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APPLICATION NUMBER:

209899Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Date: January 13, 2020

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Subject: Ozanimod, NDA 209899

Executive Summary

Ozanimod is a sphingosine 1-phosphate receptor modulator that is proposed for treatment of multiple sclerosis. One of its major metabolites, CC112273 is a MAO-B inhibitor. We were asked to address (1) the ability of an assay used by the sponsor to measure MAO-B inhibition, and (2) its ability to serve as a surrogate. The sponsor used a platelet assay to measure impact on MAO-B inhibition in a clinical trial. The platelet assay is frequently used *in vitro* as a surrogate for brain MAO-B activity and is well-established. Given the identical protein sequence of MAO-B from brain and platelet, it is reasonable to use this assay to estimate MAO-B inhibition.

However, the clinical trial the sponsor used to assess the impact of this metabolite on MAO-B was not designed appropriately to address the question of MAO-B interaction and inhibition for labeling purposes. The clinical trial enrolled healthy volunteers and no other MAO-B inhibitor was administered. As the literature shows, no clinical effects would be expected to be observed if total MAO-B inhibition is less than 80%. Therefore, the data the sponsor supplied does not eliminate the need to label for potential MAO-B inhibition and interaction with adrenergic and serotonergic acting drugs. In order to avoid labeling restrictions, the sponsor should show that the overall impact of commonly prescribed MAO-B inhibitors in conjunction with CC112273 does not exceed 80% of MAO-B activity.

Background

Ozanimod is a sphingosine 1-phosphate receptor modulator that is proposed for treatment of multiple sclerosis. It selectively binds to receptor subtypes 1 and 5 with high affinity and helps to prevent the egress of lymphocytes from lymphoid organs into circulation (Comi G, 2019). A major metabolite of ozanimod, CC112273, was identified as a monoamine oxidase (MAO) inhibitor, more selective to MAO-B than MAO-A, with an IC_{50} of 5.72nM from *in vitro* studies.

The brain has a high proportion of MAO-B receptors, predominantly located in the mitochondria of neurons, with one estimate indicating that >80% of the MAO receptors are MAO-B (Youdim MBH, 1991). Similarly, platelets express almost exclusively MAO-B and have been used as a surrogate to assess the impact of drugs on brain MAO-B levels (Youdim MBH, 1988 and 1991; Goubau C, 2014).

As part of this NDA, the sponsor has proposed (b) (4) (b) (4) since "in a clinical study (RPC01-1914) ozanimod had no inhibition effect on human platelet MAO-B activity, a biomarker for central

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MAO-B activity, compared to placebo".

Evaluation

Do you agree that platelet MAO-B activity is a reliable biomarker for central MAO-B activity? Are there any references or data showing that these are interchangeable and can be used as a surrogate biomarker for each other?

Assays to evaluate platelet MAO-B activity have been in use for decades, but there are limitations to their use and interpretation (Youdim, 1988). The DNA sequences of platelet and brain isoforms of MAO-B have been shown to be identical (Chen K, 1993). Studies comparing MAO-B activity in platelets and biopsy obtained brain tissue from study participants have had variable results, with some showing consistency (Kumlien E, 1995) and others not (Young WF, 1986). Other methods have suggested good correlation between tissue sources of MOA-B (Bench CJ, 1991).

Of importance is that it has been shown that between 80-90% of MAO-B activity must be blocked in order to observe clinical effects (Youdim, 1988; Youdim, 1991; Bench CJ, 1991, Fowler, 2015). Innumerable studies are present in the literature in which various neurotransmitters have been evaluated using platelet MAO-B assays (Ramsay RR, 2016), however, their conclusion was that PET scanning for MAO-B activity is the gold standard, especially for assessment of neurodegenerative conditions. They also suggest that while the platelet MAO-B assay is useful and inexpensive, particularly for genetic MAO-B related conditions, it should not be the first choice in assessment of MAO-B.

The data from study RPC01-1914 clearly show no differences in MAO-B activity between ozanimod and placebo treated healthy volunteers using a commercial platelet-based assay. Given the extensive literature showing the use of this assay method, and the lack of differences between the two groups, it is reasonable to conclude that there would be no effect.

However, several cited studies indicate that until 80-90% MAO-B inhibition is achieved, no clinical effects are likely to be observed. It is unclear from the data presented what level of inhibition the metabolite CC112273 could produce. Many diseases can require treatments with drugs that impact serotonin or adrenergic receptors, and this was not evaluated in the trial. It would be useful to know the level of MAO-B inhibition of CC112273 alone and with drugs that also could inhibit MAO-B and be administered concomitantly that, to determine if the resulting additive effect on MAO-B inhibition exceeds 80%. Given this level of uncertainty, it would be prudent to include labeling indicating that MAO-B inhibition is possible. If the sponsor were to demonstrate that CC112273 and potentially concomitantly administered drugs do not exceed the 80% threshold *in vitro*, using the platelet assay, it would be more reasonable to consider less labeling restriction.

Summary and Conclusions

Ozanimod is a sphingosine 1-phosphate receptor modulator that is proposed for treatment of multiple sclerosis. One of its major metabolites, CC112273 is a MAO-B inhibitor. The sponsor used a platelet assay to measure the impact on MAO-B inhibition in a clinical trial. The platelet assay used *in vitro* as a surrogate for brain MAO-B activity is well-established and given the identical sequence of brain and platelet MAO-B proteins, is reasonable to use the assay to estimate MAO-B inhibition.

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However, the clinical trial the sponsor used to assess the impact of this metabolite on MAO-B was not designed to address the question adequately. First, healthy volunteers were used, and second no other MAO-B inhibitor was administered. As the literature shows, no clinical effects would be expected to be observed if total MAO-B inhibition is less than 80%. Therefore, the data the sponsor supplied does not eliminate the need to label for potential MAO-B inhibition and interaction with adrenergic and serotonergic acting drugs. In order to avoid labeling restrictions, the sponsor would need to show that the overall impact of commonly prescribed MAO-B inhibitors in conjunction with CC112273 does not exceed 80% of MAO-B activity.

References and Supporting Documents

Bench CJ, Price GW, Lammertsma AA, Cremer JC, Luthra SK, Turton D, Dolan RJ, Kettler R, Dingemanse J, Da Prada M, et al. Measurement of human cerebral monoamine oxidase type B (MAO-B) activity with positron emission tomography (PET): a dose ranging study with the reversible inhibitor Ro 19-6327. Eur J Clin Pharmacol. 1991;40(2):169-73. PMID: 1906004.

Chen K, Wu HF, Shih JC. The deduced amino acid sequences of human platelet and frontal cortex monoamine oxidase B are identical. J Neurochem. 1993 Jul;61(1):187-90. PMID: 8515265.

Comi G, Kappos L, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, Hartung HP, Montalban X, Kubala Havrdová E, Cree BAC, Sheffield JK, Minton N, Raghupathi K, Ding N, Cohen JA; SUNBEAM Study Investigators. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. Lancet Neurol. 2019 Nov;18(11):1009-1020. doi: 10.1016/S1474-4422(19)30239-X. PMID: 31492651.

Fowler JS, Logan J, Shumay E, Alia-Klein N, Wang GJ, Volkow ND. Monoamine oxidase: radiotracer chemistry and human studies. J Labelled Comp Radiopharm. 2015 Mar;58(3):51-64. doi: 10.1002/jlcr.3247. Epub 2015 Feb 10. Review. PMID: 25678277.

Goubau C, Buyse GM, Van Geet C, Freson K. The contribution of platelet studies to the understanding of disease mechanisms in complex and monogenetic neurological disorders. Dev Med Child Neurol. 2014 Aug;56(8):724-31. PMID: 24579816.

Kumlien E, Bergström M, Lilja A, Andersson J, Szekeres V, Westerberg CE, Westerberg G, Antoni G, Långström B. Positron emission tomography with [11C]deuterium-deprenyl in temporal lobe epilepsy. Epilepsia. 1995 Jul;36(7):712-21. PMID: 7555990.

Kumlien E, Sherif F, Ge L, Oreland L. Platelet and brain GABA-transaminase and monoamine oxidase activities in patients with complex partial seizures. Epilepsy Res. 1995 Feb;20(2):161-70. PMID: 7750512.

Ramsay RR. Molecular aspects of monoamine oxidase B. Prog Neuropsychopharmacol Biol Psychiatry. 2016 Aug 1;69:81-9. PMID: 26891670.

Youdim MB, Finberg JP. New directions in monoamine oxidase A and B selective inhibitors and substrates. Biochem Pharmacol. 1991 Jan 15;41(2):155-62. PMID: 1989626.

Youdim MB. Platelet monoamine oxidase B: use and misuse. Experientia. 1988 Feb 15;44(2):137-41. PMID: 3278920.

Young WF Jr, Laws ER Jr, Sharbrough FW, Weinshilboum RM. Human monoamine oxidase. Lack of brain and platelet correlation. Arch Gen Psychiatry. 1986 Jun;43(6):604-9. PMID: 3085628.

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	209899
Submission Date	March 25, 2019
Submission Type	Standard
Brand Name	Zeposia
Generic Name	Ozanimod
Dosage Form and Strength	Capsules, 0.23 mg, 0.46 mg, 0.92 mg of ozanimod (equivalent to 0.25, 0.5 and 1 mg ozanimod HCl, respectively)
Route of Administration	Oral
Proposed Indication	Treatment of Relapsing forms of Multiple Sclerosis (RMS)
Applicant	Celgene International II Sàrl (CIS II)
OCP Review Team	Hristina Dimova, Raman Baweja, Angela Men, Atul Bhattaram, Mehul Mehta

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1. EXECUTIVE SUMMARY

The sponsor is seeking an approval for Zeposia to treat RMS. The proposed dosing regimen is 1mg once a day (QD) after a 7-day titration starting with 0.25 mg QD.

Ozanimod is a sphingosine 1-phosphate (S1P) receptor agonist, which binds selectively to S1P subtypes 1 (S1P1) and 5 (S1P5). Ozanimod causes internalization of S1P1 and retention of lymphocytes in the lymphoid tissues, as evidenced by a dose-dependent reduction in peripheral lymphocyte count. The mechanism by which ozanimod exerts therapeutic effects in relapsing multiple sclerosis (RMS) may involve reduction of lymphocyte migration into the central nervous system.

NDA 209899 for ozanimod was submitted on Dec 26, 2017 and received a Refuse to File (RTF) letter on Feb 23, 2018, mainly due to inadequate characterization of the clinical pharmacokinetics of the predominant and active metabolite of ozanimod, RP112273.

In the resubmission, the sponsor has addressed the RTF issues. The clinical pharmacology of ozanimod has been characterized in 17 Phase 1 clinical pharmacology studies. Sparse pharmacokinetic (PK) samples were also collected in three Phase 2 and 3 studies in patients with RMS for population PK and exposure-response (E-R) analyses. The submission also contains in vitro studies using human biomaterials regarding protein binding, hepatic metabolism and drug interactions, transporters, and 10 bioanalytical validation and assay reports for ozanimod and its metabolites.

The two active-controlled Phase 3 studies evaluated the efficacy of ozanimod at two dose levels, 0.5 mg and 1 mg, QD compared to interferon (IFN) β-1a (Avonex®) 30 µg weekly. In the Phase 3 program, ozanimod demonstrated superior, dose-dependent efficacy compared to Avonex in reducing annualized relapse rate (ARR), reducing the number of new and enlarging T2 lesions, and reducing the number of Gd-enhancing (GdE) lesions.

1.1 Recommendations

The office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 209899 and finds it acceptable from an OCP perspective. Key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal studies RPC01-201B [24 months] and RPC01-301 [1 year Plus] demonstrated superior, dose-dependent efficacy of ozanimod compared to Avonex in reducing annualized relapse rate (ARR), reducing the number of new and enlarging T2 lesions, and reducing the number of Gd-enhancing (GdE) lesions in RMS patients.

General dosing instructions	Initiation of ozanimod may result in transient reductions in heart rate. To mitigate these AEs, dose escalation is recommended (from 0.23mg to 0.92 mg) once daily according to the following schedule (including re-initiation after treatment interruption >14 days): o Days 1 to 4: 0.23 mg once daily o Days 5 to 7: 0.46 mg once daily o Day 8 and thereafter: 0.92 mg once daily Note: 1 mg ozanimod hydrochloride is equivalent to 0.92 mg ozanimod
Dosing in patient subgroups (intrinsic factors)	Not recommended in patients with hepatic impairment. No dose adjustment is needed in patients with renal impairment.
Extrinsic factors	• Contraindicated with MAO inhibitors e.g., phenelzine, isocarboxazid, linezolid, safinamide, selegiline, rasagiline, etc. • No dosing adjustment when ozanimod is co-administered with CYP3A inhibitors • Co-administration of ozanimod with the following is not recommended: o Strong CYP2C8 inhibitors (gemfibrozil) o Strong CYP inducers (rifampin) o BCRP Inhibitors (cyclosporine, eltrombopag, curcumin) • Labeling restrictions for concomitant use of ozanimod and drugs with adrenergic and serotonergic activity: to be determined based on input from the clinical team (consult sent to CDER OND ABPM)
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation and the formulation used in the pivotal studies (Formulation 2) are similar and do not require a bridging clinical BE study (in vitro bridging is sufficient for this level of changes). The dissolution of the clinical (Formulation 2) and registration (Formulation 3) material was similar over the pH range of 1.2 to 6.5. All 3 strengths were used in the phase 2 and phase 3 clinical trials, therefore no biowaiver is needed.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Ozanimod, a S1P receptor agonist, causes internalization of S1P1 and retention of lymphocytes in the lymphoid tissues, as evidenced by a dose-dependent reduction in peripheral lymphocyte count. The mechanism by which ozanimod exerts therapeutic effects in RMS may involve reduction of lymphocyte migration into the central nervous system.

Ozanimod is extensively metabolized in humans to several circulating active metabolites, including two major active metabolites, CC112273 and CC1084037, with similar activity and selectivity for S1P1 and S1P5 to the parent drug.

Absorption: The Tmax of ozanimod is approximately 6-8 hours. Tmax for the major active metabolite RP112273 is variable with median values between 6 and 10 hours.

Effect of food: Administration of ZEPOSIA with a high-fat, high-calorie meal (approximately 900 to 1100 calories with 500 to 600 calories from fat) had no effect on ozanimod exposure (Cmax and AUC).

Distribution: Plasma protein binding of ozanimod to human plasma proteins is approximately 98.2%. Binding of CC112273 and CC1084037 to human plasma proteins is 99.8% and 99.3%, respectively.

The mean (CV%) apparent volume of distribution of ozanimod (Vz/F) was 5590 L (27%), indicating extensive tissue distribution.

Metabolism: Ozanimod is extensively metabolized in humans with over 13 metabolites identified in plasma, urine and feces, including the active metabolites CC112273 [also referred to as RP112273], CC1084037 [also referred to as RP100798], RP101988, RP101075, RP112289, RP101442) and one circulating inactive metabolite RP101124. Ozanimod and the active metabolites have similar activity and selectivity for S1P1 and S1P5.

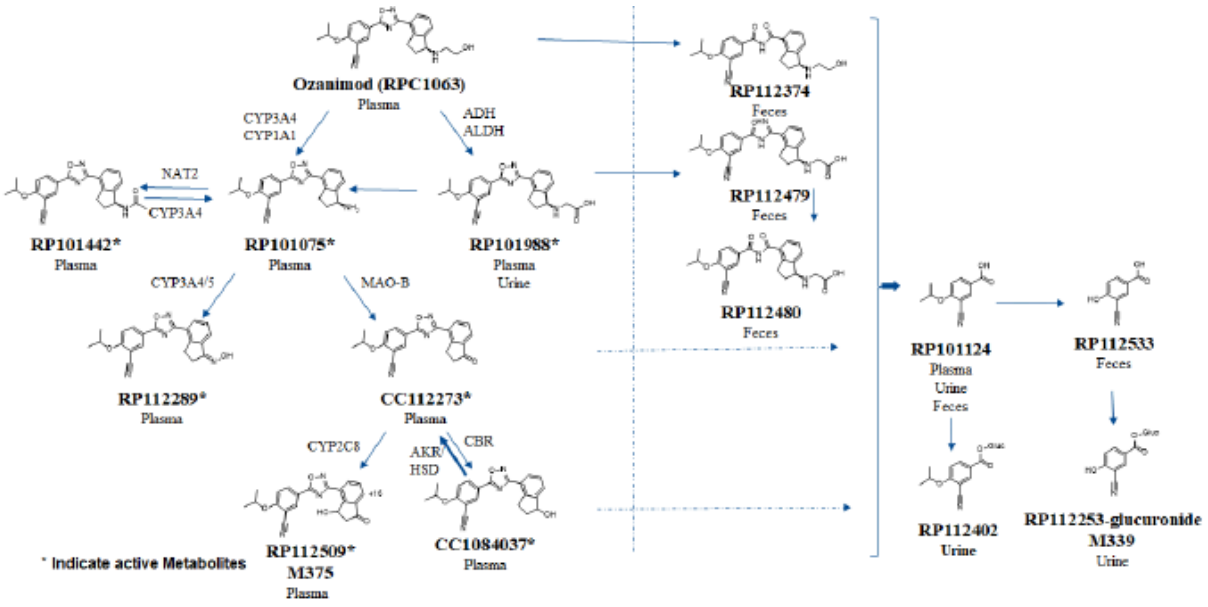
Multiple enzyme systems play a role in the metabolism of ozanimod. The oxidative pathway to form metabolite RP101988 is mediated by ALDH/ADH while formation of RP101075 by dealkylation is predominantly mediated by CYP3A4. RP101075 is N-acetylated by NAT-2 to form RP101442 or deaminated by MAO-B to form the major metabolite CC112273.

