CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209899Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	March 25, 2020
Reviewer:	Silvia Perez-Vilar, PharmD, PhD Division of Epidemiology I
Team Leader:	Catherine Callahan, PhD, MA Division of Epidemiology I
Deputy Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	ZEPOSIA (Ozanimod)
Application Type/Number:	NDA 209899
Applicant/sponsor:	Celgene Corporation
OSE RCM #:	2020-308

Expedited ARIA Sufficiency for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Ozanimod (ZEPOSIA, Celgene Corporation) is a sphingosine-1-phosphate (S1P) receptor agonist, which binds selectively to S1P subtypes 1 (S1P1) and 5 (S1P5). It is a new molecular entity (NME) and is currently not approved or marketed in any country. The proposed indication is the treatment of relapsing forms of multiple sclerosis (MS). The mechanism by which ozanimod exerts therapeutic effects in relapsing MS may involve reduction of lymphocyte migration into the central nervous system. Ozanimod is administered orally. The proposed maintenance dose of ozanimod is 1 mg per day after a seven-day dose escalation (0.25 mg per day on days 1 to 4, 0.5 mg per day on days 5 to 7). [1] Ozanimod is extensively metabolized in humans to several circulating active metabolites, including CC112273 and CC1084037. [2] The half-life of ozanimod is approximately 20 hours, while the half-life of CC112273 and CC1084037 is about 280 hours, leading to accumulation of these active metabolites (relative to the parent) after multiple dosing. [3]

The New Drug Application (NDA) submission included safety data from two phase 3 active-controlled (interferon β-1a) and one Phase 2, placebo-controlled clinical trials in adults with relapsing MS. These data were supported by placebo-controlled studies in adults with inflammatory bowel disease (IBD) and clinical pharmacology studies in healthy adult volunteers. [4] The proposed label (as of March 24, 2020) includes warnings and precautions and a medication guide for infections, bradycardia and atrioventricular conduction delays, liver injury, fetal risk, increased blood pressure, respiratory effects, and macular edema. [5]

1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of ozanimod during pregnancy. Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4%. [6,7] MS is a chronic inflammatory disease of the central nervous system leading to demyelination and

[1] ZEPOSIA (ozanimod). Draft clinical review dated February 11, 2020. Division of Neurology 2. U.S. Food and Drug Administration
[2] ZEPOSIA (ozanimod). Non-clinical primary review dated March 10, 2020. Division of Neurology 2. U.S. Food and Drug Administration
[3] See footnote 1
[4] Ibid.
[5] Proposed ZEPOSIA labeling dated March 24, 2020
[6] Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved February 3, 2020, from https://www.fda.gov/media/90160/download.
[7] Centers for Disease, C. and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep 57(1): 1-5.

neurodegeneration. The vast majority of patients with MS initially follow a relapsing-remitting course, defined by acute exacerbations from which they typically completely or incompletely recover, with periods of relative clinical stability in between. [8] MS is commonly diagnosed in women of childbearing age and its incidence is two to three times higher in women than men. Women with MS are not less fertile and do not have more difficulty in completing a pregnancy to term compared with healthy controls. [9] However, maternal MS may be associated with an increased rate of caesarean delivery and lower infant birth weights compared with women without MS. [10]

Data on pregnancy exposure during clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of ozanimod. The ozanimod clinical trials required that sexually active subjects of reproductive potential (both men and women) use an effective form of contraception for the duration of the study. A total of 36 female subjects became pregnant during the ozanimod MS trials (one twin pregnancy). Of these, 18 were reported as full term healthy infants (one infant had late intrauterine growth retardation with subsequent normal development), seven resulted in elective terminations, five led to spontaneous abortions (all in the first trimester of pregnancy), four had unknown outcomes, two led to preterm deliveries at 36 weeks gestation, and one had pregnancy complications and resulted in an infant with a congenital malformation (left kidney duplication and patent foramen ovale). [11,12] In animal studies, there were no effects on fertility in males or females dosed with ozanimod. Embryolethality and developmental effects (e.g., incomplete skeletal ossification, malpositioned vertebrae, malformed or absent arteries, anasarca, malpositioned testes, and cleft palate) occurred in pregnant rats and/or rabbits exposed to ozanimod and its metabolites during gestation. When ozanimod (0, 0.2, 1, or 5 mg/kg) was orally administered to pregnant rats during the period of organogenesis, malformations (skeletal and urogenital), post-implantation loss, and fetal lethality occurred at > 0.2 mg/kg, a dose that is 2-times higher than the maximum recommended human dose of 1 mg, on a mg/m^2 basis. At the no-effect level of 0.2 mg/kg, exposure to ozanimod and RP101124, was 8.9- and 13.7-times higher than the exposure at the maximum recommended human dose of 1 mg; exposure to the other two major human metabolites, CC112273 and CC1084037, was less than the exposure at the maximum recommended human dose. When ozanimod (0, 0.2, 0.6, or 2 mg/kg) was orally administered to pregnant rabbits during the period of organogenesis, a no-effect dose could not be determined because skeletal malformations were observed at all doses. Vascular malformations, with a no-effect dose of 0.2 mg/kg, and spontaneous abortion and embryolethality, with a no-effect dose of 0.6 mg/kg, occurred at higher doses. The lowest dose, 0.2 mg/kg, represented a dose that is 4-fold higher than the maximum recommended human dose. Exposure to ozanimod at the lowest dose of 0.2 mg/kg was 2.2-fold higher than exposure at the maximum recommended human dose; the level of the three major human metabolites did not exceed exposure at the maximum recommended human dose. When ozanimod (0, 0.2, 0.7, or 2 mg/kg) was orally administered to female rats throughout pregnancy and lactation,

[8] Katz Sand, I. (2015). "Classification, diagnosis, and differential diagnosis of multiple sclerosis." Curr Opin Neurol 28(3): 193-205.
[9] Voskuhl, R. and C. Momtazee (2017). "Pregnancy: Effect on Multiple Sclerosis, Treatment Considerations, and Breastfeeding." Neurotherapeutics 14(4): 974-984.
[10] Kelly, V. M., L. M. Nelson and E. F. Chakravarty (2009). "Obstetric outcomes in women with multiple sclerosis and epilepsy." Neurology 73(22): 1831-1836.
[11] ZEPOSIA (ozanimod). Draft clinical review dated February 11, 2020. Division of Neurology 2. U.S. Food and Drug Administration
[12] Celgene response to FDA information request received on 20 Nov 2019. Celgene Corporation

offspring exhibited an increase in activity and reactivity to touch with a no-effect dose of 0.7 mg/kg, which is 7-times higher than the maximum recommended human dose, on a mg/m^2 basis. Exposure to ozanimod and RP101124, a major human metabolite, at the no-effect dose was 30- and 40-times higher than at the maximum recommended human dose; exposure to the other two major human metabolites, CC112273 and CC1084037, was less than the exposure at the maximum recommended human dose. [13]

The currently proposed labeling, as of March 24, 2020, includes warnings and precautions for fetal risk (Section 5.4). It states that *"there are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm [see Use in Specific Populations (8.1)]. Because it takes approximately 3 months to eliminate ZEPOSIA from the body, women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA [see Use in Specific Populations (8.1)]."*
Section 8.1 (Pregnancy) states:

"*Animal Data*
Oral administration of ozanimod (0, 0.2, 1, or 5 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality, increased fetal malformations and skeletal variations (abnormal/delayed ossification), and reduced fetal body weight at the highest dose tested. No maternal toxicity was observed. At the no-effect dose (1 mg/kg/day) for adverse effects on embryofetal development, plasma ozanimod exposure (AUC) for ozanimod was approximately 60 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Oral administration of ozanimod (0, 0.2, 0.6, or 2.0 mg/kg/day) to female rabbits during organogenesis resulted in a marked increase in embryofetal mortality at the highest dose tested and increased fetal malformations (malformed blood vessels) and skeletal variations at the mid and high doses. Maternal toxicity was not observed. At the no-effect dose (0.2 mg/kg/day) for adverse effects on embryofetal development in rabbit, plasma ozanimod exposure (AUC) was approximately 2 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

Oral administration of ozanimod (0, 0.2, 0.7, or 2 mg/kg/day) to female rats throughout gestation and lactation resulted in persistent body weight reductions and long-term effects on reproductive (prolonged estrus cycle) and neurobehavioral (increased motor activity) function in offspring at the highest dose tested, which was not associated with maternal toxicity. At the no-effect dose (0.7 mg/kg/day) for adverse effects on pre- and postnatal development, plasma ozanimod exposure (AUC) was 30 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD."

Section 8.3 (Females and Males of Reproductive Potential) states:
"Contraception
Before initiation of ZEPOSIA treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for contraception during treatment with ZEPOSIA [see Use in Specific Populations (8.1)]. Because of the time it takes to eliminate the drug

[13] ZEPOSIA (ozanimod). Non-clinical primary review dated March 10, 2020. Division of Neurology 2. U.S. Food and Drug Administration

from the body after stopping treatment, the potential risk to the fetus may persist and women of childbearing age should also use effective contraception for 3 months after stopping ZEPOSIA."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☒ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: Alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☐ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

Because broad-based signal detection is not currently available, other parameters have not been assessed.

2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by DN2, as of February 11, 2020, for the PMR related to pregnancy outcomes:

"Pregnancy PMR 3809 (b) (4)
Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Zeposia during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Zeposia 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.

Milestone dates (align with the dates below):

Draft Protocol Submission:	*05/2020*
Final Protocol Submission:	*12/2020*
Annual Interim Report Submissions:	*12/2021*
	12/2022
	12/2023
	12/2024
	12/2025
	12/2026
	12/2027
	12/2028
	12/2029
	12/2030

	12/2031
Study Completion:	*12/2032*
Final Report Submission:	*12/2033*

Pregnancy 3809(b)(4):
Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3809(b)(4) (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Zeposia during pregnancy compared to an unexposed control population.
Milestone dates (align with the dates below):

Draft Protocol Submission:	*05/2020*
Final Protocol Submission:	*12/2020*
Annual Interim Report Submissions:	*12/2021*
	12/2022
	12/2023
	12/2024
	12/2025
	12/2026
	12/2027
	12/2028
	12/2029
	12/2030
	12/2031
Study Completion:	*04/2032*
Final Report Submission:	*04/2033"*

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/s/

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Medical Officer's Review of NDA 209899
Ophthalmology Consultant

NDA 209899		Submission:	3/25/2019
M.O. Review #1		Review completed:	3/11/2020

Name:	Zeposia
Sponsor:	Celgene (ozanimod)
Pharmacologic Category:	Sphingosine 1-phosphate receptor (S1P) modulators
Indications:	Multiple sclerosis

Requested: Approved S1P modulators are associated with an increased risk of macular edema (ME). Please review the findings submitted for this therapy and comment on whether a similar increased risk of macular edema exists in association with this product and what ophthalmology monitoring is indicated, if any. EDR Location: \\CDSESUB1\evsprod\NDA209899\0012

In the ozanimod clinical studies, safety assessments to evaluate the incidence of ME included Optical Coherence Tomography (OCT) evaluations and ophthalmological examinations as screening tools for potential ME. An assessment of ME was conducted by an expert panel (Macular Edema Review Panel [MERP]) who reviewed all AEs of macular edema, search terms consisting of AE preferred terms that could be associated with ME, OCT findings potentially suggestive of ME (regardless of whether an ME-related AE was reported), and ophthalmic examinations.

Subjects With Macular Edema Sponsor-Designated Events of Interest – Pool D (Safety Population)

Study Number	Subject Number Age/Sex	Treatment Group	Onset day	Action Taken	Outcome	Confounding/Risk Factor	MERP Comments
RPC01-201B	(b) (6)	Ozanimod 0.5 mg	366	DWP	Not recovered/ Not resolved Per patient report, there was no ME on follow-up examination.	Central serous choroidopathy	Central Serous Choroidopathy is a well-described disorder in which the primary pathology is subretinal (choroidal) in origin and not morphologically or anatomically related to the ME currently known to be associated with S1P modulator exposure.
RPC01-201B		Ozanimod 0.5 mg	211	DWP	Recovered/ Resolved	Prior history of ME (etiology unknown)	Cystoid macular edema, monocular, attributed to study drug. There was a prior history of ME that may have increased the risk of subsequent ME (although it was not possible to determine in which eye the prior ME had occurred).
RPC01-301		Ozanimod 0.5 mg	182	DWP	Not recovered/ Not resolved Per patient report, the condition was stable. Clarification is pending.	Ocular trauma	Investigator attributed the ME as secondary to the ocular trauma and not to study drug exposure.
RPC01-301		Ozanimod 1 mg	183	DWP	Recovered/ Resolved	History of optic neuritis. Baseline suggestive of intraocular inflammation, possible uveitis	Cystoid macular edema, monocular, attributed to study drug. Baseline external photograph demonstrating posterior synechiae of the affected eye provided clear evidence of prior intraocular inflammation.
RPC01-3001		Ozanimod 1 mg	366	No action taken	Recovering/ Resolving	Pigment epithelial detachment with possible choroidal neovascularization	Subretinal process with trace ME. Possibly represent central serous retinopathy and/or possibly related to choroidal neovascularization with pigment epithelial detachment present. Felt to be related to a choroidal process rather than intraretinal that is described with S1P related ME.
RPC01-3001		Ozanimod 1 mg	15	DWP	Resolved	Uveitis	Vitreous cells seen on OCT indicative of uveitis, previously undetected and known to be an independent cause of ME.
RPC01-3001		Ozanimod 1 mg	279	DWP	Resolved	Hx of retinopathy and optic neuritis Past medical history of "macular retinopathy" Macular pucker	Prior diagnosis of "macular retinopathy" could represent epiretinal membrane. Macular adhesion noted at Month 12 from parent study with macular pucker which could predispose to ME (left eye).
RPC01-202		Ozanimod 1 mg	22	Stopped temporarily	Resolved	Central retinal vein thrombosis	Vein occlusion known to cause ME. In vasculopathic age group at known risk for vein occlusion.
RPC01-3102		Ozanimod 1 mg	20	Dose not changed	Resolved	Central retinal vein thrombosis	Vein occlusion known to cause ME. In vasculopathic age group at known risk for vein occlusion.

DWP = drug withdrawn permanently; F = female; Hx = history; IBD = inflammatory bowel disease; M = male; ME = macular edema; MERP = Macular Edema E = open-label extension; RMS = relapsing multiple sclerosis; S1P = sphingosine-1-phosphate. 109.2; MERP Report; narratives (listing in ISS Section 22).

Reviewer's Comments: *The individual cases listed above have been reviewed. The majority of cases are not confounded. Only the cases highlighted above are likely to be confounded. There is disagreement that the rest of the cases have factors which may be confounding.*

1. Central serous is not the same as macular edema and does not necessarily predispose

patients to macular edema. Patient (b) (6) *in study RPCO1-201B should not be considered a confounded case.*

2. *A prior history of ME has minimal impact on future cases of ME. Patient* (b) (6) *should not be considered confounded.*

3. *While many forms of ocular trauma do not contribute to ME, the particular ocular trauma which occurred to patient* (b) (6) *in Study RPC01-301 is likely the cause of the macular edema.*

4. *Contrary to the applicant's statement, neither the presence of posterior synechiae or an epiretinal membrane are causes of ME. Patient* (b) (6) *should not be considered confounded.*

5. *Occasional cells in the vitreous should not be considered a diagnosis of uveitis and are highly unlikely to be the cause of macular edema. Patient* (b) (6) *should not be considered confounded.*

6. *Disagree that the epiretinal membrane observed in patient* (b) (6) *is the cause of the ME.*

7. *While the ME in the last two cases are likely to be secondary to the retinal vein occlusion, the retinal vein occlusion may be secondary to the drug product.*

The applicant has proposed the following Warnings/Precautions:

(b) (4) **Macular Edema**

(b) (4)

17 PATIENT COUNSELING INFORMATION

…

Macular Edema

Advise patients that they should contact their (b) (4) if they experience any changes in their vision. Inform patient with diabetes mellitus or a history of uveitis that their risk of macular edema maybe increased [see Warnings and Precautions (5 (b) (4).

The following edits are recommended:

5.? Macular Edema

Sphingosine 1-phosphate receptor (S1P) modulators including ZEPOSIA have been associated with an increased risk of macular edema. (b) (4) [redacted]

17 PATIENT COUNSELING INFORMATION

…

Macular Edema

Advise patients that ZEPOSIA may cause macular edema and that they should contact their healthcare provider if they experience any changes in their vision. [see Warnings and Precautions (5.?)].

