewer Comment: This case of transaminase elevation appears attributable to cholecystitis.

- At screening, Subject (b) (6) was a 50yo man who was randomized to ozanimod 1 mg. in Study RPC01-201B. The study medication was discontinued on Study Day 681 after he was hospitalized with pyrexia and a polycystic central nervous system lesion (initially deemed attributable to MS, but later attributed to infection, especially as he improved with “empirical treatment for TB, toxoplasmosis, and fungal infection;”) of note, his hospital course was complicated by a pulmonary embolism. On Study Date 736 (approximately 45 days after stopping ozanimod), he developed a moderate transaminase elevation (ALT 401 U/L, AST 93 U/L, GGT 479 U/L).

Reviewer Comment: This reviewer agrees with the Investigator that this event is much more likely to be related to the aforementioned acute medical issues (and the drugs administered to treat them) than a delayed reaction to ozanimod.

- At screening, Subject (b) (6) was a 22yo woman who was randomized to ozanimod 1 mg in Study RPC01-201B. On Day 639 of Study RPC01-3001, she was noted to have an ALT of 1436 U/L, an AST of 588 U/L, and a GGT of 216 U/L. She remained on the study medication, and the event was considered resolved when her transaminases normalized on Study Day 655. The narrative does not discuss the work-up (if any) for this very short-lived but severe transaminase elevation.
- At screening, Subject (b) (6) was a 26yo man who was randomized to ozanimod 1 mg in Study RPC01-301. On Study Day 272, he experienced a moderate transaminase elevation (AST 403 U/L, ALT 156 U/L), but these improved rapidly with temporary discontinuation of the study medication. It appears that the transaminase elevation did not recur when the study medication was resumed. It is noted that he was on acetaminophen throughout the study.
- At screening, Subject (b) (6) was a 19yo woman who was randomized to ozanimod 1 mg in Study RPC01-301 and who developed a moderate transaminase elevation (AST 458 U/L, ALT 127 U/L) on Study Day 89. The transaminase elevations corrected quickly, and she completed RPC01-301 on the study drug.

Reviewer Comment: These three additional cases of transaminase elevation are of unclear etiology but are possibly related to ozanimod, especially as liver injury is a labeled warning for two other S1P receptor modulators; however, it is reassuring that these abnormalities improved quickly, even in subjects who continued the study medication.

The following unique cases are described in the ISS as having both AST/ALT and TB elevations; cases [REDACTED] (b) (6) are discussed above.

- At screening, Subject [REDACTED] (b) (6) was a 65yo woman who had Crohn's disease and was randomized to ozanimod 1 mg in the RPC01-2201 Study. On Study Day 201, she was noted to have marked elevations in ALT, AST, GGT, ALP, and bilirubin; she was subsequently found to have metastatic pancreatic adenocarcinoma, and the study medication was discontinued on Study Day 246.

Reviewer Comment: This reviewer suspects that the onset of this case of pancreatic cancer precedes the initiation of ozanimod and notes that inflammatory bowel disease may increase the risk of pancreatic cancer; therefore, this case is deemed to be likely unrelated to ozanimod, although it is noted that malignancy (especially cutaneous malignancy) has been linked to other S1P receptor modulators.

- At screening, Subject [REDACTED] (b) (6) was a 23yo woman with a reported history of Gilbert's syndrome who was randomized to ozanimod 1 mg in Study RPC01-201B and remained on this dose of ozanimod when she transitioned to RPC01-3001. Her total bilirubin remained elevated throughout the study, with lab results ranging from 25.1 to 85.2 umol/L. On Study Day 90, she was also found to have ALT, AST, and GGT elevations (136 U/L, 57 U/L 65 U/L, respectively). The study medication was continued, and the transaminase elevations improved. She remained in the RPC01-3001 study.

Reviewer Comment: Although these lab values are initially concerning for a Hy's law case of DILI, the reported history of Gilbert's syndrome and the improved transaminases despite continued exposure to the medication in the randomized and then open-label phase of the study suggest that this is not a Hy's law case of DILI, as was suggested by an external Hepatic Advisory Board.

- At screening, Subject [REDACTED] (b) (6) was a 35yo man who was randomized to interferon β -1a in Study RPC01-301 and transitioned to ozanimod 1 mg in the RPC01-3001 extension. On Day 456 of Study RPC01-3001, he developed severe transaminase elevations (ALT 1517 U/L, AST 1377 U/L, GGT 437 U/L, TB 31.8 umol/L); however, these values normalized when rechecked on Study Day 461.

Reviewer Comment: Given the very rapid resolution of these severe hepatic laboratory abnormalities, this reviewer agrees with the hepatic advisory board that this spurious result likely represents a laboratory error.

- At screening, Subject (b) (6) was a 26yo man who was randomized to ozanimod 1 mg in Study RPC01-301 and remained on this dose in the RPC01-3001 extension. Of note, his total bilirubin was elevated at 24.6 umol/L on baseline. On Study Day 92, his ALT and AST were elevated to 136 and 68 U/L, respectively, and his TB was higher at 35.2 umol/L. A gastroenterologist suggested “medical hepatitis,” but an ultrasound with without evidence of hepatomegaly. On Study Day 112, his ALT was 131 U/ L (> 3x ULN) and his TB was 49.9 (> 2 x ULN), potentially meeting criteria for Hy’s law. Other causes of these transaminase elevations were not found; despite remaining on the study medication, his transaminases normalized, but his TB remained elevated. His TB elevated was attributed to Gilbert’s syndrome, and an external hepatic advisory panel agreed with this conclusion.

Reviewer Comment: This reviewer also agrees with the Gilbert’s syndrome hypothesis and suspect that this was not a Hy’s Law case of DILI, especially given the prolonged length of exposure to the study medication and the normalization of his transaminase early in the study.

- At screening, Subject (b) (6) was a 66yo woman who had a history of ulcerative colitis and was randomized to ozanimod 0.5 mg in the induction period of Study RPC01-202 and transitioned to ozanimod 1 mg in the open label period (OLP). On OLP Day 379, she was noted to have severe hyperbilirubinemia (TB 95.8 U/L), so the study medication was discontinued. She was then hospitalized for autoimmune hemolytic anemia (AHA) on OLP Day 386 and was treated with steroids; while in the hospital, her ALT increased to 65 U/L and her AST increased to 128 U/L. It was thought these laboratory abnormalities related to AHA, and an external Hepatic Advisory Board concluded that this case did not represent DILI. The AHA was deemed to be a complication of her ulcerative colitis.

Reviewer Comment: This reviewer agrees that this case likely relates to AHA and is not a Hy’s law case of DILI.

Additional cases of interest were sought by querying the ISS ADLBC dataset for subjects with a normal bilirubin at baseline and a bilirubin 2x ULN during the study. Twenty-four additional subjects of interest were identified, but none of these had an AST or ALT above 3X ULN, which is reassuring.

See further discussion of this adverse event of special interest in Section 8.5.1.

Reviewer Comment: The labeling of two other S1P receptor modulators include a Warning for liver injury and transaminase elevations in Section 5. Although infrequent in occurrence, it appears that transaminase elevations and seemingly reversible liver injury can also occur in subjects taking ozanimod; therefore, this reviewer recommends a similar Warning in Section 5 of the labeling for ozanimod.

Pancreatic

Descriptive statistics for amylase and hemoglobin A1C collected during the controlled treatment phase for the safety population of Pool A are shown in Table 40.

Table 40. Reviewer Table. Pancreatic Labs, controlled RRMS population (Pool A)

	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Amylase; reference range: 35 - 131 IU/L					
Mean (std) (IU/L)	58.5 (22.7)	66.9 (28.1)	57.8 (21.2)	57.4 (21.0)	57.6 (21.1)
Median (IU/L)	55	61	55	55	55
Min, max (IU,L)	4, 266	23,260	16, 271	12, 263	12, 271
# subjects > 2x ULN	2 (0.2%)	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Hemoglobin A1c; reference range: 4 - 6%					
Mean (std) (%)	5.3 (0.4)	5.2 (0.3)	5.2 (0.4)	5.2 (0.4)	5.2 (0.4)
Median (%)	5.3	5.2	5.2	5.2	5.2
Min, max (%)	3.6, 11.7	4.4, 7.0	3.6, 9.1	4.0, 9.9	3.6, 9.9
# subjects >7% but baseline < 6%	1 (0.1%)	0	2 (0.2%)	4 (0.4%)	6 (0.3%)

Source: ISS ADLBC where POOL1='Y,' SAFCFCL='Y,' BASETYPE='CORE,' and AVISIT contains 'Month' by TRT01A.

Reviewer Comment: From this analysis, it does not appear that ozanimod has a significant effect on amylase or hemoglobin A1c, so further analyses of pancreatic issues do not appear warranted at this time.

Cholesterol

Descriptive statistics for low density lipoprotein (LDL) collected from subjects in the controlled RMS population (Pool A) are shown in Table 41.

Table 41. Reviewer Table. LDL, controlled RRMS population (Pool A)

	IFN β -1a 30 mcg	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline LDL (mmol/L)				
Mean (std)	2.99 (0.87)	2.99 (0.83)	2.92 (0.85)	2.95 (0.84)
Month 6 LDL (mmol/L)				
Mean (std)	2.85 (0.83)	3.10 (0.88)	3.08 (0.94)	3.09 (0.91)
Mean Chg from baseline	-0.15	0.10	0.15	0.13
Month 12 LDL (mmol/L)				
Mean (std)	2.90 (0.85)	3.07 (0.87)	3.08 (0.96)	3.08 (0.92)
Mean Chg from baseline	-0.10	0.10	0.17	0.13
Month 18 LDL (mmol/L)				
Mean (std)	2.82 (0.86)	3.13 (0.95)	3.09 (0.92)	3.11 (0.93)
Mean Chg from baseline	-0.11	0.14	0.18	0.16
Month 24 LDL (mmol/L)				
Mean (std)	2.92 (0.90)	3.19 (0.93)	3.22 (0.94)	3.20 (0.94)
Mean Chg from baseline	0.01	0.21	0.28	0.25

Source: ISS ADLBC where POOL1='Y,' SAFCL='Y,' and BASETYPE='CORE' by TRT01A and AVISIT

Reviewer Comment: The use of ozanimod appears to cause a small but sustained increase in LDL. Increased LDL is a risk factor for cerebrovascular and cardiovascular disease and is associated with an increased risk of myocardial infarction and stroke; however, a safety signal for myocardial infarction or stroke is not noted in Sections 8.4.2 – 8.4.5 of this review. An increase in total cholesterol is described in the clinical review of safety for siponimod.

Electrolytes

Similarly, descriptive statistics of the electrolyte data for the safety population of Pool A are shown in Table 42.

Table 42. Reviewer Table. Electrolytes, controlled RRMS population (Pool A)

	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Sodium; reference range: 133 – 145 mmol/L					
Mean (std) (mmol/L)	140.6 (2.2)	142.4 (2.2)	140.9 (2.3)	140.9 (2.4)	140.9 (2.3)
Median (mmol/L)	141	142	141	141	141
Min, max (mmol/L)	123, 154	136, 150	123, 152	122, 154	122, 154
# subjects <128 mmol/L	5 (0.6%)	0	4 (0.4%)	6 (0.6%)	10 (0.5%)

	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
# subjects > 150 mmol/L	6 (0.7%)	0	6 (0.6%)	10 (1.0%)	16 (0.8%)
Potassium; reference range: 4.5 – 5.5 mmol/L					
Mean (std) (mmol/L)	4.4 (0.4)	4.2 (0.4)	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)
Median (mmol/L)	4.4	4.2	4.4	4.4	4.4
Min, max (mmol/L)	2.9, 6.6	3.4, 5.3	3.2, 6.8	3.2, 6.5	3.2, 6.8
# subjects < 3.5 mmol/L	12 (1.4%)	1 (1.1%)	13 (1.3%)	10 (1.0%)	23 (1.2%)
# subjects > 6.0 mmol/L	4 (0.5%)	0	5 (0.5%)	3 (0.3%)	8 (0.4%)
Chloride; reference range: 95-110 mmol/L					
Mean (std) (mmol/L)	103.0 (2.8)	102.6 (2.1)	103.4 (2.7)	103.5 (2.7)	103.4 (2.7)
Median (mmol/L)	103	103	103	103	103
Min, max (mmol/L)	90, 113	97, 108	93, 114	89, 114	89, 114
Calcium; reference range: 2.12-2.62 mmol/L					
Mean (std) (mmol/L)	2.4 (0.1)	2.3 (0.1)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)
Median (mmol/L)	2.35	2.32	2.35	2.35	2.35
Min, max (mmol/L)	1.7, 2.7	1.9, 2.7	1.1, 2.9	1.9, 2.9	1.1, 2.9
# subjects < 2.0	6 (0.7%)	2 (2.3%)	8 (0.8%)	6 (0.6%)	14 (0.7%)
# subjects > 2.7	2 (0.2%)	1 (1.1%)	3 (0.3%)	2 (0.2%)	5 (0.3%)
Magnesium; reference range: 0.65 – 1.05 mmol/L					
Mean (std) (mmol/L)	0.9 (0.1)	0.9	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Median (mmol/L)	0.9 (0.1)	0.9	0.9	0.9	0.9
Min, max (mmol/L)	0.4, 1.2	0.7, 1.0	0.6, 1.2	0.6, 1.2	0.6, 1.2
Phosphate; reference range: 0.81 – 1.45 mmol/L					
Mean (std) (mmol/L)	1.1 (0.2)	1.1 (0.2)	1.2 (0.2)	1.2 (0.2)	1.2 (0.2)
Median (mmol/L)	1.1	1.1	1.2	1.2	1.2
Min, max (mmol/L)	0.6, 2.1	0.7, 1.6	0.5, 1.9	0.5, 2.3	0.5, 2,3

Source: ISS ADLBC where POOL1='Y,' SAFCL='Y,' BASETYPE='CORE,' and AVISIT contains 'Month' by TRT01A.

Reviewer Comment: There does not appear to be an obvious signal for electrolyte abnormalities with ozanimod in these analyses. Despite that, this reviewer was puzzled why the ISS did not contain AEs (or SAEs) for the few subjects with seemingly severe hyponatremia (< 125mmol/L) or hypernatremia (> 150 mmol/L), so an Information Request was sent regarding this on 9/11/2019. The Applicant replied that “abnormal laboratory values should not be recorded on the AE eCRF ... clinically significant changes, in the judgement of the Investigator, in laboratory parameters (abnormalities) will be recorded as AEs.” This reviewer is surprised that these subjects were seemingly asymptomatic (and untreated), so these cases raise questions about the completeness of

the adverse event reporting and the accuracy of the laboratories performing these assays.

Renal

The effect of ozanimod on renal function is of interest, although it is noted that subjects with renal impairment (women with SCr > 1.4 mg/dL and men with SCr of > 1.6 mg/dL) were excluded from the RMS studies. Descriptive statistics of serum creatinine and blood urea nitrogen (BUN) for the safety population of Pool A are presented in Table 43. This table also contains the number of subjects with elevated urinary protein noted in the ISS ADLBU dataset.

Table 43. Reviewer Table. Renal Labs, controlled RRMS population (Pool A)

	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Serum Creatinine; reference range: 62 – 124 umol/L					
Mean (std) (umol/L)	63.2 (13.9)	68.7 (11.9)	64.1 (13.4)	64.1 (13.9)	64.1 (13.6)
Median (umol/L)	62	71	62	62	62
Min, max (umol/L)	27, 256	44, 106	27, 336	27, 309	27, 336
# subjects > 150 but baseline < 120 umol/L	1 (0.1%)	0	1 (0.1%)	2 (0.2%)	3 (0.2%)
Blood Urea Nitrogen (BUN); reference range: 1.78 – 7.14 mmol/L					
Mean (std) value	4.4 (1.2)	4.6 (1.3)	4.6 (1.2)	4.7 (1.3)	4.6 (1.2)
Median	4.3	4.6	4.3	4.6	4.6
Min, max	1.1, 12.1	1.1, 8.9	1.4, 12.5	1.4, 11.8	1.4, 12.5
# subjects > 1.5x ULN	1 (0.1%)	0	5 (0.5%)	3 (0.3%)	8 (0.4%)
Urine Protein; reference range = {Negative, Trace}					
# subjects with (+) urine protein	177 (20.0%)	3 (3.5%)	172 (17.6%)	193 (20.0%)	365 (18.8%)

Source: ISS ADLBC where POOL1='Y,' SAFCFCL='Y,' BASETYPE='CORE,' and AVISIT contains 'Month' by TRT01A.

Reviewer Comment: From this analysis, the BUN and creatinine values do not appear affected by ozanimod; however, the number of subjects with at least one positive test for urine protein is higher than expected. The lack of concerning signals in the electrolyte, BUN, and serum creatinine analyses is somewhat reassuring, but further analyses of urine protein appear to be required, especially given the following text from the ISS CSR and the Applicant's analyses of urine protein by visit in the safety population of Pool A1 (Figure 3).

"Urinary protein was detected in 16.6% in the ozanimod 1 mg group, 13.1% in the ozanimod 0.5 mg group, and 16.5% in the IFN β-1a group at baseline. The

highest incidence of urinary protein throughout the studies was recorded in the ozanimod 1 mg group (22.3%) at Month 6. On the same visit, the incidence of urinary protein was 21.9% each for the ozanimod 0.5 mg and IFN β -1a groups.”

Figure 3. Sponsor Table. Urine Protein by Visit, Pool A1

Urinalysis qualitative measurement by Visit
Pool A1, Safety Population

Parameter: Protein

Visit	IFN β -1a 30 μ g (N=885) n (%) [a]	RPC1063 0.5 mg (N=892) n (%) [a]	RPC1063 1 mg (N=882) n (%) [a]	Total RPC1063 (N=1774) n (%) [a]
Baseline[b]				
NEGATIVE	738 (83.5)	773 (86.9)	736 (83.4)	1509 (85.2)
POSITIVE	146 (16.5)	117 (13.1)	146 (16.6)	263 (14.8)
Month 3				
NEGATIVE	698 (79.7)	731 (82.9)	700 (80.3)	1431 (81.6)
POSITIVE	178 (20.3)	151 (17.1)	172 (19.7)	323 (18.4)
Month 6				
NEGATIVE	663 (78.1)	677 (78.1)	668 (77.7)	1345 (77.9)
POSITIVE	186 (21.9)	190 (21.9)	192 (22.3)	382 (22.1)
Month 9				
NEGATIVE	691 (83.2)	704 (82.1)	664 (79.0)	1368 (80.6)
POSITIVE	140 (16.8)	153 (17.9)	177 (21.0)	330 (19.4)
Month 12				
NEGATIVE	676 (82.7)	714 (85.4)	698 (83.8)	1412 (84.6)
POSITIVE	141 (17.3)	122 (14.6)	135 (16.2)	257 (15.4)
Month 15				
NEGATIVE	521 (83.1)	525 (84.1)	524 (83.3)	1049 (83.7)
POSITIVE	106 (16.9)	99 (15.9)	105 (16.7)	204 (16.3)
Month 18				
NEGATIVE	374 (85.6)	378 (84.6)	392 (86.5)	770 (85.6)
POSITIVE	63 (14.4)	69 (15.4)	61 (13.5)	130 (14.4)
Month 21				
NEGATIVE	327 (84.7)	335 (86.6)	324 (82.7)	659 (84.6)
POSITIVE	59 (15.3)	52 (13.4)	68 (17.3)	120 (15.4)
Month 24				
NEGATIVE	304 (81.3)	305 (81.1)	319 (82.6)	624 (81.9)
POSITIVE	70 (18.7)	71 (18.9)	67 (17.4)	138 (18.1)
Last On Study Drug[c]				
NEGATIVE	734 (84.7)	760 (86.3)	745 (85.5)	1505 (85.9)
POSITIVE	133 (15.3)	121 (13.7)	126 (14.5)	247 (14.1)
Last Off Study Drug[d]				
NEGATIVE	215 (87.4)	228 (88.0)	206 (83.1)	434 (85.6)
POSITIVE	31 (12.6)	31 (12.0)	42 (16.9)	73 (14.4)
Last[e]				
NEGATIVE	745 (84.9)	773 (86.9)	749 (85.3)	1522 (86.1)
POSITIVE	133 (15.1)	117 (13.1)	129 (14.7)	246 (13.9)

[a] Percentages are calculated based on the number of subjects with assessments at each visit.
[b] Baseline is defined as the last non-missing value prior to the first dose of study drug.
[c] Last On Study drug is defined as the last non-missing value while on study drug.
[d] Last Off Study drug is defined as the last non-missing value after discontinuing study drug.
[e] Last is defined as the latest non-missing value of Last On Study and Last Off Study.
Pool A1 includes studies RPC01-201 Part B and RPC01-301.

Reviewer Comment: Although there is some debate on the utility of “dipsticks” for assessing for urinary protein (McTaggart et al, 2014), the Applicant’s aforementioned

assessments of the frequency of urinary protein was concerning, especially because this finding can be a harbinger of serious kidney disease. Although the preceding BUN and serum creatinine analyses were somewhat reassuring, an Information Request (IR) was sent to the Sponsor to provide an explanation and provide context and further analyses given the percentage of subjects observed to have an elevated urinary protein at baseline or during the study. The Applicant replied on 23Oct2019 with updated analyses in which “Positive” was defined as values above “Trace” and “Trace” was considered negative and offered the following interpretation:

“In the RMS controlled studies (Pool A), the incidence of positive (greater than trace) urine protein at baseline was low and consistent across the treatment groups (< 5% in each treatment group)... incidence of positive urine protein findings remained generally stable across the treatment groups during the course of the studies.”

Given the above discussion, this reviewer reanalyzed the urine protein (defining “positive” and “negative” as the Applicant did in its 23Oct2019 IR response) for the safety population of Pool A in the ISS ADLBU dataset, and these values matched Table 1 from the Applicant’s IR response.

Table 44. Reviewer Table. Binary Urine Protein in the controlled RRMS population (Pool A)

	IFN β-1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline					
N	884	85	972	963	1935
# with (+) urine protein	39 (4.4%)	1 (1.2%)	29 (3.0%)	41 (4.3%)	70 (3.6%)
Month 3					
N	876	7	888	878	1766
# with (+) urine protein	53 (6.1%)	1 (14.3%)	35 (3.9%)	64 (7.3%)	99 (5.6%)
Month 6					
N	849	78	948	936	1884
# with (+) urine protein	44 (5.2%)	2 (2.6%)	47 (5.0%)	60 (6.4%)	107 (5.7%)
Month 9					
N	831	-	857	841	1698
# with (+) urine protein	39 (4.7%)	-	47 (5.5%)	52 (6.2%)	99 (5.8%)
Month 12					
N	817	-	836	833	1669
# with (+) urine protein	38 (4.7%)	-	28 (3.3%)	36 (4.3%)	64 (3.8%)
Month 15					
N	627	-	624	629	1253
# with (+) urine protein	34 (5.4%)	-	21 (3.4%)	19 (3.0%)	40 (3.2%)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Month 18					
N	437	-	447	453	900
# with (+) urine protein	27 (6.2%)	-	21 (4.7%)	19 (4.2%)	40 (4.4%)
Month 21					
N	386	-	387	392	779
# with (+) urine protein	19 (4.9%)	-	14 (3.6%)	23 (5.9%)	37 (4.7%)
Month 24					
N	374	-	376	386	762
# with (+) urine protein	16 (4.3%)	-	21 (5.6%)	29 (7.5%)	50 (6.5%)

Source: ISS ADLBU where POOL1='Y,' SAFCL='Y,' and BASETYPE='CORE' by TRT01A.

Reviewer Comment: Table 44 is reassuring and suggests against a signal for urinary protein elevations with ozanimod. Further analyses of the above results suggest that the urinary protein elevations were transient and potentially relating to many factors besides ozanimod, including the limited accuracy of the urinary "dipstick."

Hematology

Descriptive statistics were performed on the leukocyte, lymphocyte, hemoglobin, and platelet data collected from the controlled RMS population (Pool A). As lymphopenia is of interest due to the presumed mechanism of S1P receptor modulators, the number of subjects who had one or more lymphocyte counts below 0.5 and $0.2 \times 10^9/L$ is calculated as well. See Table 45.

Table 45. Reviewer Table. Hematology Labs, controlled RRMS population (Pool A)

	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Leukocytes; reference range: $3.7 - 11.0 \times 10^9/L$					
Mean (std) $\times 10^9/L$	6.4 (2.3)	6.7 (2.1)	5.5 (1.9)	5.2 (1.8)	5.3 (1.9)
Median $\times 10^9/L$	6.1	6.3	5.1	4.8	5.0
Min, max $\times 10^9/L$	1.7, 50.8	3, 17.5	1.4, 25.2	1.0, 21.6	1.0, 25.2
Lymphocytes; reference range: $0.9 - 3.6 \times 10^9/L$					
Mean (std) $\times 10^9/L$	1.8 (1.0)	1.8 (0.6)	1.0 (0.5)	0.8 (0.4)	0.9 (0.5)
Median $\times 10^9/L$	1.7	1.7	0.9	0.7	0.8
Min, max $\times 10^9/L$	0.3, 40.0	0.2, 3.8	0.2, 4.3	0.1, 4.8	0.1, 4.8
# subjects $< 0.5 \times 10^9/L$	10 (1.1%)	2 (2.3%)	18 (1.8%)	582 (60.3%)	600 (30.9%)
# subjects $< 0.2 \times 10^9/L$	0	0	4 (0.4%)	21 (2.2%)	25 (1.3%)
Hemoglobin; reference range: 110-155 g/L					
Mean (std) g/L	135.1 (14.9)	136.5 (14.6)	136.7 (15.1)	136.8 (15.0)	136.8 (15.0)

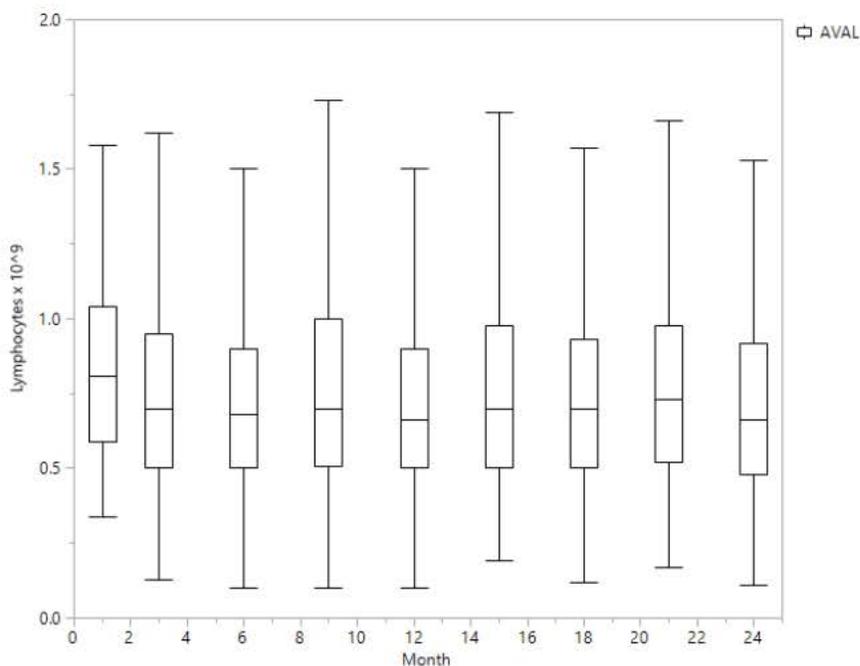
	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Median g/L	135	136	136	136	136
Min, max g/L	60, 179	93, 172	83, 186	72, 185	72, 186
Platelets; reference range: 125-375 x 10 ⁹ /L					
Mean (std) x 10 ⁹ /L	243.8 (57.3)	247.1 (72.2)	246.7 (57.4)	244.8 (60.2)	245.8 (58.8)
Median x 10 ⁹ /L	238	234	241	237	239
Min, max x 10 ⁹ /L	32, 613	142,778	49, 542	38, 609	38,609

Source: ISS ADLBC where POOL1='Y,' SAFCL='Y,' BASETYPE='CORE,' and AVISIT contains 'Month' by TRT01A.

Reviewer Comment: Comparing the ozanimod groups to the interferon beta-1 α and placebo arms, it does not appear that ozanimod has a significant impact on leukocyte count, hemoglobin, or platelet count, although it is noted that the size of the placebo arm is an order of magnitude lower than that of the other arms. Not surprisingly given the proposed mechanism of S1P receptor modulators, it appears clear that ozanimod has a dose-dependent effect on circulating lymphocyte counts.

Given ozanimod's effect on lymphocyte counts, one might question whether the effect increases with longer durations of exposure, so a plot of mean lymphocyte counts over time in subjects randomized to ozanimod 1mg in Pool A is shown in Figure 4.

Figure 4. Reviewer Figure. Mean lymphocyte counts over time with ozanimod 1 mg



Reviewer Comment: Although it appears that the drug in lymphocyte counts occurs quickly after starting ozanimod, it does not appear that lymphocyte counts continue to drop with longer exposures to ozanimod.

See further discussion of the risk of lymphopenia (and the increased risk of serious infections) with the use of ozanimod in Section 8.5.3.

8.4.7. Vital Signs

Vital signs are an essential component of safety monitoring and were checked hourly during the 6-hour observation after the first dose of the study medication was given and subsequently at periodic study visits throughout the trial. Given the labeled warnings for first dose bradyarrhythmia and atrioventricular blocks and for increased blood pressure with other S1P receptor modulators, heart rate (HR) and blood pressure changes were of special interest with ozanimod. Since pulmonary function tests were performed during the study, analyses of respiratory rate changes are not performed in this review.

Heart Rate (HR)

Descriptive statistics and change from baseline for sitting / supine heart rates (HR) obtained throughout the course of the trial are performed on the safety population of the controlled RMS population (SAFCFL, POOL1, and ANL01FL='Y,' BASETYPE='CORE,' PARC='Vital Signs,' PARAMCD='SISUSYBP')." See Table 46

Table 46. Reviewer Table. Sitting Heart Rate (HR) in controlled RMS population (Pool A)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline HR (bpm)					
N	885	88	979	965	1944
Mean (std)	69.3 (9.0)	69.4 (8.7)	68.3 (9.1)	68.6 (8.9)	68.4 (9.0)
Median	68	69	67	67	67
Min, Max	50, 111	55, 96	45, 106	49, 111	45, 111
Month 3 HR (bpm)					
N	873	87	971	954	1925
Mean (std)	72.6 (8.9)	71.6 (8.9)	71.2 (8.4)	70.8 (8.5)	71.0 (8.4)
Median	72	72	70	70	70
Min, Max	51, 107	49, 101	48, 111	51, 117	48, 117
Mean Chg from baseline	3.2	2.3	2.9	2.2	2.6
# with Chg < -10	53 (6.0%)	7 (8.0%)	68 (7.0%)	66 (6.9%)	134 (7.0%)
Month 6 HR (bpm)					

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

	IFN β-1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
N	856	81	953	940	1893
Mean (std)	71.9 (8.8)	71.4 (8.4)	70.9 (8.4)	70.3 (8.0)	70.6 (8.2)
Median	71	72	70	70	70
Min, Max	48, 112	49, 109	49, 118	45, 117	45, 118
Mean Chg from baseline	2.5	2.0	2.6	1.7	2.1
# with Chg < -10	62 (7.2%)	4 (4.9%)	58 (6.1%)	77 (8.2%)	135 (7.1%)
Month 9 HR (bpm)					
N	839	-	858	849	1707
Mean (std)	72.2 (8.6)	-	71.0 (8.3)	70.5 (8.1)	70.7 (8.2)
Median	72	-	70	70	70
Min, Max	41, 105	-	45, 113	51, 115	45, 115
Mean Chg from baseline	2.7	-	2.6	1.7	2.2
# with Chg < -10	64 (7.6%)	-	55 (6.4%)	76 (9.0%)	131 (7.7%)
Month 12 HR (bpm)					
N	826	-	839	838	1677
Mean (std)	71.1 (9.1)	-	69.9 (8.4)	69.9 (8.9)	69.9 (8.7)
Median	70	-	69	70	70
Min, Max	49, 104	-	48, 109	45, 114	45, 114
Mean Chg from baseline	1.6	-	1.4	1.2	1.3
# with Chg < -10	75 (9.1%)	-	63 (7.5%)	75 (8.9%)	138 (8.2%)
Month 15 HR (bpm)					
N	630	-	629	634	1263
Mean (std)	72.0 (8.9)	-	70.8 (8.2)	70.6 (8.3)	70.7 (8.2)
Median	70	-	70	70	70
Min, Max	50, 119	-	49, 113	46, 113	46, 113
Mean Chg from baseline	2.2	-	2.4	1.6	2.0
# with Chg < -10	61 (9.7%)	-	45 (7.2%)	48 (7.6%)	93 (7.4%)
Month 18 HR (bpm)					
N	439	-	450	458	908
Mean (std)	72.1 (8.7)	-	70.7 (7.9)	71.2 (8.4)	71.0 (8.2)
Median	72	-	70	70	70
Min, Max	51, 102	-	47, 100	51, 107	47, 107
Mean Chg from baseline	2.3	-	2.2	2.3	2.3
# with Chg < -10	42 (9.6%)	-	32 (7.1%)	40 (8.7%)	72 (7.9%)
Month 21 HR (bpm)					
N	387	-	388	399	787
Mean (std)	72.3 (9.0)	-	71.2 (8.3)	71.5 (8.1)	71.4 (8.2)
Median	70	-	70	70	70

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Min, Max	50, 107	-	48, 103	49, 100	48, 103
Mean Chg from baseline	2.7	-	2.8	2.4	2.6
# with Chg < -10	41 (10.6%)	-	22 (5.7%)	33 (8.3%)	55 (7.0%)
Month 24 HR (bpm)					
N	378	-	376	389	765
Mean (std)	72.0 (9.3)	-	70.6 (9.1)	70.4 (9.1)	70.5 (9.1)
Median	71	-	69	70	70
Min, Max	48, 114	-	48, 117	49, 103	48, 117
Mean Chg from baseline	2.4	-	2.0	1.2	1.6
# with Chg < -10	33 (8.7%)	-	30 (8.0%)	37 (9.5%)	67 (8.8%)

Reviewer Comment: It does not appear that ozanimod had a lasting clinically significant effect on HR during the conduct of the trials of the controlled RMS population.

HR was checked hourly (for six hours) after the first dose of the study medication was administered, and similar analyses of these “first dose” HRs are shown in Table 47.

Table 47. Reviewer Table. First Dose Sitting HR in controlled RMS population (Pool A)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline HR (bpm)					
N	885	88	979	965	1944
Mean (std)	69.3 (9.0)	69.4 (8.7)	68.3 (9.1)	68.6 (8.9)	68.4 (9.0)
Median	68	69	67	67	67
Min, Max	50, 111	55, 96	45, 106	49, 111	45, 111
Hour 1 HR (bpm)					
N	882	88	977	965	1942
Mean (std)	70.9 (9.6)	70.9 (9.4)	70.0 (9.5)	69.9 (9.3)	69.9 (9.4)
Median	70	71	69	69	69
Min, Max	46, 108	56, 96	47, 111	45, 120	45, 120
Mean Chg from baseline	1.6	1.5	1.7	1.3	1.5
# with Chg < -10	37 (4.2%)	4 (4.5%)	39 (4.0%)	44 (4.6%)	83 (4.3%)
Hour 2 HR (bpm)					
N	882	88	977	965	1942
Mean (std)	72.2 (9.5)	71.5	69.7 (9.4)	69.5 (9.5)	69.6 (9.4)
Median	72	70	69	68	68.5
Min, Max	50, 109	44, 99	48, 115	44, 105	44, 115

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Mean Chg from baseline	2.9	2.1	1.4	0.9	1.1
# with Chg < -10	42 (4.8%)	4 (4.5%)	62 (6.3%)	65 (6.7%)	127 (6.5%)
Hour 3 HR (bpm)					
N	882	88	977	965	1942
Mean (std)	73.7 (9.9)	72.1 (9.7)	69.1 (9.8)	68.4 (9.2)	68.7 (9.5)
Median	73	69	68	68	68
Min, Max	50, 112	54, 97	46, 120	43, 99	43, 120
Mean Chg from baseline	4.4	2.7	0.8	-0.2	0.3
# with Chg < -10	34 (3.9%)	6 (6.8%)	71 (7.3%)	75 (7.8%)	146 (7.5%)
Hour 4 HR (bpm)					
N	882	88	977	965	1942
Mean (std)	75.0 (10.6)	71.9 (9.2)	67.9 (9.1)	67.6 (9.0)	67.7 (9.0)
Median	74	70	67	66	67
Min, Max	47, 116	51, 96	45, 112	40, 100	40, 112
Mean Chg from baseline	5.7	2.5	-0.4	-1.0	-0.7
# with Chg < -10	34 (3.9%)	6 (6.8%)	92 (9.4%)	111 (11.5%)	203 (10.5%)
Hour 5 HR (bpm)					
N	883	88	977	965	1942
Mean (std)	76.1 (10.7)	72.6 (10.2)	67.4 (8.7)	67.5 (8.8)	67.4 (8.8)
Median	75	70	66	66	66
Min, Max	49, 118	50, 99	46, 114	42, 100	42, 114
Mean Chg from baseline	6.7	3.2	-0.9	-1.2	-1.0
# with Chg < -10	28 (3.2%)	7 (8.0%)	107 (11.0%)	114 (11.8%)	221 (11.4%)
Hour 6 HR (bpm)					
N	881	87	975	964	1939
Mean (std)	77.9 (11.2)	74.1 (10.0)	68.5 (8.7)	68.3 (8.8)	68.4 (8.7)
Median	77	72	68	68	68
Min, Max	52, 120	50, 100	41, 117	41, 101	41, 117
Mean Chg from baseline	8.5	4.9	0.2	-0.3	-0.0
# with Chg < -10	18 (2.0%)	3 (3.4%)	84 (8.6%)	83 (8.6%)	167 (8.6%)

Reviewer Comment: Not surprisingly given the labeled warnings for bradyarrhythmia and atrioventricular block with other S1P receptor modulators, Table 47 suggests that there can be a decrease in heart rate after administration of the first dose of ozanimod, seemingly reaching a nadir at five hours.