CC112273 is either reduced to form CC1084037 or undergoes CYP2C8-mediated oxidation to form RP101509. CC1084037 is oxidized to form CC112273 by AKR 1C1/1C2, and/or 3β- and 11β-HSD and undergoes reversible metabolism to CC112273.

The interconversion between CC112273 and CC1084037 favors CC112273.

Gut microbial flora plays an important role in vivo, via anaerobic reductive metabolism of the oxadiazole ring system in the formation of several inactive metabolites.

Metabolic Pathways for Ozanimod and Metabolites in Human



Source: Metabolite identification data from Report RPC01-1909

Elimination: After oral administration of a single oral dose of [^{14}C]-ozanimod HCl, the total mean recovery of the administered radioactivity was 63%, with 26% recovered from urine and 37% recovered from feces. The low recovery of total radioactivity is likely due to the long t½ of total radioactivity of 99 hours.

Only the minor active metabolite RP101988 was recovered in urine with approximately 4% of radioactivity (Report RCT/05). The major inactive metabolites recovered in the urine and feces were RP112402, RP112533, and RP112480. Ozanimod and the active metabolites (e.g. CC112273, CC1084037) were not present in feces.

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.

The half-life (t½) of ozanimod is approximately 20 hours, while the t½ of RP112273 and CC1084037 is about 280 hours, leading to accumulation of these active metabolites (relative to the parent) after multiple dosing. Metabolite-to-parent ratio for RP112273 is approximately 23- to 39-fold at steady state.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Initiation of ozanimod may result in transient reductions in heart rate. To mitigate these AEs, dose escalation is recommended (from 0.23mg to 0.92 mg) once daily according to the following schedule (including re-initiation after treatment interruption >14 days):

- Days 1 to 4: 0.23 mg once daily
- Days 5 to 7: 0.46 mg once daily
- Day 8 and thereafter: 0.92 mg once daily

2.2.2 Therapeutic individualization

No dose adjustment is needed in patients with renal impairment. Ozanimod is not recommended in patients with hepatic impairment.

Smokers: The 1 mg ozanimod hydrochloride dose (equivalent to 0.92 mg ozanimod) provides sufficient response in the treatment of RMS regardless of smoking status after a 7-day dose escalation scheme has been followed in RMS patients. No dose adjustment is needed for smokers.

Ozanimod is contraindicated to be used with MAO inhibitors e.g., phenelzine, isocarboxazid, linezolid, safinamide, selegiline, rasagiline, etc.

Co-administration of ozanimod with the following is not recommended:

- Strong CYP2C8 inhibitors (gemfibrozil)
- Strong CYP inducers (rifampin)
- BCRP Inhibitors (cyclosporine, eltrombopag, curcumin)

Whether additional labeling restrictions for concomitant use of ozanimod and drugs with adrenergic and serotonergic activity are needed, will be determined based on the input from the clinical team (consult sent to CDER OND ABPM).

2.3 Post-Marketing Requirements (PMRs)

1. A study to assess the effect of hepatic impairment on ozanimod and its major metabolites' pharmacokinetics when ozanimod is dosed until steady state is reached for RP112273.

2. A formal tyramine challenge study (b) (4)

2.4 Summary of Labeling Recommendations

- OCP agreed on the proposed general dosing recommendations and dose escalation of ozanimod (from 0.23mg to 0.92 mg):
  - Days 1 to 4: 0.23 mg once daily
  - Days 5 to 7: 0.46 mg once daily
  - Day 8 and thereafter: 0.92 mg once daily
- OCP agreed with the sponsor that no dose adjustment is needed based on sex, race and body weight.
- OCP agreed with the sponsor that no dose adjustment is needed for patients with renal impairment.
- (b) (4)

(b) (4). Ozanimod is not recommended in patients with hepatic impairment.

- OCP agreed with the sponsor that no dose adjustment is needed for smokers.
- (b) (4) (b) (4). Co-administration of ozanimod with strong CYP2C8 inhibitors is not recommended.
- OCP agreed with the sponsor that co-administration of inhibitors of BCRP (e.g., cyclosporine, eltrombopag) with ozanimod is not recommended.
- OCP agreed with the sponsor that no dosing adjustment is necessary when ozanimod is co-administered with CYP3A inhibitors.
- (b) (4) (b) (4). Rifampin co-administered with ozanimod significantly reduced the exposure of ozanimod major metabolites RP112273 and CC1084037.
- Ozanimod major metabolite RP112273 is formed via MAO-B; in addition, RP112273 and CC1084037 are MAO-B inhibitors. Co-administration of MAO inhibitors (e.g., phenelzine, isocarboxazid, linezolid, rasagiline, safinamide, selegiline) with ozanimod is contraindicated.
- Whether additional labeling restrictions for concomitant use of ozanimod and drugs with adrenergic and serotonergic activity are needed, will be determined based on the input from the clinical team (consult sent to CDER OND ABPM).

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Ozanimod, a S1P receptor agonist, causes retention of lymphocytes in the lymphoid tissues and a dose-dependent reduction in peripheral lymphocyte count. The mechanism by which ozanimod exerts therapeutic effects in RMS may involve reduction of lymphocyte migration into the central nervous system.

Ozanimod HCl drug product has been designed as an immediate release capsule.
Ozanimod is extensively metabolized in humans with two major active metabolites (e.g. CC112273 [also referred to as RP112273], CC1084037 [also referred to as RP100798] and one major circulating inactive metabolite RP101124. Ozanimod and the active metabolites have similar activity and selectivity for S1P1 and S1P5.

The human mass balance study was conducted late in the drug development program (results available about 4 months before the original NDA submission in Dec 2017). The major active metabolite of ozanimod RP112273 was identified in the mass balance study. Since all of the phase 1 and phase 2/3 studies were conducted before RP112273 was identified, the PK of this major metabolite were not assessed in the original NDA submission. Sponsor used retained plasma samples to quantify RP112273 in the phase 2/3 trials, and phase 1 studies, e.g. special populations and some of the DDI studies, however the samples were analyzed outside of the

long-term stability (LTS) window for RP112273 and the PK results were not acceptable. Another active disproportionate metabolite, CC1084037, was later (Aug 2018) identified. Since the results for the active metabolites would inform critical assessments related to labeling of Zeposia (general clinical pharmacology, DDIs, use in special populations), the NDA received a Refuse to File (RTF) letter on Feb 23, 2018, mainly due to inadequate characterization of the clinical pharmacokinetics of the predominant and active metabolite of ozanimod, RP112273. A Type A meeting on April 3, 2018 and a Type C, WRO (Oct. 2018) were held with the sponsor to discuss proposals to address the deficiencies described in the RTF letter.

In the NDA resubmission (March 25, 2019) the sponsor addressed the RTF issues. A 17-month LTS data for RP112273 was provided to justify the analysis of retained plasma samples for RP112273 in studies RPC01-201 Part B, RPC01-301, RPC01-1904 (hepatic impairment study), RPC01-1906 (renal impairment study) and multiple-dose study RPC01-1001 in subjects with RMS. Only samples within the stability window for RP112273 (17 months) are considered. In addition, a revised population PK (popPK) analysis and several new phase 1 studies were submitted: Phase 1 DDI studies RPC01-1912 (DDI with CYP2C8 and/or CYP3A modulators) and study RPC01-1914 (DDI with pseudoephedrine) assessing the single-dose and multiple-dose PK parameters for ozanimod and metabolites, including RP112273 and CC1084037. The results of the Phase 1 DDI study for tyramine (Study RPC01-1913) were submitted in the review cycle prior to 4-Month Safety Update to update the label.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Ozanimod and its active metabolites are S1P1 and S1P5 agonists. Ozanimod causes retention of lymphocytes in the lymphoid tissues and a dose-dependent reduction in peripheral lymphocyte count. The mechanism by which ozanimod exerts therapeutic effects in RMS may involve reduction of lymphocyte migration into the central nervous system.
Active Moieties	Major active moieties: ozanimod, CC112273, and CC1084037. Ozanimod, CC112273, and CC1084037 are approximately 6%, 73%, and 15% of circulating total active drug exposure, respectively. Several other active metabolites together contribute to the remaining 6% of circulating total active drug exposure.
QT Change	No relevant QTc prolongation effect of ozanimod's major metabolite, CC112273, was detected in the Thorough QTc study.
General Information	

Bioanalysis	Concentrations of ozanimod and its metabolites CC112273, RP101988, RP101075, RP101442, RP101124, CC1084037, and RP112289 in plasma were measured by validated bioanalytical methods. Validated high-performance liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) and stable isotope labeled internal standards were used for quantitative analysis of ozanimod and metabolites. A summary of the validation reports is included as an appendix.		
Healthy Volunteers vs Patients	The PK of ozanimod were not significantly different between healthy subjects and RMS patients based on the population analysis.		
Drug exposure at steady state following the therapeutic dosing regimen	The mean exposures (AUC0-τ) at the steady state (Day 85) following Ozanimod 1 mg, QD in Subjects with RMS were 4.5 ng*h/mL for ozanimod and 143.8 ng*h/mL for RP112273.		
Dose Proportionality	Exposure of ozanimod and CC112273 increased dose-proportionally in the dose range of 0.5 mg to 1 mg.		
Accumulation	Steady-state concentrations for ozanimod are reached within 5 to 7 days of QD dosing with approximately 2-fold drug accumulation at steady state. The mean time to steady state for CC112273 is approximately 45 days with an estimated mean accumulation ratio of approximately 16. Time to steady state and accumulation ratio for CC1084037 are expected to be similar to CC112273 since both metabolites have a similar $t_{1/2}$ and their exposure are highly correlated.		
Variability	Between-subject variability (%CV) in C_{max} and AUC_{0-24} for ozanimod, CC112237 and CC1084037 following 28-day QD dosing are similar (between 28 and 35%). In RMS patients, the inter-subject variability (%CV) was estimated for ozanimod CL/F as 23.5% and for CC112273 CL/F, Vc/F and formation rate constant as 74.5%, 25.9% and 37.2%, respectively.		
ADME			
Absorption	Co-administration with a high-fat meal showed no significant effect on the rate and the extent of absorption.		
Tmax	The Tmax of ozanimod is approximately 6-8 hours. Tmax for the major active metabolite RP112273 is variable with median values between 6 and 10 hours.		
Food Effect (high-fat)		**$AUC_{0-\infty}$**	**C_{max}**
GMR (90% CI)	Ozanimod	1.10 (1.05-1.15)	1.06 (1.02-1.14)
Distribution	Plasma protein binding of ozanimod, CC112273 and CC1084037 is 98.2%, 99.8% and 99.3%, respectively. The mean apparent volume of distribution of ozanimod (Vz/F) is 5590 L.		
Elimination			

Mean Terminal Elimination half-life	The half-life (t½) of ozanimod is approximately 20 hours t½ of RP112273 and CC1084037 is about 280 hours
Metabolism	
Primary metabolic pathway(s)	Ozanimod is extensively metabolized in humans with over 13 metabolites identified in plasma, urine and feces, including the active metabolites CC112273 [also referred to as RP112273], CC1084037 [also referred to as RP100798], RP101988, RP101075, RP112289, RP101442) and one circulating inactive metabolite RP101124. Ozanimod and the active metabolites have similar activity and selectivity for S1P1 and S1P5. Following multiple dose administration of ozanimod in healthy subjects, ozanimod, CC112273, and CC1084037 each represents approximately 6%, 73%, and 15% of circulating total active drug exposure, respectively. Multiple enzyme systems play a role in the metabolism of ozanimod. The oxidative pathway to form metabolite RP101988 is mediated by ALDH/ADH. Formation of RP101075 by dealkylation is predominantly mediated by CYP3A4. RP101075 is N-acetylated by NAT-2 to form RP101442 or deaminated by monoamine oxidase B (MAO-B) to form the major metabolite CC112273. CC112273 is either reduced to form CC1084037 or undergoes CYP2C8-mediated oxidation to form RP101509. CC1084037 is oxidized to form CC112273 by AKR 1C1/1C2, and/or 3β- and 11β-HSD and undergoes reversible metabolism to CC112273.
Excretion	After oral administration of a single oral dose of [^{14}C]-ozanimod HCl, the total mean recovery of the administered radioactivity was 63%, with 26% recovered from urine and 37% recovered from feces. The low recovery of total radioactivity is due to the long t½ of total radioactivity of 99 hours. Ozanimod, CC112273, and CC1084037 concentrations in urine were negligible, indicating that renal clearance is not an important excretion pathway for ozanimod, CC112273 and CC1084037.
Inhibitor/Inducer (in vitro)	Ozanimod and major metabolites CC112273, CC1084037 have no inhibitory effect on CYPs 1A2, 2B6, 2C19, 2C8, 2C9, 2D6, and 3A and no induction effect on CYPs 1A2, 2B6, and 3A. CC112273 and CC1084037 are MAO-B inhibitors.
Transporter Systems (in vitro)	Ozanimod, CC112273, CC1084037 and other metabolites have no inhibitory effect on P-gp, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, and MATE2-K. CC112273 and CC1084037 inhibit BCRP with an IC_{50} values of 25.2 nM and 22.8 nM, respectively. At clinically relevant concentrations of CC112273 and CC1084037, inhibition of BCRP is not expected [refer to Sect 3.3.5 for details].

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical development program of ozanimod in RMS consists of a Phase 2, randomized, double-blind, placebo-controlled study with a blinded extension period (RPC01-201A), a Phase 3, two-year, randomized, double-blind, double-dummy, active-controlled, parallel group study (RPC01-201B), a Phase 3, one-year, randomized, double-blind, double-dummy, active-controlled, parallel group study (RPC01-301), and an open-label extension (OLE) study (RPC01-3001). The active-controlled Phase 3 studies evaluated the efficacy of ozanimod at 2 dose levels, 0.5 mg and 1 mg, QD compared to interferon (IFN) β-1a (Avonex®) 30 µg weekly. In the Phase 3 program, ozanimod demonstrated superior, dose-dependent efficacy compared to Avonex in reducing annualized relapse rate (ARR), reducing the number of new and enlarging T2 lesions, and reducing the number of Gd-enhancing (GdE) lesions.

There are no clinical pharmacology-based analyses that would provide pivotal or supportive evidence of effectiveness. The Applicant states that the evidence of efficacy and safety of 0.46 and 0.92 mg doses has been obtained from Studies 201B and 301.

For primary analysis of the data from Studies 201B and 301, refer to the reviews by the Office of Neuroscience and Division of Biometrics I.