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 10, 2020

To: Kristen Haslam, Senior Regulatory Health Project Manager, Division of Neurology II (DN-II)

Tracy Peters, Associate Director for Labeling, (DN-II)

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZEPOSIA® (ozanimod) capsules, for oral use (Zeposia)

NDA: 209899/O-1

In response to DN-II's consult request dated May 6, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for Zeposia.

PI: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DN-II (Susan Daugherty) on February 26, 2020, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on March 10, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room February 11, 2020, and February 21, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Christine Bradshaw at (301) 796-6796 or Christine.Bradshaw@fda.hhs.gov.

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CHRISTINE J BRADSHAW
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 10, 2020
To:	Kristen Haslam Regulatory Project Manager **Division of Neurology II**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Christine Bradshaw, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ZEPOSIA (ozanimod)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 209899
Applicant:	Celgene Corporation

1 INTRODUCTION

On March 25, 2019, Celgene Corporation submitted for the Agency's review a resubmission of New Drug Application (NDA)/New Molecular Entity (NME) 209899 for ZEPOSIA (ozanimod) after a refusal to file letter dated February 23, 2018. ZEPOSIA (ozanimod) is indicated for the treatment of adults with relapsing forms of multiple sclerosis (MS).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II on March 26, 2019 and May 6, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZEPOSIA (ozanimod) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft ZEPOSIA (ozanimod) MG received on March 25, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on February 25, 2020.
- Draft ZEPOSIA (ozanimod) MG received on March 25, 2019 revised by the Review Division throughout the review cycle, and received by OPDP on February 29, 2020.
- Draft ZEPOSIA (ozanimod) Prescribing Information (PI) received on March 25, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on February 25, 2020.
- Draft ZEPOSIA (ozanimod) Prescribing Information (PI) received on March 25, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on February 26, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 10, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 209899
Product Name and Strength:	Zeposia (ozanimod) capsule, 0.23 mg, 0.46 mg, 0.92 mg
Applicant/Sponsor Name:	Celgene International II Sarl (Celgene)
OSE RCM #:	2018-48-4
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Celgene submitted revised saleable and sample kit carton labeling and Prescribing Information (PI), received on March 9, 2020, for Zeposia. The Division of Neurology 2 (DN 2) requested that we review the revised labeling for Zeposia (Appendix B) to determine if it is acceptable from a medication error perspective. The revised labeling replaces the term (b) (4) with "titration" per DN 2 recommendation for consistency with PI labeling of other products within the drug class.

2 CONCLUSION

The proposed labeling revisions are acceptable from a medication error perspective. We have no recommendations at this time.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 2, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 209899
Product Name and Strength:	Zeposia (ozanimod) capsule, 0.23 mg, 0.46 mg, 0.92 mg
Applicant/Sponsor Name:	Celgene International II Sarl (Celgene)
OSE RCM #:	2018-48-3
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Celgene submitted revised sample kit carton labeling, received on February 21, 2020, for Zeposia. The Division of Neurology 2 (DN 2) requested that we review the revised sample kit carton labeling for Zeposia (Appendix B) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Celgene implemented our recommendation. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Morris, C. Label and Labeling Review MEMO for Zeposia (NDA 209899). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 14. RCM No.: 2018-48-2.

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/s/

JOHN C MORRIS
03/02/2020 03:04:37 PM

BRIANA B RIDER
03/02/2020 03:08:39 PM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 19, 2020

To: Nicolas Kozauer, MD, Acting Director
Division of Neurology Products I

Through: Dominic Chiapperino, PhD, Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D. Medical Officer
Jovita Randall-Thompson, PhD, Pharmacologist
Controlled Substance Staff

Subject: **NDA 209899** (IND 109159)
Generic Name (Trade Name): ozanimod (Zeposia)
Dosages: 0.23, 0.46, and 0.92 mg orally once daily, with (b) (4) schedule
Formulations, route: Hard gelatin capsules: 0.23, 0.46, and 0.92 mg (equivalent to 0.25 mg, 0.5 mg, and 1 mg of ozanimod HCl salt, PO)
Indication(s): Treatment of relapsing multiple sclerosis (RMS) in adult patients
Sponsor: Celgene International II Sàrl
PDUFA Goal Date: March 25, 2020

Materials Reviewed:

- NDA 209884, eCTD 0012, resubmitted March 25, 2019, (originally submitted December 22, 2017)
- Drug Scheduling Proposal
- CSS review, Dr. A. Lerner, January 26, 2018
- Meeting package Auguest 29, 2018
- Meeting minutes November 9, 2018
- Evaluation of Dependence and Withdrawal of Ozanimod in MS patients, Nov 26 2019

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I. SUMMARY

1. Background

This memorandum responds to a consult request dated March 25, 2019 from the Division of Neurology Products (DNP) regarding ozanimod, trade name Zeposia (NDA 209899 and IND 109159). Ozanimod is a sphingosine 1-phosphate receptor agonist under development by Celgene International II Sàrl (Sponsor). It is a new molecular entity (NME) to be used as treatment for adult patients with relapsing forms of multiple sclerosis (RMS), given at a recommended maintenance dose of 0.92 mg orally, taken once daily.

Ozanimod is a central nervous system (CNS) active drug with its primary mode of action being an agonist at the sphingosine-1-phosphate 1 (S1P1) and 5 (S1P5) receptor subtypes. Ozanimod's therapeutic mechanism may involve the reduction of lymphocyte migration into the central nervous system, but the specific mechanism of its therapeutic effects are unknown.

Based on its pharmacology and ozanimod's potentially abuse-related AEs, CSS recommended that the Sponsor evaluate ozanimod for abuse potential (IND 109159, CSS review, Dr. A. Lerner, January 26,

2018, DARRTS). In response, the Sponsor submitted a nonclinical self-administration study and abuse-related and dependence and withdrawal adverse event assessments.

CSS requested an evaluation of dependence and withdrawal in patients with MS undergoing treatment with ozanimod (Nov 9, 2018 meeting minutes). Specifically, CSS requested an evaluation in ~ 80 MS patients using the following scales: Physician Withdrawal Checklist (PWC-20), anxiety, depression sleep scales, and Columbia-Suicide Severity Rating Scale (C-SSRS). The timepoints for these scales to be administered was: on the last day on-drug, first day off-drug, and then on the 4th and 7th days after discontinuation of the drug, followed by once a week for the following two weeks. The dependence and withdrawal monitoring would include vital sign measurements during the evaluation period.

Ozanimod is not a scheduled substance under the Controlled Substances Act (CSA). Its mechanism of action is similar to fingolimod (marketed as Gilenya, NDA 022527), a S1P-modulator with high affinity for S1P1, S1P3, S1P4, and S1P5 receptors. Fingolimod is not a controlled substance.

2. Conclusions

1. The Sponsor states that ozanimod is not chemically or pharmacologically similar to any known drug of abuse, does not produce psychoactive effects that are abuse-related, and thus has no abuse potential and is unlikely to be abused. Upon assessment of the pharmacology, chemistry, and abuse-related adverse events such as euphoria, depression, insomnia, anxiety, somnolence, and suicidality in clinical trials, CSS agrees with the Sponsor and concludes that ozanimod does not meet criteria to be scheduled under the Controlled Substance Act (CSA).

2. Ozanimod's mechanism of action is similar to that of fingolimod (Gilenya, NDA 22527); however, ozanimod is a selective agonist at S1P1 and S1P5 receptors.

3. Binding assays demonstrate that ozanimod and its metabolite CC1084037 bind to several targets associated with abuse-related effects. Ozanimod was shown to modulate the serotonin transporter (SERT), norephinephrine transporter (NET), and sodium channel. CC1084037 was shown to inhibit binding to the sigma receptor, chloride (Cl-) channel, and to modulate the adenosine 3 (A_3) and serotonin 2B ($5\text{-}HT_{2B}$) receptors, and inhibit monoamine oxidase B (MAO-B). The Sponsor conducted functional assays. The concentrations of ozanimod at the therapeutic dose of 0.92 mg are estimated to be present in the CSF or brain at concentrations several thousand-fold lower than the receptor binding values for SERT; thus, modulation of this receptor is not likely to produce a meaningful pharmacological effect. For CC1084037, there were no abuse-related signals when tested under in vivo procedures. This is supported by the lack of ozanimod-induced CNS effects in animals when evaluated in toxicological assessments.

4. In the nonclinical self-administration study conducted with ozanimod, no abuse potential signal was found (i.e., there was no difference in responding compared to placebo).

5. Abuse-related adverse events in clinical studies in healthy volunteers included euphoria, somnolence, sleep disorder insomnia, decreased appetite, increased energy and fatigue; in

clinical studies in patients with multiple sclerosis the abuse-related AEs included: depression/depressed mood, insomnia, anxiety, panic disorder, fatigue and asthenia, affective disorder, hallucinations, somnolence, memory impairments, disturbance in attention, decreased appetite, and suicidal ideation and suicide attempt. In both populations, these abuse-related AEs were not more frequent than 2.5%.

Dependence, withdrawal, and rebound were not evaluated appropriately and systematically in any clinical studies for ozanimod. The Sponsor was asked by CSS to evaluate dependence and withdrawal by collecting data from ~80 MS patients (meeting minutes, Nov 9, 2018). After one year of evaluation of withdrawal and dependence in the on-going ozanimod studies, the Sponsor provided limited data for 9 patients, 6 of whom did not yield any meaningful dependence data. This is a concerning deficiency, considering that fingolimod (marketed as GILENYA) is a drug with a similar mechanism of action and produces rebound upon abrupt discontinuation and sometimes severe and life-threatening exacerbation of MS (Havla et al., 2012; La Mantia et al., 2014; Faissner et al., 2015; Hatcher et al., 2016; Salem et al., 2016; Czlonkowska et al., 2017; Gunduz et al., 2017; Barry et al., 2019
A recent paper on fingolimod withdrawal emphasizes the presence of severe MS rebound and recommends gradual discontinuation of fingolimod, below (Fragoso et al. 2019)

> *"Twenty papers have been published reporting on 52 patients with severe MS rebound after fingolimod withdrawal. Six new patients are included in the present paper, all of them with aggressive rebound and accumulated disability sequelae. Conclusion: We recommend gradual discontinuation of fingolimod with replacement by other treatment. The washout period should not exceed 4 weeks."*

CSS defers to DN2 on how best to address potential for ozanimod to produce significant rebound of MS symptoms upon discontinuation. Our recommendation would be that product labeling convey risks of producing serious rebound upon drug discontinuation and advising to taper the drug, as the most recent scientific data suggests (see above excerpt).

3. Recommendations

1. Based on the lack of an abuse signal found with ozanimod, CSS recommends no Section 9 Drug Abuse and Dependence in the ozanimod label. Of note, the label for fingolimod, also a S1P-modulator, does not include a Section 9 Drug Abuse and Dependence. However, ozanimod labeling should clarify that there are limited, inconclusive data characterizing dependendence and withdrawal, perhaps in section 2 Dosage and Administration.

2. Because of the observance of rebound in some MS patients after abrupt discontinuation of fingolimod, additional advice to prescribers on drug tapering of ozanimod at the end of treatment or switch of therapy may be helpful (Czlonkowska et al., 2017; Barry et al., 2019; Fragoso et al., 2019).

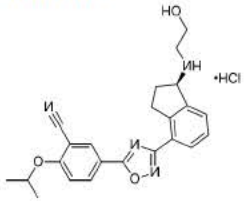
II. REVIEW AND DISCUSSION

1. Chemistry

1.1 Drug Substance

Ozanimod hydrochloride (RPC1063) chemical properties:

- chemical name
  - Base: 5-(3-{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1H-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile
  - HCl salt: 5-(3-{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1H-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile, monohydrochloride
- molecular formula is $C_{23}H_{24}N_4O_3 \cdot HCl$ (salt)
- molecular weight is 440.92 g/mol
- CAS # 1618636-37-5 (HCl salt); 1306760-87-1 (base)
- structure:



1.2 Drug Product and Recommended Dosing

Ozanimod is formulated as immediate release capsules supplied in three dosage strengths, 0.23, 0.46, and 0.92 mg. Treatment should be initiated with an oral (PO) dose of 0.23 mg of ozanimod taken once on Days 1 to 4, followed by once daily doses of 0.46 mg of ozanimod on Days 5 to 7 (b) (4) and then one 0.92 mg dose of ozanimod on Day 8 and thereafter (b) (4)

2. Pharmacokinetics in Animals

Nonclinical abuse-related studies are generally conducted in rats, therefore, ozanimod PK data collected in rats were assessed. The PK effects of ozanimod reported in other animal test species (i.e., mice, monkeys, and rabbits) evaluated by the Sponsor are not discussed in this review. Orally administered ozanimod has a bioavailability ranging from 40% to 60% in rats (Report RP-PK-001-4.0, Report RP-PK-015-1.0). Animal plasma PK data are shown below in the Sponsor's table (Table 1). Ozanimod and its metabolites, (except for RP101124 and RP101988) distribute well into the CNS in rats. Rat plasma PK data are shown below in the Sponsor's tables (Table 1 and 2).

Table 1: Summary of ozanimod (5 mg) pharmacokinetic parameters in rats

Test Article: RPC1063							
Study Number: 028993							
Species: Sprague Dawley Rats							
Sex (M/F)/Number of Animals: M/6 and F/6							
Feeding condition: Ad libitum							
Vehicle/Formulation: 0.5% carboxymethylcellulose in water.							
Method of Administration: Oral gavage							
Dose (mg/kg): 5 mg/kg							
Radionuclide: ^{14}C							
Specific Activity: 300 µCi/kg							
Sampling Time: Plasma: 2, 6, 12, and 24 hours.							
Matrix	**Sex**	**Analyte**	**t_{max} (hr)**	**$t_{½}$ (hr)**	**C_{max} (ng equiv/mL)**	**AUC_{0-24} (hr·ng equiv/mL**	**Total Radioactivity AUC_{0-24} Ratio**
Plasma	Male	Total Radioactivity	2	16.2	469	7796	NA
	Female		6	33.7	594	11568	NA
	Male	RPC1063	2	4.63	326	3219	41.3
	Female		6	4.38	384	4005	34.6
	Male	RP101124	24	NC	175	3132	40.2
	Female		24	NC	385	6975	60.3

Abbreviations: $AUC0_{-24}$ = area under the blood concentration versus time curve from time 0 to 24 hours; C_{max} = maximum blood concentration; NA = not applicable; NC = not calculated; $t_{½}$ = terminal phase half-life; t_{max} = time to maximum blood concentration.
Source: Report 028993 and 2.6.5 Pharmacokinetics Tabulated Summaries, submitted March 25, 2019, page 162.

Table 2: Summary of ozanimod (0.2, 2, and 30 mg) pharmacokinetic parameters in rats

						C_{max}		AUC_{0-24}	
Day	**Group Number**	**RPC1063 Dose (mg/kg)**	**Sex**	**T_{max} (hr)**	**$T_{1/2}$ (hr)**	**ng/mL**	**µM**	**hr*ng/mL**	**hr*µM**
1	6	0.2	M	4	8.9	3.21	0.008	37.0	0.091
1	6	0.2	F	4	5.5	3.99	0.010	55.9	0.138
1	7	2	M	4	4.6	40.3	0.100	453	1.120
1	7	2	F	2	5.8	53.4	0.132	632	1.563
1	8	30	M	4	6.6	595	1.471	8,740	21.612
1	8	30	F	4	10.3	787	1.946	11,100	27.448
28	6	0.2	M	4	9.7	3.00	0.007	37.2	0.092
28	6	0.2	F	2	6.3	7.94	0.020	91.2	0.226
28	7	2	M	4	5.7	47.4	0.117	701	1.733
28	7	2	F	2	8.7	98.2	0.243	1,130	2.794
28	8	30	M	12	NC[1]	773	1.911	13,300	32.888
28	8	30	F	4	9.1	1,460	3.610	22,900	56.627

[1]NC = Not calculated. Value could not be calculated by WinNonlin due to insufficient data points for the elimination phase.

Source: Report 026004-1, submitted March 25, 2019, page 27.

2.1 Receptor Binding and Functional Assays

The Sponsor conducted a receptor screening of off-target receptors (approximately 55 receptors, transporters, and ion channels) with ozanimod, and its metabolites CC112273, CC1084037, RP101075, RP101442, RP101988, and RP101124 (Report 100040667, CC-DISC-ET-2289, 16603, 16829, 17638, and 100032946).