See further discussion of the risk of bradyarrhythmia after the first dose of ozanimod in Section 8.5.2.

Systolic Blood Pressure (SBP)

Descriptive statistics and change from baseline for sitting / supine systolic blood pressure (BP) obtained throughout the course of the trial are performed on the safety population of the controlled RMS population (SAFCFL, POOL1, and ANL01FL='Y,' Basetype='CORE,' PARC='Vital Signs,' PARAMCD='SISUSYBP')." See Table 48.

Table 48. Reviewer Table. Sitting SBP in controlled RMS population (Pool A)

	IFN β-1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline SBP (mm Hg)					
N	885	88	979	965	1944
Mean (std)	115.9 (12.8)	115.5 (12.2)	115.6 (11.8)	116.0 (12.8)	115.8 (12.3)
Median	115	115.5	115	115	115
Min, Max	85, 171	90, 155	70, 170	85, 190	70, 190
Month 3 SBP (mm Hg)					
N	874	87	971	954	1925
Mean (std)	118.8 (12.2)	118.6 (11.9)	120.1 (12.4)	120.1 (12.8)	120.1 (12.6)
Median	120	119	120	120	120
Min, Max	90, 168	98, 150	90, 167	90, 179	90, 179
Mean Chg from baseline	3.0	3.1	4.6	4.0	4.3
# with Chg > 10	184 (21.1%)	21 (24.1%)	239 (24.6%)	229 (24.0%)	468 (24.3%)
Month 6 SBP (mm Hg)					
N	856	81	953	940	1893
Mean (std)	119.1 (12.8)	119.6 (13.4)	120.2 (12.0)	120.3 (12.3)	120.2 (12.1)
Median	120	118	120	120	120
Min, Max	90, 179	98, 175	85, 163	90, 167	85, 167
Mean Chg from baseline	3.1	3.6	4.6	4.2	4.4
# with Chg > 10	188 (22.0%)	19 (23.5%)	228 (23.9%)	216 (23.0%)	444 (23.5%)
Month 9 SBP (mm Hg)					
N	839	-	858	849	1707
Mean (std)	119.5 (12.2)	-	120.3 (11.9)	120.0 (11.9)	120.1 (11.9)
Median	120	-	120	120	120
Min, Max	90, 170	-	90, 185	80, 172	80, 185
Mean Chg from baseline	3.3	-	4.9	4.0	4.4
# with Chg > 10	195 (23.2%)	-	218 (25.4%)	206 (24.3%)	424 (24.8%)
Month 12 SBP (mm Hg)					
N	826	-	839	838	1677
Mean (std)	119.3 (12.3)	-	119.6 (11.9)	119.8 (12.9)	119.7 (12.4)

	IFN β-1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Median	120	-	120	120	120
Min, Max	90, 177	-	90, 173	88, 180	88, 180
Mean Chg from baseline	3.1	-	4.2	3.8	4.0
# with Chg > 10	180 (21.8%)	-	182 (21.7%)	199 (23.7%)	381 (22.7%)
Month 15 SBP (mm Hg)					
N	630	-	630	635	1265
Mean (std)	112.6 (12.2)	-	120.0 (12.0)	121.4 (12.7)	120.7 (12.4)
Median	120	-	120	120	120
Min, Max	85, 164	-	85, 163	90, 171	85, 171
Mean Chg from baseline	3.6	-	4.9	5.3	5.1
# with Chg > 10	151 (24.0)	-	167 (26.5%)	179 (28.2%)	346 (27.4%)
Month 18 SBP (mm Hg)					
N	439	-	450	458	908
Mean (std)	118.7 (12.9)	-	119.3 (11.3)	121.4 (13.7)	120.4 (12.6)
Median	117	-	120	120	120
Min, Max	84, 190	-	90, 155	90, 214	90, 214
Mean Chg from baseline	2.6	-	3.7	5.2	4.5
# with Chg > 10	88 (20.0%)	-	104 (23.1%)	124 (27.1%)	228 (25.1%)
Month 21 SBP (mm Hg)					
N	387	-	388	399	787
Mean (std)	119.3 (12.2)	-	120.9 (12.0)	121.6 (13.2)	121.3 (12.6)
Median	119	-	120	120	120
Min, Max	90, 160	-	90, 164	90, 174	90, 174
Mean Chg from baseline	3.3	-	5.0	5.3	5.1
# with Chg > 10	92 (23.8%)	-	111 (28.6%)	119 (29.8%)	230 (29.2%)
Month 24 SBP (mm Hg)					
N	378	-	376	389	765
Mean (std)	119.5 (12.0)	-	120.9 (12.0)	121.4 (13.3)	121.2 (12.7)
Median	120	-	120	120	120
Min, Max	90, 171	-	0, 159	90, 179	90, 179
Mean Chg from baseline	3.6	-	4.9	5.2	5.0
# with Chg > 10	89 (23.5%)	-	99 (26.3%)	124 (31.9%)	223 (29.2%)

Reviewer Comment: Table 48 suggests that there is a small but presumably clinically significant increase in SBP in the group of subjects who were randomized to ozanimod. This is not surprising since other S1P receptor modulators have a labeled warning for increased blood pressure, so this reviewer recommends that hypertension be included as a warning in Section 5 of the ozanimod labeling.

Sitting / supine SBP was checked hourly (for six hours) after the first dose of the study drug was administered, and similar analyses of these “first dose” SBPs are shown in Table 49.

Table 49. Reviewer Table. First Dose Sitting SBP in controlled RMS population (Pool A)

	IFN β-1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline SBP (mm Hg)					
N	885	88	979	965	1944
Mean (std)	115.9 (12.8)	115.5 (12.2)	115.6 (11.8)	116.0 (12.8)	115.8 (12.3)
Median	115	115.5	115	1115	115
Min, Max	85, 171	90, 155	70, 170	85, 190	70, 190
Hour 1 SBP (mm Hg)					
N	882	88	977	965	1942
Mean (std)	118.2 (12.9)	118.6 (12.3)	117.6 (12.6)	117.9 (13.1)	117.7 (12.9)
Median	118	120	118	117	117
Min, Max	80, 160	93, 170	60, 158	80, 182	60, 182
Mean Chg from baseline	2.3	3.1	2.0	1.9	1.9
# with Chg > 10	105 (11.9%)	17 (19.3%)	134 (13.7%)	117 (12.1%)	251 (12.9%)
Hour 2 SBP (mm Hg)					
N	882	88	977	965	1942
Mean (std)	117.9 (12.8)	116.8 (12.0)	117.3 (12.8)	117.7 (13.2)	117.5 (13.0)
Median	118	117	116	117	117
Min, Max	80, 160	95, 163	80, 167	80, 186	80, 186
Mean Chg from baseline	2.0	1.3	1.7	1.7	1.7
# with Chg > 10	123 (13.9%)	14 (15.9%)	142 (14.5%)	122 (12.6%)	264 (13.6%)
Hour 3 SBP (mm Hg)					
N	882	88	977	965	1942
Mean (std)	117.9 (12.6)	116.7 (12.4)	117.1 (12.4)	117.3 (13.1)	117.2 (12.7)
Median	118	115	116	117	117
Min, Max	85, 164	90, 165	80, 158	80, 181	80, 181
Mean Chg from baseline	2.0	1.2	1.5	1.3	1.4
# with Chg > 10	124 (14.0%)	12 (13.6%)	140 (14.3%)	126 (13.1%)	266 (13.7%)
Hour 4 SBP (mm Hg)					
N	882	88	977	965	1942
Mean (std)	118.0 (12.6)	116.7 (12.4)	116.8 (12.1)	117.2 (13.2)	117.0 (12.7)
Median	118	117.5	117	116	117
Min, Max	80, 165	84, 160	80, 155	80, 193	80, 193
Mean Chg from baseline	2.1	1.3	1.2	1.2	1.2

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
# with Chg > 10	120 (13.6%)	15 (17.0%)	123 (12.6%)	116 (12.0%)	239 (12.3%)
Hour 5 SBP (mm Hg)					
N	883	88	977	965	1942
Mean (std)	118.9 (13.2)	117.3 (13.2)	117.4 (12.3)	117.7 (13.7)	117.6 (13.0)
Median	120	116.5	117	117	117
Min, Max	80, 170	79, 155	80, 168	85, 210	80, 210
Mean Chg from baseline	3.0	1.8	1.8	1.7	1.7
# with Chg > 10	159 (18.0%)	15 (17.0%)	135 (13.8%)	142 (14.7%)	277 (14.2%)
Hour 6 SBP (mm Hg)					
N	881	87	975	964	1939
Mean (std)	119.8 (12.6)	118.5 (12.9)	118.4 (12.1)	118.7 (13.2)	118.6 (12.7)
Median	120	120	118	118	118
Min, Max	90, 171	87, 160	80, 158	80, 211	80, 211
Mean Chg from baseline	3.9	3.0	2.8	2.7	2.8
# with Chg > 10	168 (19.1%)	17 (19.5%)	148 (15.2%)	148 (15.4%)	296 (15.3%)

Reviewer Comment: There is a small increase in SBP after the first dose of the study medication was administered; however, it is noted that the increase was smaller in the groups that were randomized to ozanimod than the group that was randomized to interferon β -1a, so the clinical significance of this observation is unclear.

The maximum supine / sitting SBP's over 200 mm Hg is of interest; however, it is noted that these occurred in Subject (b) (6), who had a baseline SBP of 190 mm Hg; if this subject is removed from the analysis of SBP after the first dose of the study medication, the maximum supine / sitting SBP is 175 mm Hg.

Diastolic Blood Pressure (DBP)

Descriptive statistics and change from baseline for sitting / supine diastolic blood pressure (DBP) obtained throughout the course of the trial are performed on the safety population of the controlled RMS population (SAFCFL, POOL1, and ANL01FL='Y,' Basetype='CORE,' PARC='Vital Signs,' PARAMCD='SISUDIBP')." See Table 50.

Table 50. Reviewer Table. Reviewer Table. Sitting DBP in controlled RMS population (Pool A)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline DBP (mm Hg)					
N	885	88	979	965	1944
Mean (std)	73.4 (9.4)	74.9 (9.2)	73.6 (8.7)	73.4 (9.4)	73.5 (9.0)

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Median	73	74	73	73	73
Min, Max	50, 109	57, 102	46, 99	40, 114	40, 114
Month 3 DBP (mm Hg)					
N	874	87	971	954	1925
Mean (std)	75.2 (8.8)	75.7 (7.6)	75.2 (9.1)	75.1 (8.7)	75.2 (8.9)
Median	75	76	75	75	75
Min, Max	46, 105	60, 92	46, 110	50, 108	46, 110
Mean Chg from baseline	1.8	1.0	1.7	1.6	1.6
# with Chg > 10	114 (13.0%)	9 (10.3%)	123 (12.7%)	115 (12.1%)	238 (12.4%)
Month 6 DBP (mm Hg)					
N	856	81	953	940	1893
Mean (std)	75.0 (9.0)	76.3 (10.2)	75.2 (8.7)	75.0 (8.9)	75.1 (8.8)
Median	75	76	75	75	75
Min, Max	54, 109	53, 105	50, 107	46, 100	46, 107
Mean Chg from baseline	1.5	1.5	1.5	1.5	1.5
# with Chg > 10	101 (11.8%)	10 (12.3%)	124 (13.0%)	123 (13.1%)	247 (13.0%)
Month 9 DBP (mm Hg)					
N	839	-	858	849	1707
Mean (std)	75.4 (8.7)	-	75.4 (8.5)	74.6 (8.6)	75.1 (8.5)
Median	75	-	75	75	75
Min, Max	54, 112	-	51, 111	40, 112	40, 112
Mean Chg from baseline	1.9	-	2.0	1.3	1.6
# with Chg > 10	109 (13.0%)	-	123 (14.3%)	101 (11.9%)	224 (13.1%)
Month 12 DBP (mm Hg)					
N	826	-	839	838	1677
Mean (std)	75.2 (8.9)	-	75.1 (8.7)	75.1 (9.1)	75.1 (8.9)
Median	75	-	75	75	75
Min, Max	50, 114	-	52, 117	50, 111	50, 117
Mean Chg from baseline	1.7	-	1.7	1.8	1.7
# with Chg > 10	107 (13.0)	-	114 (13.6%)	116 (13.8%)	230 (13.7%)
Month 15 DBP (mm Hg)					
N	630	-	630	635	1265
Mean (std)	75.1 (8.8)	-	75.5 (9.0)	75.7 (9.4)	75.6 (9.2)
Median	75	-	75	75	75
Min, Max	52, 110	-	50, 106	50, 116	50, 116
Mean Chg from baseline	1.6	-	2.1	2.3	2.2
# with Chg > 10	97 (15.4%)	-	94 (14.9%)	97 (15.3%)	191 (15.1%)
Month 18 DBP (mm Hg)					

	IFN β-1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
N	439	-	450	458	908
Mean (std)	74.7 (9.2)	-	74.8 (8.9)	75.9 (9.3)	75.3 (9.1)
Median	74	-	74	75	75
Min, Max	51, 108	-	50, 100	52, 118	50, 118
Mean Chg from baseline	1.1	-	0.9	2.4	1.7
# with Chg > 10	56 (12.8%)	-	59 (13.1%)	77 (16.8%)	136 (15.0%)
Month 21 DBP (mm Hg)					
N	387	-	388	399	787
Mean (std)	74.4 (8.7)	-	75.4 (8.9)	75.7 (9.2)	75.6 (9.0)
Median	73	-	75	76	75
Min, Max	52, 100	-	58, 106	49, 116	49, 116
Mean Chg from baseline	0.9	-	1.4	2.0	1.7
# with Chg > 10	50 (12.9%)	-	60 (15.5%)	65 (16.3%)	125 (15.9%)
Month 24 DBP (mm Hg)					
N	378	-	376	389	765
Mean (std)	74.8 (8.7)	-	75.3 (8.9)	76.0 (9.6)	75.6 (9.3)
Median	74	-	75	75	75
Min, Max	55, 111	-	53, 101	45, 108	45, 108
Mean Chg from baseline	1.4	-	1.3	2.3	1.8
# with Chg > 10	50 (13.2%)	-	54 (14.4%)	67 (17.2%)	121 (15.8%)

Reviewer Comment: It does not appear that there is a consistent signal for a change in diastolic blood pressure in the groups randomized to ozanimod in the controlled RMS trials.

8.4.8. Electrocardiograms (ECGs)

S1P receptors are expressed on atrial myocytes cells of the cardiac conduction system, so it is not surprising that bradycardia and atrioventricular block are labeled warnings for fingolimod and siponimod. Early literature suggests that these effects were modulated by S1P3, but later literature (and the occurrence of these adverse events with an S1P1 / S1P5 receptor modulator [siponimod]) suggests involvement of other S1P subtypes, including S1P1. Due to rapid endocytosis of the S1P receptor in the setting of treatment with an S1P receptor modulator, bradyarrhythmia and atrioventricular blocks attributable to S1P receptor modulators are felt to occur several hours after initiation of the drug. The ozanimod clinical trials utilized an eight-day dose escalation (0.25mg from day 1-4, 0.5mg from day 5-7, and randomized dose of ozanimod after day 7) in an attempt to mitigate this risk.

Unless it was deemed necessary to perform electrocardiograms (ECGs) more often (e.g., abnormalities after the first dose of the study drug was administered), they were performed at screening, at baseline (before administration of the study drug), six hours after the study drug was administered, and again at 2 weeks, 12 months, and 24 months. Subjects in Study RPC01-201A also had ECGs at 3 and 6 months. Descriptive statistics of the PR interval and QTcF in the controlled RMS population (Pool A) are shown in Table 51 and Table 52, respectively.

Table 51. Reviewer Table., PR interval in controlled RRMS population (Pool A)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline PR Interval (msec)					
N	885	88	978	965	1943
Mean (std)	154.2 (20.0)	155.2 (17.5)	153.6 (21.1)	153.2 (20.2)	153.4 (20.6)
# subjects > 200	13 (1.5%)	0	21 (2.1%)	19 (2.0%)	40 (2.1%)
# subjects > 230	2 (0.2%)	0	2 (0.2%)	3 (0.3%)	5 (0.3%)
# subjects > 300	0	0	1 (0.1%)	0	1 (0.1%)
6-hour PR Interval (msec)					
N	880	88	974	959	1933
Mean (std)	153.7 (19.5)	153.7 (18.7)	155.7 (20.8)	155.4 (22.4)	155.6 (21.6)
Mean Chg from baseline	-0.5	-1.5	2.2	2.3	2.3
# subjects > 200	10 (1.1%)	2 (2.2%)	19 (2.0%)	25 (2.6%)	44 (2.3%)
# subjects > 230	2 (0.2%)	0	4 (0.4%)	5 (0.5%)	9 (0.5%)
# subjects > 300	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
2-week PR Interval(msec)					
N	879	-	881	878	1759
Mean (std)	154.7 (20.2)	-	153.4 (19.7)	154.4 (19.7)	153.9 (19.7)
Mean Chg from baseline	0.6	-	-0.2	1.1	0.5
# subjects > 200	16 (1.8%)	-	14 (1.6%)	14 (1.6%)	28 (1.6%)
# subjects > 230	2 (0.2%)	-	0	1	1 (0.1%)
# subjects > 300	0	-	0	0	0
3-month PR Interval (msec)					
N	-	85	85	82	167
Mean (std)	-	153.6 (18.5)	152.6 (24.8)	153.1 (21.3)	152.8 (23.1)
Mean Chg from baseline	-	-1.9	-0.2	0.5	0.2
# subjects > 200	-	1 (1.2%)	2 (2.4%)	0	2 (1.2%)
# subjects > 230	-	0	1 (1.2%)	0	1 (0.6%)
# subjects > 300	-	0	0	0	0
6-month PR Interval (msec)					
N	-	84	85	83	168

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Mean (std)	-	154.6 (19.0)	154.2 (20.8)	154.8 (20.6)	154.5 (20.6)
Mean Chg from baseline	-	-1.1	1.4	2.8	2.1
# subjects > 200	-	1 (1.2%)	1 (1.2%)	1 (1.2%)	2 (1.2%)
# subjects > 230	-	0	1 (1.2%)	0	1 (0.6%)
# subjects > 300	-	0	0	0	0
12-month PR Interval (msec)					
N	835	-	854	837	1691
Mean (std)	154.5 (20.5)	-	152.9 (19.9)	153.5 (19.5)	153.2 (19.7)
Mean Chg from baseline	0.17	-	-0.7	0.1	-0.3
# subjects > 200	13 (1.6%)	-	12 (1.4%)	15 (1.8%)	27 (1.6%)
# subjects > 230	4 (0.5%)	-	0	1 (0.1%)	0
# subjects > 300	0	-	0	0	0
24-month PR Interval (msec)					
N	396	-	397	409	806
Mean (std)	154.4 (20.4)	-	154.9 (18.5)	155.0 (20.1)	155.0 (19.3)
Mean Chg from baseline	-0.1	-	0.8	1.2	1.0
# subjects > 200	8 (2.0%)	-	6 (1.5%)	2 (0.5%)	8 (1.0%)
# subjects > 230	1 (0.3%)	-	1 (0.3%)	0	1 (0.1%)
# subjects > 300	0	-	0	0	0

Reviewer Comment: Although there appears to be a minimal increase in the PR interval after the first dose of ozanimod, this change is not apparent on the Week 2 or subsequent ECGs.

Table 52. Reviewer Table. QTcF in controlled RRMS population (Pool A)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline QTcF (msec)					
N	884	88	977	963	1940
Mean (std)	408.9 (19.2)	408.8 (18.7)	407.5 (18.3)	407.1 (18.2)	407.3 (18.2)
# >430 (M) or 450 (F)	27 (3.1%)	2 (2.3%)	14 (1.4%)	15 (1.6%)	29 (1.5%)
# >450 (M) or 470 (F)	2 (0.2%)	0	2 (0.2%)	1 (0.1%)	3 (0.2%)
# subjects > 480	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
6-hour QTcF (msec)					
N	867	88	969	952	1921
Mean (std)	405.4 (19.1)	405.6 (19.9)	408.9 (18.2)	408.0 (19.3)	408.5 (18.8)
Mean Chg from baseline	-3.4	-3.2	1.4	0.9	1.2

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
# >430 (M) or 450 (F)	23 (2.7%)	3 (3.4%)	15 (1.5%)	19 (2.0%)	34 (1.8%)
# >450 (M) or 470 (F)	0	0	1 (0.1%)	3 (0.3%)	4 (0.2%)
# subjects > 480	0	0	0	0	0
2-week QTcF (msec)					
N	870	-	875	873	1748
Mean (std)	407.4 (19.6)	-	408.2 (17.5)	408.3 (18.9)	408.3 (18.2)
Mean Chg from baseline	-1.3	-	1.2	1.3	1.2
# >430 (M) or 450 (F)	23 (2.6%)	-	17 (1.9%)	18 (2.1%)	35 (2.0%)
# >450 (M) or 470 (F)	5 (0.6%)	-	0	4 (0.5%)	4 (0.2%)
# subjects > 480	2 (0.2%)	-	0	1 (0.1%)	1 (0.1%)
3-month QTcF (msec)					
N	-	85	85	80	165
Mean (std)	-	407.6 (17.3)	413.0 (19.1)	409.3 (16.5)	411.2 (17.9)
Mean Chg from baseline	-	-0.3	3.2	1.5	2.3
# >430 (M) or 450 (F)	-	1 (1.2%)	1 (1.2%)	0	1 (0.6%)
# >450 (M) or 470 (F)	-	0	0	0	0
# subjects > 480	-	0	0	0	0
6-month QTcF (msec)					
N	-	83	85	83	168
Mean (std)	-	407.4 (18.1)	411.9 (17.7)	408.6 (16.5)	410.2 (17.1)
Mean Chg from baseline	-	-1.2	2.0	0.5	1.3
# >430 (M) or 450 (F)	-	1 (1.2%)	0	0	0
# >450 (M) or 470 (F)	-	0	0	0	0
# subjects > 480	-	0	0	0	0
12-month QTcF (msec)					
N	828	-	848	845	1683
Mean (std)	409.0 (19.0)	-	408.8 (17.5)	408.6 (18.7)	408.7 (18.1)
Mean Chg from baseline	0.1	-	1.5	1.6	1.5
# >430 (M) or 450 (F)	24 (2.9%)	-	21 (2.5%)	18 (2.1%)	39 (2.3%)
# >450 (M) or 470 (F)	2 (0.2%)	-	2 (0.2%)	1 (0.1%)	3 (0.2%)
# subjects > 480	0	-	0	0	0
24-month QTcF (msec)					
N	394	-	394	403	797
Mean (std)	405.9 (19.0)	-	407.4 (17.2)	407.6 (18.2)	407.5 (17.7)
Mean Chg from baseline	-2.3	-	1.4	2.0	1.6
# >430 (M) or 450 (F)	3 (0.8%)	-	6 (1.5%)	6 (1.5%)	12 (1.5%)
# >450 (M) or 470 (F)	0	-	0	0	0
# subjects > 480	0	-	0	0	0

Reviewer Comment: In subjects randomized to ozanimod, there appears to be a minimal increase in QTcF compared with baseline.

Table 53 delineates the commonly seen ECG abnormalities (and those of interest) in subjects in the controlled RMS population (Pool A).

Table 53. Reviewer Table. ECG abnormalities in controlled RMS population (Pool A)

ECG Abnormality	Baseline	Hour 6	Week 2 ¹	Month 12	Month 24
Interferon β-1a					
N	885	880	879	835	396
Right Axis Deviation	130 (14.7%)	127 (14.4%)	93 (10.6%)	93 (11.1%)	34 (8.6%)
Left Ventricular Hypertrophy	67 (7.6%)	67 (7.6%)	49 (5.6%)	31 (3.7%)	15 (3.8%)
Artifact	112 (12.7%)	79 (9.0%)	50 (5.7%)	88 (10.5%)	2 (0.5%)
Sinus Arrhythmia	93 (10.5%)	46 (5.2%)	93 (10.6%)	74 (8.9%)	37 (9.3%)
1 st degree AV block	16 (1.8%)	11 (1.3%)	16 (1.8%)	12 (1.4%)	8 (2.0%)
Short PR interval (<120 msec)	21 (2.4%)	9 (1.0%)	15 (1.7%)	11 (1.3%)	5 (1.3%)
Prolonged QT interval (>450 msec)	18 (2.0%)	12 (1.4%)	16 (1.8%)	12 (1.4%)	3 (0.8%)
Sinus bradycardia (< 50 bpm)	2 (0.2%)	0	11 (1.3%)	18 (2.2%)	3 (0.8%)
Sinus tachycardia (> 100 bpm)	7 (0.8%)	56 (6.4%)	14 (1.6%)	11 (1.3%)	8 (2.0%)
Placebo¹					
N	88	88	87	-	-
Right Axis Deviation	11 (12.5%)	10 (11.4%)	11 (12.6%)	-	-
Left Ventricular Hypertrophy	8 (9.1%)	6 (6.8%)	5 (5.7%)	-	-
Artifact	0	0	0	-	-
Sinus Arrhythmia	5 (5.7%)	8 (9.1%)	5 (5.7%)	-	-
1 st degree AV block	1 (1.1%)	2 (2.3%)	2 (2.3%)	-	-
Short PR interval (<120 msec)	0	0	0	-	-
Prolonged QT interval (>450 msec)	0	0	0	-	-
Sinus Bradycardia (<50 bpm)	0	1 (1.1%)	1 (1.1%)	-	-
Sinus Tachycardia (>100 bpm)	0	0	0	-	-
Ozanimod 0.5 mg					
N	976	972	879	852	397
Right Axis Deviation	99 (10.1%)	103 (10.6%)	72 (8.2%)	50 (5.9%)	29 (7.3%)
Left Ventricular Hypertrophy	73 (7.5%)	82 (8.4%)	34 (3.9%)	34 (4.0%)	19 (4.8%)
Artifact	104 (10.7%)	60 (6.2%)	52 (5.9%)	83 (9.7%)	3 (0.8%)
Sinus Arrhythmia	108 (11.1%)	83 (8.5%)	27 (3.1%)	28 (3.3%)	9 (2.3%)
1 st degree AV block	25 (2.6%)	18 (1.9%)	15 (1.7%)	13 (1.5%)	6 (1.5%)
Short PR interval (<120 msec)	20 (2.0%)	13 (1.3%)	18 (2.0%)	15 (1.8%)	4 (1.0%)

ECG Abnormality	Baseline	Hour 6	Week 2 ¹	Month 12	Month 24
Prolonged QT interval (>450 msec)	13 (1.3%)	3 (0.3%)	9 (1.0%)	13 (1.5%)	1 (0.3%)
Sinus Bradycardia (<50 bpm)	12 (1.2%)	17 (1.7%)	9 (1.0%)	7 (0.8%)	4 (1.0%)
Sinus Tachycardia (>100 bpm)	9 (0.9%)	4 (0.4%)	3 (0.3%)	7 (0.8%)	7 (1.8%)
Ozanimod 1 mg					
N	965	957	876	835	407
Right Axis Deviation	133 (13.8%)	129 (13.5%)	91 (10.4%)	84 (10.1%)	31 (7.6%)
Left Ventricular Hypertrophy	75 (7.8%)	77 (8.0%)	40 (4.6%)	41 (4.9%)	19 (4.7%)
Artifact	93 (9.6%)	66 (6.9%)	61 (7.0%)	90 (10.8%)	4 (1.0%)
Sinus Arrhythmia	114 (11.8%)	80 (8.4%)	27 (3.1%)	20 (2.4%)	9 (2.2%)
1 st degree AV block	22 (2.3%)	25 (2.6%)	15 (1.7%)	17 (2.0%)	2 (0.5%)
Short PR interval (<120msec)	26 (2.7%)	15 (1.6%)	12 (1.4%)	11 (1.3%)	5 (1.2%)
Prolonged QT interval (>450msec)	4 (0.4%)	9 (0.9%)	10 (1.1%)	8 (1.0%)	3 (0.7%)
Sinus Bradycardia (<50bpm)	13 (1.3%)	15 (1.6%)	10 (1.1%)	17 (2.0%)	4 (1.0%)
Sinus Tachycardia (>100bpm)	8 (0.8%)	2 (0.2%)	5 (0.6%)	9 (1.1%)	2 (0.5%)

Source: ISS ADEG AVALC where POOL1='Y,' SAFCL='Y,' and BASETYPE='CORE' by TRT01A by AVISIT

¹ Month 1 for placebo

Reviewer Comment: Right axis deviation, left ventricular hypertrophy, sinus arrhythmia, and artifacts were common ECG abnormalities, even at baseline; however, it is interesting that the percentages of these abnormalities decrease with continued follow-up, potentially suggesting either differential subject drop-out or improved ECG reading accuracy over time. Not surprisingly given the experience with other S1P receptor modulators, there appears to be a slightly increased risk of 1st degree atrioventricular block (and sinus bradycardia) six hours after the first dose of ozanimod 1mg compared to subsequent ECGs. This reviewer did not identify any cases of 2nd degree or higher atrioventricular block in this analysis, which is reassuring.

See further discussion of the risk of bradyarrhythmia and atrioventricular block, especially after the first dose of ozanimod, in Section 8.5.2.

8.4.9. QT

The Interdisciplinary Review Team for QT Studies (QT-IRT) was consulted to assess the QT effects of ozanimod. This team initially “reviewed a thorough QT study (study RPC01-102) and concluded a lack of clinically relevant effect at the worst-case scenario of ozanimod exposure of ozanimod at the 0.92 mg QD dose level ... however, the PK data acquired from study RPC01-102 was not adequate to represent steady-state exposure of CC112273, which accounts for 73% of an ozanimod dose and has an effective half-life of 10.9 days.” Resubmission of this NDA included Study RPC01-1914, which evaluated the effect of this metabolite on the QT interval; the QT-IRT concluded “no relevant QTc prolongation effect of ozanimod’s major metabolite, CC112273, was detected in this QT assessment.”

Reviewer Comment: Refer to the consults from QT-IRT for further comments (and recommendations about the labeling for ozanimod) labeling regarding the findings of these thorough QT studies.

8.4.10. Pulmonary Function Tests

S1P receptors, including S1P3, occur on the smooth muscle and the epithelium of the respiratory tract, so modulation of these receptors may lead to adverse events of the respiratory system. Indeed, dose dependent reductions in absolute forced expiratory volume over 1 second (FEV1) are labeled in Section 5 (Warnings and Precautions) of both a non-selective S1P receptor modulator (fingolimod) and a S1P1 / S1P5 selective S1P receptor modulator (siponimod) approved for RMS. The approval of both fingolimod and siponimod included a post market requirement (PMR) to further study the respiratory effects of these drugs. Given this, respiratory effects with ozanimod is an adverse event of special interest (AESI) for which pulmonary assessments were performed in the pivotal studies of ozanimod.

Pulmonary function tests, including FEV1 and forced vital capacity (FVC), were assessed in most subjects in Pool A at baseline and at 3, 6, and 12; however, it appears from the ADFA dataset that fewer than half of the subjects were tested at 24 months. The study medication was discontinued in subjects having an FEV1 or FVC less than 50% of what was predicted. Subjects who were followed at sites where diffusion capacity of the lungs for carbon monoxide (DLCO) testing was available were tested at baseline and at 6, 12, and 24 months. Results of these assessments are presented in the following tables.

Table 54. Reviewer Table. FEV1 in the controlled RMS population (Pool A)

	IFN β-1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline FEV1 (L)					
N	882	88	977	965	1942
FEV1 mean (SD)	3.5 (0.8)	3.3 (0.6)	3.5 (0.8)	3.5 (0.8)	3.5 (0.8)
3-month FEV1 (L)					
N	866	86	962	950	1912
FEV1 mean (SD)	3.5 (0.8)	3.4 (0.6)	3.4 (0.8)	3.4 (0.8)	3.4 (0.8)
FEV1 mean % chg from baseline	0.0%	1.0%	-0.9%	-1.6%	-1.3%
# with FEV1 < 80% baseline (%)	17 (2.0%)	0	29 (3.0%)	25 (2.6%)	54 (2.8%)
6-month FEV1 (L)					
N	843	84	946	935	1881
FEV1 mean (SD)	3.4 (0.8)	3.3 (0.6)	3.4 (0.8)	3.4 (0.8)	3.4 (0.8)
FEV1 mean % chg from baseline	-0.6%	-0.9%	-1.2%	-1.8%	-1.5%

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
# with FEV1 < 80% baseline (%)	20 (2.4%)	2 (2.4%)	29 (3.1%)	41 (4.4%)	70 (3.7%)
12-month FEV1 (L)					
N	822	-	833	826	1659
FVC mean (SD)	3.4 (0.8)	-	3.4 (0.8)	3.4 (0.8)	3.4 (0.8)
FEV1 mean % chg from baseline	-0.7%	-	-1.5%	-2.2%	-1.9%
# with FEV1 < 80% baseline (%)	18 (2.2%)	-	26 (3.1%)	35 (4.2%)	61 (3.7%)
24-month FEV1 (L)					
N	376	-	380	387	767
FEV1 mean (SD)	3.4 (0.8)	-	3.4 (0.8)	3.3 (0.8)	3.4 (0.8)
FEV1 mean % chg from baseline	-2.6%	-	-2.5%	-3.6%	-3.0%
# with FEV1 < 80% baseline (%)	12 (3.2%)	-	21 (5.5%)	22 (5.7%)	43 (5.6%)

Source: ISS ADFA where POOL1='Y,' SAF CFL='Y,' ANLF013='Y,' BASETYPE='CORE,' PARAM='FEV1' by TRT01A and AVISIT.

Reviewer Comment: Although the overall mean percent changes from baseline are small, Table 54 suggests that ozanimod has a potentially dose-dependent effect on FEV1, causing a relatively small subset of subjects receiving ozanimod to have an FEV1 below 80% of baseline. Although it appears that fewer than half of the subjects had testing at 24 months, the mean percent change and number of subjects with an FEV1 below baseline appears greater at this time point, so an analysis of FEV1 in Study RPC01-3001, an uncontrolled, open-label, ozanimod extension of RMS studies, is performed to assess for a continued decrement in FEV1. (The small subset of subjects who transitioned from placebo to ozanimod in Study RPC01-3001 is not considered.)

Table 55. Reviewer Table. FEV1 in Study RPC01-3001

	Transitioned from IFN β -1a 30 mcg	Transitioned from ozanimod 0.5 mg	Remained on ozanimod 1.0 mg
Baseline FEV1 (L)			
N	736	840	844
FVC mean (SD)	3.4 (0.8)	3.4 (0.8)	3.4 (0.8)
12-month FEV1 (L)			
N	707	815	815
FVC mean (SD)	3.5 (3.3)	3.4 (3.2)	3.5 (2.6)
FVC mean % chg from baseline	2.2%	3.3%	3.3%
# with FVC < 80% baseline (%)	17 (2.4%)	24 (2.9%)	10 (1.2%)
24-month FEV1 (L)			
N	47	108	123
FVC mean (SD)	3.4 (0.7)	3.2 (0.8)	3.1 (0.7)

	Transitioned from IFN β -1a 30 mcg	Transitioned from ozanimod 0.5 mg	Remained on ozanimod 1.0 mg
FVC mean % chg from baseline	-2.3%	-2.7%	-2.7%
# with FVC < 80% baseline (%)	1 (2.1%)	4 (3.7%)	5 (4.1%)

Source: RPC01-3001 ADLF where PARAM='FEV1' by TRTA and AVISIT.