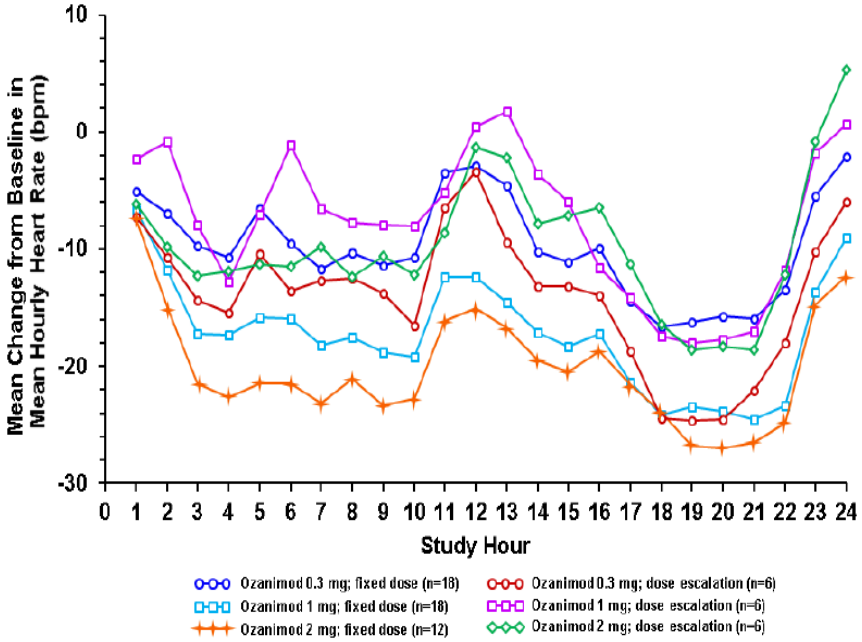
3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, by following a dose escalation scheme of ozanimod over 7 days -- more specifically, 0.23 mg once daily from day 1 to day 4, 0.46 mg once daily for days 5 to 7, and 0.92 mg once daily from day 8 onwards. Similar to other S1P receptor modulators (fingolimod, siponimod), ozanimod causes a transient, dose-dependent decrease in heart rate (HR). The dose escalation scheme is important because initiation of therapy without dose escalation may result in considerably greater reduction in heart rate.

(a) Dose Escalation Scheme

The Figure below shows the mean change from baseline in heart rate following a dose escalation scheme versus fixed dose administration of ozanimod.

Mean Changes from Daily Baseline in Mean Hourly Heart Rate for Fixed-Dose Cohorts 0.3, 1. and 2 mg on Day 1 versus Dose-escalation Cohort (0.3 mg on Day 1, 1 mg on Day 6, and 2 mg on Day 8)



Source: Page 112 of Study Report RPCS 001

As seen in the figure above, if ozanimod dose is escalated to 1 mg over a period of 6 days, there is a mean change in HR from baseline (Δ drop) of about 8 bpm between 6 and 8 hours (corresponding to the Tmax of ozanimod), whereas the 1 mg fixed dose administered on Day 1 (i.e, a 'stat' dose) shows a considerable mean change from baseline (Δ drop) of about 18 bpm between 6 and 8 hours. This change from baseline (Δ drop) is even more pronounced with the 2 mg dose, i.e., 10 bpm between 6 and 8 hours for the dose escalation scheme of 2 mg conducted over a period of 8 days versus 24 bpm between 6 and 8 hours for the fixed dose of 2 mg administered only once on day 1.

For the 0.3 mg dose there were some differences in mean change in HR from baseline between the fixed dose of 0.3 mg on day 1 versus the dose of 0.3 mg on day 1 that was involved in dose titration.

(b) Continuation of Dosing: From day 8 onwards all patients receive a dose of 1 mg (0.92 mg ozanimod base). The dose of 1 mg is selected as in the Phase 3 program, ozanimod demonstrated superior, dose-dependent efficacy compared to Avonex in reducing annualized relapse rate (ARR), reducing the number of new and enlarging T2 lesions, and reducing the number of Gd-enhancing (GdE) lesions. As per the sponsor the most frequently occurring (≥2%) related AEs by preferred term in the ozanimod 1 mg group (i.e., AEs at least possibly related to study drug) were

alanine aminotransferase increased (4.6%) and gamma-glutamyltransferase increased (4.1%). In the ozanimod 0.5 mg group, the most frequently occurring (≥2%) related AEs by preferred term were alanine aminotransferase increased (4.6%), gamma-glutamyltransferase increased (2.3%), and headache (2.1%). The most frequently occurring (≥2%) related AEs by preferred term in the IFN β-1a group were influenza like illness (4.8%), alanine aminotransferase increased (3.2%), and aspartate aminotransferase increased (2.0%). For further details refer to the review by the Safety reviewer.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Based on the results from the human mass-balance study (RPC01-1909), 26% of the dose was recovered from urine and 37% recovered from feces after oral administration of a single oral dose of [^{14}C]-ozanimod HCl. Therefore, dedicated clinical studies were conducted to assess effects of renal and hepatic impairment on the PK of ozanimod and its metabolites following single-dose administration of ozanimod.

Hepatic Impairment: The effect of hepatic impairment on the PK of ozanimod and its metabolites was evaluated in Study RPC01-1904. The PK of a single oral dose of 0.25 mg ozanimod (administered with a light meal) in subjects with mild (Child-Pugh Grade A, Group 1), and moderate (Child-Pugh Grade B, Group 2) hepatic impairment was compared with subjects with normal hepatic function (group 3), with 8 subjects in Groups 1 and 2 and 15 subjects in Group 3.

Following a single oral dose administration of ozanimod 0.25 mg, total (bound + unbound) systemic exposures (ie, $AUC_{0\text{-last}}$) for ozanimod and CC112273 in subjects with mild hepatic impairment were approximately 11% lower and 31% lower, respectively, compared to subjects with normal hepatic function.

Total systemic exposures (ie, $AUC_{0\text{-last}}$) for ozanimod and CC112273 in subjects with moderate hepatic impairment were approximately 27% higher and 33% lower, respectively, compared to subjects with normal hepatic function.

Fraction of drug unbound (Fu) for ozanimod and CC112273 were similar between all groups.

Statistical Comparison of Total (Bound + Unbound) Pharmacokinetic Parameters After Single Oral Dose Administration of 0.25 mg Between Subjects with Mild/Moderate Hepatic Impairment and Matched Subjects with Normal Hepatic Function

Primary Pharmacokinetic Endpoint	Ratio of Geometric LS Mean (90% Confidence Interval) Mild (Test) vs Normal Matched to Mild (Reference)				
	Ozanimod	RP112273	RP101988	RP101075	Total Agonist[a]
C_{max}	n = 8 vs 7 1.148 (0.898, 1.468)	n = 8 vs 7 0.775 (0.652, 0.921)	n = 8 vs 7 1.094 (0.710, 1.687)	n = 8 vs 7 0.863 (0.656, 1.134)	ND
$AUC_{0\text{-inf}}$	n = 4 vs 6 1.016 (0.758, 1.363)	ND	ND	ND	ND
$AUC_{0\text{-last}}$ ($AUC_{0\text{-12}}$ for RP101075)	n = 8 vs 7 0.886 (0.676, 1.163)	n = 8 vs 7 0.689 (0.369, 1.286)	n = 8 vs 7 1.139 (0.436, 2.975)	ND[b]	n = 8 vs 7 0.818 (0.535, 1.252)

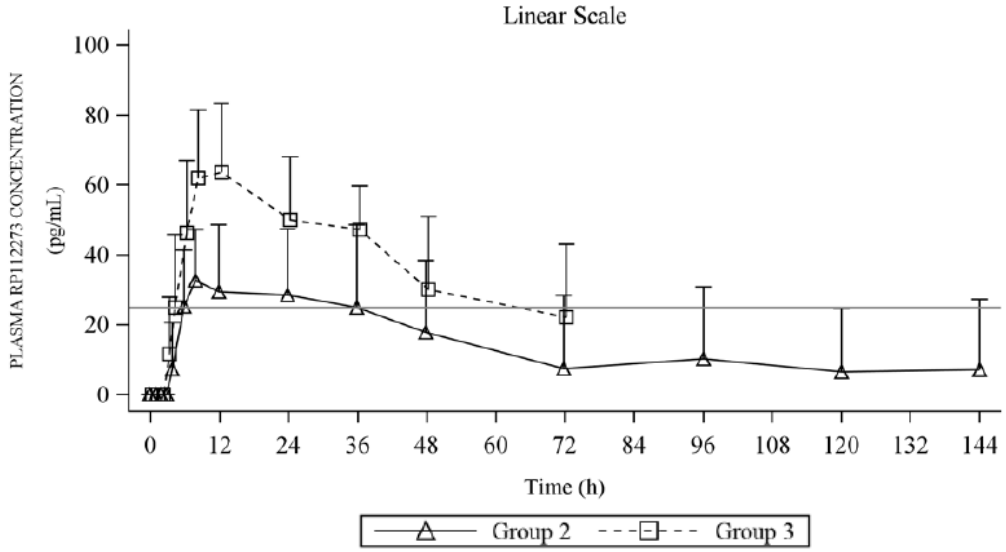
Primary Pharmacokinetic Endpoint	Ratio of Geometric LS Mean (90% Confidence Interval) Moderate (Test) vs Normal Matched to Moderate (Reference)				
	Ozanimod	RP112273	RP101988	RP101075	Total Agonist[a]
C_{max}	n = 8 1.308 (0.936, 1.828)	n = 8 0.592 (0.462, 0.759)	n = 8 1.088 (0.717, 1.651)	n = 8 1.073 (0.743, 1.550)	ND
$AUC_{0\text{-inf}}$	n = 8 vs 7 1.257 (0.925, 1.708)	ND	ND	ND	ND
$AUC_{0\text{-last}}$ ($AUC_{0\text{-12}}$ for RP101075)	n = 8 1.272 (0.933, 1.733)	n = 8 0.673 (0.317, 1.429)	n = 8 1.880 (0.979, 3.609)	ND[b]	n = 8 0.903 (0.546, 1.493)

[a] Total agonist $AUC_{0\text{-last}}$ was calculated as the sum of ozanimod, RP112273, RP101988, and RP101075 AUCs corrected for molecular weight.
[b] Comparison of $AUC_{0\text{-12}}$ for RP101075 was not done due to only 2 subjects (either as a test or reference) in each of the comparison groups.
Note: The log-transformed PK parameters were analyzed using an ANCOVA model with fixed effects for group. Age and weight were included as covariates in the model.

Source: Clinical Study Report RPC01-1904, Tables 14.2.1.3.1, 14.2.1.3.2.1, 14.2.1.3.3, 14.2.1.3.5, 14.2.1.3.6

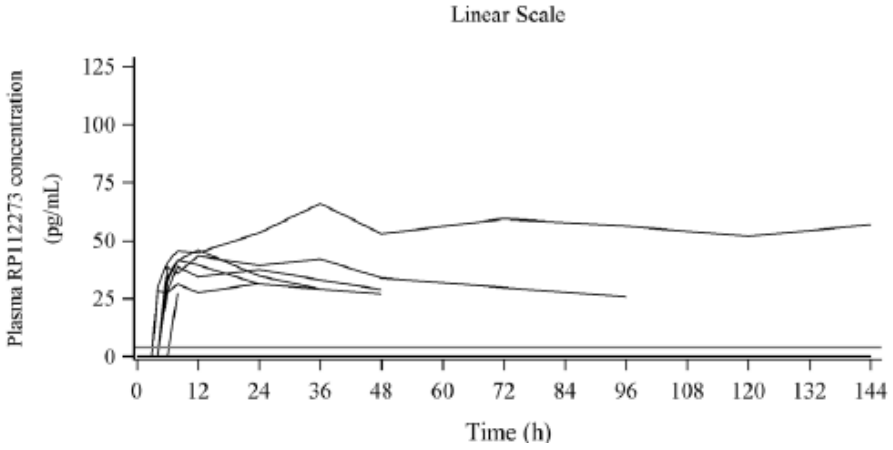
Comments: Sponsor proposes (b) (4) (b) (4) (b) (4) However, the results from study RPC01-1904 are based only on single-dose administration of ozanimod. For most subjects, concentrations of CC112273 were below the limit of quantitation (BLQ) by 60 hours in the Normal Hepatic Function group and by 48 hours in the Moderate Hepatic Impairment group.

Mean (+ SD) Plasma RP112273 Concentration-time Profiles After Single Oral Dose Administration of 0.25 mg in Subjects with Moderate Hepatic Impairment and Matched Subjects with Normal Hepatic Function (PK Population)



Abbreviations: BLQ = below the lower limit of quantification; LLOQ = lower limit of quantification; PK = pharmacokinetic; SD = standard deviation.
Note: Reference line indicates LLOQ value (25.00 pg/mL). BLQ values were replaced with 0.
Source: Figure 14.2.1.1.5

Spaghetti Plot of Plasma RP112273 Concentration Profile vs. Time: Group 2, Moderate



Source: Clinical Study Report RPC01-1904, Figure 16.2.6.2.5

CC112273 and CC1084037 are formed by metabolism, therefore their exposures are likely to decrease initially in subjects with hepatic impairment. The results from study RPC01-1904 seem to confirm this. However, at steady state, the levels of these major metabolites could potentially increase. The t½ of RP112273 and CC1084037 is about 280 hours, leading to accumulation of these active metabolites (relative to the parent) after multiple dosing. CC112273 is further metabolized by CYP2C8 to form M375 (refer to figure Metabolic Pathways for Ozanimod and Metabolites in Human). The metabolic pathways involved in the formation and/or elimination of CC112273 and CC1084037 are complex, therefore it is difficult to predict whether hepatic

impairment will lead to decreased or increased levels of RP112273 and CC1084037 at steady state. Study RPC01-1912 results show that the CYP2C8 inhibitor gemfibrozil 600 mg BID administered for three days before ozanimod administration and throughout the PK collection period of CC112273 (14 days), increased CC112273 and CC1084037 exposures (AUC_{last}) by 47% and 69%, respectively.

In addition, there are no safety data in this patient population as subjects with hepatic impairment, including mild, were excluded from the phase 2/3 trials. Liver function impairment or persisting elevations of aspartate aminotransferase (SGOT/AST) or alanine aminotransferase (SGPT/ALT) > 1.5 times the ULN, or direct bilirubin > 1.5 times the ULN) was an exclusion criterion in both 201 and 301 trials. The only subjects with hepatic impairment in the popPK dataset were from the dedicated phase 1 study 1904 (and none from the phase 2/3 studies).

Ozanimod is not recommended in patients with hepatic impairment as there are no PK or safety data in this patient population at steady state. A PMR will be issued to assess the effect of hepatic impairment on ozanimod and its major metabolites' pharmacokinetics when ozanimod is dosed until steady state is reached for RP112273.

Renal Impairment: The PK of ozanimod and active metabolites were evaluated in subjects with end stage renal disease (ESRD) and compared to matched subjects with normal renal function (8 subjects per group) in Study RPC01-1906.

Following a single oral dose administration of 0.25 mg ozanimod, systemic exposure ($AUC_{0\text{-}last}$) for ozanimod and CC112273 in ESRD subjects was approximately 27% higher and 23% lower, respectively, compared to subjects with normal renal function.

Statistical Comparison After Single Oral Dose Administration of Ozanimod 0.25 mg of Total (Bound + Unbound) and Unbound Pharmacokinetic Parameters between Subjects with ESRD and Subjects with Normal Renal Function

Primary PK Endpoint (Unit)	Ratio of Geometric LS Mean (90% Confidence Interval) ESRD (Test) vs Normal (Reference)				
	Ozanimod	RP112273	RP101988	RP101075	Total Agonist[a]
Total (bound + unbound) Parameters					
C_{max}	n = 8 0.922 (0.682, 1.247)	n = 8 0.781 (0.666, 0.917)	n = 8 1.125 (0.850, 1.488)	n = 4 vs 5 0.806 (0.615, 1.057)	ND
$AUC_{0\text{-last}}$	n = 8 1.270 (0.951, 1.696)	n = 8 0.766 (0.606, 0.969)	n = 8 1.673 (1.018, 2.750)	ND[b]	n = 8 1.006 (0.806, 1.255)
Unbound Parameters					
$C_{max,u}$	n = 8 1.054 (0.784, 1.417)	ND[c]	n = 8 1.093 (0.824, 1.450)	n = 4 vs 5 1.080 (0.754, 1.547)	ND
$AUC_{0\text{-last,u}}$	n = 8 1.450 (1.148, 1.833)	ND[c]	n = 8 1.626 (0.975, 2.710)	ND[b]	ND

Abbreviations: ANCOVA = analysis of covariance; AUC = area under the plasma concentration-time curve; $AUC_{0\text{-}12}$ = AUC from 0 to 12 hours postdose; $AUC_{0\text{-last}}$ = AUC from time 0 to last quantifiable concentration; $AUC_{0\text{-last,u}}$ = unbound $AUC_{0\text{-last}}$; C_{max} = maximum observed plasma concentration; $C_{max,u}$ = unbound C_{max}; ESRD = end stage renal disease; LS = least squares; n = number of nonzero observations; ND = not determined; PK = pharmacokinetic; vs = versus.