Disruption of binding at abuse-related targets was shown. Ozanimod (at 1 µM concentration) was shown to significantly (>50% threshold) inhibit binding at the serotonin (5-HT) transporter (SERT) and it approached significance for the norephinephrine transporter (NET) and sodium channel (both at 45%, binding inhibition). CC1084037 (at 10 µM concentration) significantly (>50% threshold) inhibited binding at the adenosine (A)3, serotonin 2B (5-HT_{2B}) and sigma receptors, and the chloride (Cl-) channel. In a separate study CC1084037 "was found in vitro to inhibit monoamine oxidase B (MAO-B) specific substrate metabolism (50% inhibitory concentration [IC_{50}] = 5.72 nM) with more than 1000-fold selectivity over the inhibition of monoamine oxidase A (MAO-A)" (Pharmacology Written Summary page 10). No other off-target interactions were identified.

Functional assays were conducted to further characterize the activity of ozanimod and CC1084037 at the above mentioned receptors, transporters, and ion channels. Seven-point dose response curves for ozanimod at SERT and for CC1084037 at A_3, and 5-HT_{2B} were determined. The IC_{50} for ozanimod at SERT and the IC_{50}s for CC1084037 at the A_3 and 5-HT_{2B} receptors were compared to the estimated steady state clinical C_{max} for ozanimod (0.604 nM) and CC1084037 (3.75 nM).

For ozanimod, an IC_{50} of 3.66 µM for SERT versus a C_{max} of 0.604 nM, thus the IC_{50} value is negligible. The concentrations of ozanimod at the therapeutic dose of 0.92 mg are estimated to be present in the CSF or brain at concentrations several thousand-fold lower than the receptor binding values for SERT.

For CC1084037, an IC_{50} = 300 nM for A3(h) and 590 nM for 5-HT_{2B} versus C_{max} = 3.75 nM mean steady-state equaled to an 80- and 400-fold difference, respectively. The IC_{50}s were more comparable to the estimated steady state clinical C_{max} for CC1084037. However, when taking into account the lack of a clinical pharmacological effect at SERT, these two receptors as well as the sigma receptor and the modulation of the chloride (Cl-) channel (see above) are not typically associated with abuse-related effects in the absence of targets highly associated (like SERT) with abuse-related effects. In support, the Sponsor points out additional findings. Ozanimod and the metabolite CC112273 when evaluated for 5-HTP-induced and MAO-B-inhibitor effects did not induce signs of serotonin syndrome in normal mice or exacerbate serotonin-induced, serotonin syndrome (Report RP-PH-008 and RP-PH-017). Coadministration of ozanimod QD over 30 days with a single dose of pseudoephedrine (60 mg on Day 30) did not potentiate the pseudoephedrine-induced blood pressure response in healthy subjects (Study RPC01-1914).

Data from the study with pseudoephedrine is also noted by the Sponsor to address CC112273 activation of MAO-B. There was no inhibitory effect on platelet MAO-B activity, a biomarker for central MAO-B activity, when compared to placebo (Study RPC01-1914).

Still, an assessment for all phases of development for abuse-related adverse event was conducted to confirm a lack of abuse signal by ozanimod.

2.2 Safety Pharmacology/Metabolites

In humans, ozanimod is metabolized to a number of circulating metabolites including CC112273, CC1084037, RP101124, RP101075, RP101988, RP101442, RP112289, and RP112509. Following PO administration of ozanimod to humans, CC112273 and CC1084037 were the two major active circulating metabolites and there is one major inactive metabolite RP101124 (Report RP-PH-001-3.0, RP-PH-002; RP-PH-010). CC112273, CC1084037, and RP101124 contribute >10% of the total drug-related exposure in the plasma. There are no unique human metabolites, with all human metabolites present in one or more animal species used for safety testing.

2.3 Findings from Toxicology Studies

The following sections include a review of ozanimod for general behavioral effects when the drug was tested in repeated-dose toxicology studies. There were no single-dose assessments.

Studies evaluating ozanimod given orally (PO) included:

1. 4 repeat-dose toxicology studies in Sprague-Dawley rats (Study RP-TX-001, 026004, 026636 and 71357)
2. 2 repeat-dose toxicology studies in CByB6F1 mice (Study RP-TX-003 and 72207)
3. 4 repeat-dose toxicology studies in Cynomolgus monkeys (Study 026005, 026006, 026715 and 30477)

Observations were gathered over multiple drug doses from 0.4 to 100 mg/kg/day. Behavioral and nervous system-related observations that were reported included the following:

- Rats (males and females):
  - at doses 0.2, 2, 30 mg/kg/day (PO) - no abnormalities were detected (functional observational battery, Study 026004)
  - at 30 mg/kg/day (PO) - salivation (males only, Study 026636)
  - at 50 mg/kg (PO) - body weight loss (RP-TX-001)
  - no relevant behavioral clinical signs were observed during recovery periods

- Mice (males and females):
  - no relevant behavioral clinical signs were noted during drug exposure and recovery periods

- Monkeys (males and females):
  - at dose 30 mg/kg/day (PO) - trembling (Study 026006 and 026715)
  - at dose 30 mg/kg/day (PO) - hunched posture (Study 026715)
  - no relevant behavioral clinical signs were observed during recovery periods

2.4 Nonclinical Abuse-related Findings

Self-administration: Report 1840-037

For self-administration, under a fixed-ratio 10 (FR10) schedule, substitution of ozanimod (0.01, 0.032, and 0.1 mg/kg/infusion) or its metabolite CC112273 (0.714, 1.43, and 2.14 µg/kg/injection) for cocaine (0.56 mg/kg/infusion) was evaluated in male and female Sprague-Dawley rats. Dose selection for ozanimod (0.01 to 0.1 mg/kg/infusion) and its metabolite covered human therapeutic C_{max} values from approximately 0.07 to 0.14 ng/mL and supratherapeutic dose levels. This is acceptable.

The methods used in this study are acceptable. According to the Sponsor, the low dose (0.01 mg/kg/infusion) was approximately equal to a human exposure of 0.4 ng/ml. Ozanimod and CC112273 exposed rats had a different pattern of responding in comparison to that reported with cocaine. The ozanimod and CC112273 response pattern was comparable to the pattern reported with vehicle. Furthermore, the group mean number of rewards for the combined ozanimod and CC112273 substitution sessions was comparable across all doses with that of the vehicle substitution. These findings indicate that ozanimod is not self-administered by animals and does not function as a positive reinforcer.

3. Clinical Pharmacology

3. 1 Pharmacokinetics: Absorption, Distribution, Metabolism, Elimination (ADME)

3.1.1. Absorption

Ozanimod and its metabolites CC112237 and CC1084037 exhibit linear PK and their maximum plasma concentration (Cmax) and area under the curve (AUC) increased proportionally over the dose range of 0.5 mg to 1 mg. Following oral administration, the median time to maximum plasma concentration (Tmax) of ozanimod was approximately 6 to 8 hours. Median Tmax for CC112273 and CC1084037 was approximately 10 hours and 16 hours, respectively.

Following multiple-dose administration, ozanimod, CC112273, and CC1084037 each represents approximately 6%, 73%, and 15% of circulating total active drug exposure, respectively. Ozanimod, CC112273, and CC1084037 contribute to approximately 94% of circulating total active drug exposure. The median times to maximum plasma concentration (Tmax) for ozanimod, CC112273, and CC1084037 were approximately 8, 10, and 16 hours, respectively. Food (high- and low-fat meals) intake did not alter exposure of ozanimod.

3.1.2. Distribution

Binding of ozanimod, CC112273 and CC1084037 to human plasma proteins is high at ~ 98.2%, 99.8%, and 99.3%, respectively.
The average apparent volume of distribution for ozanimod was greater than 5000 L, suggesting extensive tissue distribution.

3.1.3. Metabolism

Ozanimod is extensively metabolized in humans to form a number of circulating active

metabolites (CC112273, CC1084037, RP101988, RP101075, RP112289, and RP101442) and one circulating inactive metabolite (RP101124).
Multiple enzyme systems play an important role in the metabolism of ozanimod and no single enzyme system predominates the overall metabolism of ozanimod.

3.1.4. Elimination
The average apparent oral clearance (CL/F) for ozanimod was 192 L/h. The mean half-life (t½) for ozanimod was approximately 19 to 22 hours with steady-state concentrations reached within 5 to 7 days of QD dosing of ozanimod. The mean t½ of CC112273 was approximately 11 days with time to steady state of approximately 45 days and with the estimated mean accumulation ratio of approximately 16. Steady state attainment for CC1084037 is similar to CC112273 since both metabolites exhibited similar t½.
After oral administration of a single oral dose of [14C]-ozanimod HCl, approximately 26% and 37% of the radioactivity was recovered from urine and feces, respectively, primarily composed of inactive metabolites. Approximately 83% of the recovered radioactive dose was represented by compounds formed as a result of oxadiazole ring reduction and/or scission by gut microflora.

3.2 Drug/Product Interactions

- ***Other drugs***

The drugs below affect exposure of ozanimod or its metabolites; however, detailed information on drug-drug interaction is not focus of this review.
  - Gemfibrozil,
  - Rifampin
  - MAO-B inhibitors
  - Cyclosporin

- ***Food Effect***

Food (high- and low-fat meals) intake did not alter exposure of ozanimod.

- ***Sex differences***

In males CC112273 steady-state exposure was approximately 35% lower compared to females in population PK analyses.
There was a higher incidence of AEs among female subjects relative to male subjects in the ozanimod 1 mg and IFN β-1a treatment groups, which included psychiatric disorders, nervous system disorders, and gastrointestinal disorders.

4. Clinical

4.1 Clinical Development Program Summary

The clinical development program for ozanimod consisted of 23 clinical studies, and included 7

studies in relapsing forms of multiple sclerosis (RMS), ulcerative colitis (UC), and Crohn's disease (CD) and 16 clinical pharmacology and Phase 1 studies (see Table 3. Data pools). A human abuse potential study was not conducted.

The clinical program in RMS patients consisted of:

- Phase 1, multiple-dose PK/PD study (RPC01-1001)
- Phase 2, randomized, double-blind, placebo-controlled study with a blinded extension period (RPC01-201A)
- Phase 3, two double-blind, active-controlled pivotal studies with the same enrollment criteria and active comparators and endpoints:
    - RPC01- 201B, duration 24 months
    - RPC01-301, duration 12+ months
    - RPC01-3001, 1 long-term open-label extension (OLE) study

The Sponsor organized safety data into the following pools (Fig 1, below, based on Fig 4, Mod 2.5 Clinical overview, p 54):

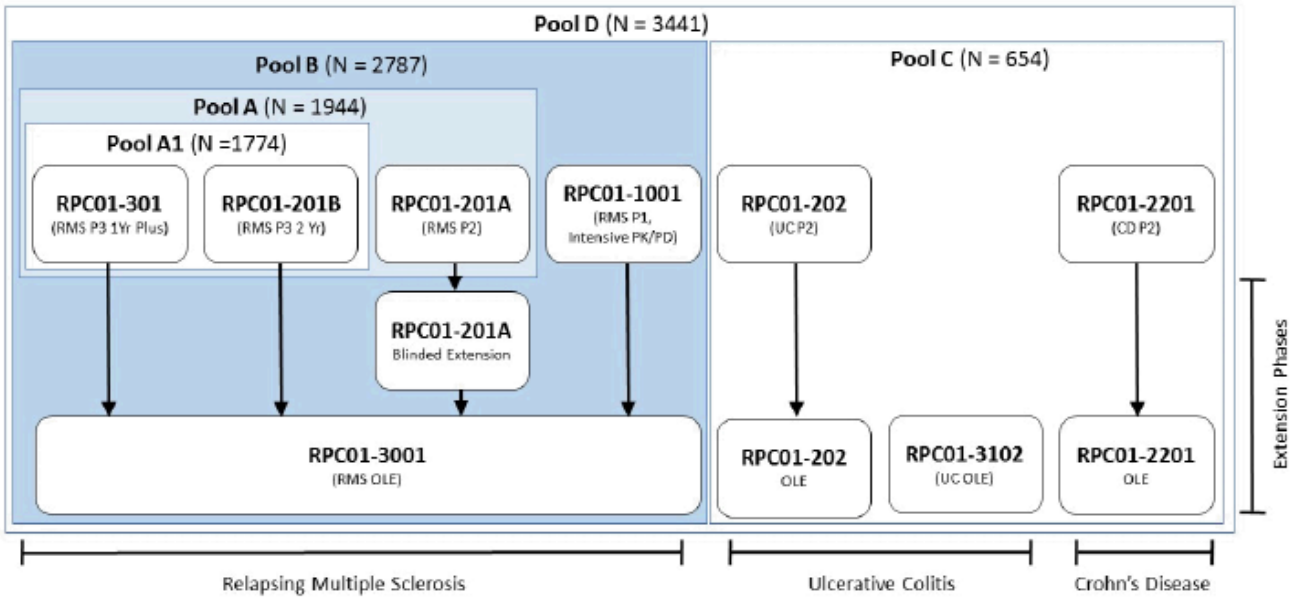
- Pool A includes all controlled RMS studies; all Phase 3 RMS controlled studies were grouped in Pool A1 while Pool A includes the placebo-controlled Phase 2 study in addition to the Phase 3 RMS studies. The Phase 3 RMS studies included an active comparator, IFN β-1a
- Pool B consisted of all RMS studies (the Phase 1 PK/PD study, the Phase 2 RMS study + blinded extension, the Phase 3 RMS controlled studies, and Phase 3 open-label extension study).
- Pool C consisted of all ulcerative colitis (UC) and Crohn's disease (CD) studies
- Pool D consisted of all RMS, UC, and CD studies (i.e., Pools B and C)
- Pool E consisted of Phase 1 studies in healthy volunteers or subjects with hepatic or renal impairment.

Table 3. Safety Analysis Pooling Strategy (based on Table 2, Mod 2.5 Overview of clinical safety, p 21)

Data Pool	Studies in Patient Data Pools
A1 (Active-controlled Phase 3 RMS Studies)	RPC01-201B, RPC01-301
A (Controlled RMS Phase 2 and 3 Studies)	Pool A1 + RPC01-201A
B (All RMS Studies)	Pool A + RPC01-201A (Blinded Extension), RPC01-1001, RPC01-3001
C (Completed IBD Phase 2 and Open-label Extension Studies)	RPC01-202 (Induction/ Maintenance Period), RPC01-202 (Open-label Period), RPC01-3102, RPC01-2201
D (All RMS + IBD Studies)	Pools B + C
E (Clinical Pharmacology)	RPCS 001, RPC01-102, RPC01-1901, RPC01-1902, RPC01-1903, RPC01-1904, RPC01-1905, RPC01-1906, RPC01-1907, RPC01-1908, RPC01-1909, RPC01-1910, RPC01-1911

IBD = inflammatory bowel disease; RMS = relapsing multiple sclerosis.

Figure 1. Safety Analysis Pooling Strategy; Numbers of Ozanimod-treated Subjects (based on Fig 4, Mod 2.5 Clinical Overview, p 54)



CD = Crohn's disease; OLE = open-label extension; P1 = Phase 1; P2 = Phase 2, P3 = Phase 3; PK = pharmacokinetics; RMS = relapsing multiple sclerosis; UC = ulcerative colitis; Yr = year.
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 ozainimod in an extension phase. Pool E (Clinical Pharmacology Studies) not shown.
Study RPC01-3101 (parent study to RPC01-3102) in an ongoing, blinded study not included in Pool C.
Study RPC01-2201 is an open-label study.

The number of subjects who were exposed to ozanimod across all patient studies (Pool D) was N= 3441 and included 3276 subjects treated with ozanimod 1 mg and 1098 subjects treated with ozanimod 0.5 mg. In this total population: 2765 subjects (84.4%) in the ozanimod 1 mg group and 938 subjects (85.4%) in the ozanimod 0.5 mg group were exposed to the drug for ≥ 12 months, and 1226 subjects (37.4%) in the ozanimod 1 mg group and 395 subjects (36.0%) in the ozanimod 0.5 mg group were exposed for ≥ 24 months.
In Pool A1 the Safety Population included 2659 subjects, ozanimod exposed subjects included 882 subjects who received at least 1 dose of ozanimod 1 mg, and 892 subjects who received at least 1 dose of ozanimod 0.5 mg, and 885 subjects who received at least 1 dose of IFN β-1a.
In Pool A1 ~ 92% of subjects were exposed to ozanimod or IFN β-1a for at least 12 months, and ~34% of subjects in Pool A1 were exposed to ozanimod or IFN β-1a for at least 24 months.

For the purpose of this review mainly patients in pools A and A1 with RMS and pool E healthy subjects will be analyzed.

4.2 Evaluation of abuse potential through all phases of clinical development

4.2.1 Abuse Potential Related Adverse Events in Phase 1 Studies

Clinical pharmacology studies were combined in Pool E and included 11 studies RPC01-102, RPC01-1901, RPC01-1902, RPC01-1903, RPC01-1904, RPC01-1905, RPC01-1906, RPC01-1907, RPC01-1908, RPC01-1909, and RPCS 001.