Reviewer Comment: With the caveat that the number of subjects tested at Month 24 was suboptimal in both Pool A and Study RPC01-3001, analysis of the FEV1 results in Table 54 and Table 55 suggests that a small subset of subjects taking ozanimod had demonstrable effects of FEV1 but does not clearly show an incremental decrease in FEV1 with prolonged exposure to this agent.

Table 56. Reviewer Table. FVC in the controlled RMS population (Pool A)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline FVC (L)					
N	882	88	977	965	1942
FVC mean (SD)	4.1 (1.0)	4.1 (0.8)	4.2 (1.1)	4.2 (1.0)	4.2 (1.0)
3-month FVC (L)					
N	866	86	963	950	1913
FVC mean (SD)	4.1 (1.0)	4.1 (0.8)	4.1 (1.0)	4.1 (1.0)	4.1 (1.0)
FVC mean % chg from baseline	0.4%	0.7%	-0.1%	-0.4%	-0.2%
# with FVC < 80% baseline (%)	26 (3.0%)	2 (2.3%)	33 (3.4%)	30 (3.2%)	63 (3.3%)
6-month FVC (L)					
N	844	84	946	935	1881
FVC mean (SD)	4.1 (1.0)	4.0 (0.8)	4.1 (1.0)	4.1 (1.0)	4.1 (1.0)
FVC mean % chg from baseline	-0.1%	-0.6%	-0.1%	-0.1%	-0.1%
# with FVC < 80% baseline (%)	22 (0.3%)	1 (1.2%)	39 (4.1%)	35 (3.7%)	74 (3.9%)
12-month FVC (L)					
N	822	-	834	826	1660
FVC mean (SD)	4.1 (1.0)	-	4.1 (1.0)	4.1 (1.0)	4.1 (1.0)
FVC mean % chg from baseline	-0.5%	-	-0.0%	-1.3%	-0.7%
# with FVC < 80% baseline (%)	23 (2.8%)	-	33 (4.0%)	32 (3.9%)	65 (4.0%)
24-month FVC (L)					
N	376	-	380	387	767
FVC mean (SD)	4.1 (1.0)	-	4.1 (1.0)	4.1 (1.0)	4.1 (1.0)
FVC mean % chg from baseline	-1.7%	-	-0.5%	-2.4%	-1.5%
# with FVC < 80% baseline (%)	15 (4.0%)	-	16 (4.2%)	22 (5.7%)	38 (5.0%)

Source: ADFA where POOL1='Y,' SAFCL='Y,' ANLF013='Y,' BASETYPE='CORE,' PARAM='FVC' by TRT01A and AVISIT.

Reviewer Comment: Similar to the FEV1 analysis above, Table 56 suggests that ozanimod may cause a small dose-dependent decrease in the mean percent change in FVC and a small subset of subjects to have an FVC below 80% of baseline. An analysis of FVC in Study RPC01-3001 follows in Table 57.

Table 57. Reviewer Table. FVC in Study RPC01-3001

	Transitioned from IFN β -1a 30 mcg	Transitioned from ozanimod 0.5 mg	Remained on ozanimod 1.0 mg
Baseline FVC (L)			
N	736	840	844
FVC mean (SD)	4.1 (1.0)	4.1 (1.0)	4.1 (1.0)
12-month FVC (L)			
N	707	815	814
FVC mean (SD)	4.0 (1.0)	4.1 (1.0)	4.1 (1.1) ¹
FVC mean % chg from baseline	-1.0%	-0.4%	0.7%
# with FVC < 80% baseline (%)	20 (2.8%)	12 (1.5%)	12 (1.5%)
24-month FVC (L)			
N	47	108	123
FVC mean (SD)	4.3 (1.0)	4.1 (1.0)	4.0 (1.0)
FVC mean % chg from baseline	0.8%	-1.2%	-1.3%
# with FVC < 80% baseline (%)	1 (2.1%)	2 (1.9%)	4 (3.2%)

Source: RPC01-3001 ADLF where PARAM='FVC' by TRTA and AVISIT.

¹ The subject with a 9865.3% increase in FVC is removed from this analysis.

Reviewer Comment: An analysis of FVC in the population that transitioned into the ozanimod open label extension (RPC01-3001) does not clearly show an incremental decrease in FVC in subjects exposed to ozanimod.

Table 58. Reviewer Table. DLCO in controlled RRMS population (Pool A)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
Baseline DLCO (mmol/min/kpa)					
N	439	73	515	509	1024
DLCO mean (SD)	9.4 (8.6)	9.0 (3.2)	9.4 (8.7)	8.8 (3.3)	9.1 (6.6)
6-month DLCO (mmol/min/kpa)					
N	-	70	69	67	136
DLCO mean (SD)	-	8.6 (2.1)	8.6 (2.2)	9.0 (3.2)	8.8 (2.8)
DLCO mean % chg from baseline	-	0.4%	6.1%	4.3%	5.2%
# with DLCO < 80% baseline (%)	-	3 (4.3%)	6 (8.7%)	7 (10.4%)	13 (9.6%)

	IFN β -1a 30 mcg	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg	Overall Ozanimod
12-month DLCO (mmol/min/kpa)					
N	417	-	421	419	840
DLCO mean (SD)	8.4 (3.8)	-	8.5 (4.2)	8.3 (4.6)	8.4 (4.4)
DLCO mean % chg from baseline	0.8%	-	3.1%	0.6%	1.8%
# with DLCO < 80% baseline (%)	40 (9.6%)	-	46 (10.9%)	62 (14.8%)	108 (12.9%)
24-month DLCO (mmol/min/kpa)					
N	228	-	229	231	460
DLCO mean (SD)	8.6 (5.2)	-	8.8 (6.4)	9.4 (8.8)	9.1 (7.7)
DLCO mean % chg from baseline	3.1%	-	6.4%	12.0%	9.2%
# with DLCO < 80% baseline (%)	35 (15.4%)	-	29 (12.7%)	43 (18.6%)	72 (15.7%)

Source: ADFA where POOL1='Y,' SAFCL='Y,' ANLF013='Y,' BASETYPE='CORE,' PARAM='DLCOHBG' by TRT01A and AVISIT.

Reviewer Comment: Although the value of the DLCO analysis is limited because many of the study subjects did not have DLCO testing performed, it appears that ozanimod may cause a mild decrement in DLCO compared with interferon β -1a.

In brief, the presence of S1P receptors in the pulmonary smooth muscle and epithelium provides biologic plausibility that modulation of these receptors may lead to respiratory effects, and the two approved S1P receptor modulators have a labeled warning for respiratory effects. This section suggests that ozanimod may have an adverse effect on respiratory function, although the magnitude of these effects (and the number of subjects with decrements over 80% of baseline) appears quite small, which suggests that this risk can be mitigated through appropriate labeling and patient education. See further comments in Section 8.5.7.

8.4.11. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Lymphopenia / Serious Infections

It is clear from the section on hematologic laboratories that lymphopenia can occur in individuals taking ozanimod, which is not surprising since the benefit of S1P receptor modulators in RMS is likely derived from their sequestration of circulating lymphocytes in secondary lymphoid tissue such as lymph nodes.

Reviewer Comment: Because it appears that ozanimod can be associated with lymphopenia, this reviewer agrees with the proposed labeling for ozanimod that a

CBC with lymphocyte count should be checked before initiating ozanimod but also recommends periodic assessments of CBC with lymphocyte count during treatment with ozanimod.

With lymphopenia, it would not be surprising to see an increased risk of infections with ozanimod. It is clear in the sections on SAEs, AEs leading to study discontinuation / drug withdrawal, severe AEs, and TEAEs (Sections 8.4.2 to Sections 8.2.5) that infections occurred frequently in the ozanimod clinical trials. An analysis of the Infections and Infestations SOC for PTs occurring 5 or more times in subjects randomized to ozanimod in the controlled RMS population (Pool A) of the ISS ADAE dataset follows in Table 59:

Table 59. Reviewer Table. Infections in the controlled RMS population (Pool A)

	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Nasopharyngitis	127	15	176	153	329
Upper respiratory tract infection	76	4	91	67	158
Urinary tract infection	35	3	46	52	98
Pharyngitis	21	4	45	35	80
Bronchitis	17	0	24	26	50
Rhinitis	15	3	25	19	44
Respiratory tract infection viral	12	0	18	24	42
Respiratory tract infection	24	1	17	23	40
Sinusitis	22	1	16	14	30
Influenza	17	0	18	10	28
Oral herpes	12	2	18	8	26
Tonsillitis	10	0	12	10	22
Cystitis	10	0	9	10	19
Gastroenteritis	7	0	6	10	16
Viral infection	10	0	7	6	13
Vaginal infection	1	1	3	7	10
Tooth abscess	5	0	3	6	9
Tracheitis	3	0	3	6	9
Herpes zoster	4	0	3	5	8
Laryngitis	2	1	2	6	8
Viral upper respiratory tract infection	5	0	5	3	8
Conjunctivitis	9	0	4	3	7
Ear infection	5	0	2	5	7

	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Pneumonia	4	0	4	3	7
Otitis media	8	1	1	4	5
Vulvovaginal mycotic infection	7	0	1	4	5

Source: ISS ADAE where TREMFL1='Y,' SAFCL='Y,' and AEBODSYS ='INFECTIONS and INFESTATIONS' by AEDECOD and TRT01A

Reviewer Comment: As infections could occur more than once in a subject, percentages are not calculated for Table 59; however, it appears that more respiratory and genitourinary infections occurred in subjects randomized to ozanimod. Herpes zoster infections are of interest but do not appear convincingly more common in the ozanimod population in this analysis. Although progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis have been reported with another S1P receptor modulator, this reviewer does not appreciate cases of these opportunistic infections in the controlled ozanimod safety population.

Given an increased risk of upper respiratory tract and genitourinary infections, this reviewer agrees that a warning / precaution for infection should be included in the labeling for ozanimod. Because the inclusion criteria for the RMS ozanimod trials required evidence of immunity to the varicella zoster virus (VZV), this reviewer also agrees with including a similar stipulation in the ozanimod labeling. In addition to the potential risk of PML, the potential risk of cryptococcal infections should be added to the labeling for ozanimod.

8.5.2. Liver Injury / Increased Hepatic Transaminases

It is clear from the section on hepatobiliary laboratories that elevations of hepatic transaminases may occur in individuals taking ozanimod, although there were no clear Hy's law cases of DILI. The following additional cases had an adverse event coded as "hepatitis" or an equivalent term while taking ozanimod.

- At screening, Subject (b) (6) was a 42yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-301 and who was deemed to have "toxic hepatitis" on Study Day 290 based on minor GGT elevations (maximum 82 U/L). Her AST, ALT, ALP, and bilirubin remained normal, and she remained on the study medication.
- At screening, Subject (b) (6) was a 29yo man who was randomized to ozanimod 1 mg in Study RPC01-301 and remained on ozanimod 1 mg in RPC01-3001. On RPC01-301 Study Day 104, he was deemed to have "toxic hepatitis," but he remained on

the study medication. His maximum ALT, AST, and GGT were 143 U/L, 57 U/L, and 268 U/L respectively; however, his bilirubin and ALP remained normal.

- At screening, Subject (b) (6) was a 38yo man who was randomized to ozanimod 0.5 mg in Study RPC01-301 and transitioned to ozanimod 1 mg in Study RPC01-3001. He reportedly had a past medical history of chronic cholecystitis and chronic pancreatitis. On RPC01-301 Study Day 180, he experienced mild “nonspecific reactive hepatitis” but remained on the study medication; he had a “reactivation” of this AE on Study RPC01-3001 Day 472 but still remained on the study medication. The narrative suggests that his maximum ALT, AST, and GGT were 107 U/L, 46 U/L, and 68 U/L, respectively; however, his total bilirubin and ALP remained normal. A confounding factor was the subject’s use of paracetamol.
- At screening, Subject (b) (6) was a 51yo woman who was randomized to ozanimod 0.5 mg in Study RPC01-301 and transitioned to ozanimod 1 mg in Study RPC01-3001. On Day 188 of Study RPC01-301 (and again on Day 386 of RPC01-3001), she experienced “hepatitis of unknown etiology, moderate activity” but continued on the study medication. The first episode was considered resolved on Study Day 274, and the second episode on Study Day 456. The narrative suggests that her maximum ALT, AST, and GGT were 158 U/L, 138 U/L, and 354 U/L. Her maximum total bilirubin was also elevated at 29.4 umol/L; however, her baseline total bilirubin was elevated at 20 mmol/L. The narrative does not suggest that much work-up was performed for the transaminase elevations and “hepatitis” AE.
- At screening, Subject (b) (6) was a 48yo woman who was randomized to ozanimod 1 mg in Study RPC01-201B and remained on this dose of ozanimod in the RPC01-3001 OLE. On Day 183 of Study RPC01-201B, she experienced mild “hepatocytolytic syndrome” but remained on the study medication; she was also noted to be taking paracetamol. The narrative suggests that her maximum ALT, AST, and GGT were 115 U/L, 55 U/L, and 168 U/L respectively, but her total bilirubin and ALP remained normal. The narrative does not suggest that much work-up was performed for this reported AE.
- At screening, subject (b) (6) was a 46yo woman with Graves’ disease who was randomized to ozanimod 0.5 mg in Study RPC01-301. She experienced mild “hepatotoxicity” on Study Day 91 but remained on the study medication; this event was deemed resolved on Study Day 183. Her ALT and AST peaked to 121 U/L and 70 U/L, but her total bilirubin remained normal.
- At screening, Subject (b) (6) was a 46yo man who was randomized to ozanimod 0.5 mg in Study RPC01-201B and transitioned to ozanimod 1 mg in the RPC01-3001

OLE. On Day 92 of Study RPC01-201B, he experienced “jaundice” and “mild hepatocytotoxic syndrome,” but the subject remained on the study medication. The highest AST and ALT noted in the narrative are 82 U/L and 46 U/L, respectively; his total bilirubin was elevated (20.5 umol/L) at baseline and peaked at 24.3 umol/L during the study.

Reviewer Comment: None of these narratives are particularly worrisome for a signal indicating a risk of irreversible hepatic injury. Given the signal for transaminase elevations and potential liver injury with ozanimod, this reviewer recommends that the labeling for ozanimod include a Warning for liver injury and hepatic transaminase elevations similar to that of the other approved S1P receptor modulators.

8.5.3. Malignancy

As noted in the sections on death, SAEs, AEs leading to study discontinuation / drug withdrawal, severe AEs, and TEAEs (Sections 8.4.1 to Sections 8.2.5), malignancies occurred during the clinical trials of ozanimod. An analysis of TEAEs in the Neoplasms Benign, Malignant, and Unspecified SOC that occurred in one or more subjects randomized to ozanimod in the controlled RMS population (Pool A) of the ISS ADAE dataset follows in Table 60.

Table 60. Reviewer Table. Malignancies in the controlled RMS population (Pool A)

	IFN β-1a 30 mcg n=885	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Melanocytic nevus	1	5	4	9
Uterine leiomyoma	8	4	3	7
Skin papilloma	1	4	1	5
Basal cell carcinoma	1	2	1	3
Lipoma	1	0	3	3
Seborrheic keratosis	0	1	2	3
Fibroma	0	0	2	2
Invasive breast carcinoma	0	1	1	2
Benign breast neoplasm	0	1	0	1
Benign neoplasm of cervix uteri	0	0	1	1
Breast cancer	0	0	1	1
Fibroadenoma of breast	1	1	0	1
Fibrous histiocytoma	0	0	1	1
Hemangioma	0	1	0	1

	IFN β -1a 30 mcg n=885	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Hemangioma of breast	0	1	0	1
Hemangioma of skin	0	0	1	1
Keratoacanthoma	0	0	1	1
Malignant melanoma in situ	0	1	0	1
Medulloblastoma	0	1	0	1
Testicular seminoma (pure) stage I	0	0	1	1

Source: ISS ADAE where TREMFL1='Y,' SAFCL='Y,' and AEBODSYS=' NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)' by AEDECOD and TRT01A

Reviewer Comment: Since the rate of malignancy was very low in the controlled RMS population, percentages are not calculated for the types of malignancies in Table 60. Although the numbers are quite low, there is a suggestion that cutaneous malignancies (and possibly breast cancer) occurred more frequently in subjects randomized to ozanimod. Especially since cutaneous malignancies are listed as a Warning or an Adverse Reaction in the labeling of other S1P receptor modulators, cutaneous malignancies should be included in Section 6 (Adverse Reactions) of the labeling for ozanimod.

8.5.4. Bradyarrhythmia and Atrioventricular Block

The analyses in Section 8.4.8 suggests that the early doses of ozanimod can be associated with bradyarrhythmia and 1st degree AV block, similar to the experience with other S1P receptor modulators; however, this reviewer did not discover any cases of second degree (or higher) AV block with ozanimod in its Phase 2/3 development program.

Due to the bradyarrhythmia and AV block noted with other S1P receptor modulators and the apparent signal for similar effects with ozanimod, the Division of Cardiovascular and Renal Products (DCaRP) was consulted early in the review of this NDA, and the conclusions of their review are summarized below:

- “Ozanimod at the doses studied results in mild dose dependent bradycardia.”
- “Administration of ozanimod has been observed in clinical studies of healthy subjects to result in first degree and second degree type 1 AV block but only at higher exposures than those expected from the recommended dose.”
- “Based on our limited evaluation of the phase 3 studies in multiple sclerosis, we were unable to identify any events of bradycardia or AV conduction defects that were of concern. 882 subjects in those studies were exposed to the recommended clinical

dose, so by the rule of three the serious cardiac event rate in clinical practice will be less than one in 274 or less than 3.6 per thousand exposed.”

- “The titration scheme used in the phase 3 studies modestly blunts the cardiac effects of ozanimod. However, titration results in the maximal cardiac effect of ozanimod occurring on day 8.”
- “If (first dose cardiac) monitoring were to be required, it would be most likely to detect cardiac effects on the eighth day of administration, not the first. Nonetheless, a need for monitoring is not obvious to us so long as the patients have both clinical characteristics and PK similar to those studied in the phase 3 study.”

The exclusion criteria for the Phase 3 clinical trials of ozanimod in RMS included a resting heart rate less than 55 bpm at screening and the following cardiac conditions:

- “Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea
- Prolonged QTcF interval (QTcF >450 msec males, >470 msec females), or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome, concurrent therapy with QT-prolonging drugs)
- Patients with other pre-existing stable cardiac conditions who have not been cleared for the study by an appropriate cardiac evaluation by a cardiologist
- Other clinically significant conduction abnormalities or any other significant cardiac condition that could jeopardize a patient’s health or put them at significant safety risk during the course of the study in the opinion of treating investigator.”

Reviewer Comment: Even though there were few cases of bradyarrhythmia and first degree atrioventricular block in the Phase 2/3 clinical trials of ozanimod, this reviewer agrees that the labeling for ozanimod should include a Warning for these. The noted delay in the maximal cardiac effect after initiation of ozanimod (eight days) probably relates to the long half-life of its active metabolites. This reviewer agrees that this delay should be included in the labeling for ozanimod, noting that it limits the utility of first dose cardiac monitoring with this particular S1P receptor modulator.

8.5.5. Hypertension

The section on Vital Signs in Section 8.4.7 suggests that ozanimod may be associated with an increase in systolic blood pressure, and the following analysis suggests that hypertension was reported more frequently as an adverse event in subjects randomized to ozanimod in the controlled RMS population (Pool A).

Table 61. Reviewer Table. TEAEs of hypertension in the controlled RMS population (Pool A)

	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Hypertension	20 (2.3%)	1 (1.1%)	33 (3.4%)	33 (3.4%)	66 (3.4%)

Source: ISS ADAE where TREMFL1='Y,' SAFCL='Y,' and AEDECOD='HYPERTENSION' by TRT01A

Reviewer Comment: Since hypertension was reported as a TEAE more frequently by subjects randomized to ozanimod, this reviewer opines that hypertension should be added to the proposed labeling of ozanimod as a Warning, especially since increased blood pressure is a Warning in the labeling for other S1P receptor modulators.

8.5.6. Macular Edema

An analysis of Pool A of the ISS ADAE dataset suggests that three subjects randomized to ozanimod developed macular edema and two others developed cystoid macular edema; of note, three subjects randomized to interferon β -1a also developed macular edema. As noted in Section 8.4, many of these had potentially confounding factors, so this analysis does not provide a clear signal for macular edema with ozanimod.

Any analysis of macular edema in Study RPC01-3001 suggests that five subjects randomized to ozanimod developed macular edema and two others developed cystoid macular edema while taking ozanimod, although some of the cases were potentially confounded as above.

Reviewer Comment: Although macular edema is a labeled Warning with other S1P receptor modulators, its correlation with ozanimod is less clear. This reviewer agrees with the proposed labeling for ozanimod that macular edema should be listed as a Warning and that an ophthalmic evaluation should be recommended for individuals with risk factors for macular edema (e.g., a history of diabetes mellitus or uveitis) prior to (and periodically during) treatment with ozanimod. In addition, a prompt ophthalmic evaluation should be recommended in individuals who develop visual changes while taking ozanimod.

8.5.7. Seizure

The sections on SAEs and TEAEs in Sections 8.4.2-8.4.5 suggests that ozanimod may be associated with an increased risk of seizure, although seizures are a recognized complication occurring in 3-5% of individuals with MS. As per Table 62, the rate of seizures was not clearly higher in subjects randomized to ozanimod.

Table 62. Reviewer Table. TEAEs of seizure in the controlled RMS population (Pool A)

	IFN β-1a 30 mcg n=885	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Epilepsy	4	2	3	5
Generalized tonic-clonic seizure	0	1	0	1
Partial seizures	1	0	0	0
Seizure	1	1	0	1

Source: ISS ADAE where TREMFL1='Y,' SAFCL='Y,' and AEDECOD contains 'Seizure' or 'Epilepsy' by TRT01A

Reviewer Comment: Since the rate of seizure was very low in the controlled RMS population, percentages are not calculated in Table 62; however, it does not appear that there is an increased risk of seizures in the active-controlled studies of ozanimod.

8.5.8. Pulmonary Effects

The section on Pulmonary Function Tests in Section 8.4.10 suggests that ozanimod may be associated with mild decreases in pulmonary function, which is a warning in the labeling of other S1P receptor modulators. The following analysis (Table 63) suggests that TEAEs relating to pulmonary function test abnormalities may have been more frequent in subjects randomized to ozanimod in the controlled RMS population (Pool A).

Table 63. Reviewer Table. Dyspnea and abnormal PFTs in the controlled RMS population (Pool A)

	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Carbon monoxide diffusing capacity decreased	6	0	4	7	11

	IFN β -1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Forced expiratory volume decreased	5	1	4	8	12
Forced vital capacity decreased	8	0	6	10	16
Pulmonary function test abnormal	0	0	0	2	2
Dyspnea	5	0	5	6	11

Source: ISS ADAE where TREMFL1='Y,' SAFCL='Y' where AEDECOD={values in first column} by TRT01A

Reviewer Comment: Since the rates of PFT abnormalities and dyspnea were very low in the controlled RMS population, percentages are not calculated in Table 63; however, it appears that PFT abnormalities were slightly more common in subjects randomized to ozanimod. This is not surprising, since respiratory effects, including a decline in pulmonary function, is noted with other S1P receptor modulators.

Due to the respiratory effects noted with other S1P receptor modulators and the apparent signal for respiratory effects with ozanimod, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) was consulted early in the review of this NDA, and the conclusions of their review are summarized below:

- “Overall, pulmonary AEs associated with ozanimod use are rare and were considered to be mostly mild or moderate ... the risk of pulmonary toxicity with ozanimod use can be mitigated through labeling and patient education.”
- “Pulmonary effects are expected based on the mechanism of action of S1P modulators and have been seen in approved S1P modulators, fingolimod and siponimod. Both fingolimod and siponimod demonstrated decreases in FEV1. In addition, fingolimod demonstrated decreases in DLCO and siponimod demonstrated decreases in FVC. The magnitude of change in pulmonary function was comparable to ozanimod.”
- “PMRs were included in the approval of both fingolimod and siponimod. Because there are outstanding PMRs designed to monitor pulmonary toxicity with long term, chronic use of the other two other drugs in this class, fingolimod and siponimod, the utility of a third PMR is arguably limited.”

This reviewer agrees that respiratory effects, including a decline in pulmonary function, should be included as a Warning in Section 5 of the labeling for

ozanimod and that the utility of a post-marketing requirement to explore this signal further is likely not merited.

8.6. Safety Analyses by Demographic Subgroups

Gender

As noted in Table 8, SAEs were uncommon in the controlled RMS population. Table 64 delineates those SAEs occurring more than one subject randomized to the proposed labeled dose of ozanimod (1 mg) in the controlled RMS population, stratified by gender.

Table 64. Reviewer Table. SAEs stratified by gender in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A)

AEDECOD	Female n=635	Male N=330
Appendicitis	1	2
Intervertebral disc disorder	0	2
Ovarian cyst	2	0

Source: ISS ADAE where AESER='Y,' TREMFL1='Y,' and TRT01A= 'RPC1063 1.0 mg' by AEDECOD and SEX.

Reviewer Comment: The numbers of SAEs in the controlled RMS population who were randomized to ozanimod 1 mg are too small to comment on gender differences with the occurrence of SAEs.

Similarly, TEAEs that occurred commonly in the controlled RMS population who received the proposed labeled dose of ozanimod 1 mg were stratified by gender as shown in Table 65.

Table 65. Reviewer Table. Common TEAEs stratified by gender in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A)

AEDECOD	Female n=635	Male N=330
Headache	206	31
Nasopharyngitis	114	39
Upper respiratory tract infection	55	12
Alanine aminotransferase increased	27	38
Influenza like illness	52	12
Gamma-glutamyltransferase increased	31	25
Urinary tract infection	48	4
Orthostatic hypotension	31	13
Back pain	30	12

AEDECOD	Female n=635	Male N=330
Dysmenorrhea	41	0
Pharyngitis	26	9
Hypertension	26	7
Abdominal pain upper	26	4
Fatigue	17	10
Bronchitis	20	6
Depression	16	9
Respiratory tract infection viral	20	4
Insomnia	18	6
Respiratory tract infection	19	4
Arthralgia	18	5
Pain in extremity	17	5
Anxiety	18	2
Rhinitis	11	8
Pyrexia	16	2
Aspartate aminotransferase increased	9	9
Nausea	13	4
Hypercholesterolemia	15	2
Toothache	14	2
Vertigo	14	1
Hepatic enzyme increased	12	3

Source: ISS ADAE where TREMFL1='Y' and TRT01A='RPC1063 1.0 mg' by AEDECOD and SEX.

Reviewer Comment: Since TEAEs could be reported more than once by the same subject, Table 65 does not contain percentages of subjects experiencing each TEAE, although recognizing that 2/3 of the subjects are women allows inferences to be made. Since headaches, urinary tract infections, and obviously dysmenorrhea are more common in women, it is not surprising that these TEAEs appear to have occurred more commonly in women randomized to ozanimod 1mg in the controlled RMS population. Similarly, it appears that hypertension may have occurred more commonly in women and that transaminase elevations may have occurred more commonly in men; however, the significance of these observations is unclear.

It also appears clear from Table 65 that nasopharyngitis, upper respiratory tract infections, and related TEAEs occurred more frequently in women than in men, so this difference will be explored further.

One might wonder if the higher frequency of upper respiratory tract infections in

women randomized to ozanimod 1mg in the controlled RMS population relates to a difference in the degree of lymphocyte sequestration in lymphoid tissue, so Table 66 explores the gender differences in lymphocyte counts in this population.

Table 66. Reviewer Table. Lymphocyte counts stratified by gender in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A)

	Female n=635	Male N=330
Mean (std) x 10 ⁹ /L	0.73 (0.39)	0.91 (0.48)
Median x 10 ⁹ /L	0.64	0.8
Min, max x 10 ⁹ /L	0.10, 4.78	0.16, 4.09
# subjects < 0.5 x 10 ⁹ /L	354 (55.7%)	108 (32.7%)
# subjects < 0.2 x 10 ⁹ /L	15 (2.4%)	6 (1.8%)

Source: ISS ADLBH where POOL1='Y,' SAFCF1='Y,' BASETYPE='CORE,' TRT01A='RPC1063 1.0mg,' AVISIT contains 'Month,' and PARAMCD='LYM' by SEX

Reviewer Comment: Table 66 shows that lymphocyte counts were somewhat lower in the population of women randomized to ozanimod 1 mg in the controlled RMS studies, an observation that may explain the somewhat higher risk of upper respiratory tract infections noted in women in Table 65. A difference in body mass index (BMI) may be an explanation for this difference in lymphocyte counts; indeed, the average BMI was 23.8 kg/m² in the women (compared to 25.2 kg/m² in the men) who were randomized to ozanimod 1 mg in the controlled RMS studies.

Age

As noted in Table 8, SAEs were uncommon in the controlled RMS population. Table 67 delineates SAEs occurring more than one subject randomized to the proposed labeled dose of ozanimod (1 mg) in the controlled RMS population, stratified by age.

Table 67. Reviewer Table. SAEs stratified by age in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A)

AEDECOD	Age ≤ 40 n=664	Age 41 - <65 N=301
Appendicitis	2	1
Intervertebral disc disorder	2	1
Ovarian cyst	1	1

Source: ISS ADAE where AESER='Y,' TREMFL1='Y,' and TRT01A='RPC1063 1.0 mg' by AEDECOD and AGEGR4.

Reviewer Comment: The numbers of SAEs in the controlled RMS population who

received ozanimod 1 mg are too small to comment on age differences with the occurrence of SAEs.

Similarly, those TEAEs that occurred commonly in the controlled RMS population who received the proposed labeled dose of ozanimod 1 mg were stratified by age as shown in Table 68.

Table 68. Reviewer Table. Common TEAEs stratified by age in subjects treated with ozanimod 1 mg in the controlled RMS population (Pool A)

AEDECOD	Age ≤ 40 n=664	Age 41 - <65 N=301
Headache	190	47
Nasopharyngitis	121	32
Upper respiratory tract infection	46	21
Alanine aminotransferase increased	47	18
Influenza like illness	51	13
Gamma-glutamyltransferase increased	27	29
Urinary tract infection	30	22
Orthostatic hypotension	28	16
Back pain	19	23
Dysmenorrhea	41	0
Pharyngitis	27	8
Hypertension	13	20
Abdominal pain upper	19	11
Fatigue	11	16
Bronchitis	18	8
Depression	14	11
Insomnia	18	6
Respiratory tract infection viral	22	2
Arthralgia	13	10
Respiratory tract infection	21	2
Pain in extremity	15	7
Anxiety	14	6
Rhinitis	16	3
Aspartate aminotransferase increased	11	7
Pyrexia	16	2
Hypercholesterolemia	7	10
Nausea	10	7
Toothache	14	2
Hepatic enzyme increased	8	7

AEDECOD	Age ≤ 40 n=664	Age 41 - <65 N=301
Vertigo	6	9

Source: ISS ADAE where TREMFL1='Y' and TRT01A='RPC1063 1.0 mg' by AEDECOD and AGER4.

Reviewer Comment: Since TEAEs could be reported more than once by the same subject, Table 68 does not contain percentages of subjects experiencing each TEAE, although recognizing that over 70% of the subjects are ≤ 40yo may allow inferences to be made. It appears that headaches and TEAEs related to upper respiratory tract infections occurred more commonly in the younger subset of the population randomized to ozanimod 1 mg in the controlled RMS studies and that hypertension occurred more commonly in the older subset of this population.

Race

Since 99.4% of the subjects randomized to ozanimod 1 mg in the controlled RMS studies classified their race as "white," subgroup analyses were not performed by race.

8.7. Specific Safety Studies/Clinical Trials

N/A

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

See malignancy subsection of 8.5.4.

8.8.2. Human Reproduction and Pregnancy

The ozanimod clinical trials required sexually active subjects of reproductive potential (both men and women) to use an effective form of contraception for the duration of the study. Unless they decided to terminate the pregnancy, the study medication was discontinued in women who became pregnant during the study; however, these women were encouraged to still be followed in the study. Information about the outcomes of all pregnancies that occurred during the study was sought.

Updated pregnancy information was received in response to an Information Request (IR) sent to the Applicant on 20Nov2019, and the pregnancies in the ozanimod RMS development program are summarized in Table 69 below. In brief, 37 female subjects became pregnant during the ozanimod RMS trials. Of these, 18 lead to presumably healthy infants, seven resulted in elective terminations, six had complications during pregnancy but seemingly had good outcomes, five lead to abnormal terminations, and

one had complications during pregnancy and resulted in an infant with a congenital malformation (left kidney duplication and patent foramen ovale).

Table 69 also shows that the female partners of five male subjects in the clinical trials of ozanimod in RMS became pregnant. One of these resulted in a miscarriage from a devitalized pregnancy, and another was complicated by mild pre-eclampsia.

Table 69. Pregnancies in Ozanimod RMS development program

Subject	Age (Yrs) ¹	Study (Drug)	Exposure During Pregnancy (Days) ²	Pregnancy Outcome / Complications
Elective terminations without known abnormalities				
(b) (6)	22	102 (ozanimod)	N/A	Elective termination
	22	201A (ozanimod 1 mg)	N/A	Elective termination
	29	201B (ozanimod 0.5 mg)	N/A	Elective termination
	30	3001 (ozanimod 1 mg)	N/A	Elective termination
	32	201B (ozanimod 1 mg)	N/A	Elective termination
	26	301 (ozanimod 1 mg)	N/A	Elective termination
	22	3001 (ozanimod 1 mg)	N/A	Elective termination
Complications				
	30	201B (ozanimod 1 mg)	N/A	Elective termination; dysfunctional uterine bleeding and placental polyp
	24	3001 (ozanimod 1 mg)	24	Anembryonic pregnancy
	18	3001 (ozanimod 1 mg)	N/A	Spontaneous abortion
	42	301 (ozanimod 1 mg)	39	Spontaneous abortion
	26	3001 (ozanimod 1 mg)	35	Spontaneous abortion
	24	3001 (ozanimod 1 mg)	41	Induced childbirth at 36 weeks; risk of pre-eclampsia and absence of fetal movement
	30	3001 (ozanimod 1 mg)	42	Infant with left kidney duplication and patent foramen ovale at 39 weeks; gestational diabetes and venous thrombosis
	32	201A (ozanimod 1 mg)	35	Healthy infant at 38 weeks; C-section for irregular heart beat ± fetal distress
	20	3001 (ozanimod 1 mg)	25	Healthy infant (with icterus) at 38 weeks; gestational diabetes
	21	3001 (ozanimod 1 mg)	33	Healthy infant at 40 weeks; C-section for oligohydramnios and asphyxia
	28	201B (ozanimod 1 mg)	69	Healthy infant at 38 weeks; vanishing twin syndrome

Subject	Age (Yrs) ¹	Study (Drug)	Exposure During Pregnancy (Days) ²	Pregnancy Outcome / Complications
(b) (6)	26	201B (ozanimod 0.5 mg)	50	Healthy infant at 38 weeks; intra-uterine growth restriction
Presumed Good Outcomes				
(b) (6)	22	3001 (ozanimod 1 mg)	29	Healthy infant at 39 weeks
(b) (6)	33	201A (ozanimod 1 mg)	25	Healthy infant at 39 weeks
(b) (6)	27	3001 (ozanimod 1 mg)	35	Healthy infant at 40 weeks
(b) (6)	26	201B (ozanimod 1 mg)	38	Healthy infant at 38 weeks
(b) (6)	31	3001 (ozanimod 1 mg)	0 ³	Healthy infant at 38 weeks
(b) (6)	31	201B (ozanimod 0.5 mg)	38	Healthy infant at 41 weeks
(b) (6)	35	201B (ozanimod 1 mg)	35	Healthy infant at 41 weeks
(b) (6)	19	201B (ozanimod 1 mg)	42	Healthy infant at 40 weeks
(b) (6)	36	201B (ozanimod 1 mg)	0 ³	Healthy infant at 40 weeks
(b) (6)	26	3001 (ozanimod 1 mg)	28	Healthy infant at 39 weeks
(b) (6)	21	3001 (ozanimod 1 mg)	25	Healthy infant at 39 weeks
(b) (6)	31	3001 (ozanimod 1 mg)	39	Healthy infant at 36 weeks
(b) (6)	33	201B (ozanimod 1 mg)	35	Healthy infant
(b) (6)	29	301 (ozanimod 0.5 mg)	N/A	Healthy infant
(b) (6)	27	3001 (ozanimod 1 mg)	33	No complications at 12 weeks
(b) (6)	19	3001 (ozanimod 1 mg)	38	Unknown
(b) (6)	30	3001 (ozanimod 1 mg)	13	Unknown
(b) (6)	18	3001 (ozanimod 1 mg)	44	Unknown
Male partners				
(b) (6)	31M	3001 (ozanimod 1 mg)	-	Miscarriage - 9 week devitalized pregnancy
(b) (6)	29M	301 (ozanimod 0.5 mg)	-	Premature infant at 36 weeks; mild pre-eclampsia
(b) (6)	33M	3001 (ozanimod 1 mg)	-	Healthy infant at 40 weeks; fetal distress with delivery
(b) (6)	24M	3001 (ozanimod 1 mg)	-	Healthy twins at 35 weeks
(b) (6)	26M	3001 (ozanimod 1 mg)	-	Unknown

¹ Age at screening

² Number of days between the last dose of study drug and the last menstrual period; not calculated for elective terminations.