[a] Total agonist $AUC_{0\text{-last}}$ was calculated as the sum of ozanimod, RP112273, RP101988, and RP101075 AUCs corrected for molecular weight.

[b] Statistical comparison with only 2 ESRD subjects with non-zero $AUC_{0\text{-}12}$ or $AUC_{0\text{-last}}$ was not appropriate and was not performed.

[c] Unbound concentrations were not determined for RP112273.

Source: Clinical Study Report RPC01-1906, Table 14.2.1.3.1, Table 14.2.1.3.2, Table 14.2.1.3.3, Table 14.2.1.3.5, and Table 14.2.1.3.6

Comments: The results from study RPC01-1906 are based only on single-dose administration of ozanimod. For most subjects, concentrations of CC112273 were BLQ after 60 hours. However, neither CC112273 and CC1084037 are renally eliminated. Therefore, renal impairment is not likely to affect the PK of these metabolites.

The differences in systemic exposures of ozanimod and CC112273 in subjects with normal renal function and patients with ESRD are not clinically meaningful. Sponsor proposes that no dosing adjustment in renal impairment is needed; we agree with this recommendation.

Race/Ethnicity

The effect of race (Japanese) was evaluated in two Phase 1 studies, RPC01-1905 (Japanese PK Bridging) and RPC01-1911 (Multiple-dose PK in Japanese and Caucasians). Study RPC01-1905 was an early phase 1 study that did not include CC112273 evaluation. However, study RPC01 1911 assessed CC112273 pharmacokinetics after multiple-dose administration of ozanimod. While CC1084037 was not evaluated in these studies, results on CC112273 are applicable for

CC1084037 since CC1084037 is an inter-converting metabolite of CC112273 and there is no known genetic polymorphism on the activity of the enzymes involved in the inter-conversion of these metabolites (CBR, AKR, and HSD).

In both studies, no clinically meaningful differences in the PK of ozanimod were observed between Japanese and Caucasian subjects for the multiple-dose regimens of ozanimod 0.5, 1, and 2 mg QD. In study RPC01-1911, no clinically meaningful differences in PK of ozanimod and CC112273 were observed between Japanese and Caucasian subjects for multiple-dose regimens of ozanimod 0.5 or 1 mg QD.

Statistical Comparison of PK Parameters on Day 1 following the First Dose of 0.25 mg Ozanimod HCl in Caucasian and Japanese Subjects

Primary PK Endpoint	Ratio of GLSM (90% CI), Japanese (Test) vs Caucasian (Reference)		
	Ozanimod	RP112273	RP101988
C_{max}	n = 33 vs. 36 0.898 (0.789, 1.021)	n = 33 vs. 36 1.111 (0.985, 1.254)	n = 33 vs. 36 0.894 (0.768, 1.042)
AUC_{tau}	n = 33 vs. 36 0.897 (0.787, 1.022)	n = 33 vs. 36 0.999 (0.877, 1.139)	n = 17 vs. 16 0.833 (0.738, 0.941)

Source: Clinical Study Report RPC01-1911, Tables 14.2.1.3.1, 14.2.1.3.2, and 14.2.1.3.3

Statistical Comparison of PK Parameters on Day 28 following Repeated Doses of 0.5 mg or 1 mg Ozanimod HCl Once Daily in Caucasian and Japanese Subjects

PK Parameter	Ratio of GLSM (90% CI), Japanese (Test) vs Caucasian (Reference)			
	Ozanimod		RP112273	
	0.5 mg	1 mg	0.5 mg	1 mg
C_{max}	1.070 (0.815, 1.404)	0.883 (0.673,1.158)	0.946 (0.643,1.393)	1.284 (0.834,1.97)
AUC_{tau}	1.124 (0.857, 1.475)	0.967 (0.730,1.281)	0.992 (0.675, 1.458)	1.428 (0.926, 2.201)

Source: Clinical Study Report RPC01-1911, Tables 14.2.1.4.1, 14.2.1.4.2, and 14.2.1.4.3

No dosage adjustment is recommended in Japanese subjects receiving multiple-dose regimens of 0.5 or 1 mg ozanimod QD.

Age: No data are available in patients aged 65 years and over.

Sex: The proposed dosing regimen should be the same for male and female patients. Steady state exposure of CC112273, the major active metabolite, was about 15% lower in males than in

females. The effect of sex on CC112273 systemic exposure is not considered to be clinically meaningful.

Body Weight: Body weight had minimal effect (less than 10%) on the exposure of metabolite -73.

Smokers versus Nonsmokers: From a PK standpoint less metabolite -73 steady state exposure (AUC) is seen in smokers than in nonsmokers. Concentrations differences for metabolite -73 between smokers and nonsmokers is about 55 % with smokers showing lower concentrations. This may possibly be due to MAO-B inhibition in smokers. Intermittent smokers had ozanimod concentrations comparable to nonsmokers. For metabolite -73 intermittent smokers had concentrations that were within the concentration values of smokers and nonsmokers.

Dose	Smoking Status	Sex	Ozanimod				CC112273			
			2-6 Hours Postdose Concentrations (pM)							
			Month 12		Month 24		Month 12		Month 24	
			n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
0.5 mg	Smoker	Male	33	287 (59, 515)	17	263 (98, 427)	32	1502 (1249, 1755)	18	2343 (1349, 3337)
		Female	30	309 (90, 529)	13	327 (160, 494)	31	2364 (1849, 2880)	13	2179 (1274, 3084)
	Non-smoker	Male	80	294 (29, 560)	75	259 (78, 439)	80	5884 (4870, 6898)	73	4816 (3982, 5650)
		Female	225	316 (90, 541)	204	307 (78, 536)	225	6398 (5822, 6974)	201	5861 (5291, 6430)
	Intermittent	Male	14	332 (0, 722)	25	280 (95, 464)	13	3278 (1945, 4611)	24	3014 (1948, 4080)
		Female	17	312 (16, 607)	17	310 (51, 569)	18	3203 (2134, 3912)	19	2951 (1803, 4099)
1 mg	Smoker	Male	25	610 (213, 1007)	21	528 (30, 1026)	25	4583 (3030, 6137)	21	3819 (2136, 5502)
		Female	31	632 (0, 1422)	27	554 (229, 879)	30	7285 (4841, 9728)	27	4071 (2851, 5292)
	Non-smoker	Male	96	545 (168, 922)	71	510 (121, 900)	98	10310 (8568, 12052)	74	9302 (7757, 10848)
		Female	210	610 (134, 1086)	184	634 (35, 1234)	207	11752 (10616, 12888)	183	12073 (10824, 13322)
	Intermittent	Male	24	509 (209, 810)	25	544 (225, 863)	25	6307 (4283, 8330)	22	5088 (2841, 7335)
		Female	14	573 (99, 1046)	19	663 (85, 1241)	14	4543 (2767, 6318)	19	6940 (3928, 9951)

Source: Page 3 of Information Request of September 24, 2019

From a PD standpoint relatively less ALC reduction is seen in smokers than in nonsmokers. It is seen that for ALC reduction a 1 mg dose in smokers is comparable to a 0.5 mg dose in nonsmokers; this is seen in both the clinical studies.

Directly comparing ALC results between smokers and nonsmokers it is seen that the overall difference, Δ, (taking into account both 0.5 mg and 1 mg doses) between nonsmokers and smokers in ALC reduction is 24 %. Individually 1 mg shows less of a difference (16%) between the two groups than the 0.5 mg group (31%).

Intermittent smokers showed ALC reduction from baseline values that were within the ALC reduction from baseline values seen for smokers and nonsmokers.

Percentage change in ALC from baseline between smokers and nonsmokers (Study 201B)

Study	Dose	Smoking Status	Number of Subjects / |ALC Percent Change from Baseline (95% CI)			
			Month 3	Month 6	Month 9	Month 12
RPC01-201B	0.5 mg	Smoker	n = 43 -27.724 (-34.9151, -20.5334)	n = 36 -44.980 (-47.6546, -42.3044)	n = 35 -32.749 (-41.7258, -23.7730)	n = 34 -31.332 (-40.8722, -21.7923)
		Non-smoker	n = 340 -44.980 (-47.6546, -42.3044)	n = 334 -46.622 (-49.3923, -43.8517)	n = 329 -45.860 (-48.8816, -42.8382)	n = 317 -47.928 (-50.7084, -45.1478)
		Intermittent Smoker	n = 54 -36.178 (-42.1981, -30.1581)	n = 52 -34.889 (-41.4047, -28.3737)	n = 53 -31.077 (-38.8845, -23.2696)	n = 52 -40.529 (-45.9306, -35.1269)
	1 mg	Smoker	n = 58 -45.182 (-51.5310, -38.8328)	n = 55 -48.255 (-53.9851, -42.5253	n = 54 -48.255 (-53.9851, -42.5253)	n = 55 -48.564 (-54.4428, -42.6857)
		Non-smoker	n = 321 -54.368 (-56.9921, -51.7444)	n = 311 -55.835 (-58.4711, -53.1994)	n = 307 -53.725 (-59.8481, -47.6023)	n = 299 -59.100 (-61.3503, -56.8502)
		Intermittent Smoker	n = 52 -54.798 (-59.9105, -49.6857)	n = 52 -53.725 (-59.8481, -47.6023)	n = 51 -54.181 (-60.1500, -48.2119)	n = 50 -57.647 (-62.8220, -52.4714)

Source: Page 10 of Information Request of September 24, 2019

Percentage change in ALC from baseline between smokers and nonsmokers (Study 301)

Study	Dose	Smoking Status	Number of Subjects / ALC Percent Change from Baseline (95% CI)			
			Month 3	Month 6	Month 9	Month 12
RPC01-301	0.5 mg	Smoker	N = 74 -34.775 (-39.3537, -30.1976)	N = 72 -35.304 (-40.5964, -30.0107)	N = 71 -26.584 (-33.8989, -19.2693)	N = 70 -35.568 (-41.0140, -30.1228)
		Non-smoker	N = 340 -47.261 (-49.5724, -44.9503)	N = 336 -47.953 (-50.2755, -45.6304)	N = 330 -43.905 (-46.6927, -41.1169)	N = 323 -49.022 (-51.4942, -46.5493)
		Intermittent Smoker	N = 34 -33.636 (-44.9635, -22.3092)	N = 35 -38.956 (-47.5940, -30.3210)	N = 35 -31.516 (-44.2582, -18.7739)	N = 35 -38.204 (-49.0445, -27.3639)
	1 mg	Smoker	N = 58 -48.798 (-56.5194, -41.0773)	N = 60 -49.112 (-55.8008, -42.4231)	N = 60 -45.637 (-53.7428, -37.5312)	N = 59 -48.959 (-57.1296, -40.7893)
		Non-smoker	N = 337 -58.852 (-61.0328, -56.6706)	N = 335 -60.361 (-62.5535, -58.1688)	N = 329 -54.768 (-57.4298, -52.1058)	N = 323 -59.606 (-62.0896, -57.1225)
		Intermittent Smoker	N = 42 -59.263 (-63.7226, -54.8036)	N = 43 -55.187 (-60.922, -49.3821)	N = 42 -48.562 (-55.3447, -41.7787)	N = 41 -50.377 (-58.4513, -42.3036)

Source: Page 11 of Information Request of September 24, 2019

Adjusted Annualized Relapse Rate, ARR, the Clinical Endpoint: For the clinical endpoint of ARR the absolute difference, Δ, (*irrespective of direction* smokers ↔ nonsmoker) in ARR lowering between smokers and nonsmokers was about 18% with overlap in confidence intervals.

Dose of 0.5 mg in smokers versus Dose of 1 mg in smokers: The results for the 0.5 mg dose in study 201B show that nonsmokers have a lower ARR than smokers (0.198 versus 0.279). In study 301 the opposite is seen for the 0.5 mg dose with smokers showing a lowering of 0.227 versus 0.260 for nonsmokers. This may be an indication of a lesser or less than optimal ARR lowering effect for smokers at the 0.5 mg dose.

In contrast to the 0.5 mg dose, the 1 mg dose shows a consistent pattern for smokers where in both studies (201B and 301) smokers show lower ARR values compared to nonsmokers (0.163 smokers versus 0.188 nonsmokers in Study 201B, and 0.159 for smokers versus 0.191 for nonsmokers in Study 301).

The 0.5 mg dose shows results in opposite directions between the two studies for the outcome of the ARR lowering effect at this dose level (i.e., 0.5 mg) for the smoking group. The 1 mg dose, where in both studies the ARR is lower in smokers than in nonsmokers, provides a clear indication that smokers can, and should, be dosed at the 1 mg dose level. The 1 mg dose appears to be optimal for both smokers and nonsmokers.

Intermittent smokers: For either dose, 0.5 mg or 1 mg the ARR results for intermittent smokers are in opposite directions (either higher or lower when compared to smokers and nonsmokers) for the two studies (201B and 301). It is important to note though that the 1 mg dose showed lower ARR results for intermittent smokers compared to either smokers or nonsmokers on two out of three occasions (Study 201B, Study 301, and pooled analysis of 201B and 301), namely study 201B and for the pooled analysis. The 0.5 mg, in contrast, shows higher ARR values on two out of the three occasions for intermittent smokers. Therefore, dosing with 1 mg seems also appropriate for intermittent smokers.

Across all scenarios mentioned above there was an overlap in 95 % confidence intervals across groups.

Thus, neither the reduced exposure of CC112273 (PK) nor the lesser ALC reduction (PD) among smokers translates into any lesser of a clinical effect in smokers compared to nonsmokers when given the 1 mg dose. Therefore, the 1 mg ozanimod hydrochloride dose (equivalent to 0.92 mg ozanimod) provides sufficient exposure and response in the treatment of RMS regardless of smoking status after a 7-day dose escalation scheme has been followed in RMS patients.

3.3.4 Are there clinically relevant food-drug interactions and what is the appropriate management strategy?

Food Effect: The effect of food on ozanimod PK was evaluated in Study RPC01-1901. This was an open-label, randomized, single dose, 3-period, crossover study with a 7-day washout between periods. Twenty-four subjects were randomized and to receive a single 1-mg dose of ozanimod in 3 separate treatment periods: fasted (Treatment A), with a high-fat meal (Treatment B), and with a low-fat meal (Treatment C).

There was no effect of either the high-fat or low-fat meal on the exposure of ozanimod and its metabolites RP101988 and RP101075, as demonstrated by the 90% CIs for the ratio of geometric LS means between fed (high-fat or low-fat) and fasted treatments for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$, which were all within the equivalence limits of 0.80 to 1.25.

Statistical Assessment of a Food Effect for Ozanimod PK Parameters (PK Evaluable Population)

Comparison		PK Parameter		Geometric LS Mean		Ratio of Geometric LS Mean (Test/ Reference)	90% Confidence Interval
Test	Reference		n	Test	Reference		
Treatment B	Treatment A	$AUC_{0\text{-inf}}$	19	5716	5216	1.096	(1.046, 1.148)
		$AUC_{0\text{-last}}$	20	5308	4806	1.104	(1.049, 1.163)
		C_{max}	20	176	167	1.058	(0.969, 1.154)
Treatment C	Treatment A	$AUC_{0\text{-inf}}$	23	5716	5394	1.060	(1.017, 1.105)
		$AUC_{0\text{-last}}$	23	5201	4927	1.056	(1.013, 1.100)
		C_{max}	23	184	171	1.077	(1.019, 1.138)

Source: Report RPC01-1901, Table 14.2.1.3.1

Comments: The major metabolite RP112273 was not measured in this study. In addition, due to the long $t_{1/2}$ (approximately 10-15 days), the 7-day washout is not adequate for RP112273 PK characterization. However, the sponsor points out that food is not expected to have an effect on the metabolism or elimination of metabolites (as observed for other metabolites RP101988 and RP101075) since food only affected the absorption of the parent drug (eg, delay gastric emptying, change gastrointestinal pH, and physically or chemically interact with a dosage form).

We agree with the sponsor's justification. Zeposia can be administered with or without food.