The total number of subjects with any exposure to ozanimod in these studies was N=496, 139 subjects had exposure longer than 22 days and 136 subjects had exposure to the therapeutic doses (0.5-1 mg) or higher (Table 4, below).
The abuse related AEs in this population were infrequent and included AEs such as somnolence, insomnia, abnormal dreams, euphoria, fatigue, decreased appetite, anxiety and energy increased and sleep abnormalities, see table 5.

Table 4. Extent of drug exposure in subjects in pool E (based on Table 9. Extent of Exposure Pool E, Safety Population, Summary of Clinical Safety, page 28)

Exposure Interval	Ozanimod < 0.5 mg (N = 151) n (%)	Ozanimod 0.5 mg (N = 38) n (%)	Ozanimod 1 mg (N = 194) n (%)	Ozanimod > 1 mg (N = 113) n (%)	Ozanimod Total (N = 496) n (%)
1 to 7 days	145 (96.0)	16 (42.1)	74 (38.1)	21 (18.6)	256 (51.6)
8 to 14 days	0	0	38 (19.6)	63 (55.8)	101 (20.4)
15 to 21 days	0	0	0	0	0
≥ 22 days	6 (4.0)	22 (57.9)	82 (42.3)	29 (25.7)	139 (28.0)

N = number randomized to treatment, n = number receiving treatment for exposure interval.
Source: ISS Table 4.6.

Table 5. Summary of abuse related adverse events for Phase 1 Studies, (based on Table 15.6 Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Pool E, ISS, page 2377, no placebo included).

Adverse Event PT	Ozanimod Doses <0.5 - >1 mg) (N=496) n (%)
Subjects with >1 TEAE	251 (50.6)
Neurological Disorders	
Somnolence	8 (1.6)
Psychiatric Disorders	
Insomnia	2 (0.4)
Abnormal dreams	3 (0.6)
Anxiety	2 (0.4)
Euphoria	2 (0.4)

Sleep disorder	1 (0.2)
Metabolism and nutrition disorders	
Decreased appetite	2 (0.4)
General Disorders	
Energy increased	1 (0.2)
Fatigue	5 (1.0)

4.2.2 Phase 2/3 Clinical Studies in Patients with RMS, Pool A and A1

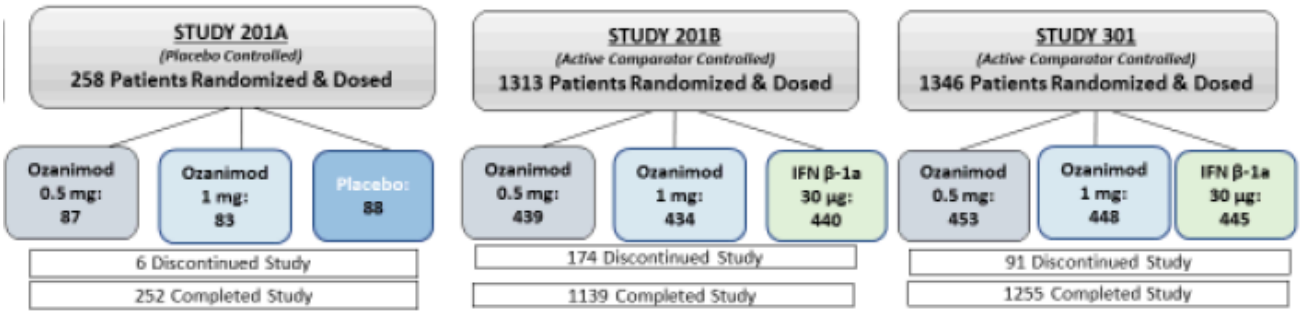
Pool A (N=1944 treated subjects only) includes following studies, see studies diagram Fig 2:

- RPC01- 201A: Duration: 24 months; Design: placebo-controlled study; Treatments: 258 (total): Ozanimod: 0.5 mg=87, 1 mg=83, Placebo-88;
- RPC01- 201B: Duration 24 months; Design: double-blind, double-dummy, active-controlled, parallel-group study; Treatments: 1313 (total): Ozanimod: 0.5 mg=439, 1 mg=434, IFN β-1a: 440
- RPC01-301: Duration 12+ months; Design: randomized, double-blind, double-dummy, active controlled, parallel group study; Treatments 1346 (total), Ozanimod: 0.5 mg=453, 1 mg=448, IFN β-1a: 445

Pool A1 (N=1774) includes studies:

- RPC01- 201B, duration 24 months
- RPC01-301, duration 12+ months

Figure 2. Diagram of Pool A studies general design, modified and based on Fig 2. Participant Flow Diagram for Ozanimod RMS Clinical Program (Pool B), Mod 2.7.4 Summary of clinical safety, p 23).



4.2.2.1 Adverse Events in Phase 2 and 3 in patients with RMS in pool A

The most frequently reported AEs in pool A in ozanimod treated patients at ≥ 1% higher incidence were: nasopharyngitis (reported in > 10%), headache, upper respiratory tract infection, alanine aminotransferase increased, influenza like illness, gamma-glutamyltransferase increased and orthostatic

hypotension, and urinary tract infection (based on Table 14.1 Incidence of Treatment-Emergent Adverse Events by Frequency Category Pool A, Safety Population, page 947, ISS-Tables).

4.2.2.2 Abuse potential related adverse events in Phase 2 and 3 in patients with RMS in pool A

Abuse-related adverse events were not frequent in ozanimod treated patients but higher than the placebo group and were generally similar to abuse AEs/neuropsychiatric AEs in the comparator group with interferon (IFN β -1a).

The most frequently reported abuse-related AEs included: depression and depressed mood, fatigue, anxiety disorders, insomnia and sleep disorders, somnolence, decreased appetite, irritability, memory impairments, there were 2 AEs of suicidality, one was suicidal ideation and one was SAE of suicidal attempt**.**

Table 6. Neuropsychiatric adverse events in study pool A including studies RPC01- 201A (with placebo) and studies RPC01- 201B, RPC01- 301 with comparator interferon (IFN β -1a). This table is based on Table 15.1. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Pool A, Safety Population, page 1056 in ISS-Tables.

Adverse Event PT	**Placebo N=88 n (%)**	**IFN β -1a 30 µg N=885 n (%)**	**Ozanimod All Doses (0.5 and 1 mg) N=1944 n (%)**
Psychiatric Disorders	6 (6.8)	78 (8.8)	153 (7.9)
Depression	1 (1.1)	25 (2.8)	49 (2.5)
Insomnia	4 (4.5)	20 (2.3)	46 (2.4)
Anxiety	0	17 (1.9)	31 (1.6)
Depressed mood	0	4 (0.5)	10 (0.5)
Anxiety disorder	0	5 (0.6)	7 (0.4)
Sleep disorder	0	1 (0.1)	4 (0.2)
Dyssomnia	0	2 (0.2)	3 (0.2)
Irritability	1 (1.1)	1 (0.1)	3 (0.2)
Panic disorder	0	1 (0.1)	2 (0.1)
Affective disorder	0	1 (0.1)	1 (<0.1)
Hallucinations	0	1 (0.1)	1 (<0.1)
Mental disorder	0	0	1 (<0.1)
Suicidal ideation	0	0	1 (<0.1)
Suicide attempt	0	0	1 (<0.1)
Nervous system disorders	21 (23.9)	140 (15.8)	323 (16.6)
Somnolence	1 (1.1)	3 (0.3)	12 (0.6)
Memory impairments	0	1 (0.1)	3 (0.2)
Disturbance in attention	1 (1.1)	4 (0.5)	3 (0.2)

Metabolism and nutrition disorders			
Decreased appetite	0	4 (0.4)	8 (0.4)
Increased appetite	0	2 (0.2)	3 (0.2)
General Disorders			
Fatigue	1 (1.1)	16 (1.8)	43 (2.2)
Asthenia	0	10 (1.1)	25 (1.3)

4.2.2.3 Safety Topics: Depression and Suicidal Ideation or Behavior

In the MS population depression is a relatively common AE and a prevalence of major depression was estimated to be 25.7%, as compared to 8.9% in the non-MS population by Patten et al., (2003) as noted by the Sponsor. However, the same author updated the estimates in 2017 showing that depressive disorders occurs in up to 50% of patients with multiple sclerosis (MS) and the prevalence estimates are generally 2-3-times higher than those of the general population (Patten et al., 2017).

There are some data which indicate that immunomodulatory treatments such as interferon alpha and beta increase risk of depression in MS patients (Goeb et al., 2005; Myint et al., 2009; Fragoso et al., 2010; Label Avonex July 2019). Fragoso et al., (2010) reported severe depression, suicide attempts, and ideation during the use of interferon beta by patients with multiple sclerosis. IFNs in general cause a number of neuropsychiatric adverse effects such as depression, irritability, anxiety, agitation, loss of appetite, fatigue, sleep disturbance, and impaired cognition (Pinto et al., 2016).
The analysis of the neuropsychiatric AEs for ozanimod indicated that though the mechanism of immunomodulatory mechanism is different than interferons, (i.e., through S1P receptors) AEs of depression, depressive disorder and anxiety are similar as in patients treated with interferon beta.

However, in spite of the well-known prevalence of depression and depressive disorders in MS patients no scales evaluating depression were administered in key safety and efficacy studies RPC01- 201A, RPC01- 201B, and RPC01-301, only C-SSRS Columbia-Suicide Severity Rating Scale was used.

The Sponsor states in Mod 2.5 Clinical Overview that S1P receptor modulators, such as ozanimod, are not known to increase the risk of depression.

However, we observed (Table 6), that MS patients treated with ozanimod had higher a incidence of depression relative to interferon and placebo. Depression and depressive disorders were higher than placebo in both interferon and ozanimod groups (3.3, 3.0 vs 1.1), and the rates for interferon were slightly higher than ozanimod (3.3 vs 3.0).
Therefore, we recommend that the label for ozanimod include a warning for depression similar to that present in IFN β-1a label (Avonex USPI, July 2019): Warnings and precautions "*Depression, Suicide, and Psychotic Disorders: advise patients to immediately report any symptoms of depression, suicidal ideation, and/or psychosis*;"

4.3 Overdose accidental and intentional

One patient (Subject (b) (6) reported an intentional overdose while being on treatment and receiving ozanimod 1 mg. The overdose occurred ~1 year after starting ozanimod 1 mg and the subject intentionally ingested over 100 pills of prescription medications which included glimepiride, lisinopril, and ozanimod. At 24 hours post-ingestion, the ozanimod concentration was 7 to 10 times higher than the average concentration at steady state, but no symptoms suggestive of overdose were reported.
Other events for this subject included depression(and a suicidal behavior). The subject was discharged from the hospital and the study drug was permanently discontinued.

There were two additional subjects reporting overdose with non-ozanimod products, one patient (subject (b) (6)) overdosed with pregabalin. The second patient (Subject (b) (6)) overdosed with zopiclone; the patient had pre-existing depression.

4.4 Diversion and Drug Accountability

The sponsor provided drug accountability data including bottle count (depot level) and capsule count (individual study subject level).
The bottle count assessment was performed for the completed Phase 2 and Phase 3 clinical studies (RPC01-201A, RPC01-201B, RPC01-301 and RPC01-202) and the completed Phase 1 study in RMS subjects (RPC01-1001).

The total amounts of unaccounted study drug was similar between ozanimod and placebo:
Study RPC01-201A: ozanimod 0.59% vs placebo 0.67%
Study RPC01-201B: ozanimod 3.49% vs placebo 3.95%
Study RPC01-301: ozanimod 0.85% vs placebo 0.62%
Study RPC01-202: ozanimod 17.91% vs placebo 18.49%
Study RPC01-1001: ozanimod 0.00%

The data presented below shows drug accontability breakdown by percentage of study drug not returned, which was designed to depict cases of potential diversion on individual level.

Drug Accountability in Phase 2 RMS Study RPC01-201A

This was a Phase 2, double-blind, randomized, placebo-controlled study which evaluated the efficacy and safety of two doses of ozanimod HCl (0.5 mg and 1 mg) administered orally for 24 weeks (core period). The study included a blinded extension period of Study RPC01-201A for subjects who completed the 24-week placebo-controlled core period. The summary of drug accountability is presented in table 5.

Table 7: Summary of Over-Compliance Rates in Study RPC01-201A (based on Table 4-21, page 70, ISS-4)

Period	Study Drug	Number of Subjects With Compliance Rate > X%				
		>110 - 120%	>120 - 130%	>130-140%	>140-150%	>150%
Core	Ozanimod (any dose)[a] (n = 258)	5	0	0	0	0
Extension	Ozanimod (any dose)[b] (n = 249)	0	0	0	0	1
Total (Combined Periods)	Ozanimod or Placebo	0	0	0	0	0

[a] There were no cases of over-compliance in the Placebo arm of the Core Period
[b] All subjects in Extension Period received ozanimod HCl (0.5 or 1 mg)

Drug Accountability in Phase 3 RMS Study RPC01-201B and RPC01-301

Studies RPC01-201B and RPC01-301 were randomized, double-blind, double-dummy, active-controlled studies examining safety and efficacy of two doses of ozanimod HCl (0.5 mg and 1 mg) orally vs IFN-1a (30 µg) intramuscularly (IM). Table 6 shows the drug accountability for both studies summarized.

Table 8. Summary of Drug Accountability for Studies RPC01-201B and RPC01-301 (based on Table 4-16, page 63, ISS-4).

Study Number	Study Drug	Number of Subjects with > X% unreturned ozanimod or placebo capsules (Number of unreturned caps/expected total number of capsules to be taken)				
		> 10 - 20%	> 20 - 30%	> 30 - 40%	> 40 - 50%	> 50%
RPC01-201B	Ozanimod Capsules[a] (n = 873)	12	5	0	0	4
	Placebo Capsules (n = 440)	4	2	0	1	2
RPC01-301	Ozanimod Capsules[a] (n = 901)	6	3	2	0	3
	Placebo Capsules (n = 445)	2	0	0	0	1

[a] Randomization was 1:1:1 for ozanimod HCl 0.5 mg, ozanimod HCl 1 mg and Avonex (ie, Placebo Ozanimod capsules)

The Sponsor also provided an analysis of "over-compliance," that is, for subjects who did not return more than 20% of their total dispensed study drug; these subjects were assessed to identify reasons for the missing study drug. The tables 8 and 9 show how many patients lost more drug in range of 10-20%, 20-30%, 30-40%, 40-50% and more than 50%.

The number of study drug lost (ozanimod tablets) in this "over-compliance" analysis ranged from 9 to 362 tablets of dispensed study drug (ISS. Table 4-17: Subjects With Over-Compliance of > 120%). In the majority of cases with higher numbers of drug missing (i.e., >200) the Sponsor identified "Data entry error"…In cases where study participants lost more than 100 study drug tablets the frequent reason was "Lost investigational product." In these cases the patient did not return to the study site or was discontinued.

Summarizing, when considering these incidents as a percentage of the number of subjects in the ozanimod or placebo groups, there was little or no difference in drug accountability. The additional data from the Sponsor on "over-compliance" may suggest that even though there was some "lost" study drug the numbers are not indicative of abuse-related drug diversion.

Drug Accountability in Phase 1 RMS Study RPC01-1001

Study # RPC01-1001 was a phase 1 randomized, open-label, multiple-dose, 12-week study in 24 RMS subjects. Table 7 provides the summary of drug accountability, which shows minimal loss of the drug.

Table 9: Summary of Drug Accountability for the study # RPC01-1001, based on table 4-19, page 68, ISS-4.

Study Drug	Number of Subjects with ≥ X% of unreturned ozanimod capsules (Number of unreturned caps/expected total # capsules to be taken)				
	10 - 20%	20 - 30%	30 - 40%	40-50%	≥ 50%
Ozanimod (any dose)[a] (n = 24)	1	2	0	0	0

[a] All subjects in study received ozanimod HCl 0.5 or 1 mg and all cases occurred during fixed dose escalation period

Drug Accountability in Phase 1 Clinical Pharmacology Studies
The Sponsor explained that subject-level drug accountability was not evaluated in the clinical pharmacology studies because drug administration in these studies was performed in-clinic by site staff or site pharmacy, thus, there was no potential for unreturned study drug by the subject due to abuse or diversion.

Conclusions from all clinical studies
The drug accountability data for ozanimod shows increased "drug loss" in some studies (e.g., study RPC01-301) however, the numbers are too low to suggest abuse-related drug diversion.