³ Stopped study drug to achieve pregnancy.

The outcome of four of the five pregnancies in subjects in the clinical trials of ozanimod in IBD is known: two resulted in healthy infants and two ended prematurely (one spontaneous abortion and one elective termination). Although not included in the response to the 20Nov2019 IR, the ISS states that there were 3 partner pregnancies in the IBD studies, of which two resulted in healthy newborns and one resulted in a

premature newborn with respiratory distress.

Reviewer Comment: Per the ISS, nonclinical studies in rats and rabbits demonstrated teratogenicity with ozanimod. Although the data regarding the effects of exposure to during ozanimod are unrevealing, the data are limited, so the labeling for ozanimod should contain a Warning for fetal risk that encourages women of child-bearing potential to use effective contraception while taking ozanimod. Also, pharmacovigilance is requested for congenital renal abnormalities with prenatal exposure to ozanimod.

The ISS states that ozanimod was excreted in the breast milk (at a 2:1 ratio relative to plasma exposure) of ozanimod-treated rats but notes “No effect of treatment was observed on parturition, offspring (F1) pup survival, sex ratios, or pup pre-weaning clinical observations.”

8.8.3. Pediatrics and Assessment of Effects on Growth

Because the clinical studies of ozanimod excluded subjects below 18 years of age, no clinical data were submitted to support a pediatric indication, so the ozanimod labeling should only indicate ozanimod for the treatment of adults with relapsing forms of MS.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Per the ISS, one subject intentionally overdosed on ozanimod. At screening, Subject (b) (6) was a 22yo woman who was randomized to interferon β -1a in Study RPC01-201B and transitioned to ozanimod 1 mg in Study RPC01-3001. On Day 344 of this extension study, she was hospitalized after a suicide attempt in which she took a total of 124 pills, including glimepiride, lisinopril, and ozanimod. An ECG at the time showed sinus bradycardia, but follow-up assessments, including lymphocyte counts and liver function tests, were reportedly normal. This reviewer’s query of the ISS ADAE dataset for rows in which AEDECOD contains “overdose” revealed two additional cases, including an overdose of pregabalin and an overdose of zopiclone.

In the ISS, the Applicant states “The effects of ozanimod on the functional observation battery and motor activity were studied in rats ... ozanimod and its major active metabolite CC112273 demonstrated no abuse potential as assessed in a behavioral assay. Ozanimod and CC112273 did not show potential for abuse liability based upon assessment in a rat self-administration study.” Further, the Applicant states “The results of the MedDRA search terms to assess drug abuse potential in ozanimod on all completed ozanimod clinical studies are summarized ... No indication of potential for drug abuse or physical dependence has been observed in the clinical programs to date.”

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Ozanimod is not currently marketed anywhere in the world, so there is no postmarketing safety experience available for review.

8.9.2. Expectations on Safety in the Postmarket Setting

Given the similarity of ozanimod to other approved S1P receptor modulators, vigilance for serious infections (including progressive multifocal leukoencephalopathy [PML], cryptococcal meningitis, and other opportunistic infections), cutaneous and other malignancies, posterior reversible encephalopathy syndrome (PRES), and severe increases in disability with drug cessation would be prudent with ozanimod.

8.9.3. Additional Safety Issues From Other Disciplines

This reviewer is unaware of any safety issues from other disciplines at this time.

8.10. Integrated Assessment of Safety

1. Infections / Lymphopenia

Administration of ozanimod causes a reduction in circulating lymphocytes, predominantly CD4+ and CD8+ subtypes, with relative sparing of neutrophils. Lymphopenia can increase the risk of infections, and the risk of upper respiratory tract infections, urinary tract infections, and herpetic infections (e.g., herpes zoster) was increased in subjects randomized to ozanimod in the controlled RMS population. Although no cases of progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis were reported in the ozanimod development program, these opportunistic infections are labeled with other S1P receptor modulators and can occur in the setting of significant lymphopenia.

Lymphocyte counts should be checked before starting, and periodically during, treatment with ozanimod. Lymphopenia and the risk of infection, including the risk of herpes infections and opportunistic infections such as PML and cryptococcal meningitis, should be described in the Warnings and Precautions section of the labeling of ozanimod.

2. Liver Injury

Ozanimod can cause elevations in AST, ALT, and GGT, but these elevations appeared reversible with discontinuation of the drug in the controlled RMS studies. Most of the transaminase elevations in the ozanimod development program were asymptomatic, and there were no reported cases of fulminant hepatic failure in these studies.

Transaminases and total bilirubin should be checked before starting, and periodically during, treatment with ozanimod. The labeling for ozanimod should include a statement regarding the risk (and symptoms) of transaminase elevation and liver injury in the Warnings and Precautions section of the labeling of ozanimod.

3. Bradyarrhythmia / AV block

S1P receptor modulators such as ozanimod are associated with bradyarrhythmia and AV block. In the controlled RMS studies, ozanimod was initiated with an 8-day dose escalation, which appeared to reduce the rate of bradycardia and cardiac TEAEs when starting the drug. Subjects with a myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization within the last 6 months, New York Heart Association Class III / IV heart failure, cardiac conduction or rhythm disorders, risk factors for QT prolongation, severe untreated sleep apnea, or a resting heart rate less than 55 bpm at baseline, were excluded from participation in the controlled RMS studies. With these exclusions and the dose escalation, there were no reported cases with a heart rate less than 40 bpm or Type 2 (or higher) AV block in the controlled RMS studies.

In order to determine whether a patient has an occult arrhythmia or to confirm an ongoing cardiac issue, all patients should have an ECG prior to initiation of ozanimod, and ozanimod should only be initiated with the dose escalation. The risk of bradyarrhythmia and AV block, and the exclusionary cardiac conditions for the controlled RMS studies, should be included in the Warnings and Precautions section of the labeling of ozanimod. The labeling should also note that the heart rate nadir after starting ozanimod likely occurs on day 8, an observation that minimizes the utility of first dose cardiac monitoring.

4. Hypertension

Similar to other S1P receptor modulators, ozanimod was associated with (usually mild) elevations in systolic blood pressure. Blood pressure should be monitored during treatment with ozanimod, and the risk of hypertension should be included in the Warnings and Precautions section of the labeling of ozanimod.

5. Respiratory Effects

Similar to other S1P receptor modulators, ozanimod was associated with a reduction in FEV1; however, the rate of dyspnea with ozanimod was not convincing greater than that of the comparators. The risk of respiratory effects should be included in the Warnings and Precautions section of the labeling of ozanimod.

6. Macular edema

Macular edema was *a priori* expected to be a treatment-related adverse event due to ozanimod's effect on vascular permeability and the experience with other S1P receptor modulators; however, the rate of macular edema with ozanimod was <1%, and some of

these cases had evidence of pre-existing factors for macular edema. The labeling for ozanimod should include a Warning for macular edema, a recommendation for baseline and follow-up ophthalmic evaluations in individuals with risk factors for macular edema, including a history of uveitis or diabetes mellitus, and a prompt ophthalmic evaluation in individuals who develop visual symptoms while taking ozanimod.

7. Malignancy

Malignancies, especially cutaneous malignancies, are noted with other S1P receptor modulators, and it is biologically plausible that decreased immunosurveillance from sequestering lymphocytes in lymphoid tissue would increase the risk of malignancy. It appears that there may be an increased risk of cutaneous malignancies (and possibly breast cancer) in the subjects randomized to ozanimod in its RMS clinical trials. In addition to including malignancies in Section 6 (Adverse Reactions) of the labeling for ozanimod, this reviewer recommends requested pharmacovigilance and timely reporting of all malignancies occurring in individuals taking ozanimod.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not deemed necessary for this NDA.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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

10.2. Nonprescription Drug Labeling

This section is not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS does not appear to be necessary for the safe use of ozanimod in the indicated population.

12. Postmarketing Requirements and Commitments

At the time of completion of this review, it appears that the postmarketing requirements will include the following:

1. A two-part study of ozanimod in pediatric patients with 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 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 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 ozanimod compared to an appropriate comparator.
2. 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 ozanimod during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to 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.
3. A pregnancy outcomes study using a different study design than provided for the (b) (4) (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to ozanimod during pregnancy compared to an unexposed control population
4. A randomized, double-blind, placebo-controlled, active-controlled (phenelzine), (b) (4) multiple-dose, parallel-group trial to investigate the pressor effect of oral tyramine during ozanimod treatment in healthy subjects.
5. A multiple-dose trial to assess the effect of hepatic impairment on the pharmacokinetics (PK) of ozanimod and its major metabolites and to determine whether a dosing adjustment of 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 ozanimod dose administration on Day 8 (following titration from 0.25 mg to 1 mg).

13. Appendices

13.1. References

Ascherio A and Munger KL. Epidemiology of multiple sclerosis: From risk factors to prevention – an update. *Semin Neurol* 2016; 36:103-114.

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

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

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

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

Confavreux C, Vukusic S, and Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain* 2003; 126: 770-782.

Confavreux C and Vukusic S. Age at disability milestones in multiple sclerosis. *Brain* 2006; 129: 595-605.

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

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

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

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

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

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

Clinical Review
David E. Jones, M.D.
NDA 209899
Zeposia (ozanimod)

McTaggart MP, Newall RG, Hirst JA, Bankhead CR, et al. Diagnostic accuracy of point-of-care tests for detecting albuminuria: a systematic review and meta-analysis. *Annals of Internal Medicine* 2014; 160: 550-557.

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

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69:292-302.

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

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

Sormani MP, Bonzano L, Roccatagliata I, Mancardi GL, Uccelli A, and Bruzzi P. Surrogate endpoints for EDSS worsening in multiple sclerosis: A meta-analytic approach. *Neurology* 2010; 75(4) 302-309.

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

Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17(2): 162-173.

Trabert B, Chen J, Devesa SS, Bray F, and McGlynn KA. International patterns and trends in testicular cancer incidence, overall and by histologic subtype, 1973-2007. *Andrology* 2015; 3(1): 4-12.

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

Wallin M, Culpepper WC, Campbell JD, Nelson LM, et al. "The prevalence of multiple sclerosis in the United States: A population based healthcare database approach." *Neurology* 2019; 92(10): e1029-e1040.

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

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

/s/

DAVID E JONES
03/25/2020 11:22:13 AM

PAUL R LEE
03/25/2020 11:30:49 AM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 19, 2019

From: Interdisciplinary Review Team for Cardiac Safety Studies
Division of Cardiovascular and Renal Products / CDER

Through: Norman Stockbridge MD, PhD
Division Director
Division of Cardiovascular and Renal Products / CDER

To: Susan B Daugherty
DN2

Subject: ABPM Consult Review NDA 209899 (SDN 013)

This memo responds to your consult to us dated 11/22/2019 regarding the interpretation of RPC01-1908 and RPC01-1914. We reviewed the following materials:

- IRT review for NDA 209899 dated 03/12/2018 ([link](#)); 06/12/2019 ([link](#));
- IRT review for IND 109159 dated 01/29/2014 ([link](#));
- DCRP consult review by Dr. Stephen Grant dated 12/11/2019 ([link](#));
- Report for study RPC01-1908 submitted to NDA 209899 (eCTD 0001 / [link](#)); and
- Report for study RPC01-1914 submitted to NDA 209899 (eCTD 0012 / [link](#));

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 IRT Responses

1.1 Comments for the Division

Question 1: For RPC01-1914, the sponsor claims that co-administration of ZEPOSIA with pseudoephedrine did not potentiate the pseudoephedrine-induced blood pressure response. ZEPOSIA increased the pseudoephedrine-induced heart rate response by approximately 3 bpm. We are trying to figure out whether the results of this study suggest that we can rule out any pressor effect enhancement by ZEPOSIA.

IRT Response: The observed blood pressure response in this study appears similar between the two treatment groups and we therefore conclude that ozanimod does not potentiate the pseudoephedrine-induced blood pressure response.

Question 2: For study RPC01-1908, do you agree that the change in PR and HR with diltiazem + ozanimod in study RPC01-1908 is clinically non-significant?

IRT Response: Diltiazem is a known L-type calcium channel blocker and is expected to prolong the PR interval. In this study, an increase in the PR interval was observed for all diltiazem treatment groups and no significant difference was observed between the treatment groups with diltiazem and those with diltiazem + ozanimod. The absence of prolongation of the PR interval for ozanimod is consistent with other ozanimod studies that we have reviewed (RPC01-102 and RPC01-1914) and we therefore conclude that the changes in PR are driven by diltiazem.

A decrease in HR of -9.6 bpm (95% CI: -13.3 to -6.0 bpm) was observed following a single 0.25-mg dose of ozanimod in group 2 of study RPC01-1908. Because the maximum time-matched difference between diltiazem ER and diltiazem ER + ozanimod was numerically less than the decrease observed with ozanimod by itself (-5 bpm [95% CI: -7.2 to -0.3 bpm]) and the maximum decreases for ozanimod and diltiazem ER + ozanimod were similar, we conclude that the observed further change in HR with diltiazem and ozanimod is not clinically significant.

Question 3a: Do you agree with the following statements: The Phase 1 drug interaction study RPC01-1914 (DDI with Pseudoephedrine) showed that co-administration of ozanimod over 30 days with a single 60 mg dose of pseudoephedrine on Day 30 did not potentiate the pseudoephedrine-induced pressor response (ie, systolic and diastolic blood pressure) in healthy subjects)?

IRT Response: Please see response to question 1 concerning the interpretation of the blood pressure findings of this study.

1.2 Internal Comments for the Division

As communicated via email, the questions related to MAO-B activity are outside the scope of our team and we are therefore omitting these questions from our review.

2 BACKGROUND

Ozanimod is a S1P receptor modulator that is being proposed for the treatment of MS. We have previously reviewed the thorough QT study, ECG data from study RPC01-1914 and patient ECG data for ozanimod and concluded that ozanimod does not prolong the QTc interval (DARRTS 01/29/2014;03/12/2018;06/12/2019). The focus of this review will be on two questions from the division related to the interpretation of HR and PR findings in a DDI study of diltiazem and ozanimod (study RPC01-1908) and if ozanimod can potentiate pressor effects of pseudoephedrine (study RPC01-1914).

2.1 Study RPC01-1908

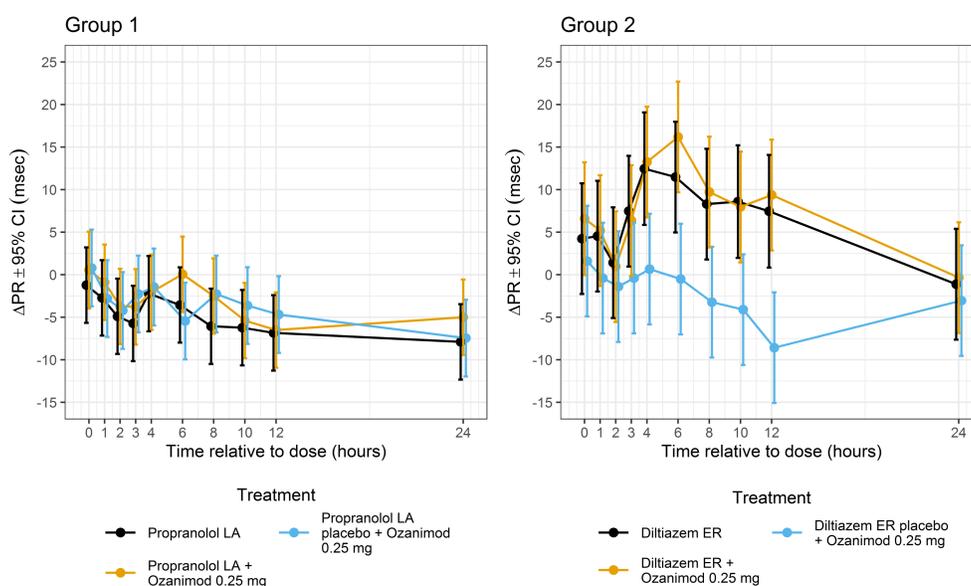
Study RPC01-1908 was a double-blind, randomized, placebo-controlled cross-over study with two groups (18 subjects each) enrolled in parallel. The treatment arms in both groups were similar and included 5 days of dosing of 80 mg propranolol long acting (LA) or 240 mg diltiazem extended-release (ER) for 5 days (or placebo) followed by a single dose of ozanimod 0.25 mg or placebo on the 5th day. The study included holter monitoring on days 1 and 5. ECGs

were extracted in triplicate from the holter at pre-dose on day 1 and at predose, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h post-dose on day 5. The reviewer was unable to locate information about ECG extraction and measurement methodology.

The data from this study were analyzed by the reviewer using a linear mixed effects model with change from period-specific baseline as the dependent variable and treatment, time, treatment * time, sequence, period and average baseline as fixed effects and a random intercept. The model was fitted to each treatment group independently.

Small decreases (mean decrease: -7.9 to -6.5 ms) were observed in Δ PR for group 1 (propranolol LA) (Figure 1). The observed decreases in this treatment group are unlikely to be drug related, because a similar decrease was observed in all treatment arms and neither ozanimod nor propranolol are known to shorten the PR interval. An increase in Δ PR was observed for treatment groups including diltiazem ER in group 2 (Figure 1). The increase in Δ PR between diltiazem ER alone and diltiazem ER + single ozanimod was not significantly different (maximum difference: 4.7 ms [95% CI: -3.1 to 12.5 ms]) and no changes in PR were observed with ozanimod by itself in this study or in the other studies that we reviewed for QT effects (DARRTS 01/29/2014;06/12/2019). The results of this analysis are consistent with those of the sponsor's analysis and suggests that the PR interval increase observed in this study is driven by diltiazem, which is expected based on diltiazem being a L-type calcium channel blocker.

Figure 1: Mean and 95% of Δ PR Time course

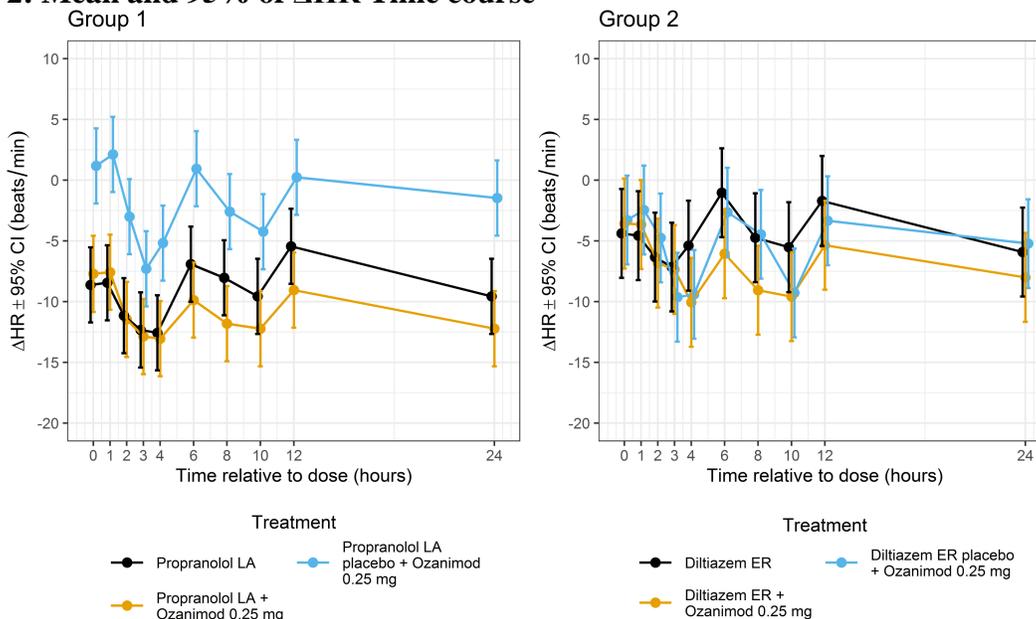


Source: Reviewer's analysis

The HR data collected in this study was analyzed using the same approach as for PR. The results of this analysis show a slight decrease in Δ HR following a single 0.25-mg dose of ozanimod of -7.3 (95% CI: -10.4 to -4.2 bpm) and -9.6 bpm (95% CI: -13.3 to -6.0 bpm), which is similar to study RPC01-102 (see review by Dr. Stephen Grant dated 12/11/2019). The maximum mean difference between propranolol LA or diltiazem ER + ozanimod 0.25 mg single dose vs propranolol LA or diltiazem alone was -3.8 bpm (95% CI: -7.2 to -0.3 bpm) and -5 bpm (95%

CI: -8.8 to -1.2 bpm), respectively. These results are similar to those of the sponsor. The further decrease observed for ozanimod + diltiazem / propranolol was less than what was observed following a single dose of ozanimod 0.25 mg and does not suggest any potential for ozanimod to potentiate the HR effects of propranolol or diltiazem.

Figure 2: Mean and 95% of Δ HR Time course



Source: Reviewer's analysis

2.2 Study RPC01-1914

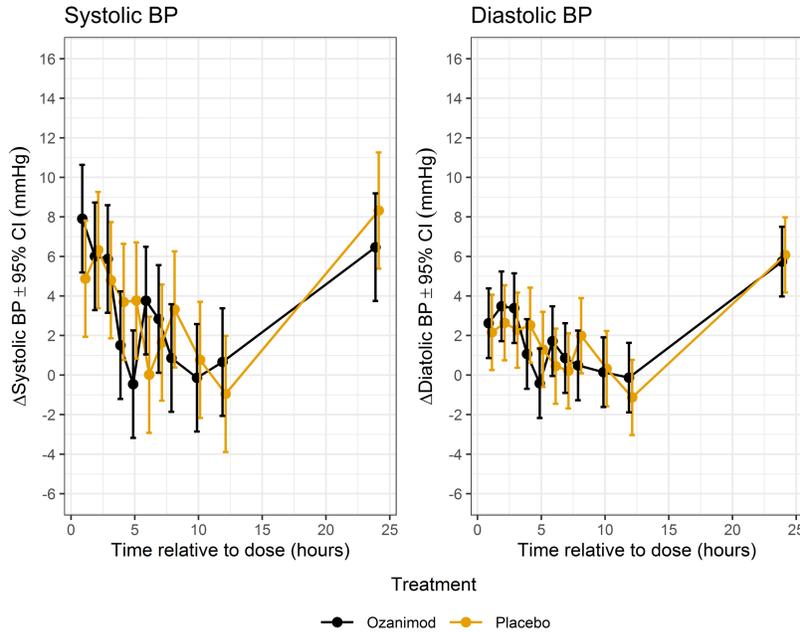
Study RPC01-1914 was a double-blind, randomized, placebo-controlled study with two treatment groups (~30 per group). Subjects in the study were randomized to receive ozanimod or placebo for 30 days with a single dose of 60 mg pseudoephedrine administered in both treatment groups on day 30. Subjects in the ozanimod group received a titrated dose of ozanimod starting at 0.25 and ending at 2 mg.

We have previously reviewed the ECG data from this study and refer the reader to our review dated 06/12/2019 for details on those findings. This review will focus on the BP data collected in this study on days 29 (before pseudoephedrine) and 30 (after single dose of pseudoephedrine). On both days, BP were collected at predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h post-dose in triplicate. The primary planned analysis for this study was maximum time-matched change from day 29 in systolic BP. The data from this study were analyzed in two ways: 1) by-time for the change from day 30 using a linear mixed effects model by BP parameter with treatment, time * treatment and average baseline as fixed effects and a random intercept and 2) change in 24-h average by BP parameter and treatment accounting for baseline BP.

An increase in the mean systolic and diastolic BP was observed on day 30 compared to day 29 (Figure 3). While, no significant difference was observed when comparing the two treatment arms the confidence limits on the difference were wide (systolic BP: 3.8 (-0.3 to 7.8) mmHg;

diastolic BP: 1.3 (-1.3 to 3.9) mmHg). The results of this analysis are like that of the sponsor's; however, the sponsor considered the maximum time-matched difference within subject, whereas the reviewer considered the maximum increase in the average difference by time.

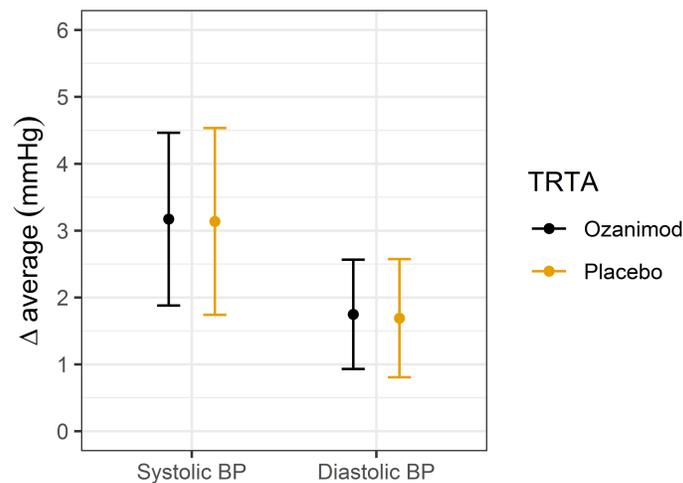
Figure 3: Mean and 95% of Δ BP Time course



Source: Reviewer's analysis

The difference in the 24-h average systolic and diastolic BP is shown in Figure 4. Consistent with the by-time analysis, an increase in systolic and diastolic BP is observed for both treatment arms and the difference between the two treatment arms are: 0.04 (-1.9 to 2) and 0.06 (-1.2 to 1.3) mmHg for systolic and diastolic BP respectively. These results are similar to the sponsor's and suggests that no changes in the 24-h average were observed between the two treatment arms.

Figure 4: Mean and 95% of 24-h average Δ BP



Source: Reviewer's analysis

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcr-ond-abpm@fda.hhs.gov

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/

LARS JOHANNESSEN
12/19/2019 01:46:15 PM

CHRISTINE E GARNETT
12/19/2019 01:47:54 PM

NORMAN L STOCKBRIDGE
12/19/2019 03:24:27 PM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 11, 2019

From: Stephen M. Grant, M.D.
Clinical Reviewer
Division of Cardiovascular and Renal Products (DCaRP)

Through: Norman Stockbridge, Ph.D., M.D.
Director
Division of Cardiovascular and Renal Products

To: Susan B Daugherty, BSN
Regulatory Health Project Manager
Division of Neurology Products (DNP)

Subject: DCaRP consult to review the effects of ozanimod, a sphingosine-1-phosphate (S1P) receptor modulator, on heart rate and cardiac conduction

On 25 March 2019 Celgene Corporation (Celgene) submitted NDA 209899 seeking approval to market ozanimod, a S1P receptor modulator, for the treatment of multiple sclerosis (MS) with a recommended dose of 1 mg qd. You asked for our opinion about the effect of ozanimod (aka RPC1063) on heart rate and cardiac conduction and whether monitoring patients to detect significant bradycardia and/or atrioventricular heart block was advisable.

We reviewed the following materials, at least in part:

- Your consult dated 27 Aug 2019
- The NDA submission dated 25 Mar 2019 including in particular
 - The Summary of Clinical Safety (section 2.7.4)
 - The clinical study reports for studies RPCS 001 (SAD/MAD), RPC01-102 (Thorough QT study), RPC01-201A (phase 2 placebo-controlled dose ranging study), RPC-201B (phase 2b active-controlled dose ranging study), and RPC01-301 (phase 3 active-controlled study intended to demonstrate superiority of ozanimod to interferon).
- Documents dated 23 Aug, 25 Nov, and 6 Dec submitted to NDA 209899 by Celgene that responded to information requests by this reviewer
- Interdisciplinary Review Team for QT studies review of RPC01-102 (Thorough QT study) dated 29 Jan 2014

- Interdisciplinary Review Team review of RPC01-1914 (placebo-controlled study of effect of ozanimod on blood pressure and HR) dated 12 Jun 2019
- Analyses of heart rate based on Holter data from study RPC01-102 and RPC01-1914 performed Dr. Lars Johannesen of the FDA Interdisciplinary Review Team
- Previous DCaRP consults dated 10 Aug 2016 and 15 Jun 2017
- Fingolimod prescribing information dated Jan 2019
- Siponimod prescribing information dated Mar 2019
- “Cardiac and vascular effects of fingolimod: Mechanistic basis and clinical implications” *Camm et. al. Am Heart J.* 2014 Nov;168(5):632-44
- “Sphingosine-1-phosphate signaling in the cardiovascular system” *Curr Opin Pharmacol.* 2007 Apr;7(2):186-92

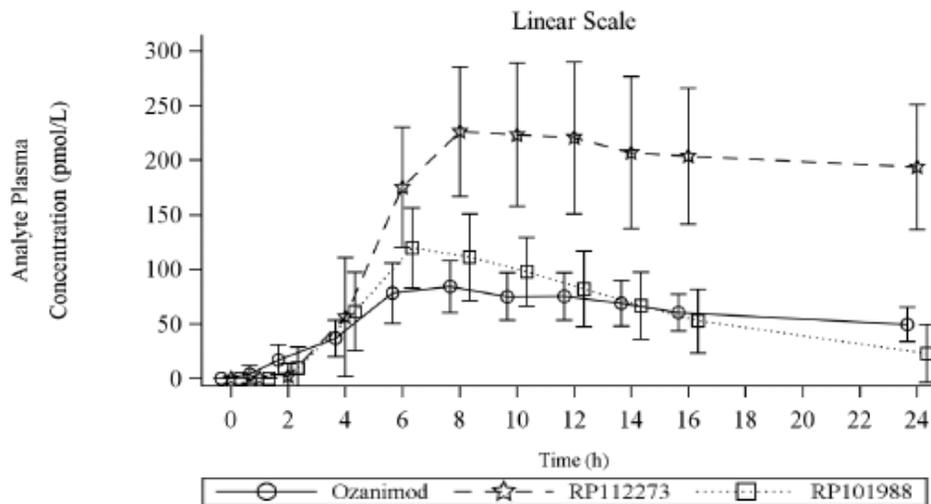
Background

The applicant, Celgene, has submitted NDA 209899 seeking approval to market ozanimod, a S1P receptor modulator, for the treatment of MS. Celgene has also conducted clinical studies of ozanimod in patients with ulcerative colitis and Crohn’s disease.

S1P receptor modulators have vagomimetic effects on the heart, apparently because of a change in inward potassium current in the sinoatrial and atrioventricular (AV) nodes. Hence, they slow the heart rate (HR), which can result in bradycardia, and prolong AV conduction, which can result in AV block. These effects are concentration dependent and are thought to occur mostly with the first dose. It is hypothesized that the first dose acts as an agonist at the S1P receptor, but subsequent doses decrease activity at this receptor.

The applicant asserts that ozanimod is relatively specific for the S1P₁ and S1P₅ receptor subtypes. It has two active metabolites, which have activity at the S1P receptor similar to the parent. Median Tmax for ozanimod is about 8 hours and Tmax for the two active metabolites, RP112273 and RP101988, is in a similar range. Inter-patient variability in exposure is reported to be low. The following figure from the NDA submission summarizes the PK:

Figure 1: Mean (SD) Plasma Concentration-Time Profiles for Ozanimod and its Active Metabolites on Day 1 Following the First Dose of Ozanimod 0.25 mg



Fingolimod is a sphingosine phosphate receptor modulator less specific for receptor subtypes than ozanimod approved for the treatment of relapsing forms of multiple sclerosis. Its T_{max} is 12 – 16 hours. Its initial label mandated ‘observation’ for 6 hours. However, the label was revised to stipulate hourly monitoring of ECG and blood pressure after the first dose for six hours and continued monitoring beyond 6 hours in specified circumstances. This change was prompted by the sudden death of a 59-year old female whose vital signs during the 6-hour observation period after the first dose of fingolimod was reported as unremarkable but who then died that night while asleep. The cause of death could not be determined.

Siponimod is a sphingosine phosphate receptor modulator with specificity for receptor subtypes similar to ozanimod that is also approved for the treatment of multiple sclerosis. Its T_{max} is about 4 hours (range 3 - 8 hours). Unlike fingolimod, the dose of siponimod is up-titrated over 6 days, which purportedly minimizes the effect on heart rate and AV conduction. The siponimod label recommends first dose monitoring of heart rate and blood pressure for six hours only for patients with sinus bradycardia (less than 55 beats per minute), first-or second-degree Mobitz type I AV block, or a history of myocardial infarction or heart failure. It recommends consultation with a cardiologist prior to initiation in patients:

- with arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs,
- with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, or uncontrolled hypertension, or
- with a history of with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block.

Clinical Development

Study RPCS 001

The initial clinical study of ozanimod was a single ascending dose study in healthy adult subjects. Heart rate was monitored via telemetry. The two figures and table below from the applicant summarizes the heart rate data from this study.