3.3.5 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

In vitro DDI studies

Potential for ozanimod (and its metabolites) as a "victim"

In vitro studies established that multiple enzyme systems play a role in the metabolism of ozanimod and its metabolites (ALDH/ADH, CYP3A4, CYP1A1, CYP2C8, NAT-2, MAO-B, CBR, AKR 1C1/1C2, 3β- and 11β-HSD, and gut microflora) with no single metabolic pathway, or enzyme system, predominating in the overall metabolism of ozanimod.
MAO-B, CYP2C8, CBR, AKR 1C1/1C2, and 3β-/11β-HSD contribute to the overall disposition of the major active metabolite CC112273. AKR 1C1/1C2 and 3β-/11β-HSD are responsible for the inter-conversion between CC112273 and CC1084037. Clinical inhibitors or inducers of CBR, AKR 1C1/1C2, or 3β-/11β-HSD have not been identified and therefore the risk of interactions due to modulation of CRB, AKR 1C1/1C2, or 3β-/11β-HSD activities is low.
Modulators of MAO-B or CYP2C8 may alter the exposure of CC112273 and consequently its direct, interconverting metabolite CC1084037. A clinical drug interaction study was conducted to evaluate the effect of CYP2C8 inhibitor on ozanimod PK. Co-administration with MAO-B inhibitors (e.g. selegiline, phenelzine) may decrease exposure of CC112273 and the exposure of its interconverting metabolite CC1084037. The potential for clinical interaction with MAO inhibitors has not been studied. However, MAO-B inhibitors are mainly indicated for the treatment of Parkinson's disease, and their use in the RMS population is anticipated to be low.
Comment: Co-administration of ozanimod with MAO inhibitors (both selective (MAO-B) and nonselective (MAO-A and MAO-B) is not recommended.
In vitro DDI studies also suggested that ozanimod may be a substrate of P-gp and the minor active metabolite RP101988 is a substrate of P-gp and BCRP. CC112273 and CC1084037 are not substrates of drug transporters. A clinical drug interaction study was conducted to evaluate the effect of P-gp and/or BCRP inhibitors on ozanimod and RP101988 PK.

Potential for ozanimod (and its metabolites) as "perpetrator"
Ozanimod and the major metabolites CC112273, CC1084037 have no inhibitory effect on CYPs 1A2, 2B6, 2C19, 2C8, 2C9, 2D6, and 3A and no induction effect on CYPs 1A2, 2B6, and 3A.
CC112273 and CC1084037 are MAO-B inhibitors.
Ozanimod, CC112273, CC1084037 and other metabolites have no inhibitory effect on P-gp, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, and MATE2-K.
CC112273 and CC1084037 inhibit BCRP with an IC_{50} values of 25.2 nM and 22.8 nM, respectively. At clinically relevant concentrations of CC112273 and CC1084037, inhibition of BCRP is not expected supported by the calculation below.

Calculation of [I]1/IC_{50} Value for BCRP Inhibition by CC112273

Dose Regimen	C_{max}[a] (nM)	F_u (%)[b]	$I_{gut} = C_{max,u}$[c] (nM)	IC_{50} (nM)	I_{gut}/IC_{50}
1 mg QD	19.41	0.239	0.04639	25	0.001856

Abbreviations: BCRP = breast cancer resistance protein; $C_{max,ss}$ = maximum plasma concentration at steady state; F_u = unbound fraction; IC_{50} = half maximal inhibitory concentration; $[I_1]$ = unbound (free) plasma $C_{max,ss}$.

[a] Mean Cmax for CC112273 1 mg QD for 12 weeks in RMS subjects (RPC01-1001 [RMS Intensive PK/PD]) was 6977 pg/mL which was converted to nM using the molecular weight of CC112273 of 359.39.
[b] Mean Fu (%) from normal subjects (RPC01-1904 [Hepatic Impairment])
[c] Cmax,u = Cmax x Fu.

Sources: Report RPC01-1001 [RMS Intensive PK/PD] CSR; Report RPC01-1904 [Hepatic Impairment] CSR

In Vivo Assessment of Drug-Drug Interactions

Effect of Other Drugs on Ozanimod and Major Metabolites

Ozanimod is initially transformed by CYPs 3A/1A1 to form the minor active metabolite RP101075. RP101075 is further transformed by MAO-B to form the major active metabolite, CC112273. CC112273 is further metabolized by CYP2C8 to form M375 and by carbonyl reductase (CBR) to form CC1084037. Therefore, a clinical study was conducted to evaluate the effect of inhibitor or inducer of CYP2C8 and/or CYP3A on the exposure of ozanimod and its major metabolites, CC112273 and CC1084037.

Co-administration of gemfibrozil (a strong inhibitor of CYP2C8) 600 mg twice daily at steady state and a single dose of ozanimod 0.46 mg resulted in no clinically meaningful changes in exposure (AUC) of ozanimod and increased exposure (AUC) of active metabolites CC112273 and CC1084037 by approximately 47% and 69%, respectively.

Effect of Gemfibrozil (Group B versus Group A) on the PK of Ozanimod and its Metabolites

Primary PK Endpoint	Ratio of Geometric LSM (90% CI), Test vs Reference					
	Ozanimod	CC112273	CC1084037	RP101988	RP112289	RP101124 (inactive)
C_{max}	n = 20 1.083 (0.9455, 1.2402)	n = 20 1.265 (0.8499, 1.1110)	n = 20 1.353 (1.1368, 1.6096)	n = 20 1.437 (1.2060, 1.7121)	n = 20 1.256 (1.0511, 1.5012)	n = 20 1.296 (1.0705, 1.5680)
AUC_{inf}	n = 19 vs 20 0.972 (0.8499, 1.1110)	ND	ND	n = 16 vs 8 1.313 (1.0530, 1.6368)	ND	n = 6 vs 9 0.974 (0.7084, 1.3393)
AUC_{last}	n = 19 vs 20 0.972 (0.8460, 1.1176)	n = 19 vs 20 1.470 (1.1083, 1.9502)	n = 19 vs 20 1.687 (1.2545, 2.2697)	n = 19 vs 20 1.555 (1.2625, 1.9157)	n = 19 1.280 (0.9732, 1.6844)	n = 19 vs 20 1.251 (0.9838, 1.5909)

Source: Report RPC01-1912, Table 14.2.3.1 and Listing 16.2.6.1

Comments: Sponsor proposes, (b) (4) (b) (4). We disagree. Co-administration of ozanimod with strong inhibitors of CYP2C8 should not be recommended since the exposures (AUC_{last}) of the active metabolites of ozanimod (CC112273, CC1084037 and RP101988) were all increased by 47-69%. In addition, the increase in AUC_{inf} of these metabolites could not be determined due to the long half-lives (potentially even more increase in AUC_{inf} than in AUC_{last}).

Coadministration of itraconazole (a strong inhibitor of CYP3A4) twice daily at steady state and a single dose of ozanimod 0.46 mg had no significant effect on ozanimod C_{max} and AUC_{inf}. Itraconazole decreased the C_{max} of the major metabolites CC112273 and CC1084037 by

approximately 21% and 22%, respectively. Coadministration with itraconazole had no effect on the AUC_{last} of CC112273 and decreased the AUC_{last} of CC1084037 by approximately 22%. Coadministration with itraconazole had no effect on the AUC_{inf} for RP101988 and RP101124 and decreased the AUC_{last} of RP112289 by approximately 26%.

Effect of Itraconazole (Group D versus Group C) on the PK of Ozanimod and its Metabolites (PK Population)

Primary PK Endpoint	Ratio of Geometric LSM (90% CI), Test vs Reference					
	Ozanimod	CC112273	CC1084037	RP101988	RP112289	RP101124 (inactive)
C_{max}	n = 20 1.026 (0.8984, 1.1719)	n = 20 0.786 (0.6942, 0.8889)	n = 20 0.775 (0.6649, 0.9041)	n = 20 0.835 (0.7319, 0.9519)	n = 20 0.862 (0.6758, 1.1006)	n = 20 1.082 (0.8624, 1.3582)
AUC_{inf}	n = 19 1.125 (0.9702, 1.3048)	ND	ND	n = 18 vs 19 0.975 (0.8639, 1.1009)	ND	n = 16 vs 17 0.960 (0.8072, 1.1422)
AUC_{last}	n = 19 1.129 (0.9692, 1.3143)	n = 19 0.945 (0.8112, 1.1016)	n = 19 0.883 (0.7547, 1.0322)	n = 19 0.949 (0.8280, 1.0881)	n = 19 0.738 (0.5751, 0.9474)	n = 19 0.955 (0.7424, 1.2280)

Source: Report RPC01-1912, Table 14.2.3.2, and Listing 16.2.6.1

No dosing adjustment is necessary when ozanimod is co-administered with CYP3A inhibitors.

Co-administration of rifampin (a strong inducer of CYP3A and P-gp, and a moderate inducer of CYP2C8) 600 mg once daily at steady state and a single dose of ZEPOSIA 0.92 mg reduced the exposure (AUC) for ozanimod, CC112273, and CC1084037 by approximately 24%, 60%, and 55%, respectively.
The clinical significance of these decreases is not known. It is possible that the decrease in exposure of ozanimod and its major metabolites could decrease the efficacy of the drug. The co-administration of ozanimod with strong CYP inducers should be avoided.

Effect of Rifampin (Group E versus Group C) on the PK of Ozanimod and its Metabolites

Primary PK Endpoint	Ratio of Geometric LSM (90% CI), Test vs Reference					
	Ozanimod	CC112273	CC1084037	RP101988	RP112289	RP101124 (inactive)
C_{max}	n = 20 0.789 (0.6759, 0.9199)	n = 20 0.868 (0.7467, 1.0093)	n = 20 0.848 (0.7201, 0.9981)	n = 20 1.378 (1.2047, 1.5757)	n = 20 1.396 (1.1602, 1.6786)	n = 20 1.069 (0.9115, 1.2542)
AUC_{inf}	n = 19 0.758 (0.6409, 0.8970)	ND	ND	n = 17 vs 19 1.050 (0.9241, 1.1922)	ND	n = 13 vs 17 0.761 (0.6544, 0.8846)
AUC_{last}	n = 19 0.749 (0.6283, 0.8928)	n = 19 0.402 (0.3193, 0.5057)	n = 19 0.446 (0.3456, 0.5767)	n = 19 1.043 (0.9031, 1.2047)	n = 19 0.796 (0.6360, 0.9970)	n = 19 0.760 (0.6319, 0.9132)

Source: Report RPC01-1912, Table 14.2.3.2 and Listing 16.2.6.1

Effect of Strong Inhibitor of BCRP on Ozanimod

The formation of the active metabolite RP101988 from ozanimod is mediated via ADH and ALDH enzymes. In vitro data show that RP101988 is a substrate of both P-gp and BCRP drug transporters.

A clinical drug interaction study (RPC01-1903) was conducted to evaluate the effect of P-gp and/or BCRP inhibitors on the single-dose PK of ozanimod and its metabolites in healthy adult subjects. Cyclosporine is a probe inhibitor of both P-gp and BCRP. Subjects received 0.25-mg ozanimod capsule with or without cyclosporine in 2 sequential treatment periods in this study.

Cyclosporine had no effect on ozanimod exposure and doubled the exposure of the minor active metabolites RP101988 and RP101075.

PK Parameter	Geometric LSM Ratio[a] (90% CI)		
	Ozanimod	RP101988	RP101075
C_{max}	0.975 (0.909, 1.045)	1.960 (1.781, 2.158)	1.966 (1.661, 2.327)
AUC_{inf}	1.013 (0.950, 1.080)	ND[b]	ND[b]
AUC_{last} (AUC_{0-12} for RP101075)	1.016 (0.950, 1.087)	2.324 (2.011, 2.686)	1.946 (1.683, 2.250)

[a] Ratio of ozanimod plus cyclosporine (Treatment B) to ozanimod alone (Treatment A).

[b] AUC0-inf was not included in the statistical analysis due to > 50% of the data missing (eg, extrapolated AUC0-inf more than 20%, R2 < 0.80, or there were < 3 points available for the determination of λz) for one or both of the treatments

Source: Report RPC01-1903, Table 14.2.1.3.1, Table 14.2.1.3.2, Table 14.2.1.3.3, and Table 14.2.1.3.4.

Comments: The effect of cyclosporine on the major metabolites RP112273 and CC1084037 was not evaluated as these metabolites have not been identified at the time this study was conducted. In addition, PK samples were not available for re-analysis to quantify RP112273 and CC1084037 (which was done for some of the more recently conducted clinical studies). The sponsor proposes the following labeling recommendations; I agree.

(b) (4)

(b) (4) *Co-administration of inhibitors of BCRP (e.g., cyclosporine, eltrombopag) with ZEPOSIA is not recommended.*

Effect of ozanimod on Other Drugs

Drug-drug interaction with oral contraceptive

Study RPC01-1907 was designed to characterize the effects of steady-state concentrations of ozanimod on the PK of an oral contraceptive containing ethinyl estradiol (EE) and norethindrone (NE) in healthy adult females. However, the major metabolites RP112273 and CC1084037 have not been identified at the time this study was conducted and the study design did not include long enough dosing with ozanimod to achieve steady state for these metabolites. Ozanimod was titrated to 1 mg (0.25 mg QD on Days 1 to 4, 0.5 mg QD on Days 5 to 7) and then 1 mg was administered QD on Days 8 to 13. On Day 12, ozanimod was co-administered with a single dose of oral contraceptive containing 35 µg EE and 1 mg NE.
The co-administration of multiple doses of ozanimod (Days 1 to 13) did not have any effect on EE or NE exposures.

Primary Pharmacokinetic Analysis (PK Population)

Primary Pharmacokinetic Endpoint	Ratio of Geometric Least Square Means (Test to Reference) and Point Estimate (90% Confidence Interval for Geometric Least Square Mean Ratio of Test to Reference)	
	Ethinyl Estradiol	Norethindrone
$AUC_{0\text{-inf}}$ (pg*h/mL)	n = 16 0.948 (0.917, 0.981)	n = 21 0.922 (0.873, 0.974)
$AUC_{0\text{-last}}$ (pg*h/mL)	n = 21 0.947 (0.916, 0.979)	n = 21 0.917 (0.866, 0.971)
C_{max} (pg/mL)	n = 21 0.999 (0.937, 1.065)	n = 21 0.924 (0.839, 1.017)

Source: Report RPC01-1907, Table 14.2.1.3

Comments: Ozanimod dosing in this study was not long enough to attain steady state for the major metabolites RP112273 and CC1084037. However, based on in vitro study data, neither RP112273 nor CC1084037 is an inhibitor or inducer of CYP enzymes. Therefore, these metabolites are not expected to have any effect on the PK of EE and NE.

Effects of Ozanimod on Drugs that Slow Heart Rate or Atrioventricular Conduction (e.g., Beta Blockers or Calcium Channel Blockers)

Ozanimod and its active metabolites are S1P receptor agonists. S1P receptor modulators are responsible for a transient, dose-dependent decrease in heart rate (HR). Therefore, a clinical study (RPC01-1908) was conducted to evaluate the cardiac effects of initiating ozanimod treatment in subjects receiving propranolol or diltiazem.

This was a double-blind, randomized, placebo-controlled, crossover study. Two groups of subjects (18 per group) were enrolled in parallel. Subjects in each group participated in 3 treatment periods, separated by a washout period of 7 to 10 days between dosing.

Group	Treatment	Day 1	Day 2	Day 3	Day 4	Day 5
1	A	Placebo for propranolol once daily (QD) x 5 days →				
						Ozanimod 0.25 mg
	B	Propranolol 80 mg QD x 5 days →				
						Placebo for ozanimod
	C	Propranolol 80 mg QD x 5 days →				
						Ozanimod 0.25 mg
2	D	Placebo for diltiazem QD x 5 days →				
						Ozanimod 0.25 mg
	E	Diltiazem 240 mg QD x 5 days →				
						Placebo for ozanimod
	F	Diltiazem 240 mg QD x 5 days →				
						Ozanimod 0.25 mg

Notes: The washout period between treatments was only one week. Due to the long $t_{1/2}$ of CC112273, carryover (measured as a treatment*period interaction) was added into all statistical models used in the analysis of PD parameters. No statistically significant carryover effects were observed.

Coadministration of ozanimod starting dose (0.25 mg) and steady-state propranolol long-acting (80 mg) or steady-state diltiazem extended release (240 mg) did not result in any additional clinically meaningful changes in HR or interval from the beginning of the P wave to the beginning of the QRS complex (PR interval) compared to either drug alone. This statement needs to be confirmed by the clinical team.

Comments: The potential pharmacokinetic (PK) interaction between ozanimod and propranolol or diltiazem could not be evaluated in this study as no results were available for the major metabolites and the washout between periods was not adequate (due to the long $t_{1/2}$ of RP112273). Also, only the effect of a single dose of ozanimod on the PK of propranolol or diltiazem could be evaluated. Considering that the accumulation ratio of the major metabolite of ozanimod RP112273 is 16, single dose results might not be representative of the (steady state) effects of ozanimod on propranolol/ diltiazem. However, since this study was designed to

capture the treatment effect at ozanimod initiation, the design may be adequate for the pharmacodynamic (PD) evaluations, e.g. HR and PR.