4.5 Dependence, Withdrawal, and Rebound

The Sponsor did not systematically evaluate dependence, withdrawal and rebound even though it is well known that immunomodulatory drugs with similar pharmacological mechanisms of action namely (e.g., Fingolimod (GILENYA)) cause severe, sometimes life-threatening withdrawal symptom of rebound in MS patients, accompanied by drastic increases in new lesions or enhancing lesions seen on MRI and increased physical disabilities (Havla et al., 2012; La Mantia et al., 2014; Faissner et al., 2015; Hatcher

et al., 2016; Salem et al., 2016; Czlonkowska et al., 2017; Gunduz et al., 2017; Evangelopoulos et al., 2018; Barry et al., 2019**).**

4.5.1 Summary of the Sponsor provided data on dependence and withdrawal

- The Sponsor obtained data for analyses of dependence and withdrawal from the RMS Parent Studies for RPC01- 3001 (Phase 2 [RPC01-201A and RPC01-201A Extension] and the active-controlled Phase 3 [RPC01-201B and RPC01-301]), N=2494

- Patients included in the analysis of dependence were treated with ozanimod for at least three months. In this group, 127 patients had at least one on-study drug vital sign assessment and one post-treatment discontinuation assessment, and 121 subjects with a last on-study drug C-SSRS assessment and a post-treatment discontinuation assessment.

- For the analysis of Adverse Events related to Drug Dependence and Withdrawal in the group of 172 subjects from the pooled Phase 2 and 3 RMS, the Sponsor used only terms: 1) associated with physical dependence and withdrawal, 2) AEs associated with the potential for abuse; 3) psychiatric AEs. The Sponsor identified after the last day of treatment onlythree subjects in this population.

    - One subject with a history of anxiety and mild anxiety during the study had AE of anxiety during the withdrawal period which likely was more severe as the subject was treated with lorazepam and aripiprazole for this AE, the description suggest withdrawal anxiety.

    - A second subject reported insomnia and dyssomnia during the study after drug discontinuation.

    - A third subject had a history of untreated depression and during the interval period between parent study and OLE developed worsening of depression, again typical withdrawal symptom. The patient had to be treated with sertraline and lorazepam for this event, which indicates increased post-withdrawal depression.

- Vital signs were measured only in 127and in different subjects at inconsistent and different time points for different patients. Thus, the presented data cannot be considered valid or representative for the population.

- Columbia-Suicide Severity Rating Scale (C-SSRS) was administered to 121 patients during the drug discontinuation period and in the same, inconsistent manneras vital signs.

The Sponsor’s provides the summary of the obtained dependence and withdrawal data (based on Evaluation of Dependence and Withdrawal of Ozanimod, data cut-off 20 Sep 2019, page 11/59):

3. STUDY RPC01-3001 DISCONTINUATION POPULATION

Of the 2494 subjects who were enrolled in Study RPC01-3001, there were 290 subjects treated with ozanimod 1 mg for approximately 3 months who discontinued treatment as of the data cut-off date of 20 Sep 2019. Of these:

- 126 subjects had a vital sign assessment at post-treatment Day 28
- 123 subjects had a C-SSRS assessment at post-treatment Day 28
- 8 subjects had a PWC-20 post-treatment assessment
- 8 subjects had a HADS post-treatment assessment
- 9 subjects had an ESS post-treatment assessment
- 3 subjects had all scales (C-SSRS, PWC-20, HADS and ESS) at all post-treatment follow-up visits up to Day 21

Additional evaluation of dependence and withdrawal was performed at the request of CSS (Meeting minutes Nov 9 2018) using Physician's Withdrawal Checklist (PWC-20), Hospital Anxiety and Depression Scale (HADS), and the Epworth Sleepiness Scale (ESS). However, this analysis was performed in nine patients instead of 80 as CSS requested.

The Sponsor further states:

"*There were 123 subjects who had a posttreatment C-SSRS assessment, 8 subjects had a post-treatment PWC-20 assessment, 8 subjects had a post-treatment HADS assessment, 9 subjects had a post-treatment ESS assessment, and 3 subjects had all scales (C-SSRS, PWC-20, HADS and ESS) at all post-treatment follow-up visits up to Day 21.*"

However, even in this very small sample, approximately half of the withdrawal scores are missing, including a withdrawal baseline on the last day on treatment. Two samples of the withdrawal data presented by the Sponsor, below.

Table 10. Example of withdrawal scores for Physician's Withdrawal Checklist (based on Table 6: Physician's Withdrawal Checklist (PWC-20) for individual subjects by visit (Discontinuation Population, Study RPC01-3001, from Dependence evaluation, page 20/59). The absence of any withdrawal data is noted for several patients.

Subject ID	LDOT (Last Assessment on Treatment)	Date of Last Dose in Study	EOT Assessment (Score / Date)	PWC-20 Score on Days post EOT Visit (Score / Date)					
				Day 1	Day 4	Day 7	Day 14	Day 21	Day 90
(b) (6)	-	(b) (6)	6 / (b) (6)	-	-	-	-	-	13 / (b) (6)
	-		11 / (b) (6)	-	-	-	-	-	-
	-		11 / (b) (6)	11 /	11 /	11 /	10 /	7 / (b) (6)	NA
	-		23 / (b) (6)	-	-	-	-	-	-

Table 9. The withdrawal data for one of eight subjects # Subject (b) (6) with the "thorough" evaluation of withdrawal (from Dependence evaluation, page 49). The absence of withdrawal data is noted.

	LDOT	End of Treatment	Day 1	Day 4	Day 7	Day 14	Day 21	Day 90
C-SSRS	0, No SIB	0, No SIB	-	-	-	-	-	-
PWC-20	-	11	-	-	-	-	-	-
HADS (Anxiety)	-	4	-	-	-	-	-	-
HADS (Depression)	-	1	-	-	-	-	-	-
ESS	-	6	-	-	-	-	-	-
Vitals								
Temp (C)	36.6	36.5	-	-	-	-	-	-
SBP (mmHg)	140	128	-	-	-	-	-	-
DBP (mmHg)	90	85	-	-	-	-	-	-
HR (bpm)	59	56	-	-	-	-	-	-

"-" = data not collected; bpm = beats per minute; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = diastolic blood pressure; ESS = Epworth Sleepiness Scale; HADS = Hospital Anxiety and Depression Scale; LDOT = last day on treatment; mm Hg = millimeters of mercury; PWC-20 = Physician's Withdrawal Checklist; SBP = systolic blood pressure; SIB = self-injurious behavior without suicidal intent.
LDOT is the last on-study drug defined as the last non-missing value prior to or at the last dose of ozanimod.
End of treatment defined as the early termination visit and after subjects' last exposure date.

4.5.2 Rebound Evaluation

Defintion
Rebound is an aspect of withdrawal and dependence. Rebound is a rapid return of the patient's original symptoms after abrupt drug discontinuation at a greater intensity than before the treatment.

Another definition addressing rebound in MS patient:

"*When this disease activity is disproportionate to the pattern observed prior to treatment initiation, patients are said to have experienced* ***rebound.***" Barry et al., 2019.

The Sponsor performed only a post hoc analysis of annualized relapse rate ARR in subjects who discontinued study drug to assess the potential for disease rebound following discontinuation of treatment in the the active-controlled Phase 3 RMS studies which included a 28-day posttreatment follow-up visit (Mod 2.7.3 Summary of Clinical Efficacy, p 125).

The Sponsor identified six relapses during this period: 1 subject in the ozanimod 1 mg dose group, 1 subject in the ozanimod 0.5 mg dose group, and 4 subjects in the IFN β-1a group.

The patient in the ozanimod 1 mg group discontinued study drug prematurely due to an AE of irritability and reported a relapse 19 days after stopping ozanimod with an increase in EDSS score from 4.5 (at the early termination visit) to 6.0, although EDSS baseline, that is pre-treatment score is not provided. Information on second patient experiencing relapse was not found.

Of note also is that analysis of annualized relapse rate (ARR) is not measure of rebound.

Reviewer's Comments and Conclusions

The Sponsor's description of the "withdrawal evaluation" and the methods the Sponsor used to obtain the data renders the dependence and withdrawal evaluation invalid and unacceptable and essentially meaningless because:
1) patients were not systematically evaluated throughout the drug discontinuation period
2) the relevant scales to evaluatewithdrawal symptoms such as depression, anxiety, and sleep scales were not used or if so, only sporadically in the final sample of nine MS patients.
3) to detect withdrawal AEs the Sponsor used only abuse, dependence, withdrawal terms and other Psychiatric Disorders SOC instead of analyzing all AEs which occurred during the withdrawal period.
4) vital signs were obtained in a nonsystematic manner, in different patients, and in different post-withdrawal periods
5) Columbia-Suicide Severity Rating Scale (C-SSRS) scores were obtained also in a nonsystematic way, in different patients in different post-withdrawal periods.
6) In the small sample of nine patients who the Sponsor claimed had administered appropriate scales, six have missing scores and fivedo not have withdrawal baseline scores, that is last day on treatment.

The label should make clear that a systematic clinical evaluation of dependence was not conducted.

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/s/

ALICJA LERNER
02/19/2020 04:14:45 PM

JOVITA F RANDALL-THOMPSON
02/20/2020 07:00:36 AM

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02/20/2020 02:54:33 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 14, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 209899
Product Name and Strength:	Zeposia (ozanimod) capsule, 0.23 mg, 0.46 mg, 0.92 mg
Applicant/Sponsor Name:	Celgene International II Sarl (Celgene)
OSE RCM #:	2018-48-2
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Celgene submitted revised container labels and carton labeling, received on February 11, 2020, for Zeposia. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for Zeposia (Appendix B) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 ASSESSMENT

Celgene implemented all of our previous recommendations. We note, Celgene also proposes three additional changes to the revised labels and labeling (Appendix A), which we evaluated and find acceptable from a medication safety perspective. However, we identified the word (b) (4) was reintroduced on the sample kit (NDA 59572-0890-97). (b) (4) do not meet the regulatory definition of a drug sample because they are intended for sale.[b]

[a] Morris, C. Label and Labeling Review for Zeposia (NDA 209899). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 23. RCM No.: 2018-48-1.
[b] See the final rule "Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Policies" (December 3, 1999, 64 FR 67720 at 67742), available at http://www.gpo.gov/fdsys/pkg/FR-1999-12-03/pdf/99-30954.pdf.

3 CONCLUSION

The revised sample kit carton labeling is unacceptable from a medication error perspective. We provide recommendations for Celgene in Section 3.1.

3.1 RECOMMENDATIONS FOR CELGENE

We recommend the following is implemented prior to the approval of this NDA:

1. We note, the use of the statement (b) (4) on the sample kit carton labeling (NDC 59572-0890-97). Remove the word (b) (4) from the sample kit carton labeling.

11 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

JOHN C MORRIS
02/14/2020 02:31:51 PM

BRIANA B RIDER
02/14/2020 02:54:14 PM

Clinical Inspection Summary

Date	02/05/2020
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Susan Daugherty, Pharm.D., Regulatory Project Manager Lawrence Rodichok, M.D., Clinical Reviewer Paul Lee, M.D., Clinical Team Leader Billy Dunn, M.D., Division Director Division of Neurology Products
NDA #	209899
Applicant	Celgene International II Sarl
Drug	Ozanimod
NME	Yes
Therapeutic Classification	Selective sphingosine 1-phosphate (S1P) 1 and 5 receptor modulator
Proposed Indication	Treatment of patients with relapsing forms of multiple sclerosis (MS)
Consultation Request Date	May 21, 2019
Summary Goal Date	February 14, 2020
Action Goal Date	March 25, 2020
PDUFA Date	March 25, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Dihenia, Likhachev, Nehrych and Zielinski were inspected in support of this New Drug Application. Based on the results of these inspection, the study (Protocol RECRPC01301) appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Celgene submitted this NDA to support the use of ozanimod for the treatment of patients with relapsing forms of multiple sclerosis (MS).

Clinical inspections were conducted for the following protocol in support of this application:

Protocol RECRPC01301

Title: "A Phase 3, Multi-center, Randomized, Double-blind, Double-dummy, Active-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients"

The primary study objective was to assess the superiority of ozanimod compared to IFN β-1a (Avonex) and to characterize the safety profile of ozanimod relative to IFN β-1a in subjects

with relapsing MS (RMS).

This was a randomized, double-blind, active controlled, parallel group study assessing the efficacy and safety of ozanimod (RPC1063) administered orally to subjects with RMS.

The primary efficacy endpoint was annualized relapse rate (ARR) during the treatment period. A relapse was defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days (a subjective definition). The new or worsening neurological symptoms also must be accompanied by objective neurological worsening, based on examination by a blinded evaluator, consistent with an increase of at least half a point on the EDSS, or 2 points on one of the appropriate Functional System (FS) scores, or 1 point on two or more of the appropriate FS scores.

The key secondary efficacy endpoints were as follows:

- The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months
- The number of gadolinium-enhancing (GdE) brain MRI lesions at Month 12

These key secondary efficacy endpoints were verified by comparing the certified copies of MRI data from the MRI reader in the central office to the MRI parameters submitted by the sponsor.

Rationale for Site Selection

Four Clinical Investigators (CIs) were identified for inspections mostly due to large enrollment and inspection history. Dr. Zielinski was inspected in July 2012 (VAI: failure to adhere to protocol). Dr. Nehrych was inspected in September 2010 (NAI). Two other CIs did not have history of FDA inspections.

III. RESULTS

1. Site #138
Bhupesh Dihenia, M.D.
3815 23rd Street
Lubbock, TX 79410
Inspection Dates: 09/16/2019 to 09/18/2019

At this site, 12 subjects were screened, 11 were enrolled, and 10 subjects completed the study. One subject withdrew consent. The subject records of all 12 screened subjects were reviewed. These records included, but were not limited to, informed consent forms, the medical histories, case report form (CRF) for each visit, the audit trail for the changes made to the CRFs, concomitant medications, the primary and the key secondary efficacy endpoint and the adverse events. The review also included the drug accountability/disposition records for the study, the monitoring records, and the site visit logs.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. Subject (b) (6) (in ozanimod 1mg group) had unspecified elevated alanine transaminase (ALT, 3 times the upper limit) at Screening, which was an exclusion criterion. However, the subject was randomized and dosed ozanimod 1 mg before the result of the repeat ALT could be obtained. The site reported this protocol deviation to the sponsor but was

advised by the sponsor to keep the subject at the study and monitor ALT. The site monitored the subject, who was able to complete the study.

2. **Site #901**
   Sergey Likhachev, M.D.
   24 F. Skorina Str.
   Minsk, 220114
   Belarus
   Inspection Dates: 09/23/2019 to 09/26/2019

At this site, 55 subjects were screened, 46 were enrolled, and 43 subjects completed the study. Three subjects discontinued the study. Subject (b) (6) (in ozanimod 0.5mg group) was withdrawn due to macular edema after blunt trauma to the eye. Subject (b) (6) (in IFN ß-1a 30 µg group) was withdrawn due to a cerebral infarction. Subject (b) (6) (in IFN ß-1a 30 µg group) withdrew consent at Month six.

An audit of the records of the 20 out of 46 enrolled subjects was conducted. These records included, but were not limited to, Independent Review Board (IRB) approvals, CV and training records, delegation of authority logs, financial disclosures, drug accountability, informed consent forms, study eligibility criteria, medical histories, physical examinations, progress notes, laboratory reports, electrocardiogram reports, concomitant medications, adverse events, protocol deviations and the primary and the key secondary data (i.e., EDSS scores, T2 lesions, and Gd enhancing lesions for all subjects were reviewed).

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

3. **Site #812**
   Tetiana Nehrych, M.D.
   7 Chernihivska Vul.
   Lviv, 79010
   Ukraine
   Inspection Dates: 09/16/2019 to 09/20/2019

At this site, 52 subjects were screened, 46 were enrolled, and 44 subjects completed the study. Two subjects discontinued the study. Subject (b) (6) (in IFN ß-1a 30 µg group) was discontinued by the PI due to elevated liver enzymes and a questionable kidney lesion. All the adverse events for this subject appeared to have been properly reported. This subject refused follow-up care due to the death of her husband. Subject (b) (6) (in ozanimod 0.5mg group) withdrew consent after Visit 1.