Figure 2: Change from Predose Baseline in Mean Hourly Heart Rate (beats/minute) by Dose in Study RPCS001

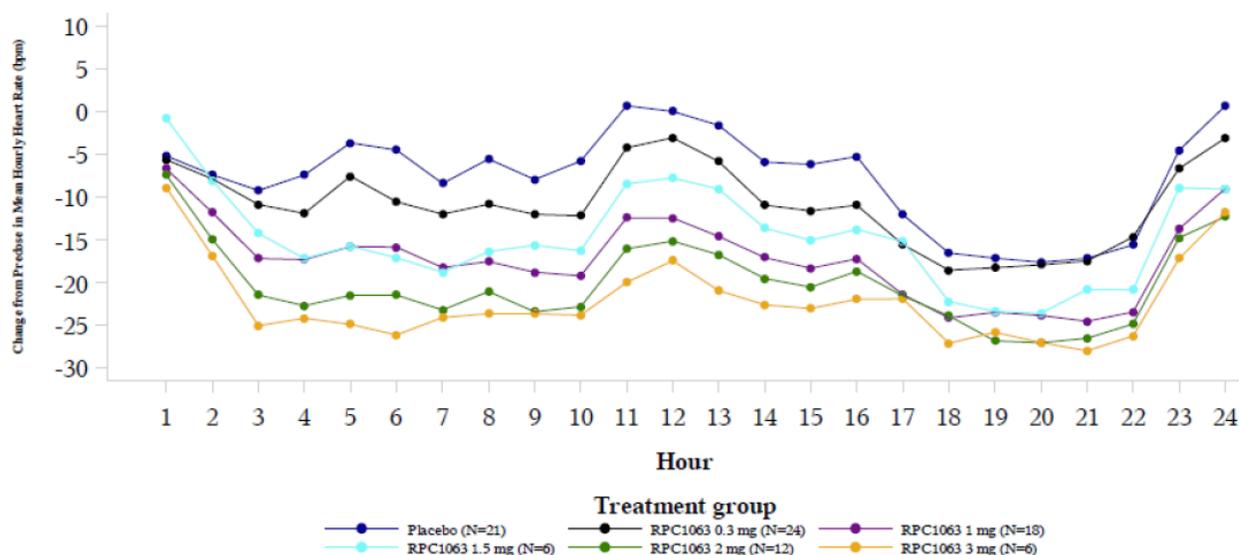


Figure 3: Difference of the Mean Change from Baseline in Hourly Heart Rate (beats/minute) by Ozanimod Dose Compared to Placebo in Study RPCS001

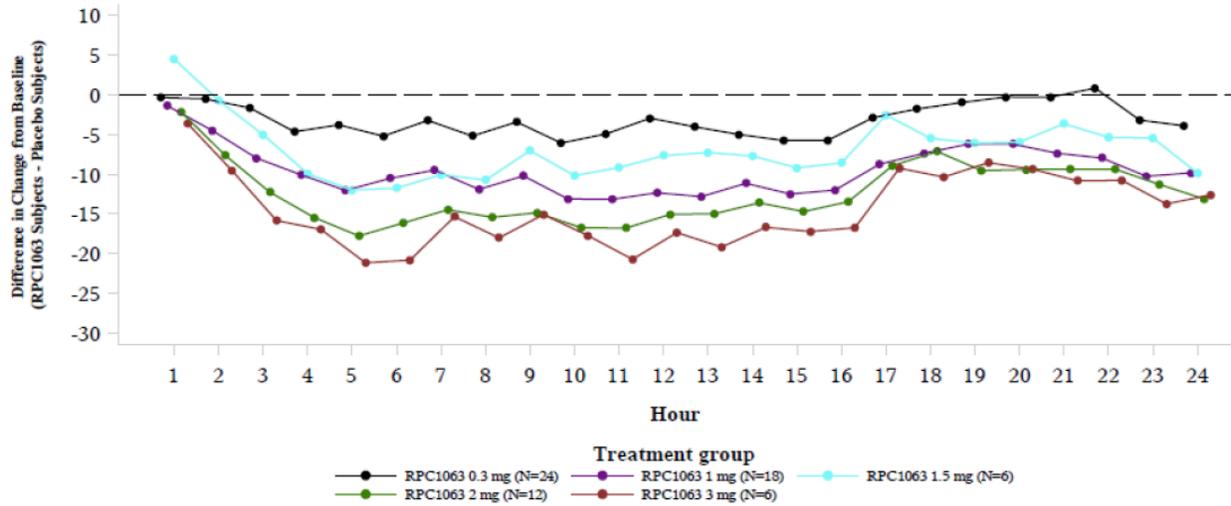


Table 1: Difference of the Mean Change from Baseline in Hourly Heart Rate (beats/minute) by Ozanimod Dose Compared to Placebo in Study RPCS001

Hour	Dose				
	0.3 mg	1 mg	1.5 mg	2 mg	3 mg
1	-0.5 bpm	-1.5 bpm	4.4 bpm	-2.2 bpm	-3.7 bpm
2	-0.5 bpm	-4.4 bpm	-0.7 bpm	-7.6 bpm	-9.5 bpm
3	-1.7 bpm	-8.0 bpm	-5.0 bpm	-12.2 bpm	-15.8 bpm
4	-4.5 bpm	-9.9 bpm	-9.8 bpm	-15.3 bpm	-16.8 bpm
5	-3.9 bpm	-12.1 bpm	-12.1 bpm	-17.9 bpm	-21.2 bpm
6	-6.1 bpm	-11.4 bpm	-12.6 bpm	-17.0 bpm	-21.7 bpm
7	-3.6 bpm	-9.8 bpm	-10.4 bpm	-14.8 bpm	-15.7 bpm
8	-5.3 bpm	-12.0 bpm	-10.8 bpm	-15.5 bpm	-18.1 bpm
9	-4.1 bpm	-10.9 bpm	-7.7 bpm	-15.5 bpm	-15.7 bpm
10	-6.4 bpm	-13.4 bpm	-10.5 bpm	-17.0 bpm	-18.0 bpm
11	-4.9 bpm	-13.1 bpm	-9.1 bpm	-16.8 bpm	-20.7 bpm
12	-3.1 bpm	-12.5 bpm	-7.8 bpm	-15.2 bpm	-17.5 bpm
13	-4.2 bpm	-13.0 bpm	-7.5 bpm	-15.2 bpm	-19.3 bpm
14	-5.0 bpm	-11.2 bpm	-7.7 bpm	-13.6 bpm	-16.7 bpm
15	-5.4 bpm	-12.2 bpm	-8.9 bpm	-14.4 bpm	-16.9 bpm
16	-5.7 bpm	-12.0 bpm	-8.5 bpm	-13.4 bpm	-16.7 bpm

17	-3.5 bpm	-9.3 bpm	-3.2 bpm	-9.5 bpm	-9.9 bpm
18	-2.0 bpm	-7.6 bpm	-5.7 bpm	-7.4 bpm	-10.6 bpm
19	-1.1 bpm	-6.3 bpm	-6.2 bpm	-9.7 bpm	-8.7 bpm
20	-0.3 bpm	-6.2 bpm	-6.0 bpm	-9.4 bpm	-9.4 bpm
21	-0.3 bpm	-7.4 bpm	-3.7 bpm	-9.4 bpm	-10.8 bpm
22	0.9 bpm	-7.8 bpm	-5.2 bpm	-9.3 bpm	-10.7 bpm
23	-2.1 bpm	-9.2 bpm	-4.4 bpm	-10.2 bpm	-12.7 bpm
24	-3.8 bpm	-9.7 bpm	-9.7 bpm	-13.0 bpm	-12.5 bpm

Conclusions:

- Ozanimod results a dose dependent reduction in heart rate that peaks about 6 to 12 hours after administration, which is consistent with Tmax of ozanimod and its active metabolites.
- The maximal reduction in heart rate after administration of the highest dose studied, 3 mg, compared to placebo is about 20 beats per minute.

Additionally, the applicant reports that three subjects in the 3 mg dose group and one in the 1.5 mg dose group had symptomatic bradycardia and at least one subject had type 1 second degree AV block but none required any treatment.

Study RPC01-102

In the phase 2 and 3 studies, the dose of ozanimod was titrated as follows:

Table 2: Ozanimod Dose Escalation Regimen

Ozanimod Treatment Group	Day Number		
	Days 1 to 4	Days 5 to 7	Day 8
0.5 mg	0.25 mg	0.5 mg	0.5 mg
1 mg	0.25 mg	0.5 mg	1 mg

Study RPC01-102 was a thorough QT study in which 60 healthy male and female adult subjects received ozanimod monotherapy titrated from an initial ozanimod dose of 0.25 mg to 0.5 mg, then 1 mg, and finally to 2 mg (the suprathreshold dose) using the dosing scheme in table 2 above, except that subjects had an additional up-titration to 2 mg on day 11. Subjects had Holter monitors performed for 24 hours after initiation and after each increase in dose (i.e., on days 1, 5, 8, and 11). Lars Johannesen of the FDA Interdisciplinary review team analyzed the Holter monitor heart rate data from study RPC01-102 and provided the following figures and table:

Figure 4: Change from Predose Baseline in Mean Hourly Heart Rate (beats/minute) by Ozanimod Dose after Titration in Study RPC01-102

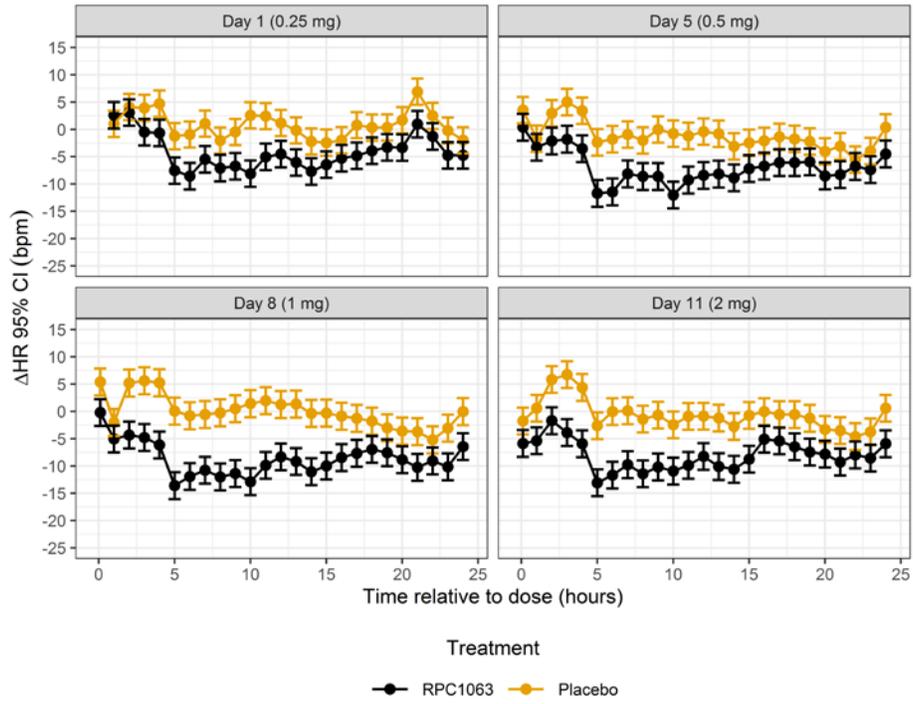


Figure 5: Difference of the Mean Change from Baseline in Heart Rate (beats/minute) by Ozanimod Dose after Titration Compared to Placebo in Study RPC01-102

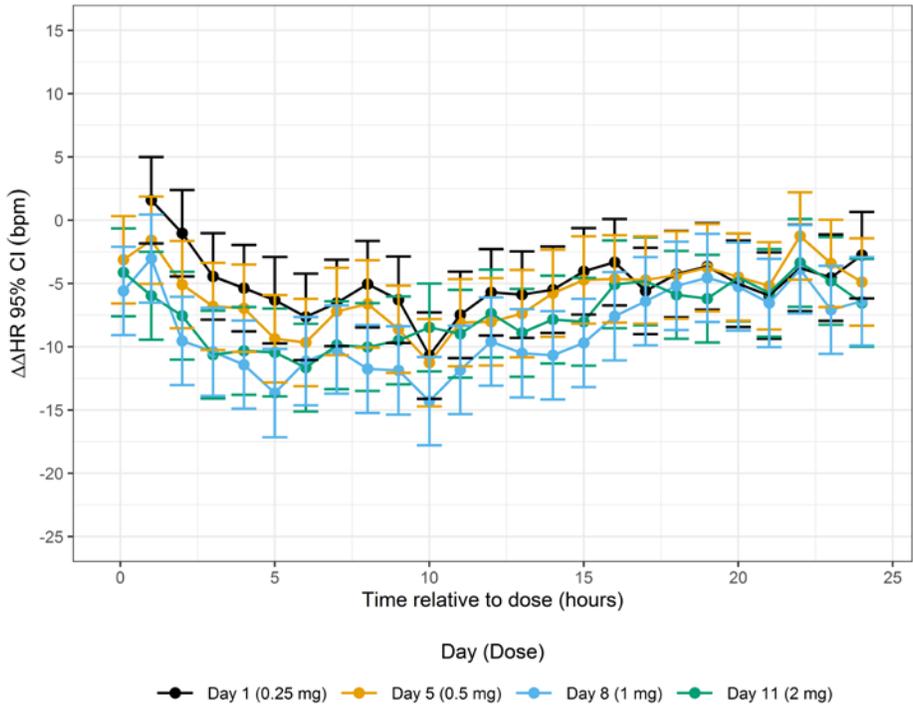


Table 3: Difference of the Mean Change from Baseline in Hourly Heart Rate (beats/minute) by Ozanimod Dose After Titration Compared to Placebo in Study RPC01-102

Hour	DOSE and DAY			
	0.25 mg (day 1)	0.5 mg (day 5)	1 mg (day 8)	2 mg (day 11)
1	1.6 bpm	-1.6 bpm	-3.0 bpm	-6.0 bpm
2	-1.0 bpm	-5.1 bpm	-9.5 bpm	-7.5 bpm
3	-4.4 bpm	-6.8 bpm	-10.4 bpm	-10.6 bpm
4	-5.4 bpm	-7.0 bpm	-11.4 bpm	-10.3 bpm
5	-6.3 bpm	-9.4 bpm	-13.7 bpm	-10.4 bpm
6	-7.6 bpm	-9.7 bpm	-11.1 bpm	-11.6 bpm
7	-6.5 bpm	-7.2 bpm	-10.2 bpm	-9.9 bpm
8	-5.0 bpm	-6.6 bpm	-11.7 bpm	-10.0 bpm
9	-6.3 bpm	-8.6 bpm	-11.9 bpm	-9.5 bpm
10	-10.7 bpm	-11.3 bpm	-14.3 bpm	-8.5 bpm
11	-7.5 bpm	-8.1 bpm	-11.8 bpm	-9.0 bpm
12	-5.7 bpm	-8.0 bpm	-9.6 bpm	-7.4 bpm
13	-5.9 bpm	-7.4 bpm	-10.5 bpm	-8.9 bpm
14	-5.5 bpm	-5.8 bpm	-10.7 bpm	-7.8 bpm
15	-4.0 bpm	-4.7 bpm	-9.7 bpm	-8.0 bpm
16	-3.3 bpm	-4.6 bpm	-7.6 bpm	-5.1 bpm
17	-5.6 bpm	-4.7 bpm	-6.4 bpm	-4.8 bpm
18	-4.3 bpm	-4.3 bpm	-5.2 bpm	-5.9 bpm
19	-3.6 bpm	-3.7 bpm	-4.6 bpm	-6.2 bpm
20	-5.0 bpm	-4.5 bpm	-5.2 bpm	-4.5 bpm
21	-6.0 bpm	-5.2 bpm	-6.5 bpm	-5.7 bpm
22	-3.8 bpm	-1.2 bpm	-3.9 bpm	-3.4 bpm
23	-4.5 bpm	-3.4 bpm	-7.1 bpm	-4.8 bpm
24	-2.8 bpm	-4.9 bpm	-6.4 bpm	-6.5 bpm

Conclusions:

1. The peak effect on heart rate for all doses of ozanimod occurs between hours 6 and 10, which is consistent with Tmax of ozanimod and its active metabolites.
2. Each increase in dose from doses 0.25 mg to 1.0 mg results in a greater reduction in heart rate compared to preceding doses. However, the increase in heart rate reduction for 2.0 mg is less than that for 1.0 mg dose.

3. The titration scheme results in a modest blunting of the reduction in heart rate based on a comparison of heart rate after administration of 1 mg in study RPC01-102 compared to administration of 1 mg without titration in study RPCS 001, as shown in the table below:

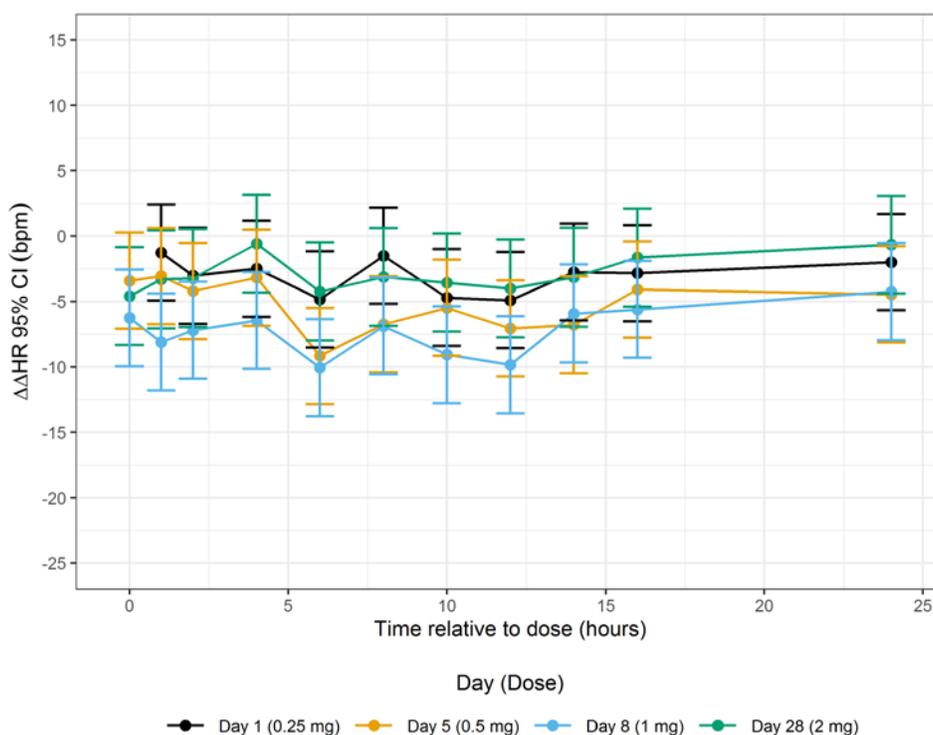
Table 4: Comparison of the Mean Change in Hourly Heart Rate (in beats/minute) from Baseline Compared to Placebo after administration of 1 mg of Ozanimod without Titration in Study RPCS 001 and with Titration in Study RPC01-102

Hour	DOSE, DAY, and STUDY	
	1 mg (day 1) Study RPCS001	1 mg (day 8) Study RPC01-102
1	-1.5 bpm	-3.0 bpm
2	-4.4 bpm	-9.5 bpm
3	-8.0 bpm	-10.4 bpm
4	-9.9 bpm	-11.4 bpm
5	-12.1 bpm	-13.7 bpm
6	-11.4 bpm	-11.1 bpm
7	-9.8 bpm	-10.2 bpm
8	-12.0 bpm	-11.7 bpm
9	-10.9 bpm	-11.9 bpm
10	-13.4 bpm	-14.3 bpm
11	-13.1 bpm	-11.8 bpm
12	-12.5 bpm	-9.6 bpm
13	-13.0 bpm	-10.5 bpm
14	-11.2 bpm	-10.7 bpm
15	-12.2 bpm	-9.7 bpm
16	-12.0 bpm	-7.6 bpm
17	-9.3 bpm	-6.4 bpm
18	-7.6 bpm	-5.2 bpm
19	-6.3 bpm	-4.6 bpm
20	-6.2 bpm	-5.2 bpm
21	-7.4 bpm	-6.5 bpm
22	-7.8 bpm	-3.9 bpm
23	-9.2 bpm	-7.1 bpm
24	-9.7 bpm	-6.4 bpm

Study RPC01-1914

Study RPC01-1914 was a phase 1 study in which 56 healthy subjects were randomized 1:1 to either placebo for 30 days or to ozanimod 0.25 mg on days 1 to 4, 0.5 mg on days 5 to 7, 1 mg on days 8 to 10, and 2 mg QD on days 11 to 30. Holter monitoring was performed on days -1, 1, 5, 8, and 28. Lars Johannesen of the FDA Interdisciplinary review team analyzed the Holter monitor heart rate data from study RPC01-102 and provided the following figure:

Figure 6: Difference of the Mean Change from Baseline in Hourly Heart Rate (beats/minute) by Ozanimod Dose after Titration Compared to Placebo in Study RPC01-1914



Conclusion: At least at day 28 the heart rate effect of ozanimod at a dose twice the recommended clinical dose is minimal. This finding supports the hypothesis that the first dose acts as an agonist at the S1P receptor, but subsequent doses decrease activity at this receptor.

Study RPCS RPC01-201A

In this study 258 patients with MS were randomized to either 0.5 mg or 1.0 mg of ozanimod titrated as shown in table 1 or to placebo for 24 weeks. Subjects with resting HR less than 55 bpm, ischemic heart disease, myocardial infarction, congestive heart failure, stroke, sick sinus syndrome, recurrent syncope, second-degree or higher atrioventricular block or “other clinically significant conduction abnormalities,” severe untreated sleep apnea, or diabetes were not eligible to enroll. All subjects underwent Holter monitoring on days 1 and the first 75 subjects also underwent Holter monitoring on days 5 and 8. The heart rate data is summarized in the figures and table supplied by the applicant below:

Figure 7: Mean Hourly Heart Rate (+/- SE) on Day 8 in Study RPC01-201A

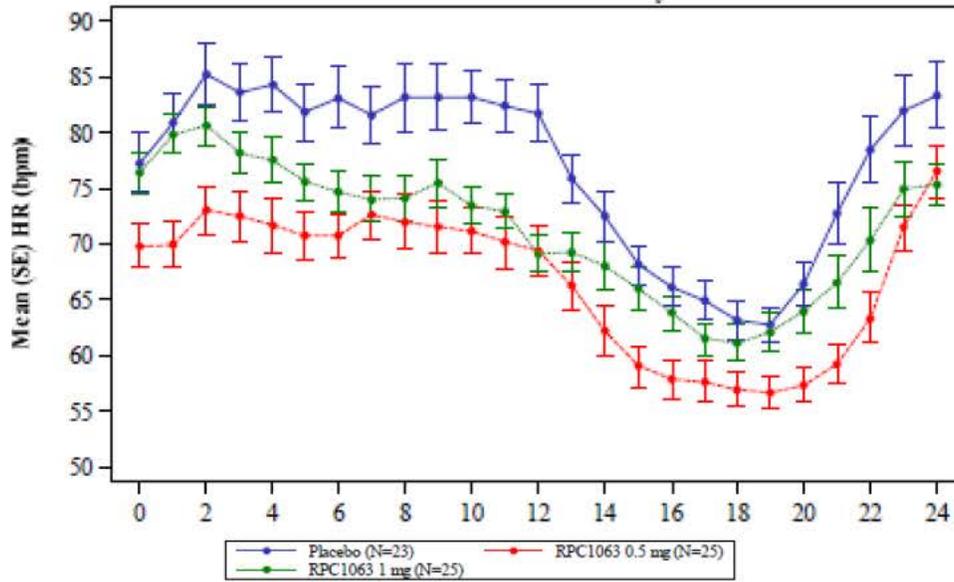
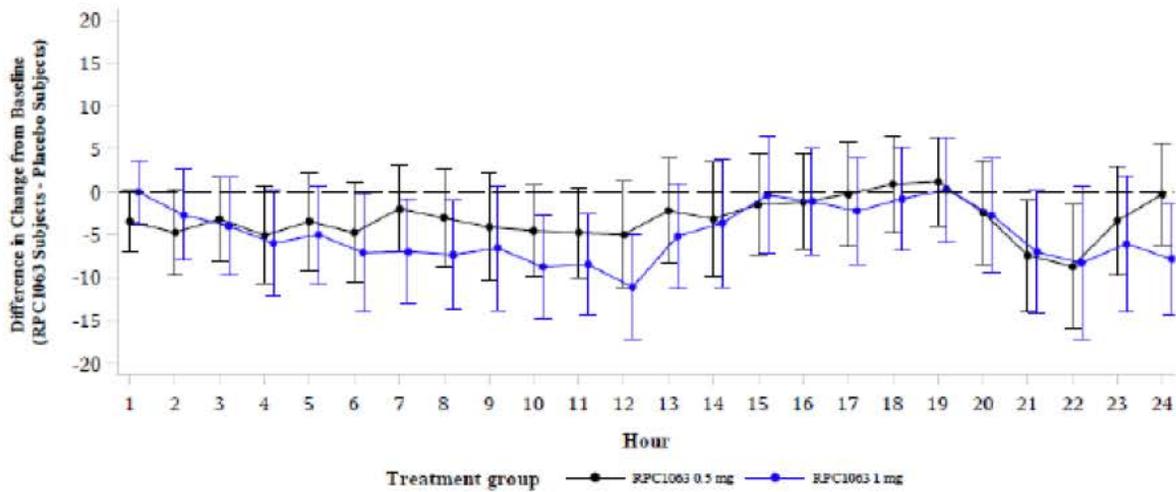


Figure 8: Difference of the Mean Change from Baseline in Hourly Heart Rate (beats/minute) on Day 8 Ozanimod (0.5 & 1 mg) Compared to Placebo in Study RPC01-201A



CI = confidence interval; RPC1063 = ozanimod HCl

Note: The difference represents the mean change from baseline in heart rate of subjects treated with ozanimod 0.25 mg (N = 161) minus the mean change from baseline in heart rate of subjects treated with placebo (N = 85). The figure includes subjects with a baseline and any postdose heart rate; N is the maximum number of subjects across the 24-hour period. The vertical bars indicate 95% confidence intervals.

Table 5: Difference of the Mean Change in Hourly Heart Rate (beats/minute) from Baseline by Ozanimod Dose After Titration Compared to Placebo in Study RPC01-201A

Hour	DOSE and DAY			
	0.25 mg (day 1)	0.5 mg (day 5)	0.5 mg (day 8)	1 mg (day 8)
1	0.3 bpm	-3.2 bpm	-3.5 bpm	-0.1 bpm
2	-0.4 bpm	-4.4 bpm	-4.7 bpm	-2.7 bpm
3	-1.8 bpm	-5.8 bpm	-3.2 bpm	-4.0 bpm
4	-5.3 bpm	-7.9 bpm	-5.1 bpm	-6.0 bpm
5	-7.0 bpm	-7.7 bpm	-3.5 bpm	-5.0 bpm
6	-7.5 bpm	-9.5 bpm	-4.8 bpm	-7.1 bpm
7	-6.7 bpm	-8.3 bpm	-2.0 bpm	-7.0 bpm
8	-7.0 bpm	-5.0 bpm	-3.1 bpm	-7.3 bpm
9	-5.6 bpm	-6.0 bpm	-4.1 bpm	-6.6 bpm
10	-6.8 bpm	-5.6 bpm	-4.5 bpm	-8.8 bpm
11	-6.2 bpm	-7.4 bpm	-4.8 bpm	-8.5 bpm
12	-6.5 bpm	-5.3 bpm	-5.0 bpm	-11.1 bpm
13	-6.1 bpm	-4.2 bpm	-2.2 bpm	-5.2 bpm
14	-5.3 bpm	-0.2 bpm	-3.2 bpm	-3.7 bpm
15	-4.6 bpm	-1.3 bpm	-1.5 bpm	-0.4 bpm
16	-4.8 bpm	0.0 bpm	-1.2 bpm	-1.1 bpm
17	-4.7 bpm	0.9 bpm	-0.3 bpm	-2.2 bpm
18	-3.6 bpm	1.3 bpm	0.9 bpm	-0.8 bpm
19	-3.0 bpm	2.7 bpm	1.2 bpm	0.2 bpm
20	-2.7 bpm	2.9 bpm	-2.4 bpm	-2.7 bpm
21	-3.7 bpm	3.5 bpm	-7.4 bpm	-7.0 bpm
22	-4.5 bpm	-0.1 bpm	-8.7 bpm	-8.3 bpm
23	-7.7 bpm	-0.8 bpm	-3.4 bpm	-6.1 bpm
24	-7.9 bpm	-4.4 bpm	-0.3 bpm	-7.9 bpm

Conclusion: The effect of ozanimod on heart rate in patients with multiple sclerosis who meet cardiac eligibility criteria is similar to that of the healthy subjects in study RPC01-102. Hence assessments of heart rate in healthy subjects can be used to provide labeling recommendations for use in patients.

Studies RPCS RPC01-201B and RPC01-301

Studies RPCS RPC01-201B and RPC01-301 were both randomized, double-blind, active-controlled studies comparing the efficacy and safety of ozanimod to IFN β -1 in MS patients. In

the two studies about 2666 subjects were enrolled and randomized to IFN β -1, 0.5 mg ozanimod, or 1 mg ozanimod for 24 months; about 882 were administered 1 mg ozanimod. Cardiac exclusion criteria were similar to those for study RPC01-201. Vital signs were measured hourly for six hours after the initial dose of ozanimod but Holter monitoring was not performed.

In response to a request from this reviewer, the applicant submitted information about all subjects who were monitored for more than 6 hours, treated or hospitalized for bradycardia or AV block, or who discontinued investigational product and had an adverse event of bradycardia or other cardiac conduction abnormality or syncope reported, regardless of whether discontinuation was attributed to the cardiac abnormality or syncope. The applicant provided narratives for nine subjects and PK data for those for whom it was available. This reviewer reviewed the information submitted. None of the events raise any particular concerns, i.e., none disclosed symptomatic or serious bradycardia or AV conduction defects. One subject ((b) (6)) who administered a single dose of 0.25 mg of ozanimod on day 1 deserves discussion. He had a heart rate of 60 at baseline that decreased to 50 at hour 6, which resulted in admission and extended monitoring. He had nonspecific symptoms and normal blood pressure. He was hospitalized for four days (i.e., for several days after expected Tmax) and administered nightly doses of atropine to increase nocturnal heart rate. The subject's exposure to ozanimod and active metabolites is reported to be low. He discontinued from the study. Given the low exposure, lack of concerning symptoms, and normal blood pressure, this event cannot readily be attributed to administration of ozanimod.

ASSESSMENT:

1. Ozanimod at the doses studied results in mild dose dependent bradycardia
2. Administration of ozanimod has been observed in clinical studies of healthy subjects to result in first degree and second degree type 1 AV block but only at higher exposures than those expected from the recommended dose.
3. The titration scheme used in the phase 3 studies modestly blunts the cardiac effects of ozanimod. However, titration results in the maximal cardiac effect of ozanimod occurring on day 8. We recommend this observation be disclosed in the label.
4. A comprehensive evaluation of the safety data base for ozanimod is beyond the scope of this review. Based on our limited evaluation of the phase 3 studies in multiple sclerosis, we were unable to identify any events of bradycardia or AV conduction defects that were of concern. 882 subjects in those studies were exposed to the recommended clinical dose, so by the rule of three the serious cardiac event rate in clinical practice will be less than one in 274 or less than 3.6 per thousand exposed.
5. The determination of the utility of first dose monitoring is in part dependent on the benefit of ozanimod because monitoring is likely to be cumbersome for the prescribing physician and patient and so likely to discourage use. Further, if monitoring were to be required, it would be most likely to detect cardiac effects on the eighth day of administration, not the first. Nonetheless, a need for monitoring is not obvious to us so long as the patients have both clinical characteristics and PK similar to those studied in the phase 3 study. We understand that interindividual variability in exposure is expected to be low. But if there are any drug-drug interactions or genetic variations in drug metabolizing enzymes that will increase exposure to ozanimod and/ or its active metabolites, patients with higher than usual exposure should be monitored.

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/

STEPHEN M GRANT
12/11/2019 11:57:10 AM

NORMAN L STOCKBRIDGE
12/11/2019 12:21:52 PM

**DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION**

Date: November 22, 2019
To: Division of Neurology Products (DNP)
From: Natalie Pica, Medical Officer, DPARP
Through: Miya Paterniti, Medical Team Leader, DPARP
Through: Banu Karimi-Shah, Acting Deputy Director, DPARP
Subject: Zeposia (ozanimod)

General Information

NDA/IND#: 209899
Sponsor: Celgene
Drug product: Zeposia (ozanimod)
Request from: Division of Neurology Products
Date of request: May 6, 2019
Date received: May 7, 2019
Requested completion date: November 30, 2019
Materials reviewed: Siponimod DPARP consult (17 JAN 2019), fingolimod DPARP consult (30 AUG 2011), Type A face-to-face meeting minutes (27 APR 2018), Type C Written Responses (09 NOV 2018, 15 FEB 2019)

I. Introduction

This is a Medical Officer response to the consultation request from the Division of Neurology Products (DNP), to review pulmonary function results for NDA 209899 for ozanimod (also known as RPC1063 and Zeposia), a sphingosine-1-phosphate (S1P) receptor modulator proposed for the treatment of relapsing multiple sclerosis (RMS). DNP has also requested for the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to specifically comment on whether there is adequate characterization of the effects of this therapy on pulmonary testing parameters to inform labeling and whether postmarketing studies are needed to characterize the degree or persistence of these effects.

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system. RMS includes patients with relapsing-remitting MS (RRMS) as well as secondary progressive MS (SPMS) with superimposed relapses. MS is thought to be a result of demyelination and axonal damage of neurons in the CNS by autoreactive lymphocytes. It is hypothesized that inhibition of these processes could slow disease progression and reduce incidences of relapse.

The clinical program for ozanimod included a phase 2, randomized, double-blind, placebo-controlled trial with a blinded extension period (RPC01-201A), two, pivotal, phase 3, randomized, double-blind, active-controlled trials (RPC01-201B and RPC01-301), and a long-term open-label extension (OLE) trial (RPC01-3001). Based on the known side effect

profile of S1P modulators, special attention was directed to the assessment for pulmonary adverse events.

Table of Contents

I. Introduction.....	1
II. Background.....	6
III. Clinical Trial Summary	7
A. Trial RPC01-201A.....	7
B. Trial RPC01-201B.....	9
C. Trial RPC01-301	11
D. Trial RPC01-3001	13
IV. Review of Pulmonary Safety	15
A. Trial RPC01-201A – Placebo-controlled period	15
B. Trial RPC01-201A - Blinded Extension Period	19
C. Trial RPC01-201B.....	22
D. Trial RPC01-301	27
E. Trial RPC01-3001	33
V. Integrated Review of Pulmonary Safety.....	37
A. Demographics.....	37
B. Extent of Exposure	37
C. Analysis of Adverse Events.....	37
D. Death and Serious Adverse Events.....	38
E. Pulmonary Function Measurements	38
F. Pulmonary Safety Conclusions	41
VI. Labeling Recommendations	43

Table of Tables

Table 1: RPC01-201A (Placebo-Controlled Period), Participant Demographics, ITT Population	9
Table 2: Trial RPC01-201B, Patient Demographics, ITT Population	10
Table 3: Trial RPC01-301, Patient Demographics, ITT Population	13
Table 4: Trial RPC01-3001, Patient Demographics, ITT Population	15
Table 5: Adverse Events (Occurring \geq 1% in Any Ozanimod Treatment Group and Reported at a Higher Rate Than Placebo): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-201A (Placebo-Controlled Period), Safety Population	16
Table 6: Mean Change From Baseline in FEV1, FVC, and DLCO at Weeks 12 and 24, Study RPC01-201A, Placebo-Controlled Period (Safety Population)	17
Table 7: Adverse Events (\geq 1% in Any Treatment Group): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-201A (Blinded Extension Period), Ozanimod Population	20
Table 8: Adverse Events (Occurring \geq 1% in Any Ozanimod Treatment Group and Reported at a Higher Rate Than IFN- β): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-201B (Safety Population)	23
Table 9: Mean Change From Baseline in FEV1, Trial RPC01-201B (Safety Population) ..	24
Table 10: Mean Change From Baseline in FVC, Trial RPC01-201B (Safety Population) ..	25
Table 11: Outlier Analysis of Pulmonary Function Testing, Trial RPC01-201B (Safety Population)	27
Table 12: Adverse Events (Occurring \geq 1% in Any Ozanimod Treatment Group and Reported at a Higher Rate Than IFN β -1a): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-301 (Safety Population)	28
Table 13: Mean Change From Baseline in FEV1, Trial RPC01-301 (Safety Population) ..	29
Table 14: Mean Change From Baseline in FVC, Trial RPC01-301 (Safety Population) ..	30
Table 15: Outlier Analysis of Pulmonary Function Testing, Trial RPC01-201B (Safety Population)	33
Table 16: Adverse Events (\geq 1% in Any Treatment Group): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-3001 (Safety Population)	34
Table 17: Serious Adverse Events Related to Pulmonary Safety, Trial RPC01-3001 (Safety Population)	34
Table 18: Mean Change From Open-Label Extension Baseline in FEV1, Trial RPC01-3001 (Safety Population)	35
Table 19: Mean Change from Open-Label Extension Baseline in FVC, Trial RPC01-3001 (Safety Population)	35
Table 20: Outlier Analysis of Pulmonary Function Testing, Trial RPC01-3001 (Safety Population)	36
Table 21: Adverse Events (Occurring \geq 1% in an Ozanimod Treatment Group and Reported at a Higher Rate Than IFN β -1a): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Pooled Active-Controlled Trials (Safety Population)	38

Table 22: Mean Change From Baseline in FEV1, Pooled Active-Controlled Trials (Safety Population)	39
Table 23: Mean Change From Baseline in FVC, Pooled Active-Controlled Trials (Safety Population)	40

Table of Figures

Figure 1: Study Design of Placebo-Controlled and Blinded Extension Portions of RPC01-201A.....	8
Figure 2: Study Design of RPC01-201B.....	10
Figure 3: Study Design of RPC01-301	12
Figure 4: Parent Studies for Open-Label Extension Trial RPC01-3001	14
Figure 5: Mean Change From Baseline (95% Confidence Intervals) in FEV1 at Week 12 and 24 (Panel A, Liters; Panel B, % Predicted), Trial RPC01-201A, Placebo-Controlled Period (Safety Population)	18
Figure 6: Mean Change From Baseline (95% Confidence Intervals) in FVC at Week 12 and 24 (Panel A, Liters; Panel B, % Predicted), Study RPC01-201A, Placebo-Controlled Period (Safety Population)	19
Figure 7: Change From Baseline in % Predicted FEV1, Study RPC01-201A, Blinded Extension Period (Ozanimod Population).....	21
Figure 8: Change From Baseline in % predicted FVC, Trial RPC01-201A, Blinded Extension Period (Ozanimod Population).....	22
Figure 9: Change From Baseline in DLCO (Corrected for Hemoglobin), Study RPC01-201A, Blinded Extension Period (Ozanimod Population)	22
Figure 10: Mean Change From Baseline (95% Confidence Intervals) in FEV1 (Panel A, Liters; Panel B, % Predicted), Trial RPC01-301(Safety Population)	31
Figure 11: Mean Change From Baseline (95% Confidence Intervals) in FVC (Panel A, Liters; Panel B, % Predicted), Trial RPC01-301(Safety Population)	32

II. Background

Ozanimod is an oral sphingosine-1-phosphate (S1P) receptor agonist which binds selectively to S1P subtypes 1 (S1P1) and 5 (S1P5), with little activity to other S1P receptors. Agonists of S1P receptors are thought to retain autoreactive lymphocytes within lymphoid tissues, inhibiting migration across the blood-brain barrier. It is hypothesized that this retention decreases cell-mediated demyelination related to MS (1).