Sponsor claims that no PK interactions between RP112273 and propranolol or diltiazem are expected based on their metabolic pathways: we agree. While diltiazem has been reported to be an inhibitor and a substrate of CYP3A4, CYP3A strong inhibitors had no effect on the exposure of ozanimod and its major metabolites based on the results of study RPC01-1912.

In vitro data showed that ozanimod major metabolites CC112273 and CC1084037 are MAO inhibitors. The minor metabolite RP101075 also inhibits MAO-A and MAO-B.
Monoamine oxidase inhibition can lead to peripheral or central neurotransmitter accumulation. Monoamine oxidase inhibitors, when taken in combination with vasoconstrictors, such as pseudoephedrine (PSE), or high dietary tyramine can cause sudden blood pressure elevations that may lead to hypertensive crises (Bainbridge, 2008).
Therefore, clinical studies were conducted to evaluate the effect of ozanimod on blood pressure and heart rate response to PSE and the effect of ozanimod on pressor response to oral tyramine in healthy subjects.

RPC01-1914 was a randomized, double-blind, placebo-controlled study to assess the potential of ozanimod to enhance pressor **responses to pseudoephedrine** in healthy subjects.
Pseudoephedrine is a sympathomimetic agent which is found in many over-the-counter medicines to relieve nasal congestion. Pseudoephedrine displaces norepinephrine from storage vesicles in presynaptic neurons, thereby releasing norepinephrine into neuronal synapses where it stimulates primarily alpha-adrenergic receptors. Monoamine oxidase inhibitors may reduce the deamination of norepinephrine, leading to pressor effect enhancement.
The ozanimod dosing regimen 2 mg (or 1.84 mg) QD in this study was selected to achieve CC112273 C_{max} on Day 28 similar to CC112273 C_{max} at steady state ($C_{max,ss}$) range observed in RMS patients following 12-week dosing of ozanimod 0.92 mg QD.
Due to the long terminal elimination half-life of CC112273 of approximately 15 to 16 days, a crossover study design was considered not feasible, therefore this study had a parallel-arm design. Subjects received placebo or ozanimod QD for 30 days (including the initial 10-day dose escalation). On Day 30, a single oral dose of PSE 60 mg was co-administered with placebo or ozanimod. On Days 29 and 30, blood pressure (BP) and heart rate (HR) for cardiovascular endpoints were measured in triplicate at pre-dose and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after dosing. The primary cardiovascular endpoint was the Day 30 maximum time-matched change from Day 29 in supine blood pressure (SBP).

Effect of Ozanimod on PSE-Induced Pressor Response: Day 30 Maximum Time-Matched Change from Day 29 for SBP, DBP, and HR (PP Population)

Cardiovascular Parameters (Units)	Mean (SD)		LS Means		LS Means Difference (Test minus Reference)	90% CI for LS Means Difference (Test minus Reference)
	Ozanimod + PSE (Test) N = 28	Placebo + PSE (Reference) N = 24	Ozanimod + PSE (Test) N = 28	Placebo + PSE (Reference) N = 24		
SBP (mmHg)	15.50 (5.418)	14.64 (5.952)	15.49	14.63	0.86	(-1.81, 3.53)
DBP (mmHg)	9.63 (3.683)	8.96 (4.444)	9.74	9.10	0.64	(-1.23, 2.51)
HR (bpm)	13.91 (5.350)	10.90 (4.637)	13.76	10.73	3.03	(0.71, 5.35)

Source: Report RPC01-1914, Table 14.2.2.1.2

Co-administration of ZEPOSIA with pseudoephedrine did not potentiate the pseudoephedrine-induced blood pressure response. ZEPOSIA increased the pseudoephedrine-induced heart rate response by approximately 3 bpm.
The significance of the HR increase will be evaluated by the clinical team (consult sent to CDER OND ABPM).

There was no effect of multiple dose administration of ozanimod on the exposure of PSE.

Effect of Multiple Doses of Ozanimod on a Single Dose of PSE (PK Population)

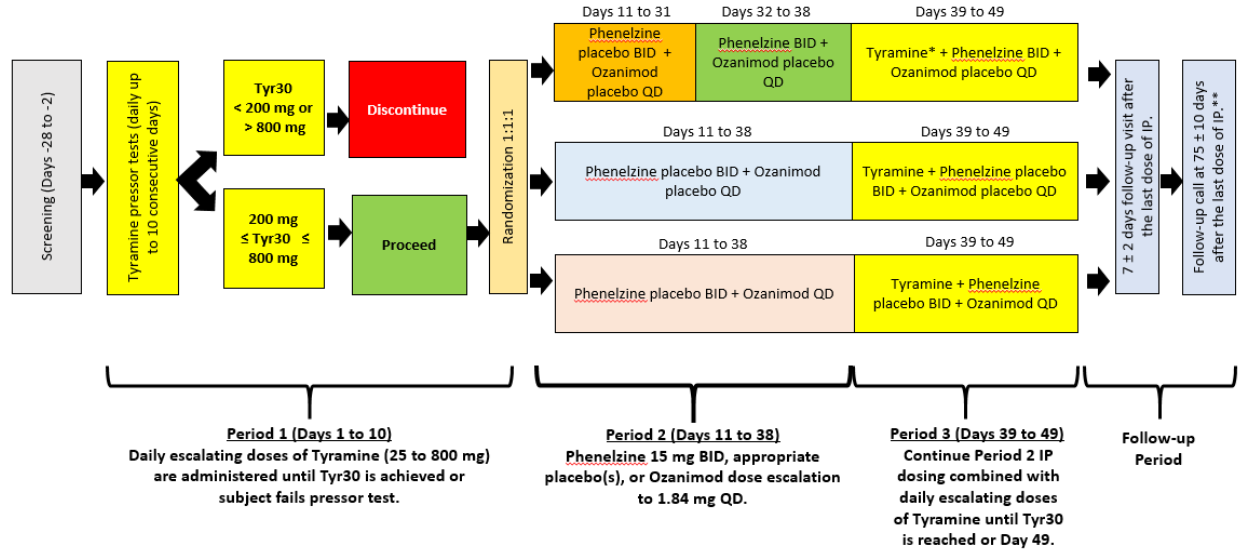
PSE Primary PK Endpoint (Units)	Geometric LS Means		Ratio of Geometric LS Means (Test to Reference)	90% CI for Ratio of Geometric LS Means
	Ozanimod + PSE (Test) N = 28	Placebo + PSE (Reference) N = 24		
C_{max} (ng/mL)	256	262	0.979	0.922, 1.040
AUC_{0-24} (ng*h/mL)	2450	2383	1.028	0.935, 1.130

Source: Report RPC01-1914, Table 14.2.1.5

In addition, pharmacodynamic (PD) blood samples for monoamine oxidase B (MAO-B) activity in platelets were collected at screening, pre-dose on Days 1, 5, 8, 26 to 30, and at 12 hours post-dose on Days 1 and 28. CC112273 and CC1084037 had no inhibitory effect on human platelet MAO-B activity, a biomarker (per the sponsor) for central MAO-B activity, compared to placebo. However, the reliability of this biomarker to predict MAO-B inhibition needs to be confirmed (consult).

Effect of ozanimod on pressor response when co-administered with oral tyramine

A study was conducted to evaluate the potential effect of ozanimod on pressor response when co-administered with oral tyramine in healthy adult subjects. **Study RPC01-1913** was a double-blind, placebo- and positive-controlled study.



*A lower dose of Tyramine will be administered in the Phenelzine treatment group compared with other treatment groups.
** Data for the 75 ± 10 days post-last dose of IP follow-up will be collected and reported in a separate Phase 1 extension study (Protocol RPC01-1915).

Comments: The design of the study could have been improved by including two dosing levels for ozanimod (helping establish dose-response) and by including another positive control (e.g. selegiline or rasagiline) similar to the tyramine DDI study design for safinamide and Azilect. These two provisions could have helped in interpreting the results of this study, which showed unexpected significant effect on pressor response in the placebo group.

The effect of ozanimod on pressor response to oral tyramine were assessed by Tyr30 and TSF. Tyr30 was the tyramine dose required to increase systolic blood pressure by at least 30 mm Hg from daily-defined baseline in 3 consecutive measurements within 4 hours after tyramine dosing. Tyramine sensitivity factor (TSF) was the ratio of Tyr30 in Period 1 over Tyr30 in Period 3. During Period 1, the median Tyr30 was similar between all 3 treatment groups (400 mg). During Period 3, the median Tyr30 was the lowest in the placebo group (25 mg), followed by the phenelzine (75 mg) and ozanimod (200 mg) groups. Consequently, the median TSF was the highest (14.0) in the placebo group, followed by the phenelzine (5.17) and ozanimod (2.00) groups. These results revealed an unexpected significant placebo effect as the placebo group was expected to show a median TSF of approximately 1.

Effect of Placebo, Phenelzine, and Ozanimod on Pressor Response to Oral Tyramine as Assessed by Tyr30 and Tyramine Sensitivity Factor

Parameter (Unit)	Statistics	Placebo (N = 22)	Phenelzine (N = 22)	Ozanimod (N = 21)
Period 1 Tyr30 (mg)	n	22	22	21
	Mean (SD)	427 (142)	400 (97.6)	357 (117)
	Median	400	400	400
	Min, Max	200, 700	200, 600	200, 600
Period 3 Tyr30 (mg)	n	22	22	21
	Mean (SD)	166 (198)	70.5 (47.9)	204 (184)
	Median	25.0	75.0	200
	Min, Max	12.5, 600	6.25, 175	12.5, 600
TSF	n	22	22	21
	Mean (SD)	15.7 (15.1)	13.5 (16.9)	6.5 (8.31)
	Median	14.0	5.17	2.00
	Min, Max	0.3, 56.0	1.6, 64.0	0.6, 32.0
	GM	6.82	7.77	3.10
	GM CV%	345	133	190
	95% CI	9.0, 22.4	6.0, 21.0	2.7, 10.2

Source: Report RPC01-1913, Tables 14.2.3.1 and 14.2.3.3

Statistical Analyses of Log-Transformed Tyramine Sensitivity Factor to Assess the Effect of Ozanimod on Pressor Response to Oral Tyramine

Comparison	Number of Subjects		Geometric LS Means		Ratio of Geometric LS Means (Test to Reference)	90% CI for Ratio of Geometric LS Means (Test to Reference)
	Test	Reference	Test	Reference		
Ozanimod (Test) vs. Placebo (Reference)	21	22	3.16	6.34	0.4988	(0.2367, 1.051)
Phenelzine (Test) vs. Placebo (Reference)	22	22	7.65	6.51	1.1741	(0.5875, 2.3461)

Source: Report RPC01-1913, Tables 14.2.3.3.1.1 and 14.2.3.3.2.1

Summary: The results of the study are uninterpretable and can not be used to support labeling.

A PMR will be issued to conduct a formal tyramine challenge study (b) (4).

Labeling Comments:

Sponsor proposes to include the following information in Section 12.3 of Zeposia label:

(b) (4)

This information is not appropriate to be included in Sect 12.3 for the following reasons:

- Labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular, per 21 CFR 201.56(a)(2).
- Nonclinical animal information should generally be included in subsection 13.2 Animal Toxicology and/or Pharmacology unless it is necessary for the understanding of pharmacology data in humans, per guidance Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.

The proposed by the sponsor labeling language implies (b) (4)

(b) (4)

Whether Zeposia label should include (b) (4)

(b) (4) needs to be discussed with the clinical team (consult sent to CDER OND ABPM).

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Two immediate release capsule formulations have been used in ozanimod clinical development (Formulation 1 and Formulation 2). A third formulation, Formulation 3, is the proposed commercial formulation. All three formulations use the same excipients (microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate). All formulations were designed as immediate release products in a hard gelatin capsule. A

comparison of the formulations is provided in the table below.

Composition of the Development and Registration/Commercial Formulations

	Composition (mg)									
	Development							Registration/Commercial		
	Formulation 1 (Process 1)				Formulation 2 (Process 2)			Formulation 3 (Process 3)		
	Strengths (mg)									
Formulation Component	**0.1**	**0.25**	**0.5**	**1.0**	**0.25**	**0.5**	**1.0**	**0.25**	**0.5**	**1.0**
Ozanimod HCl	0.10	0.25	0.50	1.00	0.25	0.50	1.00	0.25	0.50	1.00
Microcrystalline cellulose, (b) (4) (b) (4)	(b) (4)									
Colloidal silicon dioxide										
Croscarmellose sodium										
Magnesium stearate										
Total theoretical capsule components weight (mg)										

Source: Module 3, Section 3.2.P.2.2, Table 2

The registration/commercial drug product (Formulation 3) was introduced to simplify the manufacturing process and (b) (4). Formulation 3 utilizes the same quantitative and chemical formulation as Formulation 1 and Formulation 2, however (b) (4) (b) (4)

The changes in (b) (4) and manufacturing process/equipment are considered (b) (4) as assessed via US FDA Guidance for Industry 'Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, 1995' and 'Manufacturing Equipment Addendum, 2014'.

Comparative dissolution testing was performed for representative batches of Formulation 2 and Formulation 3 drug product. Dissolution data demonstrate that the formulations are equivalent.

Comments: This claim was confirmed by the OPQ team. The sponsor has demonstrated the similarity in the dissolution profiles to establish the in vitro bridging. This is sufficient to bridge the formulations and no in vivo BE study is needed.

4. APPENDICES

4.1: Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Ozanimod and its metabolites CC112273, CC1084037, RP101988, RP112289, RP101075, RP101442, and RP101124 were quantified in plasma (and urine, ozanimod, RP101988, RP101075, RPC101442 and CC112273 only) using validated high-performance liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods.

In addition, ethinyl estradiol, norethindrone, itraconazole, gemfibrozil, diltiazem, propranolol, pseudoephedrine and tyramine, were also quantified by validated LC-MS/MS methods. Assay interference evaluations were performed; these compounds did not interfere with the quantitation of ozanimod and its metabolites.

The validation results are summarized below.