A review of the records of 20 out of 46 enrolled subjects was conducted. These records included, but were not limited to, informed consent, study eligibility, protocol deviations, the primary and the secondary endpoints, concomitant medications, and adverse events.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

4. **Site #426**
   Tomasz Zielinski, M.D.
   Jaworowa 34/1
   Katowice, Slaskie 40-650
   Poland
   Inspection Dates: 09/02/2019 to 09/06/2019

At this site, 27 subjects were screened, 26 were enrolled, and 22 subjects completed the study. Subject (b) (6) (in ozanimod 0.5mg group) and Subject (b) (6) (in IFN ß-1a 30 µg group) discontinued due to MS relapse. Subject (b) (6) (in ozanimod 0.5mg group) withdrew consent. Subject (b) (6) (in IFN ß-1a 30 µg group) discontinued due to flu-like symptoms. The records of 20 out of 26 enrolled subjects were reviewed. These recorded included, but were not limited to, study training records, delegation logs, FDA 1572, financial disclosures, and drug accountability, informed consent forms, study eligibility, medical histories, physical examinations, progress notes, concomitant medications, the primary endpoint data and the MRI lesions, adverse events, and protocol deviations.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. The inspector discussed with the clinical investigator that one serious adverse event of abscess of a surgical wound was reported 2 months late. This protocol deviation was reported to the sponsor and the FDA.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
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cc:
Central Doc. Rm. NDA 209899
DPP /Project Manager/Susan Daugherty
DPP/Division Director/Billy Dunn
DPP/Medical Officer/Lawrence Rodichok
DPP/Clinical Team Leader/Paul Lee
OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 23, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 209899
Product Name and Strength:	Zeposia (ozanimod) capsule, 0.23 mg, 0.46 mg, 0.92 mg
Applicant/Sponsor Name:	Celgene International II Sarl (Celgene)
OSE RCM #:	2018-48-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Celgene submitted revised container labels and carton labeling, received on January 3, 2020, for Zeposia. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for Zeposia (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 ASSESSMENT

Table 1. Identified Issues and Recommendations for Celgene (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Trade and Sample Container Labels and Carton Labeling (All NDC)			
1.	The prominence of the established name statement [that is, (ozanimod) capsules] can	As currently presented, the established name statement is presented in (b) (4) font, which may not provide adequate	We recommend you improve the contrast between the established name statement and the background.

[a] Morris, C. Label and Labeling Review for Zeposia (NDA 209899). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 16. RCM No.: 2018-48.

Table 1. Identified Issues and Recommendations for Celgene (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	be improved.	contrast between it and the (b) (4) background on some of the panels of the carton labeling and container labels.	
2.	The patient labeling will include a medication guide (MG); however, the MG statement is not present on the Principal Display Panel (PDP).	Not in accordance with 21 CFR 208.24(d).	Add the MG statement to the PDP. The statement should state how the MG is provided (for example, enclosed, accompanying). For example: Dispense the enclosed medication guide to each patient.
Starter Pack (NDC 59572-810-07, (b) (4), 59572-810-97)			
	The net quantity statement is expressed as follows: (b) (4)	The net quantity statement on the 7-count starter packs and 37-count starter kits are not expressed consistently, which may lead to confusion. Also, the symbol "-" may be misinterpreted.	Consider revising the net quantity statement to read: "This pack contains 7 capsules for dosing over 7 days. The contents of this pack are as follows:" or a similar statement. Also, consider alternatives ways to express the quantity. For example: 0.23 mg capsules (quantity: 4) Four 0.23 mg capsules Four capsules (0.23 mg per capsule) Lastly, ensure the format for expressing the net quantity statement on the 7-count starter packs and 37-count starter kits are consistent.
30-count bottles: **Trade [Saleable (NDC 59572-820-30), Non-saleable (** (b) (4) **Sample (NDC 59572-0820-97)**			
1.	The strength statement	The strength statement	Ensure the proprietary and

Table 1. Identified Issues and Recommendations for Celgene (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	remains more prominent than the established name [that is, (ozanimod) capsules] and has the same amount of prominence as the proprietary name on the principal display panel (PDP).	competes in prominence with the proprietary and established names on the PDP.	established names appear more prominent than the strength statement on the PDP. To accomplish this, consider relocating the graphic that appears in front of the proprietary name to allow for the font size of the proprietary and established names to be increased, decrease the size of the strength statement, or address this concern by other means.
Trade Starter Kit (NDC 59572-0890-91) Sample Kit (NDC 59572-0890-97)			
1.	The net quantity statement is expressed as follows: (b) (4)	The net quantity statement on the 37-count starter kits and 7-count starter packs are not expressed consistently, which may lead to confusion. Also, it may be unclear that the number in parentheses (for example, (4) 0.23 mg capsules) is the quantity.	Consider revising the net quantity statement to read: "This Starter Kit contains 37 capsules for titration over 7 days up to the prescribed maintenance dose of one 0.92 mg capsule taken once daily. The contents of the Starter Kit, which are not to be sold separately, are as follows:" or a similar statement. Also, consider alternatives ways to express the quantity. For example: 0.23 mg capsules (quantity: 4) Four 0.23 mg capsules Four capsules (0.23 mg per capsule) Lastly, ensure the format for expressing the net quantity statement on the 37-count starter kits and 7-count starter packs are consistent.

3 CONCLUSION

The revised carton labeling and container labels are unacceptable from a medication error perspective. We provide recommendations for Celgene in Table 1.

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BRIANA B RIDER
01/23/2020 07:39:21 PM

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Name: (b) (4)
City, Country:
EI Dates:
FDA Participants: Byungja E. Marciante, National BIMO Expert, ORA/OBIMO/DBIMO I
Charles Bonapace, Pharmacologist, CDER/OTS/OSIS
Zhou Chen, Pharmacologist, CDER/OTS/OSIS
Mark J Seaton, Regulatory Officer, CDER/OTS/OSIS

Inspection Summary

This was a FY2019 GLP surveillance inspection. A five-item Form FDA 483 was issued to management at the close-out of this inspection for deficiencies related to personnel training, archives, and SOP deviations. Four items were discussed with management, related to inadequate response to system monitor alarms, the use of "study director directives", SOPs not reflecting current practice, and SOPs not defining test article disposition. The final classification is voluntary action indicated (VAI). After review of the establishment inspection report, the reviewers conclude that the data from the audited studies are reliable for Agency review.

Studies Audited During This Inspection

Study No.:	AF00PS.2G3R (b) (4). RP112273
Study Title:	28-Day Repeated Dose Toxicity and Toxicokinetic Study in CByB6F1 Mice
Study Initiation Date:	8/11/2017
Final Report Date:	10/15/2018
Study Director:	Marie E. McKeon
Test Article:	RP112273
Relevant FDA Application:	NDA 209899
Review Division:	DNP

Study No.:	AF26AJ.502ICH (b) (4)
Study Title:	Bacterial Reverse Mutation Assay
Study Initiation Date:	4/13/2018
Final Report Date:	7/18/2018
Study Director:	Emily Dakoulas
Test Article:	MD9150004
Relevant FDA Application:	(b) (4)
Review Division:	DNP

Background: (b) (4) offers contract research services in the area of genetic toxicology and analytical services. Those are the only GLP compliant activities relevant to CDER. Since the previous inspection, (b) (4) has stopped offering 6-month carcinogenicity studies utilizing the rasH2 transgenic mouse as well as 28-day dose range finding studies. Likewise, (b) (4) no longer offers histopathology and clinical pathology services.

Prior Inspection: The previous inspection of this nonclinical laboratory was completed on (b) (4) and was classified as NAI. Form FDA 483, Inspectional Observations, was not issued.

Current Inspection: The current inspection was a FY2019 GLP surveillance inspection conducted from [redacted]. The inspection covered the conduct and oversight of various GLP studies. The inspection also covered the firm's compliance with the FD&C Act, applicable compliance programs and regulations. During the inspection, the following areas were given coverage: Quality Assurance Unit, archives, training, vivarium, test article storage areas, cage washing area, feed / bedding storage, analytical laboratories, incubators, balances, weights, and animal housing.

At the conclusion of the current inspection, a close-out meeting was held with firm's management. During this meeting, a five item Form FDA 483, Inspectional Observations was issued to the firm. Four items were discussed with management. The observations (in bold type below) cited on Form FDA 483 and items discussed with management, a summary of the firm's written responses to the observations and discussion items dated [redacted] respectively, and my evaluation of the firm's responses follow.

OBSERVATION 1:

[redacted]

Firm's Response:
The firm acknowledged the observation. [redacted]

OSIS Evaluation:
The firm's response is adequate. [redacted]

OBSERVATION 2:

[redacted]

Firm's Response:
The firm acknowledged the observation [redacted]

OSIS Evaluation:
The firm's response is adequate. [redacted]

(b) (4)

OBSERVATION 3:

(b) (4)

Firm's Response:
The firm acknowledged the observation (b) (4) (b) (4).

OSIS Evaluation:
The firm's response is adequate (b) (4) (b) (4)

OBSERVATION 4:

(b) (4)

Firm's Response:
The firm acknowledged the observation (b) (4) (b) (4)

OSIS Evaluation:
The firm's response is adequate. (b) (4) (b) (4)

OBSERVATION 5:

(b) (4)

Firm's Response:
The firm acknowledged the observation. (b) (4) (b) (4)

OSIS Evaluation:
The firm's response is adequate. [redacted]

Discussion item 1
[redacted]

Discussion item 4
[redacted]

Firm's Responses:
[redacted]

OSIS Evaluation:
The firm's responses to the discussion items are adequate, [redacted]

Recommendations:

- The data from studies AF00PS.2G3R [redacted] RP112273 and AF26AJ.502ICH [redacted] are reliable, and the reviewers recommend that the data be accepted for Agency review.
- Based on the GLP workload at the firm, the next surveillance inspection should be conducted in four years (FY2023).
- Recommended HQ classification: Voluntary Action Indicated (VAI)

Zhou Chen, M.D., Ph.D.
Pharmacologist

Mark J. Seaton, Ph.D., DABT
Regulatory Officer

Inspection Type: _X_ Routine Surveillance ____ Directed
FDA-483 Issued: ____ No _X_ Yes
Letter Issued: __ None _X_ Inspection Close-Out Letter

Date Assigned: 4/4/2019
Date EIR Received by Reviewer: 10/9/2019
1st Draft Review Completed: 10/28/2019

Inspection Conclusion: VAI
District Decision: VAI
Final HQ Classification: VAI

cc: via DARRTS

CDER-OSIS-GLP@fda.hhs.gov
OSIS/Kassim/Fenty-Stewart/Johnson
OSIS/DNDBE/Bonapace/ChenZ/Seaton
DNP/Christopher Toscano/Non-clinical Reviewer (NDA 209899)
DNP/Susan Daugherty/Regulatory Project Manager (NDA 209899)
DNP/Edward Fisher/Non-clinical Reviewer [redacted] (b) (4)
DNP/Stephanie Parncutt/Regulatory Project Manager [redacted] (b) (4)
ORA/OBIMO/ Byungja E. Marciante
Draft: MJS 10/28/2019
Edits: ZC 10/30/2019; CB 11/1/2019
OSIS File: GLP0984
ECMS: Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/GLP Program/[redacted] (b) (4) USA /FY2019: 6-AUG-2019/Post-Inspection Folder/EIR & EIR Review

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/s/

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CHARLES R BONAPACE
11/06/2019 06:55:28 AM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 209899
Submission Number	012
Submission Date	3/26/2019
Date Consult Received	3/26/2019
Clinical Division	DNP

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

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review dated 03/12/2018 (NDA 209899) and 01/29/2014 (IND 109159) in DARRTS;
- Population PK analysis of ozanimod and its metabolite (Submission 0012);
- Proposed label (Submission 0012); and
- Study rpc-01-1914 protocol, study report, and QTc analysis (Submission 0012).

1 SUMMARY

No relevant QTc prolongation effect of ozanimod's major metabolite, CC112273 (previously labeled as RP112273), was detected in this QT assessment.

The effect of CC112273 was evaluated in study RPC01-1914. Study RPC01-1914 was a double-blind, placebo-controlled, parallel-arm study in 56 subjects; 28 subjects received ozanimod monotherapy. The highest dose evaluated was ozanimod 1.84 mg once daily (QD), which covers 1.8-times the predicted therapeutic exposure and 1.2-times the highest clinically relevant exposure of CC112273 at the proposed therapeutic dose (0.92 mg QD). The data from study RPC01-1914 was analyzed using exposure-response analysis as the primary analysis, which did not suggest that CC112273 is associated with significant QTc prolonging effect – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (section 5.1), central tendency analysis (section 0), categorical analysis (section 4.4), and previous QT-IRT reviews of ozanimod.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration (Metabolite)	ΔΔ (ms)	90% CI (ms)
QTc	Ozanimod 0.23 mg QD	70.9 pg/mL	0.5	(-1.7, 2.8)
QTc	Ozanimod 0.46 mg QD	332.8 pg/mL	0.5	(-1.7, 2.7)
QTc	Ozanimod 0.92 mg QD	750.5 pg/mL	0.5	(-1.7, 2.7)
QTc	Ozanimod 1.84 mg QD	6051.7 pg/mL	0.2	(-3.0, 3.4)

Previously the QT-IRT 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 (IND 109159, dated 01/29/2014 in DARRTS). 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. Based on totality of evidence, the QT-IRT proposed to include the negative findings and the limitations of the TQT study, and to communicate the categorical analysis results from Phase 3 trials in the product label (NDA 209899, dated 03/12/2018 in DARRTS).

Based on the sponsor's simulations from their population PK model, the predicted $C_{max,ss}$ for 0.92 mg QD is 7937 pmol/L (3499.6 pg/mL). Gemfibrozil, an inhibitor of CYP2C8, increased $AUC_{0\text{-last}}$ of metabolite CC112273 by 47%. Using the predicted $C_{max,ss}$ for 0.92 mg QD of 3499.6 pg/mL, the metabolite CC112273 exposure is expected to increase to 5144.4 pg/mL. This worst-case scenario for CC112273 exposure is lower than the mean CC112273 exposures observed in Study RPC01-1914 (6051.7 pg/mL) at the supra therapeutic dose of 1.84 mg ozanimod on Day 28 by a margin of 17%.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable

2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0012. Our changes are highlighted (addition, ~~deletion~~). This is a suggestion only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

Reviewer's comments: *In general we agree with the sponsor's proposed label language in section 12.2.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

This QT assessment is based on data collected from Study RPC01-1914. Study RPC01-1914 is a Phase 1, randomized, double-blind, placebo-controlled, parallel-arm study in which 56 subjects were randomized such that 28 subjects received ozanimod once daily (QD) and 28 received matching placebo from Days 1 to 30. The subjects randomized to

ozanimod received 0.23 mg QD on Days 1 to 4, 0.46 mg QD on Days 5 to 7, 0.92 mg QD on Days 8 to 10, and 1.84 mg QD on Day 11 until Day 30 (or early termination). The primary analysis is concentration-QTc analysis. Refer to Appendix 5.1 for a detailed review of the sponsor's QT assessment plan.

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

The sponsor presented exposure-response analysis as the primary analysis. The sponsor provided by time exploratory analysis of QTcP. FDA reviewer performed by time analysis for QTcF. Both sponsor analysis and FDA analysis show QT prolongation. Please see section 0 for additional details.

3.2.1.1 Assay Sensitivity

The sponsor did not propose assay sensitivity methods.

3.2.1.1.1 QT bias assessment

Not applicable

3.2.2 Categorical Analysis

Sponsor did not provide the categorical analysis results. FDA reviewer performed standard categorical analysis. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

No deaths or SAEs were reported. One subject in the placebo group experienced a TEAE resulting in discontinuation of the study.

3.2.4 Exposure-Response Analysis

The sponsor's final model differs from the reviewer's final model.

The sponsor assessed 15 different C-QTc modeling scenarios where 3 analytes (ozanimod, CC112273 or CC1084037) were each assessed as the independent variable in 5 models (base model without concentration effect, linear without inter-individual variability [IIV] on slope, linear with IIV on slope, E_{max}, and power model). The sponsor utilized the population correction for QT values (QTcP).

The sponsor reported that the E_{max} model was considered the best modeling approach. However, magnitude of the maximum effect was small (E_{max} < 2 ms) and was estimated with low precision (standard error ≥ estimate). Inclusion of more than one analyte in a single model resulted in physiologically implausible parameter estimates (e.g. negative E_{max} values) that was likely due to correlation among the analytes.

Overall, three separate E_{max} models were developed such that each of the 3 analytes was included in a model. The E_{max} model for CC1084037 performed better than the E_{max} models for ozanimod and CC112273 in terms of the Akaike Information Criterion. The E_{max} estimates were 0.972, 1.26, and 1.39 ms for the ozanimod, CC112273, and CC1024037 models. The EC_{50} estimates were 195, 482, and 57.4 pmol/L for the ozanimod, CC112273, and CC1024037 models.