It is important to assess the potential pulmonary toxicity of any drug used for the treatment of MS, as patients with MS may be at an increased risk for respiratory issues related to muscle weakness. Moreover, because S1P regulates the functions of airway smooth muscles during inflammation and airway remodeling and has been implicated in the development of lung disease (2, 3), an assessment of pulmonary safety is critical for any therapeutic that activates S1P signaling. As such, DPARP has previously been consulted to assess the pulmonary safety of two other drugs within this class, fingolimod and siponimod. Because pulmonary toxicity was appreciated during these clinical trial programs, DPARP recommended additions to various sections of product labeling as well as the addition of postmarketing requirements (PMR) for both fingolimod and siponimod, as described below.

Fingolimod is a S1P modulator and was approved as Gilenya under NDA 22527 in 2010 for the treatment of relapsing forms of MS in patients 10 years of age and older. During the development program, dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in patients treated with fingolimod as early as 1 month after treatment initiation. In 2-year, placebo-controlled trials in adult patients, the reduction from baseline in the % predicted values for FEV1 at the time of last assessment on drug was 2.8% for the approved dose of Gilenya compared to placebo. For DLCO, the reduction from baseline in % predicted values at the time of last assessment on drug was 3.3% for Gilenya and 0.5% for placebo. While the changes in FEV1 were thought to be reversible, there were insufficient data to determine the reversibility of DLCO changes. Of note, several patients discontinued Gilenya in the extension trial due to dyspnea. It is recommended in the prescribing information that spirometric evaluation of respiratory function and evaluation of DLCO should be performed during therapy with fingolimod, if clinically indicated. Following approval, a PMR was issued for an observational, prospective, parallel cohort (patients newly prescribed fingolimod vs. patients receiving other disease modifying therapy) trial in RMS patients which would include the assessment of pulmonary toxicity amongst other safety outcomes. The final report submission for the PMR is expected to be completed in December 2020.

Siponimod, another S1P modulator, was recently approved in March 2019 as Mayzent under NDA 209884 for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. Similar dose-dependent reductions in FEV1 were seen during the clinical trial assessment of siponimod. Decline in FEV1 occurred as early as 3 months after treatment initiation. In a placebo-controlled trial in adult patients, the decline in absolute FEV1 from baseline compared to placebo was 88 mL (95% CI: 139, 37) at 2 years. The mean difference between siponimod-treated patients and patients receiving placebo in %

predicted FEV1 at 2 years was 2.8% (95% CI: -4.5, -1). There were insufficient data to determine the reversibility of these decreases. As with fingolimod, spirometric evaluation of respiratory function is recommended during therapy with siponimod if clinically indicated, and a PMR was issued following approval to further study pulmonary safety. The final report submission for the PMR is expected in December 2027.

Ozanimod was originally studied under IND 109159. The Applicant is seeking approval of 0.23 mg, 0.46 mg and 0.92 mg capsules, which is equivalent to 0.25 mg, 0.5 mg, and 1 mg of ozanimod HCL. The lower doses capsules will be used for a 7-day dose escalation period at the start of ozanimod treatment; 0.92 mg capsules are to be used daily for the duration of treatment with ozanimod. Discussion of the clinical data will refer to the ozanimod HCL doses; labeling will refer to the strengths of the finished product.

The ozanimod clinical program included a phase 2, randomized, double-blind trial with a 24-week placebo-controlled period and a blinded extension period for ~3.5 years (RPC01-201A, up to 39 months), two double-blind, active-control trials of ~2 years duration (RPC01-201B, 24 months; RPC01-301; up to 22 months), and an ongoing open-label extension trial (RPC01-3001). Given that Trials RPC01-201B and RPC01-301 share the same enrollment criteria, active comparators, and endpoints, these data were pooled to provide a more robust assessment of safety.

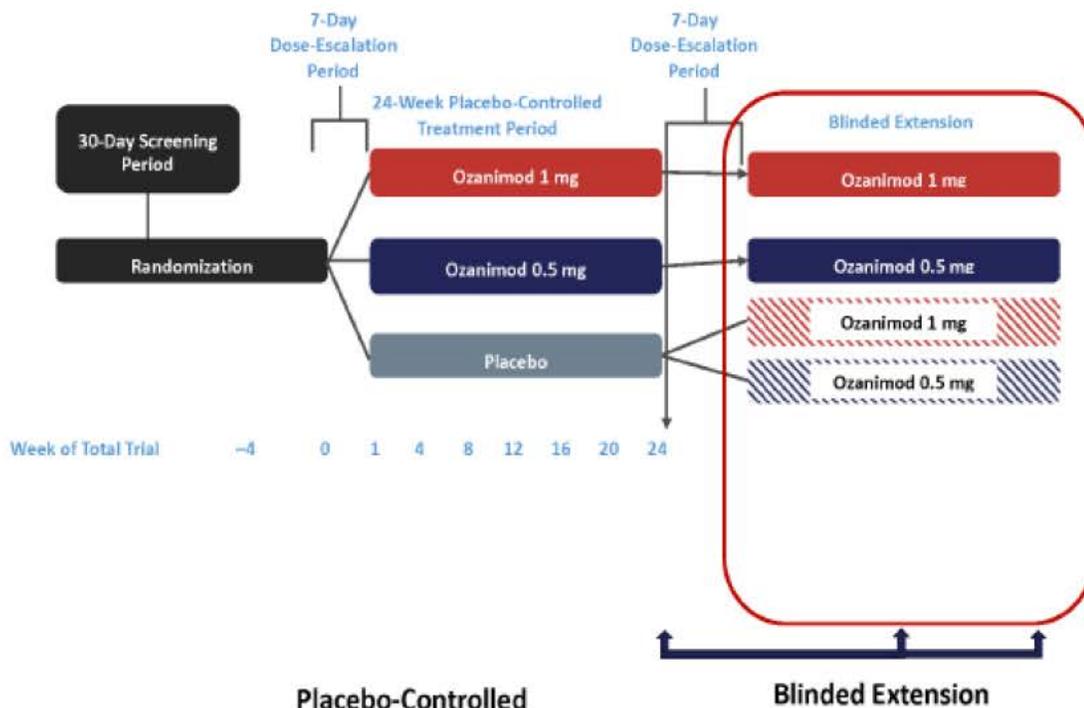
III. Clinical Trial Summary

A. Trial RPC01-201A

Study Design

Trial RPC01-201A was a 24-week randomized, double-blind, placebo-controlled trial with a blinded extension period. During the placebo-controlled period, patients were randomized to receive 0.5 mg or 1 mg of ozanimod, or placebo. Following screening, all subjects in the ozanimod groups had an initial 7-day dose-escalation period which included 0.25 mg daily on Days 1-4 and 0.5 mg daily on Days 5-7 to mitigate the reductions in heart rate that can be seen when ozanimod is not up-titrated. Patients then received randomized ozanimod treatment. At the conclusion of the 24-week treatment period, the study was unblinded for efficacy and safety analysis. Patients were then offered to be included in an optional blinded-extension period for ~3 years. Patients receiving ozanimod continued to receive their assigned dose, while patients on placebo were randomized 1:1 to ozanimod 0.5 mg or 1 mg (referred to as the placebo-0.5 mg or placebo-1 mg treatment arms). All patients participating in the blinded extension received a 7-day dose escalation period to avoid unmasking of patients already receiving ozanimod (Figure 1). The primary efficacy endpoint was mean cumulative total number of gadolinium-enhancing (GdE) lesions from Week 12 to Week 24.

Figure 1: Study Design of Placebo-Controlled and Blinded Extension Portions of RPC01-201A



Source: Figure 1, Clinical Study Report RPC01-201A Extension, Page 22

Study medication was discontinued if a participant was not able to comply with protocol requirements or developed an intercurrent illness that was not consistent with protocol requirements. Of note, study medication was also discontinued for pulmonary complications, defined as FEV1 or FVC <50% of predicted values. Any patients who discontinued study medication participated in an early termination visit, as well as a safety follow-up visit 4 weeks later if they had not withdrawn consent or been lost to follow-up.

Trial Participants

RPC01-201A enrolled 258 RMS patients ages 18-55 years without exclusion of specific pulmonary conditions. FEV1 or FVC was required to be >70% of predicted values for study enrollment.

Demographic Characteristics

The majority of patients in Trial RPC01-201A were female (64%) and white (98%). The average age was 38.5 years. In this multicenter study, 90% of the patients enrolled were from Eastern Europe; 51% were from Poland. There were no notable differences between treatment groups (Table 1).

Approximately 80% (n=205) of patients reported non-MS medical history; 9% (n=23) reported a respiratory issue as part of their medical history (Table 1). Of the 11 (4%) participants that reported a history of asthma, 10 (4%) reported this as an active medical issue.

Table 1: RPC01-201A (Placebo-Controlled Period), Participant Demographics, ITT Population

Demographic Parameter	Placebo n=88	Ozanimod 0.5 mg n=87	Ozanimod 1 mg n=83	Total N=258
Sex				
Female	62 (71%)	60 (69%)	59 (71%)	181 (64%)
Male	26 (30%)	27 (31%)	24 (29%)	77 (30%)
Age (years)				
Mean (SD)	39.0 (9)	38.1 (9)	38.4 (9)	38.5 (9)
Race				
White	87 (99%)	84 (97%)	83 (100%)	254 (98%)
Black	1 (1%)	2 (2%)	0 (0%)	3 (1%)
Asian	0 (0%)	1 (1%)	0 (0%)	1 (0.4%)
Ethnicity				
Not Hispanic or Latino	88 (100%)	86 (99%)	81 (98%)	255 (99%)
Hispanic or Latino	0 (0%)	1 (1%)	2 (2%)	3 (1%)
Region				
Eastern Europe	78 (89%)	79 (91%)	76 (92%)	233 (90%)
Western Europe	6 (7%)	4 (5%)	3 (4%)	13 (5%)
North America	4 (5%)	4 (5%)	4 (5%)	12 (5%)
Medical history				
Subjects with non-MS medical history	67 (76%)	69 (79%)	69 (83%)	205 (80%)
Respiratory	11 (13%)	8 (9%)	4 (5%)	23 (9%)

Source: Generated by FDA reviewer

All subjects in the ITT population were analyzed according to the treatment they were randomized to receive

*Sponsor coded respiratory data as “respiratory”

Of the 252 subjects who completed the placebo-controlled period, 249 elected to enter the blinded extension period. One hundred sixty-six subjects continued the ozanimod dose that was started at the beginning of trial; the placebo group was randomized to 0.5 mg (“placebo-0.5 mg”) or 1 mg of ozanimod (“placebo-1 mg”). These 249 subjects are referred to as the “Ozanimod Population” by the Applicant. This group includes all individuals who received at least 1 dose of study drug and had any postbaseline assessment in the blinded extension period.

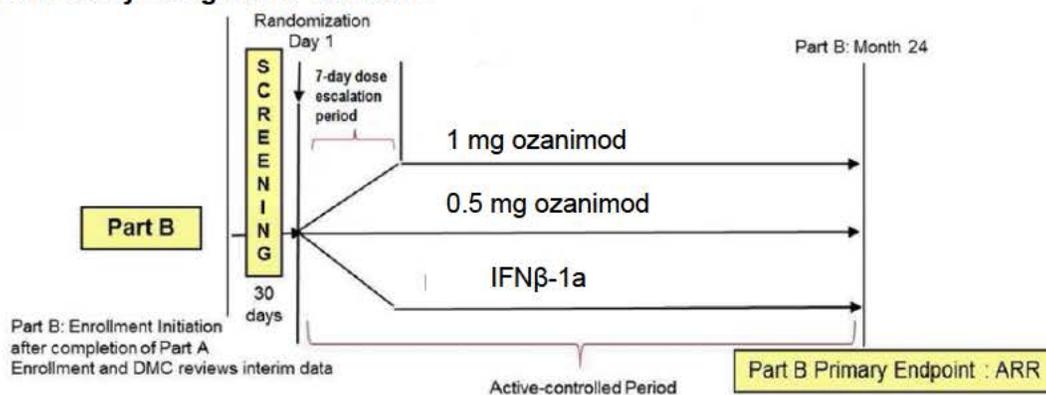
Demographic characteristics in the blinded extension were similar to those of the placebo-controlled period.

B. Trial RPC01-201B

Study Design

Trial RPC01-201B is a phase 3, randomized, double-blind, double-dummy, active-controlled parallel group, 24-month trial to evaluate the efficacy and long-term safety of ozanimod in patients with RMS. Following screening, participants were randomized 1:1:1 to 0.5 mg or 1 mg of ozanimod or active control, 30 ug IM of IFN β -1a (Avonex, Biogen) (Figure 2). All subjects in the ozanimod groups had an initial 7-day dose-escalation period which included 0.25 mg daily on Days 1-4 and 0.5 mg daily on Days 5-7. Ozanimod was administered daily and IFN β -1a was administered weekly. The primary efficacy endpoint was annual relapse rate at the end of Month 24.

Figure 2: Study Design of RPC01-201B



Source: Figure 1, Clinical Study Report RPC01-201B, Page 24

Subjects who completed the trial were invited to enroll in an open label extension study, RPC01-3001, or asked to complete the study with a safety follow-up visit 28 days after last dose of treatment.

Criteria for treatment or trial discontinuation were similar to those used for Trial RPC01-201A.

Trial Participants

In RPC01-201B, 1320 RMS patients ages 18-55 years were randomized to treatment. Of these subjects, 1313 received study drug. The inclusion and exclusion criteria were similar to Trial RPC01-201A. As in Trial RPC01-201A, specific pulmonary conditions were not defined within the exclusion criteria. FEV1 or FVC was required to be >70% for study enrollment.

Demographic Characteristics

In Trial RPC01-201B, participants were also mostly female (67%) and white (98%). The average age of participants in this trial was 35.5 years. The majority of participants were from Eastern Europe (86%). Of those patients who reported a medical history in addition to their MS diagnosis, 11% reported a respiratory, thoracic, or mediastinal disorder.

Table 2: Trial RPC01-201B, Patient Demographics, ITT Population

Demographic Parameter	IFNβ-1a 30 ug n=440	Ozanimod 0.5 mg n=439	Ozanimod 1 mg n=434	Total N=1313
Sex				
Female	304 (69%)	287 (65%)	291 (67%)	882 (67%)
Male	137 (31%)	152 (35%)	142 (33%)	431 (33%)

Demographic Parameter	IFNβ-1a 30 ug n=440	Ozanimod 0.5 mg n=439	Ozanimod 1 mg n=434	Total N=1313
Age (years)				
Mean (SD)	35.1 (9)	35.4 (9)	36 (9)	35.5 (9)
Race				
White	432 (98%)	431 (98%)	428 (99%)	1291 (98%)
Black or African American	7 (2%)	6 (1%)	5 (1%)	18 (1%)
Other	1 (0.2%)	2 (1%)	0 (0%)	3 (0.2%)
Asian	1 (0.2%)	0 (0%)	0 (0%)	1 (0.1%)
Ethnicity				
Not Hispanic or Latino	436 (99%)	433 (99%)	423 (98%)	1292 (98%)
Hispanic or Latino	5 (1%)	6 (1%)	10 (2%)	21 (2%)
Region				
Eastern Europe	379 (86%)	378 (86%)	374 (86%)	1131 (86%)
Western Europe	40 (9%)	40 (9%)	36 (8%)	116 (9%)
North America	16 (4%)	16 (4%)	16 (4%)	48 (4%)
South America	6 (1%)	5 (1%)	7 (2%)	18 (1%)
Medical history				
Subjects with any medical history besides MS	370 (84%)	377 (86%)	362 (84%)	1109 (85%)
Respiratory, thoracic, and mediastinal disorders*	59 (13%)	28 (6%)	51 (12%)	138 (11%)

All subjects in the ITT population were analyzed according to the treatment they were randomized to receive

*Sponsor coded respiratory data within "respiratory, thoracic and mediastinal disorders" SOC

Source: Generated by FDA reviewer

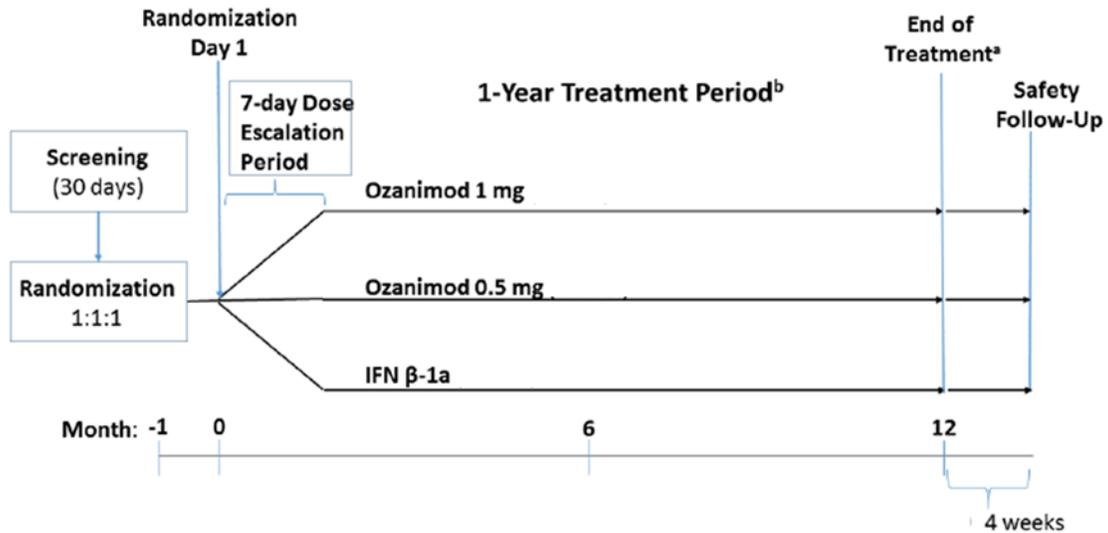
C. Trial RPC01-301

Study Design

Trial RPC01-301 used the same enrollment criteria, dosing, active comparators, and endpoints as Trial RPC01-201B. Trial RPC01-301 is a phase 3, randomized, double-blind, double-dummy, active-controlled parallel group to evaluate the efficacy and long-term safety of ozanimod in patients with RMS. Participants were treated until the last active subject received 12 months of treatment, which included a 22-month time period (Figure 3).

The primary efficacy endpoint was annual relapse rate at the end of Month 12. At trial completion, participants were invited to enroll in an open label extension (RPC01-3001) or return for a safety follow-up visit 4 weeks after their last dose.

Figure 3: Study Design of RPC01-301



^{a,b} Treatment continued for at least 12 months; the end of treatment occurred when the last active subject received 12 months of treatment.

Source: Adapted from Figure 1, Clinical Study Report RPC01-301, Page 18

Trial Participants

Trial RPC01-301 enrolled 1346 RMS patients ages 18-55 years. Inclusion and exclusion criteria were the same as Trial RPC01-201B. FEV1 or FVC was required to be >70% for study enrollment.

Demographic Characteristics

As with the other trials in the ozanimod program, most participants in Trial RPC01-301 were female (66%) and white (100%). The majority of patients enrolled in this trial were from Eastern Europe (93%). Seven percent of participants reported a medical history that was related to a respiratory, thoracic, or mediastinal disorder at screening (Table 3).

Table 3: Trial RPC01-301, Patient Demographics, ITT Population

Demographic Parameter	IFN β -1a 30 ug n=448	Ozanimod 0.5 mg n=451	Ozanimod 1 mg n=447	Total N=1346
Sex				
Female	300 (67%)	311 (69%)	283 (63%)	894 (66%)
Male	148 (33%)	140 (31%)	164 (37%)	452 (34%)
Age (years)				
Mean (SD)	35.9 (9)	36 (9)	34.8 (9)	35.6 (9)
Race				
White	447 (100%)	447 (99%)	446 (100%)	1340 (100%)
Asian	0 (0%)	1 (0.2%)	1 (0.2%)	2 (0.1%)
Black or African American	0 (0%)	2 (0.4%)	0 (0%)	2 (0.1%)
Other	1 (0.2%)	1 (0.2%)	0 (0%)	2 (0.1%)
Ethnicity				
Not Hispanic or Latino	446 (100%)	448 (99%)	442 (99%)	1336 (99%)
Hispanic or Latino	2 (0.4%)	3 (1%)	5 (1%)	10 (1%)
Region				
Eastern Europe	419 (94%)	419 (93%)	415 (93%)	1253 (93%)
Western Europe	16 (4%)	17 (4%)	17 (4%)	50 (4%)
North America	11 (3%)	13 (3%)	12 (3%)	36 (3%)
New Zealand	2 (0.4%)	2 (0.4%)	3 (1%)	7 (1%)
Medical history				
Subjects with any medical history	362 (81%)	369 (82%)	358 (80%)	1089 (81%)
Respiratory, thoracic, and mediastinal disorders*	36 (8%)	34 (8%)	30 (7%)	100 (7%)

Source: Generated by FDA reviewer

All subjects in the ITT population were analyzed according to the treatment they were randomized to receive

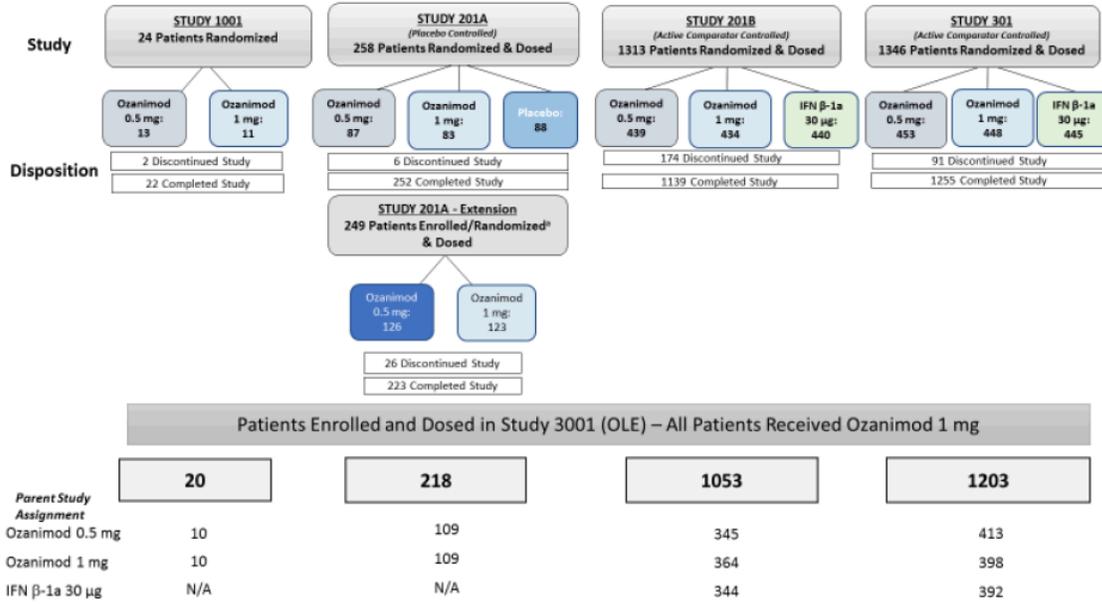
*Sponsor coded respiratory data within "respiratory, thoracic and mediastinal disorders" SOC

D. Trial RPC01-3001

Study Design

Trial RPC01-3001 is a multi-site, OLE trial that began October 16, 2015. While the trial is still ongoing, a data cut-off date of June 30, 2018 was used to generate the clinical study report submitted with this NDA application. The OLE was designed to further characterize longer-term safety and efficacy. Enrollment was offered to patients who had completed Trials RPC01-201 and RPC01-301, as well as Trial RPC01-1001, which was a phase 1, randomized, open-label, 12-week PK trial in patients with RMS and is not reviewed in this document (Figure 4).

Figure 4: Parent Studies for Open-Label Extension Trial RPC01-3001



IFN=interferon, OLE=open-label extension, RMS=relapsing multiple sclerosis

^aPlacebo-treated subjects in Trial RPC01-201A enrolled into the 201A extension study were randomized 1:1 to ozanimod 1 mg or 0.5 mg; ozanimod-treated subjects enrolled into the 201A extension continued their respective treatment.

Source: Figure 2, Summary of Clinical Safety, page 23

Patients could be removed from the OLE if it was thought that continued participation was not safe or in the best interest of the participant. Participants could withdraw at any time, though completion of early termination and safety visits was encouraged. Of note, the protocol also required consultation of the Medical Monitor if pulmonary function tests (PFT) declined to <50% of predicted values. Subjects with confirmed decline in PFT values to <50 % of predicted values would be discontinued from ozanimod.

Trial Participants

In addition to completing one of the parent trials, patients were required to be in otherwise good health and not receiving any prohibited concomitant medications.

Demographic Characteristics

As of the data cut-off date, 2495 (95%) of the 2639 subjects that completed the parent trials consented to participate in the OLE. Of the 2495 subjects who consented, one subject did not receive study medication. The ITT and safety populations therefore includes 2494 participants.

As with the parent trials, most participants in the OLE were female (70%), white (99%), and were enrolled in sites in Eastern Europe (90%). The average participant age was 38 years. Of patients who reported a medical history besides MS, 8% reported a respiratory, thoracic or mediastinal disorder (Table 4).

Table 4: Trial RPC01-3001, Patient Demographics, ITT Population

Demographic Parameter	Pooled Parent Treatment Groups					
	Placebo-OZ 0.5 mg n=37	Placebo- OZ 1 mg n=35	IFN β -1a 30 ug n=740	Ozanimod 0.5 mg n=838	Ozanimod 1 mg n=844	All subjects N=2494
Sex						
Female	27 (73%)	27 (77%)	500 (68%)	568 (68%)	546 (65%)	1668 (70%)
Male	10 (27%)	8 (23%)	240 (32%)	270 (32%)	298 (35%)	826 (33%)
Age (years)						
Mean (SD)	43.5 (8)	39.5 (9)	37.4 (9)	37.7 (9)	37.6 (9)	37.7 (9)
Race						
White	37 (100%)	35 (100%)	738 (100%)	826 (99%)	838 (99%)	2474 (99%)
Black or African American	0 (0%)	0 (0%)	1 (0.1%)	7 (1%)	6 (1%)	14 (1%)
Asian	0 (0%)	0 (0%)	0 (0%)	3 (0.4%)	0 (0%)	3 (0.1%)
Other	0 (0%)	0 (0%)	1 (0.1%)	2 (0.2%)	0 (0%)	3 (0.1%)
Ethnicity						
Not Hispanic or Latino	37 (100%)	35 (100%)	736 (100%)	830 (99%)	829 (98%)	2467 (99%)
Hispanic or Latino	0 (0%)	0 (0%)	4 (1%)	8 (1%)	15 (2%)	27 (1%)
Region						
Eastern Europe	34 (92%)	30 (86%)	675 (91%)	755 (90%)	752 (89%)	2246 (90%)
Rest of World	3 (8%)	5 (14%)	65 (9%)	83 (10%)	92 (11%)	248 (10%)
Medical history						
Subjects with any medical history	30 (81%)	25 (71%)	608 (82%)	700 (84%)	686 (81%)	2049 (82%)
Respiratory, thoracic, and mediastinal disorders*	0 (0%)	0 (0%)	74 (10%)	50 (6%)	72 (9%)	196 (8%)

OZ=ozanimod

Source: Generated by FDA reviewer

All subjects in the ITT population were analyzed according to the treatment they were randomized to receive

*Sponsor coded respiratory data within "respiratory, thoracic and mediastinal disorders" SOC

IV. Review of Pulmonary Safety

A. Trial RPC01-201A – Placebo-controlled period

Safety Population

The safety population for the placebo-controlled period of Trial RPC01-201A included all patients who received at least one dose of study drug. All participants in the safety population were analyzed according to the highest dose of ozanimod that was received and includes 258 participants.

Disposition and Extent of Exposure

Of the 258 trial participants, 98% of patients completed the 24-week study. The average drug exposure was similar across treatment groups.

There were no discontinuations due to adverse events. Of the six patients that stopped study drug, 1 (placebo) was lost to follow-up, and 4 (n=2, placebo; n=1, 0.5 mg ozanimod;

n=1, 1 mg ozanimod) voluntarily withdrew. One participant was randomized and received treatment of 0.5 mg ozanimod for 9 days, but then was withdrawn when it was noted that this individual did not meet inclusion criteria.

Analysis of Adverse Events

AEs were monitored from time of first dose until 28 days following the last dose of treatment. Decreases in pulmonary function testing (PFT) were reported in 2 individuals, both in the 1 mg ozanimod treatment arm (Table 5). Eleven (4%) participants reported an AE that is related to the Respiratory, Thoracic and Mediastinal Disorders SOC, though these events were generally evenly distributed across treatment groups, were mostly singular in number, and did not appear to be dose-dependent.

Table 5: Adverse Events (Occurring ≥ 1% in Any Ozanimod Treatment Group and Reported at a Higher Rate Than Placebo): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-201A (Placebo-Controlled Period), Safety Population

Adverse Event	Placebo n=88	Ozanimod 0.5 mg n=87	Ozanimod 1 mg n=83	Total n=258
Investigations Related to Pulmonary Function Testing				
Pulmonary function test decreased	0 (0%)	0 (0%)	2 (2%)	2 (1%)
Carbon monoxide diffusing capacity decreased	0 (0%)	0 (0%)	1 (1%)	1 (0.4%)
Respiratory, Thoracic, and Mediastinal Disorders				
Asthma	4 (5%)	6 (7%)	1 (1%)	11 (4%)
Cough	1 (1%)	2 (2%)	1 (1%)	4 (2%)
Rhinorrhea	1 (1%)	2 (2%)	0 (0%)	3 (1%)
Productive cough	0 (0%)	1 (1%)	0 (0%)	1 (0.4%)
Oropharyngeal pain	0 (0%)	1 (1%)	0 (0%)	1 (0.4%)

Source: Adapted from Table 14.3.1.10, RPC01-201 Part A CSR, page 479

Deaths and Serious Adverse Events

There were no deaths nor SAEs related to pulmonary safety during the placebo-controlled portion of Trial RPC01-201A.

Pulmonary Function Testing

Pulmonary function testing, which included FEV1 and FVC, was performed using American Thoracic Society/European Respiratory Society (ATS/ERS) criteria at screening, Week 12 (Month 3), Week 24 (Month 6), and at end of study or at early termination. DLCO was assessed at similar timepoints at available sites. If any abnormalities in pulmonary function were detected, patients were followed until resolution or until no further improvement was expected, based on a follow-up period of no less than 3 months. Decline in FEV1, FVC or DLCO were considered to be an event of special interest by investigators.

A decline in mean change from baseline was seen in FEV1, FVC, and DLCO measurements in both placebo and ozanimod-treated groups (Table 6, Figure 5, and Figure 6). Compared to placebo, mean change from baseline was found to be statistically significantly different for FEV1 (% predicted), FVC (L), and FVC (% predicted) in the 0.5

mg ozanimod arm and for FEV1 (L) in the 1 mg ozanimod arm at Week 12 (Table 6). At Week 24, treatment differences were not statistically significant for any FEV1 or FVC parameter. DLCO differences were not statistically significant at either timepoint. Changes in PFT parameters in the placebo-controlled portion of Trial RPC01-201A were therefore not found to be dose-dependent, progressive, nor sustained.

Table 6: Mean Change From Baseline in FEV1, FVC, and DLCO at Weeks 12 and 24, Study RPC01-201A, Placebo-Controlled Period (Safety Population)

Change From Baseline^a	Placebo N=88	Ozanimod 0.5 mg N=87	Ozanimod 1 mg N=83
Week 12 – FEV1 (L)			
n	86	85	82
Mean (SD)	0.023 (0.29)	-0.100 (0.52)	-0.081 (0.31)
Mean difference from placebo (95% CI, p-value ^b)		-0.123 (-0.25, 0.004) p=0.06	-0.104 (-0.19, -0.01) p=0.02
Week 12 – FEV1 (% predicted)			
n	86	85	82
Mean (SD)	0.23 (8.73)	-4.24 (15.7)	-2.04 (8.78)
Mean difference from placebo (95% CI, p-value ^b)		-4.47 (-8.3, -0.64) p=0.02	-2.27 (-4.94, 0.4) p=0.09
Week 12 – FVC (L)			
n	86	85	82
Mean (SD)	0.02 (0.32)	-0.16 (0.58)	0.04 (0.59)
Mean difference from placebo (95% CI, p-value ^b)		-0.18 (-0.31, -0.04) p=0.01	0.03 (-0.12, 0.17) p=0.7
Week 12 – FVC (% predicted)			
n	86	85	82
Mean (SD)	0.35 (8.01)	-5.22 (15.56)	0.55 (8.4)
Mean difference from placebo (95% CI, p-value ^b)		-5.57 (-9.30, 1.84) p=0.004	0.2 (-2.3, 2.7) p=0.87
Week 12 – DLCO corrected for hemoglobin (mmol/min/kpa)			
n	32	19	27
Mean (SD)	-0.17 (4.14)	2.05 (10.4)	0.26 (6.5)
Mean difference from placebo (95% CI, p-value ^b)		2.22 (-1.91, 6.36) p=0.29	0.44 (-2.37, 3.24) p=0.76
Week 24 -FEV1 (L)			
n	84	83	80
Mean (SD)	-0.04 (0.28)	-0.12 (0.49)	-0.1 (0.37)
Mean difference from placebo (95% CI, p-value ^b)		-0.08 (-0.2, 0.04) p=0.21	-0.06 (-0.16, 0.04) p=0.22
Week 24 – FEV1 (% predicted)			
n	84	84	80
Mean (SD)	-0.73 (8.78)	-2.46 (16.12)	-1.43 (11.44)
Mean difference from placebo (95% CI, p-value ^b)		-1.74 (-5.69, 2.21) p=0.39	-0.7 (-3.83, 2.43) p=0.66

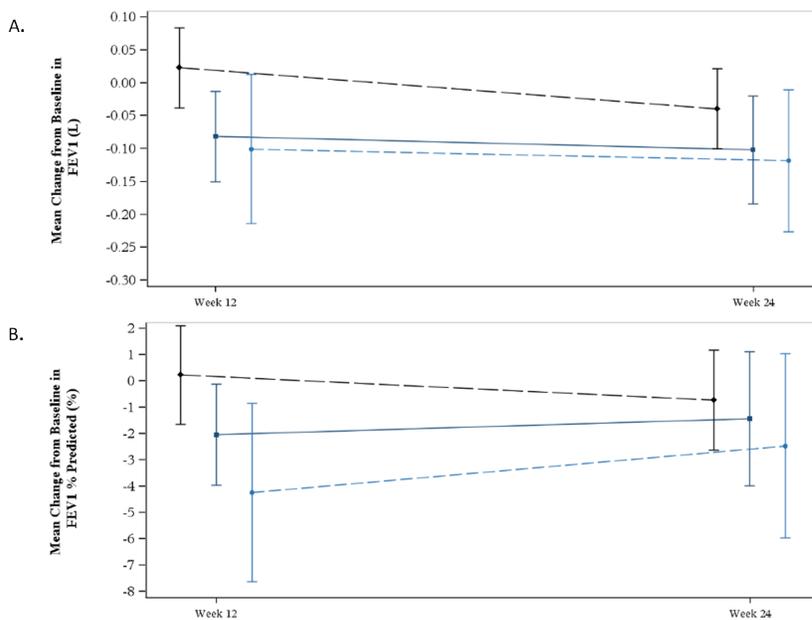
Change From Baseline ^a	Placebo N=88	Ozanimod 0.5 mg N=87	Ozanimod 1 mg N=83
Week 24 – FVC (L)			
n	84	84	80
Mean (SD)	-0.04 (0.43)	-0.1 (0.55)	0.03 (0.63)
Mean difference from placebo (95% CI, p-value ^b)		-0.06 (-0.21, 0.09) p=0.42	0.07 (-0.09, 0.24) p=0.4
Week 24 – FVC (% predicted)			
n	84	84	80
Mean (SD)	-1.13 (11.62)	-2.6 (15.01)	0.35 (10.76)
Mean difference from placebo (95% CI, p-value ^b)		-1.44 (-5.53, 2.65) p=0.49	1.48 (-1.97, 4.94) p=0.4
Week 24 – DLCO corrected for hemoglobin (mmol/min/kpa)			
n	70	68	66
Mean (SD)	-0.34 (2.92)	-0.39 (3.78)	-0.06 (1.82)
Mean difference from placebo (95% CI, p-value ^b)		-0.05 (-1.18, 1.09) p=0.94	0.28 (-0.55, 1.11) p=0.5

^a Baseline is defined as the last non-missing value prior to the first dose of the study drug

^b p-value is the nominal p-value based on a simple t-test comparison without any multiplicity adjustment

Source: Table 3, Celgene Response to Information Request Received on 25 Jul 2019, page 47-56

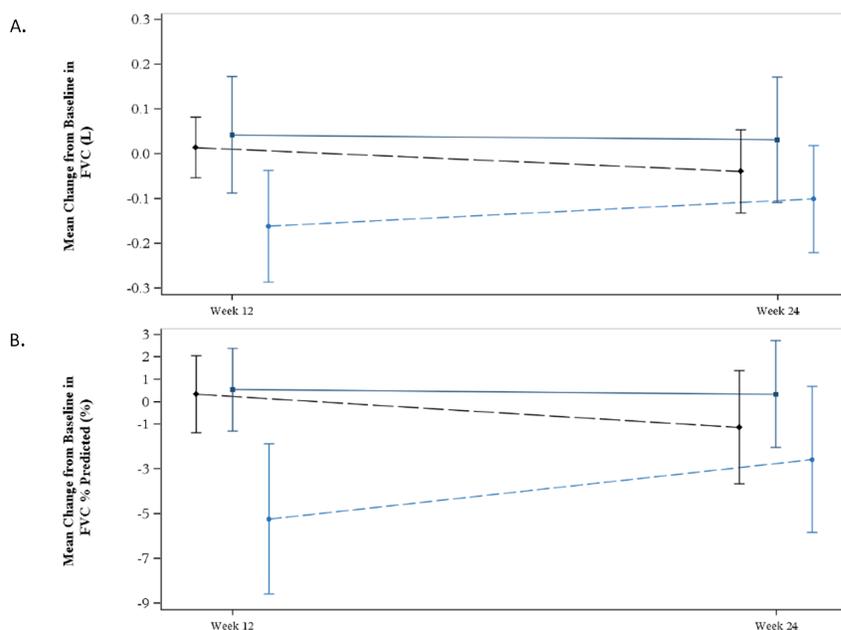
Figure 5: Mean Change From Baseline (95% Confidence Intervals) in FEV1 at Week 12 and 24 (Panel A, Liters; Panel B, % Predicted), Trial RPC01-201A, Placebo-Controlled Period (Safety Population)



Black diamond=placebo, blue circle=ozanimod 0.5 mg, blue square=ozanimod 1 mg

Source: Figures 3.1 and 3.2, Celgene Response to Information Request Received on 25 Jul 2019, pages 10-11

Figure 6: Mean Change From Baseline (95% Confidence Intervals) in FVC at Week 12 and 24 (Panel A, Liters; Panel B, % Predicted), Study RPC01-201A, Placebo-Controlled Period (Safety Population)



Black diamond=placebo, blue circle=ozanimod 0.5 mg, blue square=ozanimod 1 mg
 Source: Figures 3.3 and 3.4, Celgene Response to Information Request Received on 25 Jul 2019, pages 12-13

B. Trial RPC01-201A - Blinded Extension Period

Safety Population

The “Ozanimod Population” is used in safety and efficacy analyses of the blinded extension period of Trial RPC01-201A. This population includes patients who received at least one dose of ozanimod and had at least one postbaseline assessment.