(b) (4) Study 025998: Ozanimod (RPC1063) Human Plasma Method Validation

Species: Human	Matrix: Plasma	Anticoagulant: EDTA (K_2, K_3)	Stabilizer: N/A
Method: Protein Precipitation	Regression model: Linear, $1/x^2$		GLP Status: Yes
Identification of Sample	Concentration (pg/mL)	Method Performance	
		Accuracy (% RE)	Precision (% CV)
Calibration range	40.0-10000	-1.5 to 2.5	≤ 6.6
Intra-day QC	40 (LLOQ)	5.3	5.5
	120, 800, 5000, 8000	4.1 to 9.4	≤ 6.3
Inter-day QC	40 (LLOQ)	7.3	6.5
	120, 800, 5000, 8000	1.6 to 5.8	≤ 5.9
Stability			
Bench stability for 4.9 h (RT)	120, 8,000	-5.0 to -0.1	≤ 7.1
Freeze-thaw (3 cycle)	120, 8,000, 20000 (LQC, HQC, DilQC)	-7.6 to 2.0	≤ 4.7
Long term for 462 d at -20°C	120, 8,000	-11.5 to -6.7	≤ 2.9
Long term for 462 d at -80°C	120, 8,000	-5.9 to -2.5	≤ 6.2
Processed sample for 261 h (4-10°C)	120, 8,000	-4.1 to -1.7	≤ 4.2

(b) (4) Study 178930: Ozanimod (RPC1063), RP101075, RP101442, and RP101988 Human Plasma Method Validation

Species: Human	Matrix: Plasma	Anticoagulant: K_2EDTA	Stabilizer: N/A
Method: Liquid-Liquid Extraction	Regression model: Linear, $1/x^2$		GLP Status: Yes

Identification of Sample	Concentration (pg/mL)	Method Performance	
		Accuracy (% RE)	Precision (% CV)
Calibration range	4.00-2000 (RPC1063); 4.00-2000 (RP101075); 8.00-4000 (RP101442); 16.0-4000 (RP101988)	-1.25 to 2.50 -1.10 to 1.00 -2.95 to 3.38 -1.50 to 2.50	≤ 5.39 ≤ 6.75 ≤ 3.70 ≤ 8.26
Intra-day QC	LLOQ 4.00 (RPC1063); 4.00 (RP101075); 8.00 (RP101442); 16.0 (RP101988)	 -3.25 to 1.50 -4.75 to 8.25 -6.50 to 5.63 -5.00 to 4.38	 ≤ 6.87 ≤ 7.48 ≤ 5.75 ≤ 18.3
	12.0, 100, 1600 (RPC1063); 12.0, 100, 1600 (RP101075); 24.0, 200, 3200 (RP101442); 48.0, 200, 3200 (RP101988)	-2.00 to 4.17 -1.56 to 4.17 -3.78 to 3.75 -3.88 to 6.88	≤ 3.47 ≤ 3.86 ≤ 4.28 ≤ 8.15
Inter-day QC	LLOQ 4.00 (RPC1063); 4.00 (RP101075); 8.00 (RP101442); 16.0 (RP101988)	 -0.250 -0.250 -2.25 -1.25	 6.54 7.47 7.51 14.0
	12.0, 100, 1600 (RPC1063); 12.0, 100, 1600 (RP101075); 24.0, 200, 3200 (RP101442); 48.0, 200, 3200 (RP101988)	-0.813 to 2.50 1.00 to 3.00 -2.72 to 2.08 -2.22 to 5.42	≤ 3.10 ≤ 3.04 ≤ 3.33 ≤ 7.45

Stability			
Bench stability for 6 h (RT)	12.0, 1600 (RPC1063); 12.0, 1600 (RP101075); 24.0, 3200 (RP101442); 48.0, 3200 (RP101988)	-6.19 to -5.83 -2.38 to 0.00 -5.94 to 1.67 -3.13 to 3.13	≤ 3.11 ≤ 5.07 ≤ 0.495 ≤ 1.53
Freeze-thaw (6 cycle)[a]	12.0, 1600 (RPC1063); 12.0, 1600 (RP101075); 24.0, 3200 (RP101442); 48.0, 3200 (RP101988)	-0.438 to 3.33 -5.25 to 5.83 -5.09 to 7.08 1.41 to 1.67	≤ 2.14 ≤ 2.34 ≤ 6.81 ≤ 0.893
Long term for 1109 d at -70°C	12.0, 1600 (RPC1063); 12.0, 1600 (RP101075); 24.0, 3200 (RP101442); 48.0, 3200 (RP101988)	-10.5 to -6.67 -3.33 to -2.56 -14.2 to -10.8 -10.2 to -2.71	≤ 2.84 ≤ 5.74 ≤ 5.42 ≤ 5.14
Long term for 403 d at -20°C	12.0, 1600 (RPC1063); 12.0, 1600 (RP101075); 24.0, 3200 (RP101442); 48.0, 3200 (RP101988)	5.00 to 5.25 -8.33 to -2.75 -10.3 to -7.50 5.09 to 5.83	≤ 4.85 ≤ 6.94 ≤ 2.34 ≤ 7.78

(b) (4) Study 187077: CC112273, CC1084037, and RP112289 Human Plasma Method Validation

Species: Human	Matrix: Plasma	Anticoagulant: K_3EDTA	Stabilizer: N/A
Method: Supported Liquid Extraction	Regression model: Linear, $1/x^2$		GLP Status: Yes
Identification of Sample	Concentration (pg/mL)	Method Performance	
		Accuracy (% RE)	Precision (% CV)
Calibration range	25.0-10000 (CC112273) 4.00-1600 (CC1084037) 4.00-1600 (RP112289)	-2.44 to 4.00 -2.38 to 2.50 -1.75 to 2.75	≤ 2.78 ≤ 6.34 ≤ 7.60
Intra-day QC	LLOQ 25.0 (CC112273) 4.00 (CC1084037) 4.00 (RP112289)	 -6.40 to 8.00 12.0 to 14.5 -2.00 to 16.5	 ≤ 9.81 ≤ 8.91 ≤ 13.8
	75.0, 500, 8000 (CC112237) 12.0,75.0,1200 (CC1084037) 12.0,75.0,1200 (RP112289)	 -11.2 to 2.27 -8.27 to 4.17 -7.33 to 9.17	 ≤ 4.28 ≤ 5.32 ≤ 4.50
Inter-day QC	LLOQ 25.0 (CC112273) 4.00 (CC1084037) 4.00 (RP112289)	 0.00 13.0 6.25	 9.20 7.18 12.5
	75.0, 500, 8000 (CC112237) 12.0,75.0,1200 (CC1084037) 12.0,75.0,1200 (RP112289)	 -6.20 to -1.20 -4.67 to -0.833 -4.80 to 0.833	 ≤ 4.18 ≤ 5.17 ≤ 7.26
Stability			
Bench stability for 32.5 h (4°C)	75, 8000 (CC112273) 12, 1200 (CC1084037) 12, 1200 (RP112289)	-3.21 to -1.20 -1.75 to 2.50 -3.33 to -1.67	≤ 1.98 ≤ 2.15 ≤ 3.48
Freeze-thaw (6 cycles, -70°C/Ice Bath)	75, 8000 (CC112273) 12, 1200 (CC1084037) 12, 1200 (RP112289)	-3.10 to 0.800 --2.17 to 0.00 -3.67 to 2.50	≤ 1.42 ≤ 6.37 ≤ 4.09

A 17-month LTS data for RP112273 was provided to justify the analysis of retained plasma samples for RP112273 in studies RPC01-201 Part B, RPC01-301, RPC01-1904 (hepatic impairment study), RPC01-1906 (renal impairment study) and multiple-dose study RPC01-1001 in subjects with RMS (refer to Section 3.1).

The assays performance during the samples analysis was evaluated in each of the clinical studies. Assays performance parameters, including incurred sample reanalysis (ISR), were adequate for ozanimod and its metabolites. The only exception was the minor metabolite RP101075: there were ISR failures with analysis across multiple studies, however RP101075 contributes less than 1% of the total drug exposure.

Additional Issues in Study RPC01-1913

Tyramine assay: The total number of samples selected for the assessment of incurred sample reproducibility was 184; however only 181 were assessed because 3 ISR samples required

deactivation being out of bias (>15.0%). For each reproducibility result, the relative difference from the original result was calculated. For at least 2/3 of the samples, the absolute relative difference had to be ≤ 20.0%. Of the 181 results, 76 did not meet acceptance criteria resulting in a 58.0% acceptance rate.

Dihydroxyphenylglycol (DHPG): the samples are not within the validated stability period.

Comments: These results are of little relevance considering that the results of this study are uninterpretable due to a significant effect on pressor response in the placebo group.

4.2: Pharmacometrics Review

INTRODUCTION

Ozanimod HCl (RPC1063) is an orally bioavailable sphingosine 1-phosphate 1 receptor (S1P1R) and S1P5R agonist that causes internalization of S1P1 thereby impacting SIP-mediated lymphocyte migration. Ozanimod is for the treatment of Relapsing Multiple Sclerosis (RMS) in adult patients. The mechanism by which ozanimod exerts its therapeutic effects is unknown but may involve the alteration of lymphocytes in areas of inflammation. Ozanimod, its major active metabolite CC112273 ("-73"), and minor metabolite CC1084037 ("-37") each represent approximately 6%, 73%, and 15% of circulating total active drug exposure, respectively; CC1084037 which is the minor metabolite is a direct and inter-converting metabolite of CC112273 which is the major metabolite.

The primary efficacy endpoint in Phase 3 clinical studies for RMS was Annualized Relapse Rate (ARR) which is derived based on the number of confirmed relapse events.

Peripheral Absolute Lymphocyte Count (ALC) is a pharmacodynamic (PD) biomarker endpoint for S1P1R modulators. A dose dependent reduction in ALC from baseline was observed in clinical studies. An E-R relationship for metabolite -73 and ALC is seen (PK/PD); however, there is no PK-PD relationship between the parent drug ozanimod and ALC.

Smokers have about 55 % lower steady state exposure (AUC) of the major active metabolite -73, than nonsmokers (PK). Lower concentrations of metabolite -73 result in about 24 % less mean reduction in absolute lymphocyte count, ALC (PD), in smokers than in nonsmokers. However, neither the reduced exposure of metabolite -73 (PK) nor the lesser ALC reduction (PD) among smokers translates into any lesser of a clinical effect (i.e., the lowering of ARR) in smokers compared to nonsmokers when given the 1 mg dose. The 1 mg dose appears to be the optimal dose for both smokers and nonsmokers. Therefore, as far as dosing is concerned, the 1 mg ozanimod hydrochloride dose (equivalent to 0.92 mg ozanimod) provides sufficient exposure and response in the treatment of RMS regardless of smoking status after a 7-day dose escalation scheme has been followed in RMS patients.

The population pharmacokinetic review describes the exposure of the major active metabolite, -73 (PK) to the reduction in ALC (PD), and, on PK, and PD differences between smokers and nonsmokers.

Recommendation:

The Office of Clinical Pharmacology has reviewed the information in the submission for its Pharmacometrics component and it is in agreement with the sponsor's analysis and findings.

A. Results of Sponsor's Analysis

OBJECTIVES

Study 0003

The objectives of the analysis were to develop a population PK model to characterize the pharmacokinetics of the major active metabolite -73 in adult subjects, and further to investigate the effects of covariates on it.

Study 0004

The objectives of this analysis were to develop an E-R model to characterize the relationship between exposure of the major active metabolite -73 and Absolute Lymphocyte Count (ALC), the Pharmacodynamic marker.

DATA

Study 0003

A total of 9402 PK samples from 1687 subjects were included in the population PK analysis of metabolite -73. Metabolite -73 plasma concentrations were measured using fresh samples from Study RPC01-1910 and RPC01-1911. Metabolite -73 concentrations were determined retrospectively using retained plasma samples after Studies RPC01-1001, RPC01-1904, RPC01-1906, RPC01-301 and RPC01-201B had been completed. Only samples collected within the 17-month long term stability (LTS) period for CC112273 were included in the analysis. Approximately 62% of the subjects were females, and approximately 95% were White. Most of the subjects were RMS patients (89.9%), and the remaining subjects were healthy (10.2%). Overall, 19.2% of the subjects were current smokers. Subjects had a median (range) age of 36 (18 to 70) years and body weight of 68 (40 to 149) kg.

Study 0004

The dataset included 1937 subjects with 17285 ALC measurements following placebo or ozanimod treatment. The analysis also included 9069 quantifiable CC112273 concentrations determined within the 17-month LTS period from a total of 1641 subjects. The E-R analysis of ALC utilized response data from two Phase 1 studies in healthy subjects (RPC01-1910 and RPC01-1911) and three studies in RMS patients (Phase 1: RPC01-1001; Phase 3: RPC01-201B and RPC01-301).

METHODS

Population PK Model for Metabolite -73

Study 0003

A population PK model was developed to characterize the concentration-time profiles of ozanimod's major active metabolite, CC112273, in healthy subjects and patients with RMS. The

PK of CC112273 was adequately described by a two-compartment model with first order formation rate of CC112273, a lag time for appearance of CC112273 and first-order elimination of CC112273. Covariates studied in the CC112273 model included sex, current smoker, hepatic impairment, body weight, baseline bilirubin level and RMS patient on apparent clearance (CL/F); sex, hepatic impairment and body weight on V2/F; and sex, hepatic impairment and body weight on K12. Interindividual variability (IIV) was about 74 % for CL/F of metabolite -73.

Study 0004

PK-PD Models for Ozanimod

A PK-PD model was developed to correlate ALC with the observed concentrations of metabolite -73 in healthy subjects and RMS patients using the non-linear mixed effects method. The effect of -73 concentrations on ALC is described by an indirect response model incorporating an inhibitory Emax model. Our analysis verified the sponsor's findings.

SOFTWARE

Study 0003

Source data were received from the sponsor in SAS format. NONMEM 7 ready datasets were constructed by the Ann Arbor Pharmacometrics Group (A2PG) using SAS (version 9.3), S-plus (version 8.2) and/or R (version 3.1.2 or higher) software.

Study 0004

The E-R analysis for CC112273 and ALC was performed using the nonlinear mixed effects modeling methodology of NONMEM software (Version 7.3). Data post-processing was performed using SAS (version 9.3), SPlus (version 8.2) or R (version 3.1.2 or higher).

B. Population Pharmacokinetic Analysis:

Sponsor's Analysis:
Study 0003

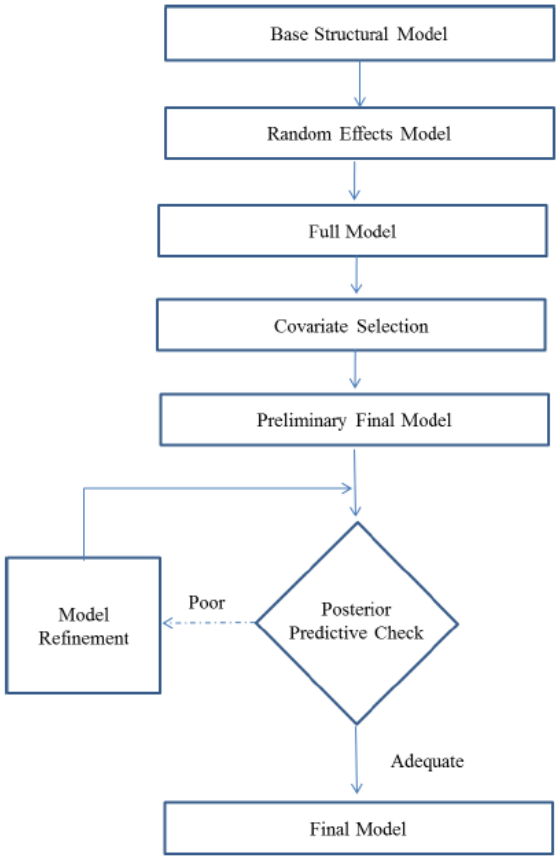
Base Structure Model Development

The initial model describing the disposition of metabolite -73 was a two-compartment model with first-order formation rate of CC112273 and first-order elimination.

Full Model Development

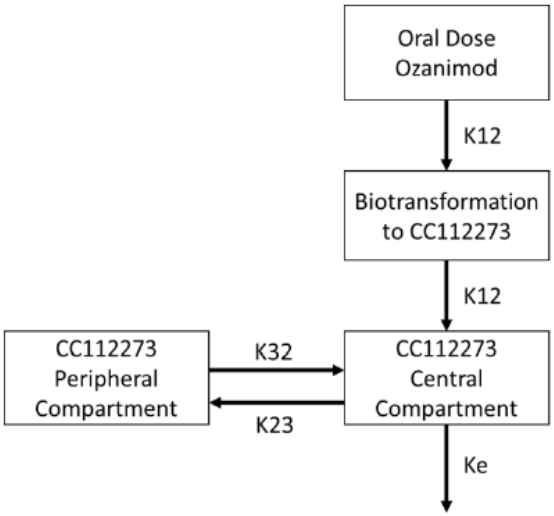
The studying of covariates included age, body weight, sex, race, population (healthy subject or RMS patient), smoking status, hepatic impairment, ESRD, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin and creatinine clearance (CRCL).

Figure 1: Flow Chart of Model Development



Source: Page 22 of Study Report A2PG-0003

Figure 2: Metabolite -73 -- Base Pharmacokinetic Model Diagram



Source: Page 38 of Study Report A2PG-0003

The PK parameters for Metabolite -73 in the Final model are shown in Table 1.