Please see section 4.5 for details on the Reviewer's analyses.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcP for the primary analysis. The Reviewer used QTcF as the primary analysis. Despite of a mean decrease in heart rate close to 10 bpm between 6 and 12 hour postdose at the 0.46 mg QD and 0.92 mg QD dose levels, the observed heart rate changes do not appear to be dose- or exposure-dependent. Because the HR effect is mild and transient, and is not present at the high dose level, we propose to use QTcF as the primary endpoint. (See Sections 4.3.2 and 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

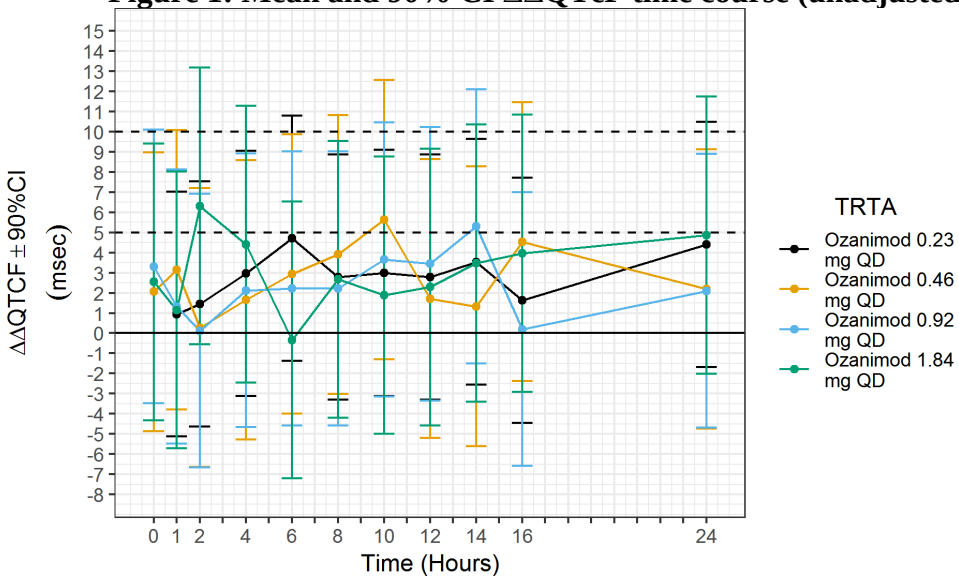
Not applicable.

4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used mixed model to analyze the ΔQTcF effect of the ozanimod by scheduled study day. The model includes treatment, time, time and intreatment interaction as fixed effects. Subjects were included in the model as a random effect. Baseline values were also included in the model as a covariate. Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The largest upper bound of the 90% confidence interval on ΔΔQTcF is 13.2 ms for ozanimod 1.84 mg QT on day 28.

Figure 1: Mean and 90% CI ΔΔQTcF time course (unadjusted CIs).



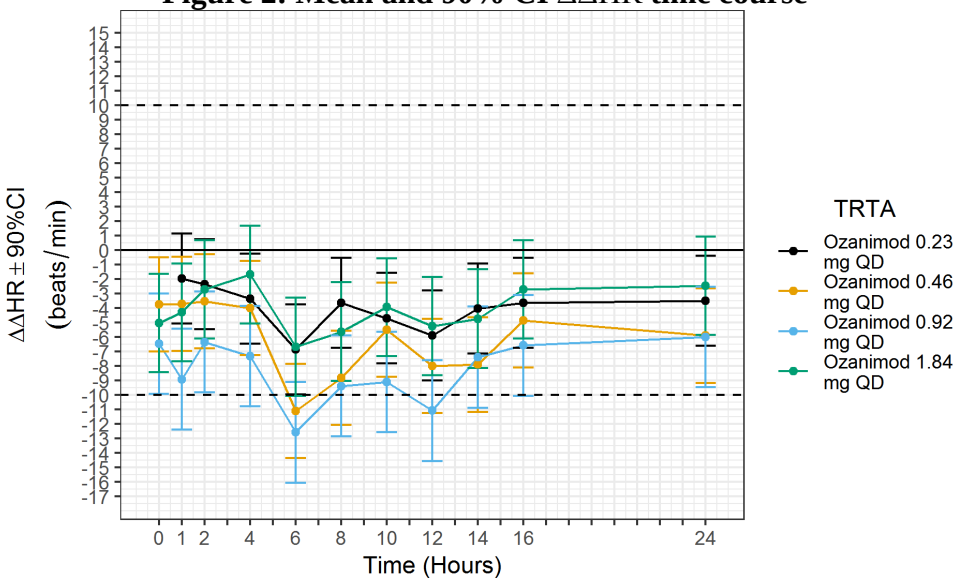
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

The same statistical analysis was performed based on HR (Figure 2). The largest upper limits of 90% CI for the HR mean differences between different dose level of ozanimod groups and placebo are less than 2 beats/min. However, HR shortening effect is observed. The smallest lower limit is -16.1 ms for ozanimod 0.92 mg QD on day 8.

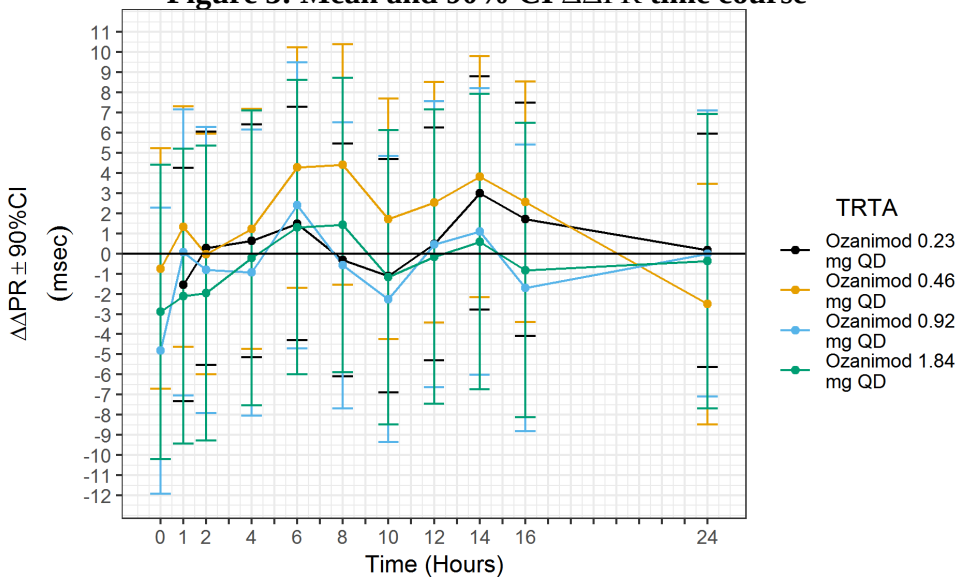
Figure 2: Mean and 90% CI ΔΔHR time course



4.3.3 PR

The same statistical analysis was performed based on PR interval (Figure 3). The largest upper limits of 90% CI for the PR mean differences between ozanimod 0.23 mg QD on day 1 and placebo is 8.8 ms, between ozanimod 0.46 mg QD on day 5 and placebo is 10.4 ms, between ozanimod 0.92 mg QD on day 8 and placebo is 9.5 ms, and between ozanimod 1.84 mg QD on day 28 and placebo is 8.7 ms. Border line shortening effect also observed for ΔΔPR (smallest lower bounds: -11.9 ms for ozanimod 0.93 mg QT on day 8 and -10.2 ms for ozanimod 1.84 mg QD on day 28).

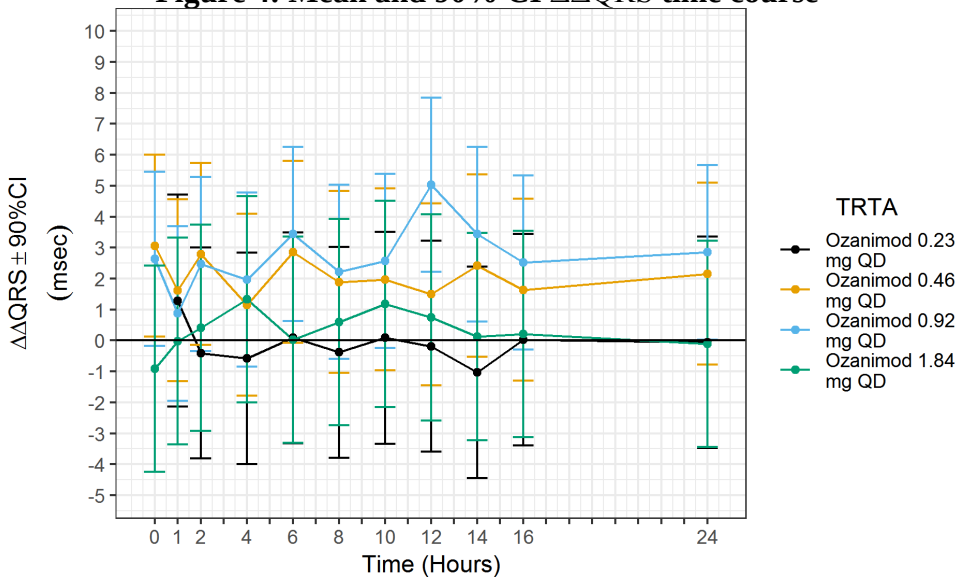
Figure 3: Mean and 90% CI ΔΔPR time course



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the QRS mean differences between ozanimod 0.92 mg QD on day 8 and placebo is 7.8 ms.

Figure 4: Mean and 90% CI ΔΔQRS time course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Table 2 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 2: Categorical Analysis for QTcF

Treatment	Total (N)		Value <= 450 msec		450 msec < Value <= 480 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ozanimod 0.23 mg QD	(b) (6)	280	(b) (6) (92.9%)	278 (99.3%)	(b) (6) (7.1%)	2 (0.7%)
Ozanimod 0.46 mg QD		308	(b) (6) (89.3%)	304 (98.7%)	(b) (6) (10.7%)	4 (1.3%)
Ozanimod 0.92 mg QD		308	(b) (6) (100.0%)	308 (100.0%)	0	0
Ozanimod 1.84 mg QD		308	(b) (6) (100.0%)	308 (100.0%)	0	0
Placebo		1080	(b) (6) (96.2%)	1078 (99.8%)	(b) (6) (3.8%)	2 (0.2%)

Table 3 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 3: Categorical Analysis of ΔQTcF

Treatment	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ozanimod 0.23 mg QD	(b) (6)	280	(b) (6) (100.0%)	280 (100.0%)	(b) (6)	0
Ozanimod 0.46 mg QD		308	(b) (6) (100.0%)	308 (100.0%)		0
Ozanimod 0.92 mg QD		308	(b) (6) (92.9%)	306 (99.4%)	(b) (6) (7.1%)	2 (0.6%)
Ozanimod 1.84 mg QD		308	(b) (6) (100.0%)	308 (100.0%)	(b) (6)	0
Placebo		1080	(b) (6) (92.3%)	1078 (99.8%)	(7.7%)	2 (0.2%)

4.4.2 PR

The outlier analysis results for PR are presented in Table 4. There are 1 subject in ozanimod 0.23 mg QD group, 2 subjects in ozanimod 0.46 mg QD group, 3 subjects in ozanimod 0.92 mg QD group and 2 subjects in ozanimod 1.84 mg QD group, who experienced PR interval greater than 200 ms. One subject ((b) (6)) experienced PR interval greater than 200 ms at all dose levels of ozanimod and one subject ((b) (6)) experienced PR interval greater than 220 ms which was >25% increase from baseline PR (176 ms).

Table 4: Categorical Analysis for PR

Treatment	Total (N)		Value <= 200 msec		200 msec < Value <= 220 msec		Value > 220 msec & <= 25%		Value > 220 msec & > 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ozanimod 0.23 mg QD	(b) (6)	280	(b) (6) (96.4%)	273 (97.5%)	(b) (6) (3.6%)	7 (2.5%)	(b) (6)	0	(b) (6)	0
Ozanimod 0.46 mg QD		308	(b) (6) (92.9%)	304 (98.7%)	(b) (6) (7.1%)	4 (1.3%)		0		0
Ozanimod 0.92 mg QD		308	(b) (6) (89.3%)	296 (96.1%)	(b) (6) (7.1%)	11 (3.6%)		0	(3.6%)	1 (0.3%)

Treatment	Total (N)		Value <= 200 msec		200 msec < Value <= 220 msec		Value > 220 msec & <= 25%		Value > 220 msec & > 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ozanimod 1.84 mg QD	(b) (6)	308	(b) (6) (92.9%)	304 (98.7%)	(b) (6) (7.1%)	4 (1.3%)	(b) (6)	0	(b) (6)	0
Placebo		1080	(b) (6) (92.3%)	1060 (98.1%)	(b) (6) (3.8%)	19 (1.8%)	(3.8%)	1 (0.1%)		0

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 5. There are two subjects who experienced QRS interval greater than 110 ms in ozanimod 0.92 mg QD and ozanimod 1.84 mg QD groups.

Table 5: Categorical Analysis for QRS

Treatment	Total (N)		Value <= 100 msec		100 < Value <= 110 msec		Value > 110 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ozanimod 0.23 mg QD	(b) (6)	280	(b) (6) (78.6%)	249 (88.9%)	(b) (6) (21.4%)	31 (11.1%)	(b) (6)	0
Ozanimod 0.46 mg QD		308	(b) (6) (75.0%)	258 (83.8%)	(b) (6) (25.0%)	50 (16.2%)		0
Ozanimod 0.92 mg QD		308	(b) (6) (82.1%)	276 (89.6%)	(b) (6) (14 %)	31 (10.1%)	(3.6%)	1 (0.3%)
Ozanimod 1.84 mg QD		308	(b) (6) (82.1%)	266 (86.4%)	(b) (6) (14.3%)	41 (13.3%)	(b) (6) (3.6%)	1 (0.3%)
Placebo		1080	(b) (6) (69.2%)	1041 (96.4%)	(b) (6) (30.8%)	39 (3.6%)	(b) (6)	0

4.4.4 HR

There are no subjects who experienced HR greater than 100 bpm in different dose levels of ozanimod. When subjects are counted in their minimum categories, there are 2, 1 and 2 subjects who experienced HR less than 45 bpm in ozanimod 0.23 mg QD, 0.46 mg QD and 0.92 mg QD group respectively.

Table 6: Categorical Analysis for HR (minimum)

Treatment	Total (N)		Value <= 45 beats/min		45 beats/min< Value <= 100 beats/min		Value > 100 beats/min
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Obs.
Ozanimod 0.23 mg QD	(b) (6)	280	(b) (6) (7.1%)	2 (0.7%)	(b) (6) (92.9%)	278 (99.3%)	0
Ozanimod 0.46 mg QD		308	(b) (6) (3.6%)	2 (0.6%)	(b) (6) (96 %)	306 (99.4%)	0
Ozanimod 0.92 mg QD		308	(b) (6) (7.1%)	4 (1.3%)	(b) (6) (92.9%)	304 (98.7%)	0
Ozanimod 1.84 mg QD		308	(b) (6)	0	(b) (6) (100.0%)	308 (100.0%)	0
Placebo		1080	(7.7%)	2 (0.2%)	(b) (6) (92.3%)	1075 (99.5%)	3 (0.3%)

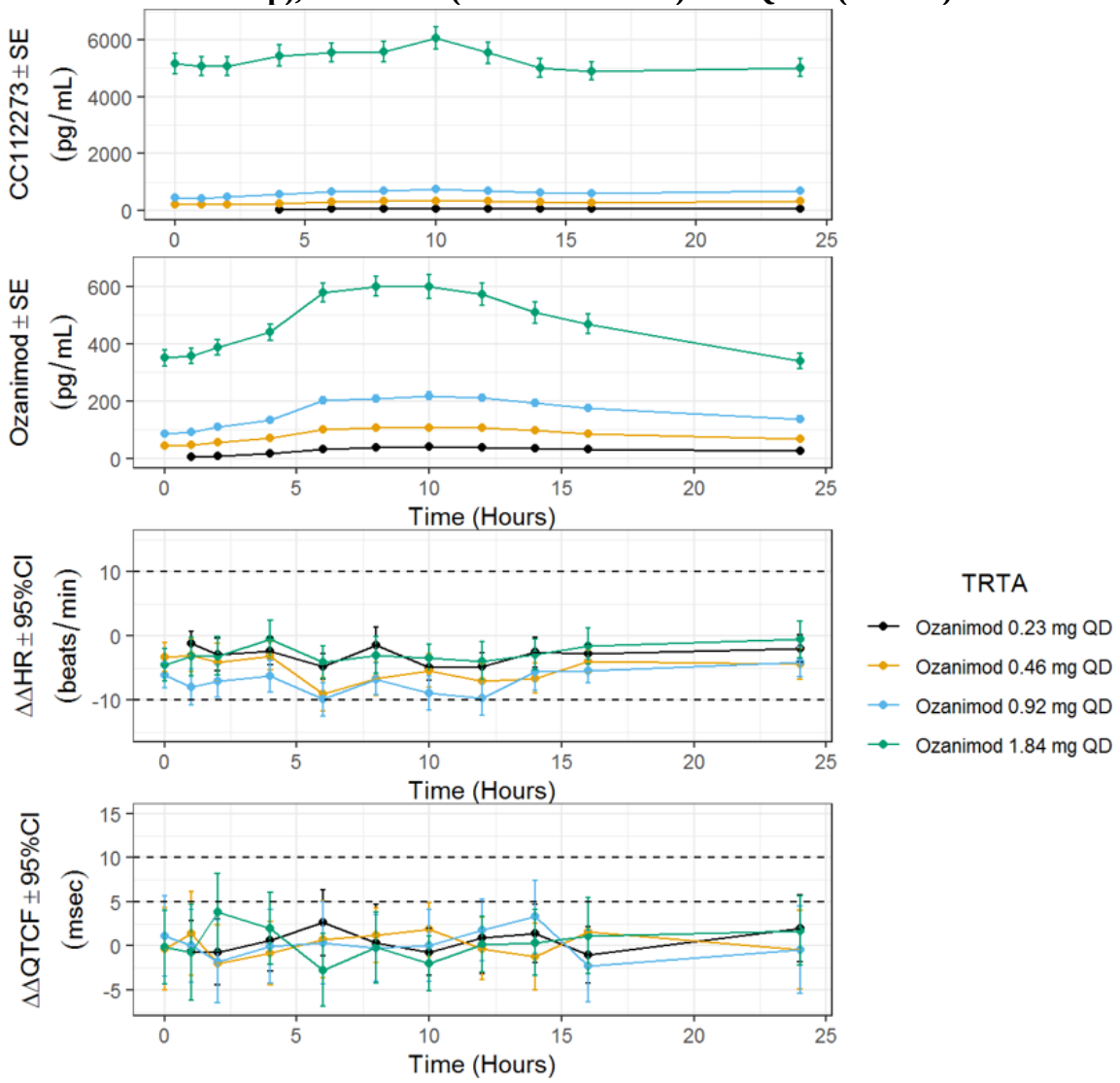
Note: Subjects were counted in their minimum categories.