The safety results for the blinded extension period include cumulative safety from the placebo-controlled period (Weeks 1 to 24) for subjects who received ozanimod during that period. The remainder of the safety data (for patients who received placebo until Week 24) was derived from the beginning of the open-label extension period up until Week 120 (Year 2).

Disposition and Extent of Exposure

Twenty-six patients discontinued study drug. While 4 participants discontinued treatment due to an AE, none of these discontinuations were related to pulmonary toxicity.

Of the 252 patients who completed the placebo-controlled period of this trial, 249 enrolled in the blinded extension period. Three subjects declined enrollment, though this was not related to a pulmonary safety issue.

Ninety percent of participants remained on study drug during the blinded extension period. Overall, treatment exposure was balanced across the treatment arms.

Analysis of Adverse Events

Decreases in pulmonary function test measurements were reported in four participants during the blinded extension period (Table 7). These events were comparable across treatment arms and were generally rare. Twenty-three participants reported events related to the Respiratory, Thoracic and Mediastinal Disorders SOC (Table 7). Of note, cough (n=6, 2%) and asthma (n=5, 2%) were more frequently reported than productive cough (n=1, 0.4%), upper respiratory tract inflammation (n=1, 0.4%), wheezing (n=1, 0.4%), and dyspnea (n=1, 0.4%). All pulmonary AEs were determined to be mild, with the exception of one moderate event of “pulmonary function test decreased” in a patient exposed to 1 mg of ozanimod. Overall, pulmonary AEs were mostly reported in participants exposed to 0.5 mg of ozanimod, suggesting that these effects are not dose dependent, though it is difficult to draw conclusions due to the rarity of events overall. Of note, the participant who reported dyspnea (“short breath” verbatim term) did not experience a concomitant decrease in pulmonary function testing. The dyspnea was reported to have resolved without interruption of ozanimod use.

Table 7: Adverse Events (≥ 1% in Any Treatment Group): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-201A (Blinded Extension Period), Ozanimod Population

Adverse Event	Placebo-OZ 0.5 mg n=41	Ozanimod 0.5 mg n=42	Placebo-OZ 1 mg n=85	Ozanimod 1 mg n=81	Total n=249
Investigations related to pulmonary function testing					
Pulmonary function test decreased	0 (0%)	1 (1%)	1 (2%)	3 (1%)	4 (2%)
Vital capacity decreased	0 (0%)	0 (0%)	0 (0%)	2 (3%)	2 (1%)
Forced expiratory volume decreased	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders					
Oropharyngeal pain	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (0.4%)
Cough	4 (10%)	12 (14%)	1 (2%)	6 (7%)	23 (9%)
Asthma	1 (2%)	4 (5%)	0 (0%)	3 (4%)	8 (3%)
Epistaxis	1 (2%)	3 (4%)	0 (0%)	2 (3%)	6 (2%)
Dysphonia	1 (2%)	2 (2%)	0 (0%)	2 (3%)	5 (2%)
Throat irritation	0 (0%)	1 (1%)	1 (2%)	0 (0%)	2 (1%)
Productive cough	1 (2%)	1 (1%)	0 (0%)	0 (0%)	2 (1%)
Rhinorrhea	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Upper respiratory tract inflammation	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0.4%)
Wheezing	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0.4%)
Dyspnea	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0.4%)

OZ=ozanimod

The safety results for the blinded extension period include cumulative safety from the placebo-controlled period (Weeks 1 to 24) for subjects who received ozanimod during that period. The remainder of the safety data (for patients who received placebo until Week 24) was derived from the beginning of the open label extension period up until Week 120 (Year 2).

Source: Adapted from Table 14.3.1.2 ext, RPC01-201a EXT - Tables, page 79

Deaths and Serious Adverse Events

No deaths nor serious adverse events related to pulmonary safety occurred during the blinded extension period.

Pulmonary Function Testing

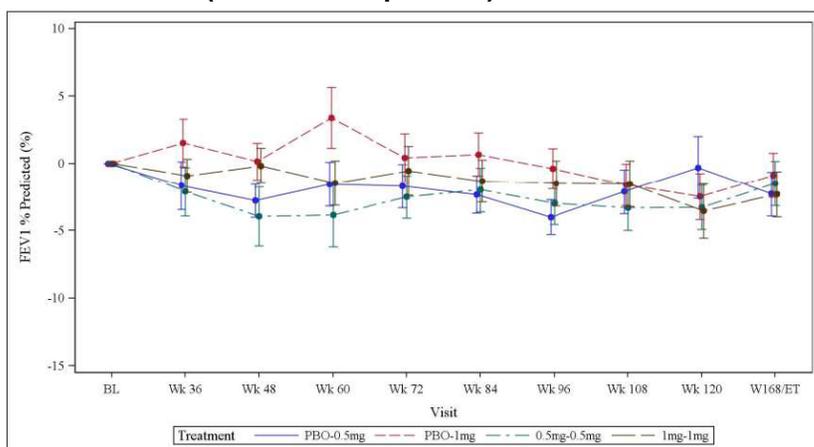
Pulmonary function testing using American Thoracic Society/European Respiratory Society (ATS/ERS) criteria was performed every 12 weeks during the blinded extension,

as well as at end of study or at early termination. DLCO was assessed at similar timepoints at available sites. If any abnormalities in pulmonary function were detected, patients were followed until resolution or no further improvement was expected, based on a follow-up period of not less than 3 months.

Pulmonary events of special interest were defined as decline in FEV1, FVC, and DLCO in the blinded extension period. Baseline measurements were used as reference points for analysis of data in the placebo-controlled period; the last non-missing measurement performed prior to the first dose of ozanimod was used as the reference point for analysis of data generated in the blinded extension.

While there were small changes from baseline in % predicted FEV1 and FVC, or DLCO, this did not appear to be dose-dependent nor an effect that worsened over time (Figure 7, Figure 8, and Figure 9).

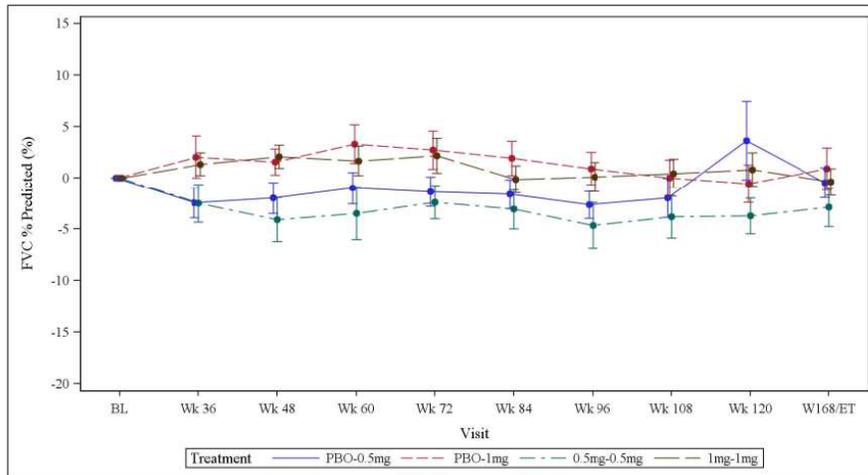
Figure 7: Change From Baseline in % Predicted FEV1, Study RPC01-201A, Blinded Extension Period (Ozanimod Population)



Baseline is defined as the last non-missing assessment performed prior to the first dose of ozanimod in either the placebo-controlled study or the blinded extension

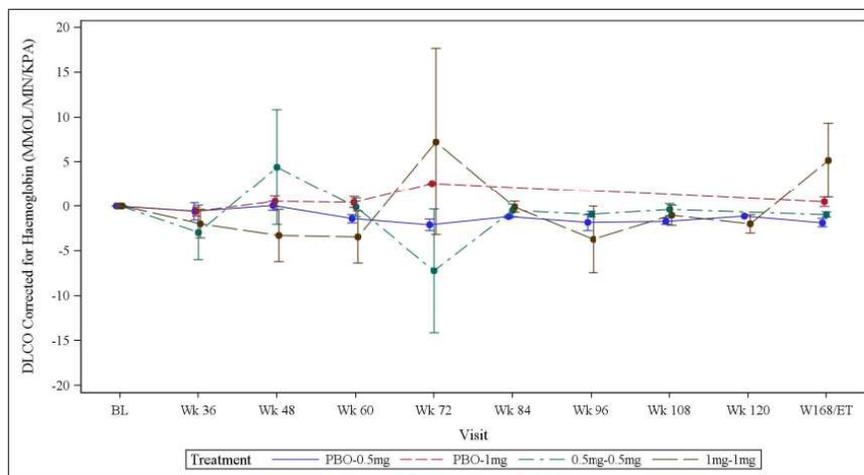
Source: Figure 14.3.4.3.ext, RPC01-201A EXT – Figures, page 2

Figure 8: Change From Baseline in % predicted FVC, Trial RPC01-201A, Blinded Extension Period (Ozanimod Population)



Baseline is defined as the last non-missing assessment performed prior to the first dose of ozanimod in either the placebo-controlled study or the blinded extension
 Source: Figure 14.3.4.4.ext, RPC01-201A EXT – Figures, page 3

Figure 9: Change From Baseline in DLCO (Corrected for Hemoglobin), Study RPC01-201A, Blinded Extension Period (Ozanimod Population)



Baseline is defined as the last non-missing assessment performed prior to the first dose of ozanimod in either the placebo-controlled study or the blinded extension
 Source: Figure 14.3.4.5.ext, RPC01-201A EXT – Figures, page 4

C. Trial RPC01-201B

Safety Population

The safety population for Trial RPC01-201B includes 1313 RMS patients. These patients received at least one dose of study drug. Participants were analyzed according to the highest dose of study drug received.

Disposition and Extent of Exposure

Of the 175 patients who discontinued study drug and 174 patients who discontinued from the study, 45 participants discontinued due to an AE. None of the discontinuations related to AEs were a result of a pulmonary safety issue.

Of the 1313 patients who received study drug, 1138 (87%) completed the 24-month trial. Patients were exposed to drug for a mean duration of 22 months which was similar across treatment groups.

Analysis of Adverse Events

AEs were monitored from the time of first dose until end of study or until the first dose of the OLE. The highest incidence of reported decreases in pulmonary function measurements were reported in the 1 mg ozanimod-treated groups (Table 8). This rate (2%) was low, however, and comparable to what was seen for the 0.5 mg ozanimod group (1%) and IFN-treated (1%) groups. The rates of total AEs in the Respiratory, Thoracic, and Mediastinal Disorders SOC were the same across treatment groups (Table 8). While there were some AEs that were reported at slightly higher rates in the ozanimod groups than those of the IFN-treated group, these events were rare and occurred $\leq 1\%$ of patients treated with ozanimod. The AEs in Table 8 were considered to be mild.

Table 8: Adverse Events (Occurring $\geq 1\%$ in Any Ozanimod Treatment Group and Reported at a Higher Rate Than IFN- β): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-201B (Safety Population)

Adverse Event	IFN β -1a	Ozanimod	Ozanimod	Total N=1313
	30 ug n=440	0.5 mg n=439	1 mg n=434	
Investigations related to pulmonary function testing	6 (1%)	3 (1%)	10 (2%)	19 (1%)
Respiratory, thoracic and mediastinal disorders	41 (9%)	41 (9%)	37 (9%)	119 (9%)
Epistaxis	0 (0%)	4 (1%)	2 (1%)	6 (1%)
Nasal congestion	1 (0.2%)	0 (0.0%)	2 (1%)	3 (0.2%)
Dysphonia	1 (0.2%)	2 (1%)	0 (0%)	3 (0.2%)
Asthma	0 (0%)	2 (1%)	1 (0.2%)	3 (0.2%)
Nasal septum deviation	0 (0%)	1 (0.2%)	2 (1%)	3 (0.2%)

Source: Adapted from Table 14.3.1.2, RPC01-201B - Tables, Page 79

Deaths and Serious Adverse Events

Two deaths were reported in patients who were enrolled in Trial RPC01-201B. One individual receiving 1 mg ozanimod developed pulmonary embolism during the OLE (Trial RPC01-3001) following surgical repair of a fracture and subsequent hospitalization; this was also considered to be serious adverse event. The other death, as well as other serious adverse events related to Trial RPC01-201B, were not related to pulmonary safety.

Pulmonary Function Testing

Pulmonary function testing was performed using American Thoracic Society/European Respiratory Society (ATS/ERS) criteria at screening, at Month 3, Month 6, Month 12, and Month 24. DLCO was assessed at screening, Month 12, and Month 24 at available sites. PFTs were also performed at an early termination visit, if applicable. If any pulmonary

abnormalities were detected, patients were followed until resolution or until no further improvement was expected, based on a follow-up period of not less than 3 months.

Pulmonary events of special interest were again defined as decline in FEV1, FVC, and DLCO (corrected from hemoglobin). Changes from baseline were comparable across treatment groups (Table 9 and Table 10), with declines in pulmonary function test measurements for all groups over time. When comparing change from baseline with 1 mg ozanimod to active control treatment, the mean treatment difference in FEV1 was only statistically different at Month 12 (-0.05 L, 95% CI: -0.1, -0.003, nominal p=0.04). A statistically significant treatment difference was not seen when comparing change from baseline as measured by FEV1 (% predicted) at this time and at any other timepoint. When comparing 0.5 mg to active control, a treatment difference was seen in FVC (% predicted) for the last postbaseline value (1.92%, 95% CI: 0.14, 3.7, nominal p=0.03) and was not seen when considering FVC in liters. Because statistically significant changes are only seen in one determination of FEV1 or FVC at a given timepoint, it is difficult to draw definitive conclusions regarding PFT results for Trial RPC01-201B. No statistically significant changes were noted for DLCO (results not shown).

Table 9: Mean Change From Baseline in FEV1, Trial RPC01-201B (Safety Population)

Change From Baseline^a	IFN β-1a 30 ug N=440	Ozanimod 0.5 mg N=439	Ozanimod 1 mg N=434
Month 3 – FEV1 (L)			
n	427	425	426
Mean (SD)	-0.04 (0.41)	-0.05 (0.39)	-0.07 (0.35)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.004 (-0.06, 0.05) p=0.89	-0.03 (-0.08, 0.02) p=0.28
Month 3 – FEV1 (% predicted)			
n	427	424	425
Mean (SD)	-1.13 (12.52)	-1.24 (10.81)	-1.78 (10.45)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.1 (-1.68, 1.47) p=0.9	-0.64 (-2.19, 0.91) p=0.42
Month 6 – FEV1 (L)			
n	411	419	416
Mean (SD)	-0.07 (0.39)	-0.06 (0.46)	-0.11 (0.37)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.002 (-0.06, 0.06) p=0.95	-0.04 (-0.09, 0.008) p=0.1
Month 6 – FEV1 (% predicted)			
n	412	418	415
Mean (SD)	-1.27 (11.71)	-1.14 (14.18)	-2.2 (11.57)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.135 (-1.64, 1.91) p=0.88	-0.93 (-2.51, 0.66) p=0.25
Month 12 – FEV1 (L)			
n	406	404	406
Mean (SD)	-0.07 (0.34)	-0.1 (0.4)	-0.12 (0.38)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.03 (-0.08, 0.02) p=0.29	-0.05 (-0.1, -0.003) p=0.04
Month 12 – FEV1 (% predicted)			
n	406	404	405
Mean (SD)	-1.59 (9.97)	-2.3 (10.6)	-2.72 (11.38)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.71 (-2.13, 0.71) p=0.33	-1.12 (-2.6, 0.35) p=0.14

Change From Baseline^a	IFN β-1a 30 ug N=440	Ozanimod 0.5 mg N=439	Ozanimod 1 mg N=434
Month 24 – FEV1 (L)			
n	376	378	387
Mean (SD)	-0.11 (0.44)	-0.1 (0.41)	-0.15 (0.37)
Mean difference from IFN β-1a (95% CI, p-value ^b)		0.01 (-0.06, 0.07) p=0.88	-0.04 (-0.1, 0.02) p=0.19
Month 24 – FEV1 (% predicted)			
n	376	378	387
Mean (SD)	-2.06 (11.1)	-1.23 (15.23)	-0.6 (43.58)
Mean difference from IFN β-1a (95% CI, p-value ^b)		0.83 (-1.08, 2.74) p=0.39	1.47 (-3.08, 6.01) p=0.53
Last postbaseline value prior to EOT – FEV1 (L)			
n	432	433	430
Mean (SD)	-0.11 (0.42)	-0.1 (0.41)	-0.13 (0.37)
Mean difference from IFN β-1a (95% CI, p-value ^b)		0.01 (-0.04, 0.07) p=0.63	-0.03 (-0.08, 0.03) p=0.36
Last postbaseline value prior to EOT – FEV1 (% predicted)			
n	432	432	429
Mean (SD)	-2.09 (10.96)	-1.21 (14.89)	-0.44 (41.53)
Mean difference from IFN β-1a (95% CI, p-value ^b)		0.874 (-0.87, 2.62) p=0.33	1.65 (-2.41, 5.71) p=0.42

EOT = end of treatment

^a Baseline is defined as the last non-missing value prior to the first dose of the study drug

^b p-value is the nominal p-value based on a simple t-test comparison without any multiplicity adjustment

Source: Table 2, Celgene Response to Information Request Received on 25 Jul 2019, page 24-33

Table 10: Mean Change From Baseline in FVC, Trial RPC01-201B (Safety Population)

Change From Baseline^a	IFN β-1a 30 ug N=440	Ozanimod 0.5 mg N=439	Ozanimod 1 mg N=434
Month 3 – FVC (L)			
n	427	426	426
Mean (SD)	-0.02 (0.53)	-0.03 (0.55)	-0.07 (0.52)
Mean difference from IFN β-1a (95% CI, p-value ^b)		-0.01 (-0.08, 0.07) p=0.85	-0.05 (-0.12, 0.02) p=0.19
Month 3 – FVC (% predicted)			
n	427	425	425
Mean (SD)	-0.24 (13.96)	-0.32 (13.6)	-1.18 (12.41)
Mean difference from IFN β-1a (95% CI, p-value ^b)		-0.08 (-1.93, 1.78) p=0.93	-0.94 (-2.72, 0.83) p=0.3
Month 6 – FVC (L)			
n	412	419	416
Mean (SD)	-0.06 (0.45)	-0.03 (0.59)	-0.1 (0.55)
Mean difference from IFN β-1a (95% CI, p-value ^b)		0.03 (-0.04, 0.1) p=0.41	-0.41 (-0.11, 0.03) p=0.24
Month 6 – FVC (% predicted)			
n	412	418	415
Mean (SD)	-1 (11.81)	-0.03 (14.81)	-1.93 (12.67)
Mean difference from IFN β-1a (95% CI, p-value ^b)		0.98 (-0.85, 2.8) p=0.29	-0.93 (-2.6, 0.75) p=0.28

Change From Baseline^a	IFN β-1a 30 ug N=440	Ozanimod 0.5 mg N=439	Ozanimod 1 mg N=434
Month 12 – FVC (L)			
n	406	405	406
Mean (SD)	-0.07 (0.38)	-0.06 (0.56)	-0.13 (0.52)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.01 (-0.06, 0.08) p=0.77	-0.06 (-1.12, 0.004) p=0.07
Month 12 – FVC (% predicted)			
n	406	404	405
Mean (SD)	-1.18 (9.83)	-0.87 (13.78)	-2.14 (11.97)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.31 (-1.34, 1.96) p=0.71	-0.96 (-2.47, 0.55) p=0.21
Month 24 – FVC (L)			
n	376	378	387
Mean (SD)	-0.09 (0.53)	-0.06 (0.58)	-0.14 (0.54)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.04 (-0.04, 0.12) p=0.36	-0.04 (-0.12, 0.03) p=0.27
Month 24 – FVC (% predicted)			
n	376	378	387
Mean (SD)	-1.36 (11.89)	0.38 (15.22)	-2.11 (12.66)
Mean difference from IFN β -1a (95% CI, p-value ^b)		1.74 (-0.22, 3.69) p=0.08	-0.754 (-2.5, 0.99) p=0.4
Last postbaseline value prior to EOT – FVC (L)			
n	432	433	430
Mean (SD)	-0.1 (0.52)	-0.05 (0.55)	-0.13 (0.52)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.05 (-0.02, 0.12) p=0.18	-0.03 (-0.1, 0.04) p=0.36
Last postbaseline value prior to EOT – FVC (% predicted)			
n	432	432	429
Mean (SD)	-1.47 (11.83)	0.45 (14.58)	-1.96 (12.35)
Mean difference from IFN β -1a (95% CI, p-value ^b)		1.92 (0.14, 3.69) p=0.03	-0.5 (-2.12, 1.12) p=0.55

EOT = end of treatment

^a Baseline is defined as the last non-missing value prior to the first dose of the study drug

^b p-value is the nominal p-value based on a simple t-test comparison without any multiplicity adjustment

Source: Adapted from Table 2, Celgene Response to Information Request Received on 25 Jul 2019, page 34-43

While the average changes in pulmonary function are comparable across treatment groups, it should be noted that some patients demonstrated greater declines in pulmonary function during the conduct of this trial. Proportions of participants who had <80% of baseline PFT at any postbaseline visit or <80% in percent-predicted measurements are comparable between the IFN β -1a and ozanimod 0.5 mg treatment groups; rates were slightly higher in the 1 mg treatment arm, suggesting that some of these pulmonary changes may be dose-dependent (Table 11).

Table 11: Outlier Analysis of Pulmonary Function Testing, Trial RPC01-201B (Safety Population)

Test	IFN β-1a 30 ug n=440	Ozanimod 0.5 mg n=439	Ozanimod 1 mg n=434
<80% of baseline PFT at any postbaseline visit			
FEV1	31/432 (7%)	36/433 (8%)	43/430 (10%)
FVC	37/432 (9%)	33/433 (8%)	44/430 (10%)
DLCO	54/263 (21%)	55/262 (21%)	84/264 (32%)
<80% at any postbaseline visit			
FEV1 % predicted	56/432 (13%)	38/435 (9%)	69/430 (16%)
FVC % predicted	58/432 (13%)	37/435 (9%)	69/430 (16%)

DLCO=diffusing capacity of lungs for carbon monoxide; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; PFT=pulmonary function test

^a Denominators for percentages are the total number of subjects with a baseline and at least one postbaseline assessment

^b Denominators for percentages are the total number of subjects with at least one postbaseline assessment

Source: Table 51, Clinical Study Report RPC01-201B, Page 215

D. Trial RPC01-301

Safety Population

The safety population for Trial RPC01-301 includes 1346 RMS patients. These patients received at least one dose of study drug and were analyzed according to the highest dose of study drug received.

Disposition and Extent of Exposure

All 1346 patients that were randomized received at least one dose of study drug. Ninety-one subjects discontinued study drug. Thirty-six discontinued drug related to an AE, though none of these were related to pulmonary safety.

Overall treatment duration of exposure was comparable across the three treatment arms. A majority of participants remained on study drug for ≥ 12 months (88%).

Analysis of Adverse Events

AEs were monitored from the time of first dose until end of study or until the first dose of the OLE. As in Trial RPC01-201B, the highest incidence of reported decreases in pulmonary function measurements were reported in the 1 mg ozanimod-treated group. This rate (2%) was also low, and comparable to what was seen for the 0.5 mg ozanimod group (0.2%) and IFN-treated (1%) groups. The incidence of total AEs related to Respiratory, Thoracic, and Mediastinal Disorders were also comparable across treatment groups. Oropharyngeal pain was the only AE reported at a rate of $\geq 1\%$ and at a higher rate than what was reported for the active control group (

Table 12). While events of dyspnea were appreciated in the ozanimod treatment group (n=2, 0.4%), these events were mild, rare, and without notable concomitant change in PFT.

Table 12: Adverse Events (Occurring \geq 1% in Any Ozanimod Treatment Group and Reported at a Higher Rate Than IFN β -1a): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-301 (Safety Population)

Adverse Event	IFN β -1a 30 ug n=445	Ozanimod 0.5 mg n=453	Ozanimod 1 mg n=448	Total Ozanimod N=901
Investigations Related to Pulmonary Function Testing	3 (1%)	1 (0.2%)	9 (2%)	10 (1%)
Forced vital capacity decreased	2 (0.4%)	0 (0%)	5 (1%)	7 (1%)
Forced expiratory volume decreased	0 (0%)	0 (0%)	3 (1%)	3 (0.3%)
Respiratory, thoracic and mediastinal disorders	13 (3%)	16 (4%)	19 (4%)	35 (4%)
Oropharyngeal pain	2 (0.4%)	2 (0.4%)	4 (1%)	6 (1%)

Source: Adapted from Table 14.3.1.2, RPC01-301 – Tables, Page 486 - 514

Deaths and Serious Adverse Events

No deaths occurred during the conduct of this trial. No serious adverse events related to pulmonary safety were reported.

Pulmonary Function Testing

PFT was performed using American Thoracic Society/European Respiratory Society (ATS/ERS) criteria at screening, Month 3, Month 6, and Month 12. DLCO was assessed at screening and every 12 months at available sites. PFTs were also performed if clinically indicated or at the early termination visit, if applicable. If pulmonary abnormalities were detected, patients were followed until resolution or until no further improvement was expected, based on a follow-up period of not less than 3 months.

Pulmonary events of special interest were again defined as decline in FEV₁, FVC, and DLCO (corrected from hemoglobin). When considering treatment with 0.5 mg ozanimod compared to IFN β -1a, a mean treatment difference of -0.05 L (95% CI: -0.1, -0.01, nominal p=0.01) and -1.4% (95% CI: -2.58, -0.21, nominal p=0.02) in FEV (L) and FEV (% predicted), respectively, was seen at Month 3. These treatment differences do not appear to be sustained, as there were no other differences when comparing active control to the 0.5 mg of ozanimod treatment, except at Month 6 for FEV (% predicted) (Table 13 and Figure 10). A decrease was seen in the 0.5 mg ozanimod treatment group compared to active control at Month 6 for FVC (% predicted), though this was not seen for any other FVC measurement (Table 14 and Figure 11). While it appears that there was an improvement in lung function at Month 18, this phenomenon is likely a result of smaller sample size (Table 14, Figure 10, and Figure 11). There were no statistically significant differences between 0.5 mg ozanimod and IFN treatment when comparing change from baseline in DLCO.

When comparing changes from baseline between the IFN β -1a treated group and the 1 mg ozanimod treatment group, statistically significant declines in FEV₁ and FVC were seen (Table 13 and Table 14). For FEV₁, these differences were appreciated in both absolute and % predicted measurements at Months 3 and 12, as well as when considering the last postbaseline value. A treatment difference was also seen at Month 6 for the 1 mg ozanimod cohort, though only in % predicted FEV₁. The treatment differences seen are small (58-81 mL or 1.7-2.6%) and may not be clinically significant, but are sustained. While it appears that there was an improvement in lung function at Month 18, this, again, might be an

artifact of sample size (Table 13, Table 14, Figure 10, and Figure 11). A statistically significant treatment difference for FVC (absolute and % predicted values) was only seen at Month 3, when comparing 1 mg ozanimod to IFN treatment (Table 14 and Figure 11). There were no statistically significant differences between 1 mg ozanimod and IFN treatment when comparing changes from baseline in DLCO (data not shown).

Taken together, these data are suggestive of a safety signal related to ozanimod use as early as Month 3, which appears to be dose-dependent and sustained, especially for FEV1 measurements.

Table 13: Mean Change From Baseline in FEV1, Trial RPC01-301 (Safety Population)

Change From Baseline^a	IFN β-1a 30 ug n=445	Ozanimod 0.5 mg n=453	Ozanimod 1 mg n=448
Month 3 – FEV1 (L)			
n	437	449	442
Mean (SD)	0.01 (0.34)	-0.04 (0.3)	-0.07 (0.34)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.05 (-0.1, -0.01) p=0.01	-0.081 (-0.13, -0.04) p=0.0005
Month 3 – FEV1 (% predicted)			
n	437	449	442
Mean (SD)	0.41 (8.93)	-0.99 (9.05)	-2.19 (10.06)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-1.4 (-2.58, -0.21) p=0.02	-2.6 (-3.85, -1.34) p<0.001
Month 6 – FEV1 (L)			
n	430	442	439
Mean (SD)	-0.01 (0.36)	-0.05 (0.38)	-0.05 (0.37)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.04 (-0.09, 0.01) p=0.13	-0.04 (-0.09, 0.01) p=0.13
Month 6 – FEV1 (% predicted)			
n	430	442	438
Mean (SD)	0.38 (10.1)	-1.103 (10.7)	-1.29 (10.36)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-1.49 (-2.87, -0.10) p=0.04	-1.67 (-3.03, -0.31) p=0.02
Month 12 – FEV1 (L)			
n	413	427	420
Mean (SD)	-0.01 (0.43)	-0.05 (0.37)	-0.07 (0.37)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.04 (-0.09, 0.01) p=0.15	-0.07 (-0.12, -0.01) p=0.02
Month 12 – FEV1 (% predicted)			
n	413	427	420
Mean (SD)	0.47 (10.91)	-0.69 (10.41)	-2.13 (11.05)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-1.16 (-2.6, 0.29) p=0.12	-2.59 (-4.09, -1.1) p=0.007
Month 18 – FEV1 (L)			
n	25	27	22
Mean (SD)	0.01 (0.31)	0.01 (0.35)	-0.08 (-0.24)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.01 (-0.18, 0.19) p=0.94	-0.08 (-0.25, 0.08) p=0.32
Month 18 – FEV1 (% predicted)			
n	25	27	22
Mean (SD)	0.93 (7.95)	0.68 (7.54)	-0.172 (8.93)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.25 (-4.57, 4.07) p=0.91	-1.1 (-6.06, 3.86) p=0.66

Change From Baseline^a	IFN β-1a 30 ug n=445	Ozanimod 0.5 mg n=453	Ozanimod 1 mg n=448
Last postbaseline value prior to EOT – FEV1 (L)			
n	439	450	445
Mean (SD)	-0.01 (0.43)	-0.05 (0.37)	-0.07 (0.38)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.036 (-0.09, 0.02) p=0.18	-0.058 (-0.11, -0.005) p=0.03
Last postbaseline value prior to EOT – FEV1 (% predicted)			
n	439	450	445
Mean (SD)	0.29 (11.15)	-0.84 (10.85)	-1.91 (11.24)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-1.13 (-2.58, 0.32) p=0.13	-2.2 (-3.68, -0.72) p=0.004

EOT = end of treatment

^a Baseline is defined as the last non-missing value prior to the first dose of the study drug

^b p-value is the nominal p-value based on a simple t-test comparison without any multiplicity adjustment

Source: Table 1, Celgene Response to Information Request Received on 25 Jul 2019, page 1-10

Table 14: Mean Change From Baseline in FVC, Trial RPC01-301 (Safety Population)

Change From Baseline^a	IFN β-1a 30 ug N=440	Ozanimod 0.5 mg N=439	Ozanimod 1 mg N=434
Month 3 – FVC (L)			
n	437	449	442
Mean (SD)	-0.003 (0.45)	-0.02 (0.45)	-0.08 (0.49)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.016 (-0.08, 0.04) p=0.59	-0.08 (-0.14, -0.01) p=0.02
Month 3 – FVC (% predicted)			
n	437	449	442
Mean (SD)	0.09 (11.18)	-0.62 (11.42)	-1.79 (13.28)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.71 (-2.2, 0.78) p=0.35	-1.87 (-3.5, -0.25) p=0.02
Month 6 – FVC (L)			
n	430	442	439
Mean (SD)	0.01 (0.46)	-0.03 (0.5)	-0.02 (0.53)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.042 (-0.11, 0.02) p=0.2	-0.03 (-0.1, 0.03) p=0.32
Month 6 – FVC (% predicted)			
n	430	442	439
Mean (SD)	0.85 (11.43)	-0.87 (12.19)	-0.49 (13.68)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-1.73 (-3.3, -0.15) p=0.03	-1.34 (-3.02, 0.34) p=0.12
Month 12 – FVC (L)			
n	413	427	420
Mean (SD)	-0.01 (0.51)	-0.01 (0.49)	-0.05 (0.51)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.01 (-0.06, 0.07) p=0.88	-0.034 (-0.1, 0.04) p=0.33
Month 12 – FVC (% predicted)			
n	413	427	420
Mean (SD)	0.43 (12.33)	-0.09 (11.3)	-0.92 (13)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.51 (-2.12, 1.09) p=0.53	-1.35 (-3.07, 0.38) p=0.13

	IFN β -1a 30 ug N=440	Ozanimod 0.5 mg N=439	Ozanimod 1 mg N=434
Change From Baseline^a			
Month 18 – FVC (L)			
n	25	27	22
Mean (SD)	0.03 (0.4)	0.12 (0.42)	0.11 (0.29)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.09 (-0.14, 0.32) p=0.45	0.075 (0.13, 0.28) p=0.47
Month 18 – FVC (% predicted)			
n	25	27	22
Mean (SD)	1.91 (9.21)	3.11 (9.42)	4.66 (8.76)
Mean difference from IFN β -1a (95% CI, p-value ^b)		1.2 (-3.99, 6.4) p=0.64	2.75 (-2.55, 8.05) p=0.3
Last postbaseline value prior to EOT – FVC (L)			
n	439	450	445
Mean (SD)	-0.03 (0.54)	-0.01 (0.5)	-0.04 (0.51)
Mean difference from IFN β -1a (95% CI, p-value ^b)		0.01 (-0.06, 0.08) p=0.71	-0.016 (-0.08, 0.05) p=0.66
Last postbaseline value prior to EOT – FVC (% predicted)			
n	439	450	445
Mean (SD)	0.07 (13.62)	-0.26 (11.88)	-0.71 (13.05)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.32 (-2.01, 1.36) p=0.71	-0.78 (-2.54, 0.98) p=0.39

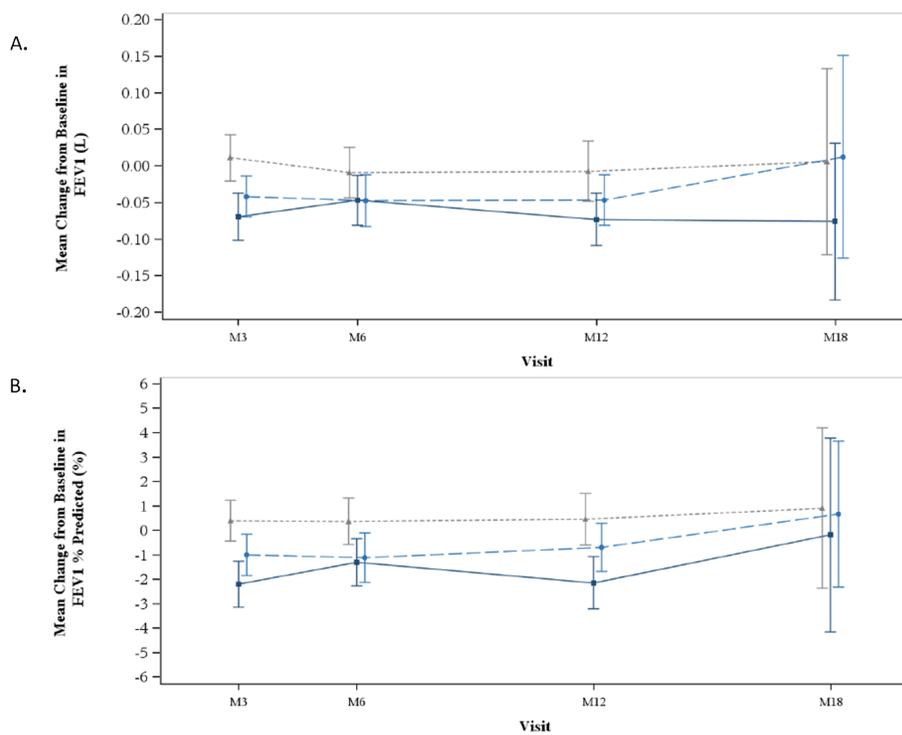
EOT = end of treatment

^a Baseline is defined as the last non-missing value prior to the first dose of the study drug

^b p-value is the nominal p-value based on a simple t-test comparison without any multiplicity adjustment

Source: Adapted from Table 1, Celgene Response to Information Request Received on 25 Jul 2019, page 11-20

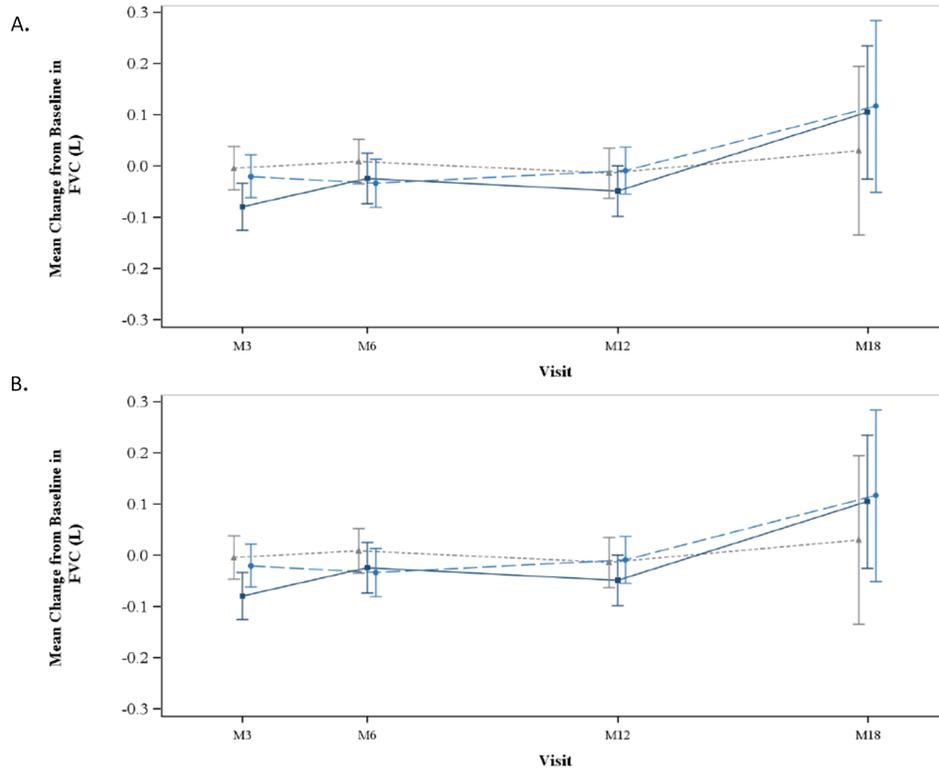
Figure 10: Mean Change From Baseline (95% Confidence Intervals) in FEV1 (Panel A, Liters; Panel B, % Predicted), Trial RPC01-301(Safety Population)



Grey triangles=IFN β -1a, light blue circles=ozanimod 5 mg, dark blue squares=ozanimod 1 mg

Source: Figure 1, Celgene Response to Information Request Received on 25 Jul 2019, Appendix 2 – Statistical Figures, pages 1-2

Figure 11: Mean Change From Baseline (95% Confidence Intervals) in FVC (Panel A, Liters; Panel B, % Predicted), Trial RPC01-301(Safety Population)



Grey triangles=IFNβ-1a, light blue circles=ozanimod 5 mg, dark blue squares=ozanimod 1 mg
 Source: Figure 1, Celgene Response to Information Request Received on 25 Jul 2019, Appendix 2 – Statistical Figures, pages 3-4

In Trial RPC01-301, some patients demonstrated more significant declines in pulmonary function than others. Ozanimod-treated groups had slightly higher percentages of participants who had <80% of baseline PFT at any postbaseline visit, compared to IFNβ-1a treatment. The percentages of those with <80% percent-predicted measurements at any postbaseline visit were comparable across treatment arms (Table 15).

Table 15: Outlier Analysis of Pulmonary Function Testing, Trial RPC01-201B (Safety Population)

Test	IFN β-1a 30 ug N=445	Ozanimod 0.5 mg N=453	Ozanimod 1 mg N=448
<80% of baseline PFT at any postbaseline visit^a			
FEV1	19/439 (4%)	25/450 (6%)	24/445 (5%)
FVC	20/439 (5%)	27/450 (6%)	15/445 (3%)
DLCO	12/153 (8%)	15/153 (10%)	16/156 (10%)
<80% at any postbaseline visit^b			
FEV1 % predicted	46/442 (10%)	46/450 (10%)	38/445 (9%)
FVC % predicted	57/442 (13%)	41/450 (9%)	51/445 (12%)

DLCO=diffusing capacity of lungs for carbon monoxide; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; PFT=pulmonary function test

^a Denominators for percentages are the total number of subjects with a baseline and at least one postbaseline assessment

^b Denominators for percentages are the total number of subjects with at least one postbaseline assessment

Source: Table 51, RPC01-201B – Study Report Body, page 212

E. Trial RPC01-3001

Safety Population

The OLE safety population as of the data cutoff date includes all enrolled participants who received at least one dose of ozanimod.

Disposition and Extent of Exposure

As of the data cutoff date, 2495 patients consented to participation in the OLE, with 2494 receiving study drug. Of the 30 participants that discontinued treatment due to AEs, 1 participant who received 1 mg ozanimod in the parent trial withdrew due to dyspnea after developing this symptom on Day 8 of the OLE. Following study drug discontinuation, they recovered on Day 13. There were no abnormal PFTs for this subject nor were there any additional pulmonary-related AEs listed for this subject (Table 16).

Of the 2494 patients receiving ozanimod in OLE, 2323 (93%) subjects were continuing to receive ozanimod at the time of the data cutoff. The average treatment duration of all participants at time of data cutoff was 19 months.

Analysis of Adverse Events

AEs related to PFTs abnormalities were rare, representing 1% of the OLE participants (Table 16).

One-hundred twenty-seven participants (5%) experienced an AE that was considered a Respiratory, Thoracic and Mediastinal Disorder (Table 16). The most common respiratory AE, cough was reported in 30 participants (1%) (Table 16).

Events of oropharyngeal pain (n=2, received 0.5 mg ozanimod in parent trial) and pulmonary embolism following surgical repair of a lower limb fracture (n=1, received 1 mg ozanimod in the parent trial) were considered severe AEs. The remainder of AEs were considered to be mild or moderate.

Table 16: Adverse Events (≥ 1% in Any Treatment Group): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Trial RPC01-3001 (Safety Population)

Adverse Event	Placebo- Oz 0.5 mg n=37	Placebo- Oz 1 mg n=35	IFN β-1a 30 µg n=736	Ozanimod 0.5 mg n=840	Ozanimod 1 mg n=846	Totals N=2494
Investigations related to pulmonary function testing	0 (0%)	0 (0%)	5 (1%)	8 (1%)	2 (0.2%)	15 (1%)
Forced expiratory volume decreased	0 (0%)	0 (0%)	2 (0.3%)	4 (1%)	1 (0.1%)	7 (0.3%)
Respiratory, thoracic and mediastinal disorders	2 (5%)	1 (3%)	36 (5%)	47 (6%)	41 (5%)	127 (5%)
Cough	2 (5%)	0 (0%)	9 (1%)	9 (1%)	10 (1%)	30 (1%)
Oropharyngeal pain	0 (0%)	0 (0%)	6 (1%)	15 (2%)	8 (1%)	29 (1%)
Epistaxis	0 (0%)	0 (0%)	6 (1%)	2 (0.2%)	1 (0.1%)	9 (0.4%)
Rhinitis allergic	0 (0%)	0 (0%)	4 (1%)	2 (0.2%)	3 (0.4%)	9 (0.4%)
Asthma	0 (0%)	1 (3%)	1 (0.1%)	1 (0.1%)	4 (1%)	7 (0.3%)
Respiratory disorder	0 (0%)	0 (0%)	0 (0%)	4 (1%)	2 (0.2%)	6 (0.2%)

Source: Adapted from Table 14.3.1.2, RPC01-3001 – Tables, Page 1721-1763

Deaths and Serious Adverse Events

Two patients died while receiving study drug during the OLE; one died of craniocerebral injury after being hit by a train and the other died of pulmonary embolism following a 38-day hospitalization for surgical repair of lower limb fracture. A third subject died after discontinuing study drug and the cause of death was not specified.

Three (0.1%) participants experienced serious adverse events (Table 17). These events were singular and rare, and occurred at similar rates irrespective of treatment in the parent trial.

Table 17: Serious Adverse Events Related to Pulmonary Safety, Trial RPC01-3001 (Safety Population)

Adverse Event	Placebo- Ozanimod 0.5 mg n=37	Placebo- Ozanimod 1 mg n=35	IFN β-1a 30 µg n=736	Ozanimod 0.5 mg n=840	Ozanimod 1 mg n=846	Totals N=2494
Respiratory, thoracic and mediastinal disorders	0 (0%)	0 (0%)	2 (0.3%)	0 (0.0%)	1 (0.1%)	3 (0.1%)
Pleurisy	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	1 (<0.1%)
Pulmonary embolism	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	1 (<0.1%)
Epistaxis	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	1 (<0.1%)

Source: Table 14.3.2.1, RPC01-3001 – Tables, Page 2263 - 2272

Pulmonary Function Testing

FEV1 and FVC will be assessed every 12 months during the OLE, as well as at end of trial (EOT) or at early termination (ET) using American Thoracic Society/European Respiratory Society (ATS/ERS) criteria. DLCO will only be assessed at the EOT/ET where locally available. Abnormal PFTs are to be repeated within <30 days. As in the other trials, any abnormalities detected are to be followed until resolution or until no further improvement is expected by the Investigator (based on a follow-up period of not less than 3 months).

Changes from baseline in PFT parameters are shown in Table 18. A small decline in FEV1 (-0.88% predicted) was appreciated at Month 12; declines in both absolute value and % predicted FEV1 were appreciated at Month 24. Similarly, a small decline in FVC (-0.07% predicted) was appreciated at Month 12; declines in both absolute and % predicted FVC were seen at Month 24. DLCO was not determined to be affected by ozanimod treatment in OLE, though this was only assessed at EOT/ET where available.

Table 18: Mean Change From Open-Label Extension Baseline in FEV1, Trial RPC01-3001 (Safety Population)

Change From Baseline^a	Total (OLE) Ozanimod 1 mg N=2494
Month 12 – FEV1 (L)	
n	2382
Mean (SD)	0.07 (2.91)
Min, max	-2.48, 88.71
Month 12 – FEV1 (% predicted)	
n	2382
Mean (SD)	-0.88 (11.46)
Min, max	-220, 85.4
Month 24 – FEV1 (L)	
n	345
Mean (SD)	-0.09 (0.32)
Mean difference from IFN β-1a (95% CI, p-value ^b)	-2, 1.5
Month 24 – FEV1 (% predicted)	
n	345
Mean (SD)	-2.12 (9.77)
Min, max	-44.8, 25

^a Baseline is defined as the last non-missing value prior to the first dose of the study drug in the OLE
Source: Table 14.3.5.5.2, RPC01-3001 – Tables, page 3562 - 3563

Table 19: Mean Change from Open-Label Extension Baseline in FVC, Trial RPC01-3001 (Safety Population)

Change From Baseline^a	Total (OLE) Ozanimod 1 mg N=2494
Month 12 – FVC (L)	
n	2382
Mean (SD)	0.22 (11.65)
Min, Max	-3, 568.2
Month 12 – FVC (% predicted)	
n	2382
Mean (SD)	-0.07 (12.43)
Min, Max	-164, 209
Month 24 – FVC (L)	
n	345
Mean (SD)	-0.05 (0.47)
Min, Max	-2.4, 4.3
Month 24 – FVC (% predicted)	
n	345
Mean (SD)	-1.23 (12.82)
Min, Max	-44.5, 93.24

^a Baseline is defined as the last non-missing value prior to the first dose of the study drug in the OLE
Source: Table 14.3.5.5.2, RPC01-3001 – Tables, page 3564 - 3565

When considering PFT changes determined to be outliers, 60 (3%) subjects and 51 (2%) subjects reported FEV1 or FVC values that were <80% of baseline, respectively. One hundred-eighty (7%) subjects and 169 (7%) subject reported FEV1 and FVC (% predicted) <80 at any postbaseline value (Table 20).

Table 20: Outlier Analysis of Pulmonary Function Testing, Trial RPC01-3001 (Safety Population)

Test	Total (OLE) Ozanimod 1 mg
<80% of baseline PFT at any postbaseline visit ^a	
FEV1	60/2434 (3%)
FVC	51/2434 (2%)
<80% at any postbaseline visit ^b	
FEV1 % predicted	180/2436 (7%)
FVC % predicted	169/2436 (7%)

DLCO=diffusing capacity of lungs for carbon monoxide; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; PFT=pulmonary function test

^a Denominators for percentages are the total number of subjects with a baseline and at least one postbaseline assessment

^b Denominators for percentages are the total number of subjects with at least one postbaseline assessment

Source: Table 43, Interim Clinical Study Report RPC01-3001, Page 139

Of note, FEV1 and FVC declines of <50% predicted were determined to be AESI in the OLE; this affected 3 participants (0.1%).

Two participants were found to have FEV1 decreases of <50% predicted:

- (1) Subject was a 48-year-old white male who was enrolled in parent Trial RPC01-201B where he was exposed to 733 days of ozanimod 0.5 mg daily and 730 days of weekly placebo IM injection. He then enrolled in the OLE and received 1 mg ozanimod. On Day 361 of Trial RPC01-3001, FEV1 was 1.39L (43% of predicted value). His FVC was 3.59 L (91% of predicted value). It was noted that the subject was “nervous” at the time of testing. He continued study medication and FEV1 was determined to be 3.43 L (105% of predicted) on Day 401.
- (2) Subject was a 19-year old white female who was enrolled in parent Trial RPC01-301, where she was exposed to ozanimod 1 mg daily for 454 days and 449 day of weekly placebo IM injection. The patient’s FEV1 at baseline was 75% predicted. Over the course of the Trial RPC01-301, FEV1 declined to FEV1 47% predicted. The patient then enrolled in Trial RPC01-3001 and was determined to have an FEV1 of 1.5 L (45% predicted) on Day 364. This decline was not associated with symptoms. It was determined that this subject did not correctly know how to participate in pulmonary function testing, and the subject continued on ozanimod. On Day 514, FEV1 was determined to be 1.9L (56% of predicted) and determined to be “recovered/resolved” by investigators.

One participant was found to have FEV1 and FVC decrease of <50% predicted:

- (1) Subject was a 50-year-old white female who was enrolled in parent Trial RPC01-301, where she was exposed to 671 days of ozanimod 1 mg daily and 670 days of weekly placebo IM injection. She then enrolled in the OLE and received 1 mg ozanimod. On Day 212 of Trial RPC01-3001, her FEV1 was

found to be 1.24 L (42% predicted) and FVC was 1.61 L (43% predicted). She did not have any pulmonary symptoms at this time but “voluntarily withdrew” from the trial on this date. PFTs performed on Day 288 yielded similar results; FEV1 was determined to be 1.14 L (39% predicted) and FVC was 1.42L (38% predicted). The patient was seen by a pulmonologist on Day 299 and was reported to have a normal exam. The subject reported that breathing “had not been any different over the last several months.”

V. Integrated Review of Pulmonary Safety

In order to provide a more robust assessment of safety, the two active-controlled trials, Trials RPC01-201B and RPC01-301, were pooled to create a safety database of 2659 participants. Both trials were ~2 years in duration.

A. Demographics

The demographics of the pooled active-controlled trials are similar to that of the overall clinical program for ozanimod. Most participants were female and white, and enrolled in sites in Eastern Europe. Approximately 20% of patients were active smokers.

B. Extent of Exposure

The mean duration of exposure for the two active-controlled trials is approximately 18 months and represents a total of 1300 subject-years in both ozanimod treatment groups. The majority of patients were exposed to ozanimod for at least 12 months. These exposures are sufficient for a robust analysis of safety.

A total of 3% of participants withdrew due to an AE, though none were related to pulmonary safety.

C. Analysis of Adverse Events

The portion of participants with AEs related to pulmonary investigations was slightly higher in the ozanimod 1 mg group (2%) compared to active control (1%) in the pooled active-controlled trials. The incidence of AEs related to the Respiratory, Thoracic and Mediastinal Disorders SOC were equivalent across treatment groups (Table 21).

Table 21: Adverse Events (Occurring \geq 1% in an Ozanimod Treatment Group and Reported at a Higher Rate Than IFN β -1a): Investigations Related to Pulmonary Function Testing and Respiratory, Thoracic and Mediastinal Disorders, Pooled Active-Controlled Trials (Safety Population)

Adverse Event	IFN β-1a 30 μg n=885	Ozanimod 0.5 mg n=892	Ozanimod 1.0 mg n=882	Totals N=2659
Investigations related to pulmonary safety	9 (1%)	4 (0.4%)	21 (2%)	34 (1%)
Carbon monoxide diffusing capacity decreased	3 (0.3%)	2 (0.2%)	4 (1%)	9 (0.3%)
Forced expiratory volume decreased	2 (0.2%)	0 (0%)	6 (1%)	8 (0.3%)
Respiratory, Thoracic, and Mediastinal Disorders	54 (6%)	57 (6%)	56 (6%)	167 (6%)
Catarrh	2 (0.2%)	4 (0.4%)	5 (1%)	11 (0.4%)
Epistaxis	0 (0%)	5 (1%)	3 (0.3%)	8 (0.3%)

Source: Table 15.2, ISS-Tables, page 1118

Via monoamine oxidase-B (MAO-B) enzymatic reaction, ozanimod is metabolized to CC112273. Because of differential activity of MAO-B in smokers and in males, the exposure to this major circulating metabolite is predicted to be 52% lower in smokers compared to non-smokers and 35% lower in males compared to females. As such, a subgroup analysis of AEs was conducted.

When considering smoking status, non-smokers had a slightly higher rate of PFT abnormalities than smokers. AEs within the Respiratory, Thoracic, and Mediastinal SOC were also higher in the non-smoker groups, though this phenomenon was also appreciated in the IFN treated group (data not shown).

The number of adverse events related to abnormal PFT does not appear to be affected by sex; rates in males and females was comparable across treatment groups. AEs within the Respiratory, Thoracic, and Mediastinal SOC were slightly higher in females, though this was appreciated in both IFN and ozanimod-treated individuals (data not shown).

D. Death and Serious Adverse Events

There were four deaths in the development program of ozanimod for the treatment of MS. One subject, a 48-year-old male subject who received 1 mg ozanimod for > 24 months in Trial RPC01-301 and in the OLE, died of pulmonary embolism. This was thought to be related to a 38-day hospitalization for surgical repair of a limb fracture. Of note, this was the only death and serious adverse event related to pulmonary safety.

E. Pulmonary Function Measurements

When comparing mean change from baseline in 1 mg ozanimod compared to IFN β -1a treatment for the pooled active-controlled trials, a statistically significant treatment difference of -0.06 L (95% CI: -0.09, -0.02, nominal p=0.001) and -1.6% (95% CI: -2.63, -0.04, nominal p=0.001) in FEV (L) and FEV (% predicted), respectively, was seen at Month 3 (Table 22). A statistically significant treatment difference between 1 mg ozanimod and IFN β -1a for FEV1 (in L and % predicted) was also appreciated at 6 and 12 months (Table 22). These decreases relative to active control treatment were also seen with FVC (L) and FVC (% predicted) at Month 3, but not in DLCO (data not shown).

Interpretations regarding sustainability and reversibility of effect should be viewed with caution, as sample sizes after Month 12 are notably smaller than those in the early months of the trials. Similarly, while statistically significant changes in DLCO were not detected at any timepoint, the sample sizes are smaller than those where FEV1 and FVC data is available.

Table 22: Mean Change From Baseline in FEV1, Pooled Active-Controlled Trials (Safety Population)

Change From Baseline^a	IFN β-1a 30 ug N=885	Ozanimod 0.5 mg N=892	Ozanimod 1 mg N=882
Month 3 – FEV1 (L)			
n	864	874	868
Mean (SD)	-0.02 (0.38)	-0.05 (0.34)	-0.07 (0.35)
Mean difference from IFN β -1a (95% CI, p-value ^b)		-0.03 (-0.06, 0.01) p=0.1	-0.06 (-0.09, -0.02) p=0.002
Month 3 – FEV1 (% predicted)			
n	864	873	867
Mean (SD)	-0.35 (10.9)	-1.11 (9.94)	-1.98 (10.25)
Mean difference from placebo (95% CI, p-value ^b)		-0.76 (-1.74, 0.23) p=0.13	-1.63 (-2.63, -0.04) p=0.001
Month 6 – FEV1 (L)			
n	841	861	855
Mean (SD)	-0.04 (0.38)	-0.06 (0.42)	-0.08 (0.37)
Mean difference from placebo (95% CI, p-value ^b)		-0.02 (-0.06, 0.02) p=0.34	-0.04 (-0.08, -0.005) p=0.03
Month 6 – FEV1 (% predicted)			
n	842	860	853
Mean (SD)	-0.43 (10.92)	-1.12 (12.5)	-1.7 (10.97)
Mean difference from placebo (95% CI, p-value ^b)		-0.69 (-1.81, 0.43) p=0.22	-1.31 (-2.35, -0.26) p=0.01
Month 12 – FEV1 (L)			
n	819	831	826
Mean (SD)	-0.04 (0.39)	-0.07 (0.37)	-0.1 (0.38)
Mean difference from placebo (95% CI, p-value ^b)		-0.03 (-0.07, 0.004) p=0.08	-0.06 (-0.1, -0.02) p=0.002
Month 12 – FEV1 (% predicted)			
n	819	831	825
Mean (SD)	-0.55 (10.5)	-1.47 (10.53)	-2.42 (11.21)
Mean difference from placebo (95% CI, p-value ^b)		-0.92 (-1.93, 0.01) p=0.08	-1.86 (-2.91, -0.81) p=0.001
Month 18 – FEV1 (L)			
n	25	27	22
Mean (SD)	0.01 (0.31)	0.01 (0.35)	-0.08 (0.24)
Mean difference from placebo (95% CI, p-value ^b)		0.01 (-0.12, 0.19) 0.02 p=0.94	-0.08 (-0.25, 0.08) p=0.32
Month 18 – FEV1 (% predicted)			
n	25	27	22
Mean (SD)	0.93 (7.95)	0.68 (7.54)	-0.17 (8.93)
Mean difference from placebo (95% CI, p-value ^b)		-0.25 (-4.57, 4.07) p=0.91	-1.1 (-6.06, 3.86) p=0.66

Change From Baseline^a	IFN β-1a 30 ug N=885	Ozanimod 0.5 mg N=892	Ozanimod 1 mg N=882
Month 24 – FEV1 (L)			
n	376	378	387
Mean (SD)	-0.11 (-.44)	-0.1 (0.41)	-0.15 (0.37)
Mean difference from placebo (95% CI, p-value ^b)		0.01 (-0.06, 0.07) p=0.88	-0.04 (-0.01, 0.02) p=0.19
Month 24– FEV1 (% predicted)			
n	376	378	387
Mean (SD)	-2.06 (11.1)	-1.23 (15.23)	-0.6 (43.58)
Mean difference from placebo (95% CI, p-value ^b)		0.83 (-1.08, 2.74) p=0.39	1.47 (-3.08, 6.01) p=0.53

^a Baseline is defined as the last non-missing value prior to the first dose of the study drug

^b p-value is the nominal p-value based on a simple t-test comparison without any multiplicity adjustment

Source: Table 4, Celgene Response to Information Request Received on 25 Jul 2019, Page 57-104

Table 23: Mean Change From Baseline in FVC, Pooled Active-Controlled Trials (Safety Population)

Change From Baseline^a	IFN β-1a 30 ug N=885	Ozanimod 0.5 mg N=892	Ozanimod 1 mg N=882
Month 3 – FVC (L)			
n	864	875	868
Mean (SD)	-0.01 (0.49)	-0.02 (0.5)	-0.07 (0.5)
Mean difference from IFN β-1a (95% CI, p-value ^b)		-0.01 (-0.06, 0.04) p=0.63	-0.06 (-0.11, -0.01) p=0.01
Month 3 – FVC (% predicted)			
n	864	873	867
Mean (SD)	-0.07 (12.62)	-0.47 (12.52)	-1.49 (12.86)
Mean difference from placebo (95% CI, p-value ^b)		-0.4 (-1.58, 0.78) p=0.51	-1.42 (-2.6, -0.21) p=0.02
Month 6 – FVC (L)			
n	842	861	855
Mean (SD)	-0.3 (0.46)	-0.03 (0.55)	-0.06 (0.54)
Mean difference from placebo (95% CI, p-value ^b)		-0.01 (-0.05, 0.04) p=0.78	-0.04 (-0.08, -0.01) p=0.13
Month 6 – FVC (% predicted)			
n	842	860	854
Mean (SD)	-0.06 (11.65)	-0.46 (13.52)	-1.19 (13.21)
Mean difference from placebo (95% CI, p-value ^b)		-0.41 (-1.61, 0.8) p=0.51	-1.13 (-2.32, 0.05) p=0.06
Month 12 – FVC (L)			
N	819	832	826
Mean (SD)	-0.04 (0.45)	-0.03 (0.53)	-0.09 (0.52)
Mean difference from placebo (95% CI, p-value ^b)		0.01 (-0.04, 0.06) p=0.74	-0.05 (-0.09, 0.001) p=0.05
Month 12 – FVC (% predicted)			
n	819	831	825
Mean (SD)	-0.37 (11.18)	-0.47 (12.57)	-1.52 (12.510)
Mean difference from placebo (95% CI, p-value ^b)		-0.1 (-1.25, 1.05) p=0.87	-1.15 (-2.29, 0.002) p=0.05

Change From Baseline^a	IFN β-1a 30 ug N=885	Ozanimod 0.5 mg N=892	Ozanimod 1 mg N=882
Month 18 – FVC (L)			
n	25	27	22
Mean (SD)	0.03 (0.4)	0.12 (0.42)	0.1 (0.29)
Mean difference from placebo (95% CI, p-value ^b)		0.09 (-0.14, 0.32) p=0.45	0.08 (-0.13, 0.28) p=0.47
Month 18 – FVC (% predicted)			
n	25	27	22
Mean (SD)	1.91 (9.21)	3.11 (9.42)	4.66 (8.76)
Mean difference from placebo (95% CI, p-value ^b)		1.2 (-3.99, 6.4) p=0.64	2.75 (-2.55, 8.05) p=0.3
Month 24 – FVC (L)			
n	376	378	387
Mean (SD)	-0.01 (0.53)	-0.06 (0.58)	-0.14 (0.54)
Mean difference from placebo (95% CI, p-value ^b)		0.04 (-0.04, 0.12) p=0.36	-0.04 (-0.12, 0.03) p=0.27
Month 24– FVC (% predicted)			
n	376	378	387
Mean (SD)	-1.36 (11.89)	0.38 (15.22)	-2.11 (12.66)
Mean difference from placebo (95% CI, p-value ^b)		1.74 (-0.22, 3.69) p=0.08	-0.75 (-2.5, 0.99) p=0.4

^a Baseline is defined as the last non-missing value prior to the first dose of the study drug

^b p-value is the nominal p-value based on a simple t-test comparison without any multiplicity adjustment

Source: Table 4, Celgene Response to Information Request Received on 25 Jul 2019, Page 57-104

F. Pulmonary Safety Conclusions

DPARP's assessment of pulmonary safety focuses on a 6-month placebo-controlled trial in 258 subjects and two-active controlled trials, ~2 years in length in 1313 and 1346 subjects, respectively. The pulmonary safety analyses are further supported by uncontrolled extension periods in 2744 subjects. Pulmonary function changes were not consistent or robust in the individual trials; however, the pooled analyses did demonstrate dose-dependent changes in FEV1 and FVC as early as Month 3. The changes in FEV1 were sustained through Month 12, while the changes in FVC were not statistically significant at other timepoints. The change from baseline in absolute FEV1 and FVC at Month 3 was -60 mL (-90, -20) and -60 mL (-110, -10), respectively. The change from baseline in percent-predicted FEV1 and FVC at Month 3 was -1.63 (-2.63, -0.04) and -1.42 (-2.6, -0.21), respectively. The magnitude of change for FEV1 was sustained through Month 12. Statistically significant changes in FEV1 were not noted after Month 12, however, this is limited by the decreases in sample size after Month 12. Although FEV1 and FVC were generally stable in uncontrolled extension periods (up to 22 and 39 months), there is insufficient information to determine the reversibility of the decrease in FEV1 or FVC after drug discontinuation due to limited follow-up.

Overall, pulmonary AEs associated with ozanimod use are rare and were considered to be mostly mild or moderate. Reports of dyspnea following ozanimod use were rare and were not associated with changes in PFT parameters, including the one participant who withdrew from the OLE trial (RPC01-3001) due to dyspnea. Considering both the mild-

moderate severity and rarity of these adverse events overall, the risk of pulmonary toxicity with ozanimod use can be mitigated through labeling and patient education.

Pulmonary effects are expected based on the mechanism of action of S1P modulators and have been seen in approved S1P modulators, fingolimod and siponimod. Both fingolimod and siponimod demonstrated decreases in FEV1. In addition, fingolimod demonstrated decreases in DLCO and siponimod demonstrated decreases in FVC. The magnitude of change in pulmonary function was comparable to ozanimod. Both fingolimod and siponimod also noted several subjects discontinuing due to dyspnea compared to the ozanimod trials which also noted one subject discontinuing for dyspnea. Overall, the pulmonary safety profile for the S1P modulators are comparable.

PMRs were included in the approval of both fingolimod and siponimod. Because there are outstanding PMRs designed to monitor pulmonary toxicity with long term, chronic use of the other two other drugs in this class, fingolimod and siponimod, the utility of a third PMR is arguably limited. While it is unclear if the pulmonary effects for ozanimod are reversible, a trial designed to assess reversibility following drug discontinuation would be unethical, given the concern that stopping S1P modulators can cause worsening of MS symptoms (4-6). It is also unclear if pulmonary function will decline over time. A comparator group would be required to adequately assess pulmonary function decline over time; however, as S1P receptor modulators are considered to be part of standard of care, a comparator group may not be feasible. While a trial to assess the risk of special populations could yield additional safety information, it was shown for other S1P modulators that treatment of those with COPD and asthma are affected similarly to those without respiratory disease at doses approved for RMS treatment (5, 6). At this time, we are therefore not recommending a PMR for ozanimod, though it is possible that we would recommend the issuance of one in the setting of new clinical data from the PMR trials of fingolimod or siponimod.

VI. Labeling Recommendations

Based on our review of pulmonary function safety, we recommend that ozanimod, like other S1P receptor modulators, include verbiage reflecting observed changes in pulmonary function testing as well as the respiratory effects that were seen during the clinical development program, as outlined below.

In HIGHLIGHTS OF PRESCRIBING INFORMATION, under WARNINGS AND PRECAUTIONS:

- “Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated.”

In SECTION 5 WARNINGS AND PRECAUTIONS:

- “Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in patients treated with ZEPOSIA as early as 3 months after treatment initiation. In pooled analyses of (b) (4), the decline in absolute FEV1 from baseline (b) (4) was 60 mL (95% CI: -100, -20) at 12 months. The mean difference (b) (4) in percent predicted FEV1 at 12 months was 1.9% (95% CI: -2.9, -0.8). Dose-dependent reductions in FVC (absolute value and %-predicted) were also seen at Month 3 in pooled analyses comparing (b) (4) (60 mL, 95% CI (-110, -10); 1.4%, 95% CI: (-2.6, -0.2)), though significant reductions were not seen at other timepoints. There is insufficient information to determine the reversibility of the decrease in FEV1 or FVC after drug discontinuation. (b) (4) one patient discontinued ZEPOSIA due to dyspnea. Spirometric evaluation of respiratory function should be performed during therapy with ZEPOSIA if clinically indicated.”

In SECTION 6 ADVERSE REACTIONS:

- “Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and forced vital capacity (FVC) were observed in patients treated with ZEPOSIA [see Warnings and Precautions]”

Comment to DNP: AEs related to changes in spirometry within the Investigations SOC should be pooled together as “Pulmonary function test abnormal” and included in any AE table or description of AEs included in Section 6.

In SECTION 12.2 PHARMACODYNAMICS:

- “Pulmonary Function: “Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and forced vital capacity (FVC) were observed in patients treated with ZEPOSIA [see *Warnings and Precautions*]”

In SECTION 17 PATIENT COUNSELING INFORMATION:

- “Respiratory Effects: Advise patients that they should contact their (b) (4) if they experience new onset or worsening dyspnea [see *Warnings and Precautions*]”

References

1. Groves A, Kihara Y, Chun J. Fingolimod: direct CNS effects of sphingosine 1-phosphate (S1P) receptor modulation and implications in multiple sclerosis therapy. *J Neurol Sci* 2013; 328: 9-18.
2. Ammit AJ, Hastie AT, Edsall LC, Hoffman RK, Amrani Y, Krymskaya VP, Kane SA, Peters SP, Penn RB, Spiegel S, Panettieri RA, Jr. Sphingosine 1-phosphate modulates human airway smooth muscle cell functions that promote inflammation and airway remodeling in asthma. *FASEB J* 2001; 15: 1212-1214.
3. Mohammed S, Harikumar KB. Sphingosine 1-Phosphate: A Novel Target for Lung Disorders. *Front Immunol* 2017; 8: 296.
4. FDA warns about severe worsening of multiple sclerosis after stopping the medicine Gilenya (fingolimod). 2018. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-severe-worsening-multiple-sclerosis-after-stopping-medicine-gilenya-fingolimod>.
5. GILENYA (fingolimod) prescribing information. 2019. Available from: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gilenya.pdf>.
6. MAYZENT (siponimod) prescribing information. 2019. Available from: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/mayzent.pdf>.

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/

NATALIE M PICA
11/22/2019 08:21:15 AM

BANU A KARIMI SHAH
11/22/2019 08:22:06 AM