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between exposure and ΔQTcF. The Day 28 time period was selected to represent steady-state exposure of a major metabolite, CC112273, which was not represented in previous exposure-response analyses for QT (see the review of IND 109159 dated 01/29/2014 in DARRTS for additional details). The CC112273 metabolite represents 73% of circulating total active drug exposure. As such, along with ozanimod, the reviewer's exposure-response analyses also focused on metabolite CC112273.

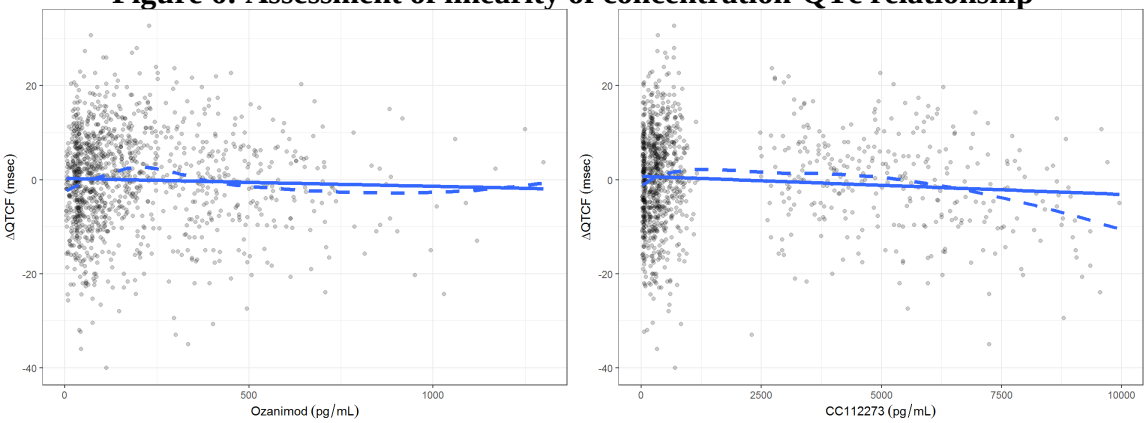
Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship. An evaluation of the time-course of drug concentration and changes in ΔΔHR and ΔΔQTcF is shown in Figure 5. A decrease in mean HR of up to 10 bpm is apparent from 6-12 hours post-dose. However, there is no apparent dose-response relationship for ΔΔHR. For example, a 3-fold and 5-fold increase in ozanimod exposure and metabolite exposure was observed when comparing PK at the 0.92 mg QD level to the 1.84 mg QD level. However, despite the exposure increase, the magnitude of ΔΔHR decreased over this range. Overall, the exploratory exposure-response analysis does not suggest a significant relationship between ΔHR vs. ozanimod or metabolite concentration. Also, there is no apparent signs of hysteresis for either ΔΔHR or ΔΔQTcF (please refer to Figure 5).

Figure 5: Time course of metabolite concentration (top), parent concentration (2nd from top), heart rate (2nd from bottom) and QTcF (bottom)



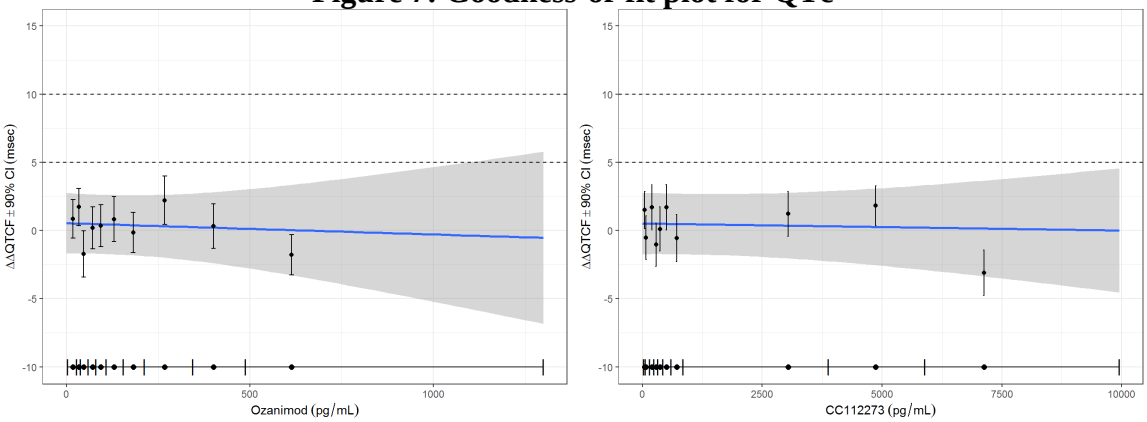
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between concentration and ΔQTcF and supports the use of a linear model for ozanimod. For metabolite CC112273, a linear model was used as it describes the central tendency of the ΔQTcF data well for the majority of the exposure measurements (i.e.) up to ~ 7500 pg/mL.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied and the goodness-of-fit plot is shown in Figure 7. The model used ΔQTcF as the dependent variable, ozanimod or metabolite concentration as the exposure covariate, and study treatment, time, study day, and centered baseline as the fixed effects; a random effect by subject was included on the intercept and slope. Predictions from the concentration-QTc model for CC112273 are provided in Table 1.

Figure 7: Goodness-of-fit plot for QTc



The sponsor utilized an E_{max} modeling approach in the three final models to describe the relationship between QT and ozanimod, CC112273, or metabolite CC1084037. Though the sponsor's model differs from the reviewer's, both the sponsor's and the reviewer's analyses suggest a lack of clinically relevant effect on QTc at the 0.92 mg QD dose.

4.5.1 Assay sensitivity

The exposure of CC112273 is expected to cover 1.8-times of the predicted $C_{max,ss}$ and 1.2-times of the highest clinically relevant exposure at the proposed therapeutic dose. The finding of this study is consistent with that from previous evaluations. A formal test for assay sensitivity is not considered necessary.

4.6 SAFETY ASSESSMENTS

No additional safety analyses were conducted. See section 3.2.3.

4.7 OTHER ECG INTERVALS

No clinically meaningful effects on PR and QRS intervals.

5 APPENDIX

5.1 EVALUATION OF QT ASSESSMENT PLAN

1. Product Information			
Generic Name	Ozanimod	Brand Name	ZEPOSIA (proposed name)
Drug class	agonist for the sphingosine 1-phosphate receptor subtypes 1 and 5		
Combination product	No		
Indication	for the treatment of adults with relapsing forms of multiple sclerosis		
Therapeutic Dose	0.92 mg QD		
Maximum Tolerated Dose	Not determined. No Grade 3 adverse events were reported for single doses of up to 3 mg, for repeated doses up to 2 mg for 7 days, or for repeated doses up to 1.5 mg for 28 days.		
Dosage Form	Capsule	Route of Administration	Oral

2. Safety Pharmacology 2.1 In vitro
The ozanimod concentration to achieve 50% inhibition (IC50) of the hERG channel current (a surrogate for IKr, the rapidly activating delayed rectifier cardiac potassium current) was 0.21 µM, a value > 300 times the Cmax with a clinical ozanimod dose of 1 mg. The metabolite RP112273 had an IC50 of 0.6 µM, a value > 30 times the Cmax with a clinical ozanimod dose of 1 mg at steady state (total drug). At 1 µM, the metabolites RP101988, RP101075, RP101442, and RP101124 inhibited the channel < 50%.
2.2 In vivo
No new information provided. Refer to previous QT-IRT reviews dated 03/12/2018 (NDA 209899) and 01/29/2014 (IND 109159) in DARRTS.

3. Clinical cardiac safety
No new information provided. Refer to previous QT-IRT reviews dated 03/12/2018 (NDA 209899) and 01/29/2014 (IND 109159) in DARRTS.

4. QT Studies 4.1 Primary Studies								
Protocol number / Population	**ECG Quality**		**Arms**		**Sample size**		**ECG & PK assessments**	
	Assessment	**Ok?**	**Arms**	**High dose covers?**	**No subjects**	**Ok?**	**Timing**	**Ok?**

Protocol number: RPC-01-1914 Population: Healthy volunteers	Central read? Yes Blinded? Yes Method? Unknown Replicates? Yes	Yes	Highest dose: 1.92 mg QD Placebo: Yes Positive control: No	High dose exposure exceeds worst case scenario for metabolite CC112273 exposure by 17%.	54	Unknown	Baseline: Other Timing: on Days -1, 1, 5, 8, and 28, at predose, 1, 2, 4, 6, 8, 10, 12, 14, 16 and 24 hours	Yes
Reviewer's comments: *The ECG sampling schedule supports the use of time-matched baseline (used in the Reviewer's analysis). It is not clear how baseline was defined in the sponsor's population PK/PD model.*								

4.2 Secondary Studies (Not Applicable)

4.3 Data pooling (Not Applicable)

5. Analysis plan

5.1 Study Objective related to QT

What QTc effect size is the analysis trying to exclude?	10 ms (E14)

5.2 Dose Justification

Sponsor's Rationale: The ozanimod dosing regimen in this study was selected to achieve CC112273 maximum observed plasma concentration within the dosing interval (Cmax) on Day 28 similar to the Cmax at steady state (Cmax,ss) in RMS patients at the therapeutic dose of 0.92 mg once daily (QD). Ozanimod treatment in the Phase 2 and 3 studies included a 7-day dose escalation (0.23 mg QD on Days 1 to 4, 0.46 mg QD on Days 5 to 7) followed by a maintenance dose of either 0.46 or 0.92 mg QD on Day 8 and thereafter. Another multiple-dose regimen consisting of the same 7-day dose escalation, followed by 0.92 mg QD on Days 8 to 10 and a maintenance dose of 1.84 mg QD on Day 11 and thereafter was safely evaluated in the Phase 1 studies RPC01-102 and RPC01-1911 in healthy volunteers. Results from the Phase 1 study RPC01-1911 coupled with pharmacokinetic (PK) simulation showed that a multiple dosing regimen of 1.84 mg QD for 28 days (including the 10-day dose escalation) resulted in CC112273 Cmax distribution on Day 28 similar to the Cmax,ss range observed in RMS patients following 12-week dosing of ozanimod. Food (high-fat or low-fat breakfast) has no effect on the absorption of ozanimod.

Reviewer comment*: The main impetus for this QT assessment is the attempt to characterize the effect of the steady-state exposures of the major metabolite CC112273, which has a half-life of ~10 days, on QT, and was not covered in the previous TQT assessment (please refer to IND 109159 dated 01/29/2014 in DARRTS for details). The sponsor predicts Cmax,ss for 0.92 mg QD is 3499.6*

pg/mL based on population PK modeling. The maximum mean CC112273 exposures observed in Study RPC01-1914 (6051.7 pg/mL) at the supra therapeutic dose of 1.84 mg ozanimod are ~70% higher. However, as gemfibrozil increases CC112273 exposure by 47%, then the worst-case scenario is CC112273 exposure of 5144.4 pg/mL. Thus, the worst-case scenario is concomitant gemfibrozil resulting in CC112273 metabolite exposure (5144.4 pg/mL) which is still lower than the maximum mean CC112273 exposures observed in Study RPC01-1914 (6051.7 pg/mL) at the supra therapeutic dose of 1.84 mg ozanimod. However, the margin for the worst-case scenario coverage drops from ~70% to 17% (6051.7/5144.4 = 1.17).

5.3 QT correction method	
Is an HR increase or decrease greater than 10 bpm?	Unknown
Primary method for QT correction	Other (QTcP)

Reviewer's comments:

- *The sponsor's graphical evaluation of the relationships of time-matched change from baseline in HR (ΔHR) with plasma ozanimod, CC112273 and CC1084037 concentration does not appear to suggest significant exposure-response relationships.*
- *The sponsor examined the correlations between RR and QTcF, QTcB, or QTcP with regression lines using data from placebo and pre-dose samples (drug-free data) to assess whether the correction factors have suitably removed the correlation between QT and RR. The QTc endpoint demonstrating the least correlation with heart rate was selected as the primary endpoint.*

5.4 Assay Sensitivity		
Assay sensitivity methods proposed by sponsor	☐ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment	☐ Not applicable (objective is large mean effects) ☒ Other (The sponsor did not propose to evaluate assay sensitivity.)

5.5 Central Tendency Analysis **5.5.1 Investigational drug**	
Primary analysis	No
Did the sponsor use IUT or descriptive statistics?	Unknown
For IUT: Does the sponsor use MMRM to analyze longitudinal values that considers the correlation across time-points or use ANCOVA by time-point without considering correlation?	Unknown
For IUT: Is the MMRM model specified correctly with regards to covariance structure, covariates, etc?	Unknown

5.5.2 Positive control	
Primary analysis	N/A
Did the sponsor adjust for multiplicity?	Unknown

5.6 Concentration-QTc analysis 5.6.1 Investigational drug	
Primary analysis	Yes
What is the dependent variable in the sponsor's model?	Unknown (The sponsor used absolute QTc value.)
White paper model?	No
Which concentration covariate(s) are included in the model?	Multiple - Univariate
Did the sponsor propose an assessment of delayed effects?	Yes
Did the sponsor propose an assessment of linearity?	Yes
Did the sponsor propose model selection criteria?	Yes
What methods did the sponsor use for predicting the QT effect?	☐ Model-based confidence intervals ☒ Bootstrap-derived confidence intervals
4.6.2 Positive control	
Primary analysis	N/A
Same model as investigational drug	N/A

5.7 Categorical analysis					
QTc?	No	PR?	No	HR?	No
ΔQTc?	No	QRS?	No	T-wave morphology?	No

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/s/

NAN ZHENG
06/12/2019 09:52:25 AM
Michael Bewernitz is the primary clinical pharmacology reviewer.

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DALONG HUANG
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MICHAEL Y LI
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LARS JOHANNESEN
06/12/2019 01:47:46 PM

CHRISTINE E GARNETT
06/12/2019 04:03:05 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 17, 2018

To: Nahleen Lopez, Regulatory Project Manager
Division of Neurology Products (DNP)

Tracy Peters, Associate Director for Labeling, DNP

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for Zeposia (ozanimod), capsules for oral use

NDA: **209899**

This memo is in response to DNP's labeling consult request dated January 5, 2018. Reference is made to a Refuse to File letter that was issued on February 23, 2018. Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DNP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Christine Bradshaw at (301) 796-6796 or Christine.Bradshaw@fda.hhs.gov.

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/s/

CHRISTINE J BRADSHAW
05/17/2018