Table 1: Pharmacokinetic Parameter Estimates for CC112273 in the Final Model

Parameter	Estimate	ASE	%RSE	95% CI	Units
CL/F	10.0	0.680	6.8	(8.70, 11.4)	L/hr
V2/F	294	18.8	6.4	(257, 331)	L
K12	0.0238	0.00144	6.1	(0.0209, 0.0266)	hr^{-1}
K23	0.112	0.00349	3.1	(0.105, 0.119)	hr^{-1}
K32	0.0134	0.00052	3.9	(0.0124, 0.0145)	hr^{-1}
ALAG1	0.701	0.0249	3.6	(0.653, 0.750)	hr
Sex on CL/F	-0.348	0.0309	8.9	(-0.409, -0.288)	-
Smok on CL/F	1.09	0.101	9.2	(0.893, 1.29)	-
Hep on CL/F	1.58	0.571	36.1	(0.462, 2.70)	-
WT on CL/F	-0.633	0.101	16.0	(-0.832, -0.435)	-
BILI on CL/F	-0.142	0.0397	27.9	(-0.220, -0.0643)	-
Patient on CL/F	0.415	0.0998	24.0	(0.220, 0.611)	-
Sex on V2/F	0.601	0.0763	12.7	(0.452, 0.751)	-
Hep on V2/F	-0.641	0.0851	13.3	(-0.808, -0.474)	-
WT on V2/F	1.72	0.108	6.3	(1.51, 1.93)	-
Sex on K12	0.653	0.108	16.5	(0.442, 0.863)	-
Hep on K12	-0.631	0.0694	11.0	(-0.767, -0.495)	-
WT on K12	0.867	0.146	16.9	(0.580, 1.15)	-
Proportional Residual Error					
RV	13.6	0.112		(13.4, 13.8)	CV%
IIV					
CL/F	74.5			(71.9, 77.1)	CV%
V2/F	25.9			(22.4, 29.1)	CV%
K12	37.2			(32.7, 41.2)	CV%
OFV	-20870.368				

ASE = asymptotic standard error; %RSE = percent relative standard error; CI = confidence interval; CV% = percent coefficient of variation; RV = residual variability; IIV = interindividual variability; OFV = objective function value; CL/F = apparent clearance; V2/F = apparent central distribution volume; K12 = formation rate constant for CC112273; K23 = distribution rate constant between central and peripheral compartments; K32 = distribution rate constant between peripheral and central compartments; ALAG1 = lag time associated with CC112273 formation; Smok = current smoker; Hep = mild or moderate hepatic impairment; WT = body weight; BILI = total bilirubin; Patient = relapsing multiple sclerosis (RMS) patient

Source: Page 46 of Study Report A2PG-0003

Table 2: Model-Predicted Steady State PK Parameters for CC112273 in Patients with RMS Following Ozanimod 0.92 mg QD

Parameter	Mean[a]	Median[a]	90% Prediction Interval[a]
$AUC_{0-\tau,ss}$ (pmol·hr/L)	237588	186691	(38813, 603393)
$C_{min,ss}$ (pmol/L)	9616	7497	(1394, 24828)
$C_{max,ss}$ (pmol/L)	10071	7937	(1781, 25321)

[a] N=754 RMS patients in Study RPC01-201B and Study RPC01-301 that had ozanimod dose escalated to 0.92 mg

PK = pharmacokinetic; RMS = relapsing multiple sclerosis; QD = once daily; $AUC_{0-\tau,ss}$ = steady state area under the plasma drug concentration-time curve over the 24- hour dosing interval; $C_{min,ss}$ = steady state minimum plasma drug concentration; $C_{max,ss}$ = steady state maximum plasma drug concentration; hr = hour

Source: Page 56 of Study Report A2PG-0003

Reviewer's Analysis and Comments for Population PK:

A population PK model was developed to characterize the concentration-time profiles of ozanimod's major active metabolite, -73 in patients with RMS. The reviewer performed NONMEM runs with NONMEM Version VII. The minimum value objective function (MVOF) obtained was - 18,482.311. This is very similar to the MVOF value obtained by the sponsor.

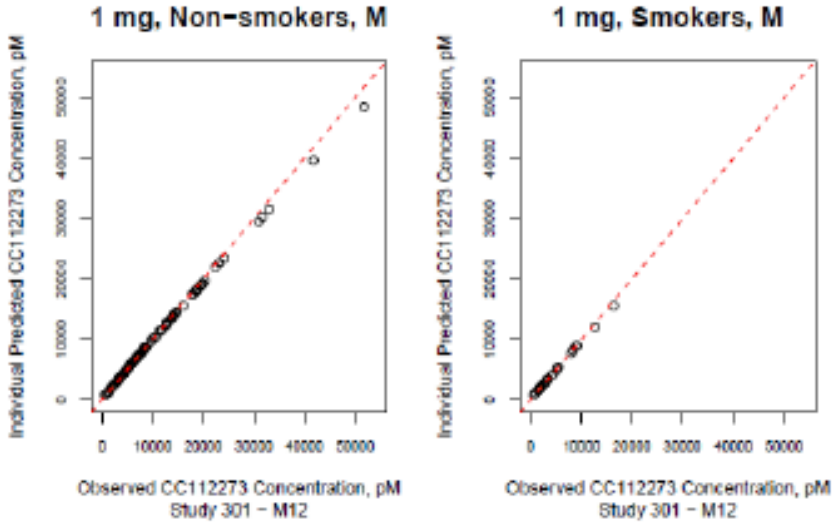
The reviewer was able to replicate the results of the sponsor. The population parameter estimates (e.g., of clearance, volume of distribution etc.) and the corresponding between subject variability (% BSV) agree and match with the values obtained by the sponsor.

Population pharmacokinetic analysis performed by the sponsor and replicated by the reviewer shows that smoking is an important covariate that influences ozanimod exposure in patients. Smokers consistently showed less metabolite -73 concentrations than nonsmokers. Smokers had approximately 55% lower -73 steady state exposure (AUC) than non-smokers which may be attributed to the lower MAO-B activity in smokers compared with non-smokers.

Observed and Predicted Concentrations: A great degree of concordance is seen between the observed concentrations and their corresponding predicted concentrations for the major active metabolite -73 for each group, i.e., smokers, nonsmokers, for males and females, for both the 0.5 mg dose and for the 1 mg dose, and in both the clinical studies (201B and 301). The difference between observed and predicted concentrations is less than 5 %.

A characteristics concordance plot between observed and predicted concentrations of metabolite -73 is shown in Figure 3.

Figure 3: Concordance plot between observed and predicted concentrations of metabolite -73



Source: Page 7 of Information Request of September 24, 2019

Covariates and Observed Concentrations: Table 3 shows the observed concentrations for 0.5 mg and 1 mg doses in male and female smokers, in male and female nonsmokers, and male and female intermittent smokers. The sponsor mentions that intermittent smokers were those who at some visits were noted as smokers and at other visits were noted as nonsmokers.

Table 3: Covariates and Observed Concentrations:

Dose	Smoking Status	Sex	Ozanimod				CC112273			
			2-6 Hours Postdose Concentrations (pM)							
			Month 12		Month 24		Month 12		Month 24	
			n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
0.5 mg	Smoker	Male	33	287 (59, 515)	17	263 (98, 427)	32	1502 (1249, 1755)	18	2343 (1349, 3337)
		Female	30	309 (90, 529)	13	327 (160, 494)	31	2364 (1849, 2880)	13	2179 (1274, 3084)
	Non-smoker	Male	80	294 (29, 560)	75	259 (78, 439)	80	5884 (4870, 6898)	73	4816 (3982, 5650)
		Female	225	316 (90, 541)	204	307 (78, 536)	225	6398 (5822, 6974)	201	5861 (5291, 6430)
	Intermittent	Male	14	332 (0, 722)	25	280 (95, 464)	13	3278 (1945, 4611)	24	3014 (1948, 4080)
		Female	17	312 (16, 607)	17	310 (51, 569)	18	3203 (2134, 3912)	19	2951 (1803, 4099)
1 mg	Smoker	Male	25	610 (213, 1007)	21	528 (30, 1026)	25	4583 (3030, 6137)	21	3819 (2136, 5502)
		Female	31	632 (0, 1422)	27	554 (229, 879)	30	7285 (4841, 9728)	27	4071 (2851, 5292)
	Non-smoker	Male	96	545 (168, 922)	71	510 (121, 900)	98	10310 (8568, 12052)	74	9302 (7757, 10848)
		Female	210	610 (134, 1086)	184	634 (35, 1234)	207	11752 (10616, 12888)	183	12073 (10824, 13322)
	Intermittent	Male	24	509 (209, 810)	25	544 (225, 863)	25	6307 (4283, 8330)	22	5088 (2841, 7335)
		Female	14	573 (99, 1046)	19	663 (85, 1241)	14	4543 (2767, 6318)	19	6940 (3928, 9951)

Source: Page 3 of Information Request of September 24, 2019

Sex – Males and Females: The observed concentrations of ozanimod and metabolite -73 between males and females are comparable with males showing about 15 % lower concentrations than females. This difference in exposure between males and females is not considered to be clinically meaningful.

Smokers versus Nonsmokers: Concentration differences between smokers and nonsmokers is about 55 % with smokers showing lower concentrations than nonsmokers.

Intermittent smokers: Intermittent smokers had ozanimod concentrations comparable to nonsmokers. For metabolite -73 intermittent smokers had concentrations that were within the concentration values of smokers and nonsmokers.

Table 4: Predicted Concentrations of Ozanimod and metabolite -73

Dose	Smoking Status	Sex	Ozanimod				CC112273			
			2-6 Hours Postdose Concentrations (pM)							
			Month 12		Month 24		Month 12		Month 24	
			n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
0.5 mg	Smoker	Male	33	242 (114, 370)	17	223 (166, 279)	32	1503 (1256, 1750)	18	2293 (1347, 3240)
		Female	30	259 (131, 387)	13	273 (171, 374)	31	2348 (1852, 2844)	13	2166 (1296, 3035)
	Non-smoker	Male	80	240 (117, 362)	75	228 (109, 346)	80	5755 (4803, 6707)	73	4733 (3934, 5533)
		Female	225	260 (149, 372)	204	259 (141, 376)	225	6300 (5753, 6848)	201	5775 (5233, 6317)
	Intermittent	Male	14	241 (108, 374)	25	233 (140, 326)	13	3209 (1939, 4479)	24	2942 (1940, 3944)
		Female	17	280 (103, 457)	17	241 (153, 329)	18	2997 (2140, 3854)	19	2916 (1818, 4014)
1 mg	Smoker	Male	25	493 (327, 659)	21	480 (218, 743)	25	4498 (3021, 5975)	21	3774 (2178, 5370)
		Female	31	515 (178, 852)	27	508 (293, 722)	30	7101 (4818, 9383)	27	4046 (2873, 5218)
	Non-smoker	Male	96	472 (259, 684)	71	438 (255, 621)	98	10112 (8464, 11760)	74	9163 (7685, 10642)
		Female	210	519 (266, 771)	184	513 (213, 813)	207	11589 (10506, 12673)	183	11886 (10693, 13080)
	Intermittent	Male	24	443 (280, 605)	25	481 (312, 650)	25	6161 (4241, 8082)	22	5010 (2862, 7159)
		Female	14	503 (216, 789)	19	522 (252, 791)	14	4538 (2815, 6260)	19	6834 (3952, 9716)

Source: Page 4 of Information Request of September 24, 2019

C) Pharmacokinetics/Pharmacodynamics (PK/PD)

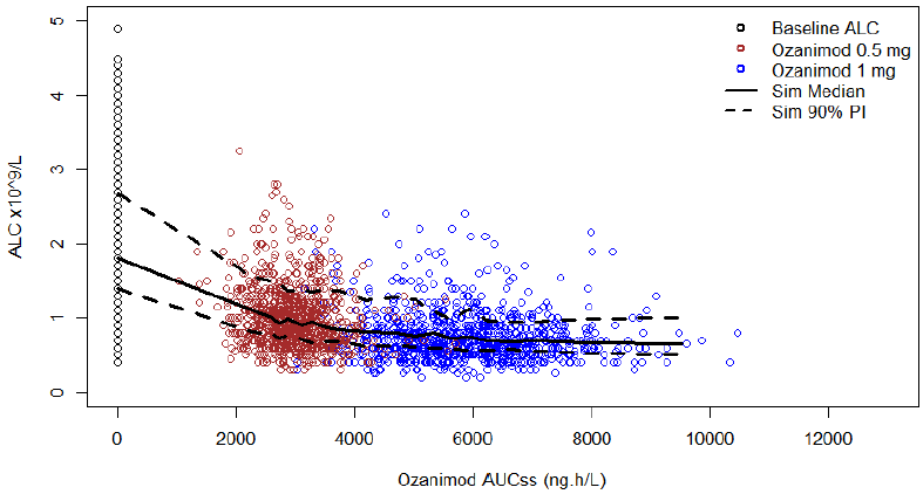
Reviewer's Analysis and Comments for Population PK/PD: The reviewer performed NONMEM runs with NONMEM Version VII. The MVOF value obtained was - 44,759.493. This is very similar to the MVOF value obtained by the sponsor.

The reviewer was able to replicate the results of the sponsor. The population parameter estimates (e.g., of clearance, volume of distribution etc.) and the corresponding between subject variability (% bsv) agree and match with the values obtained by the sponsor.

PD - Absolute Lymphocyte Count (ALC)

Ozanimod: No relationship was observed between the exposure (AUCss) of the parent drug ozanimod and ALC reduction between ozanimod AUCss of 1500 ng.hr/L and 10500 ng.hr/L (see Figure 4). In this region of AUCss it is seen that increasing ozanimod AUCss (x-axis) does not show any difference in the span of values of ALC (y-axis).

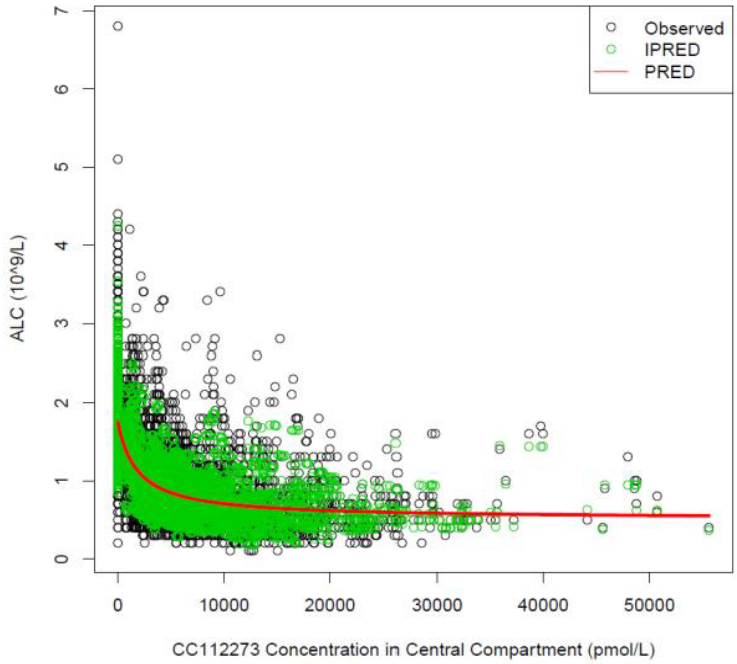
Figure 4: Ozanimod AUCss versus ALC



Source: Page 28 of Report RMS-358-2

Metabolite -73: An E-R model was developed for ALC reduction with ozanimod treatment that included estimation of baseline ALC and drug effect parameters based on metabolite -73 exposure. ALC measurements demonstrated a significant reduction with increasing metabolite -73 concentrations that was described by an Emax model (see Figure 5).

Figure 5: Metabolite-73 concentrations versus ALC



Source: Page 44 of Study Report A2PG-0004

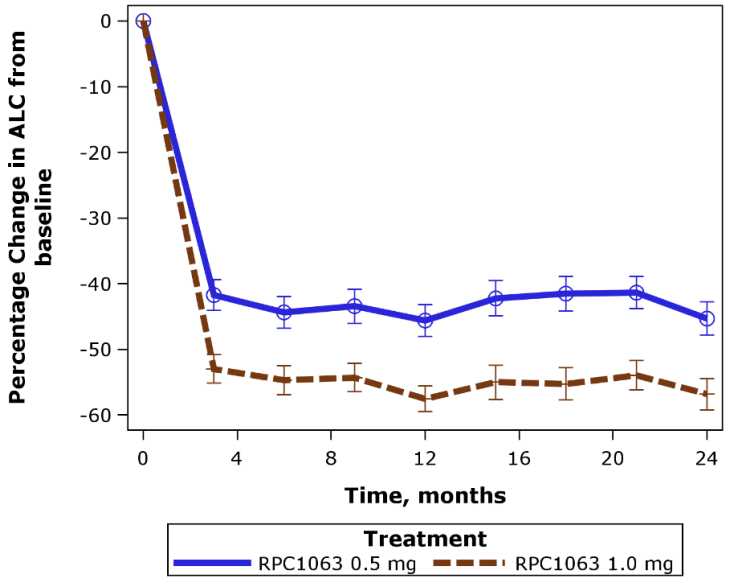
Reviewer's Comment: Metabolite -73 appears to be a better marker than ozanimod for Exposure (PK) - ALC (PD) assessments.

Reduction in ALC by 0.5 mg and 1 mg ozanimod dose:

Figures 6 and 7 show the percentage change in ALC from baseline versus time for both the 24 month clinical study (study 201B) and for 12 month clinical study (study 301). In both studies it is seen that the 1 mg dose of ozanimod shows greater reduction in ALC from baseline than the 0.5 mg dose from baseline.

Study 201B

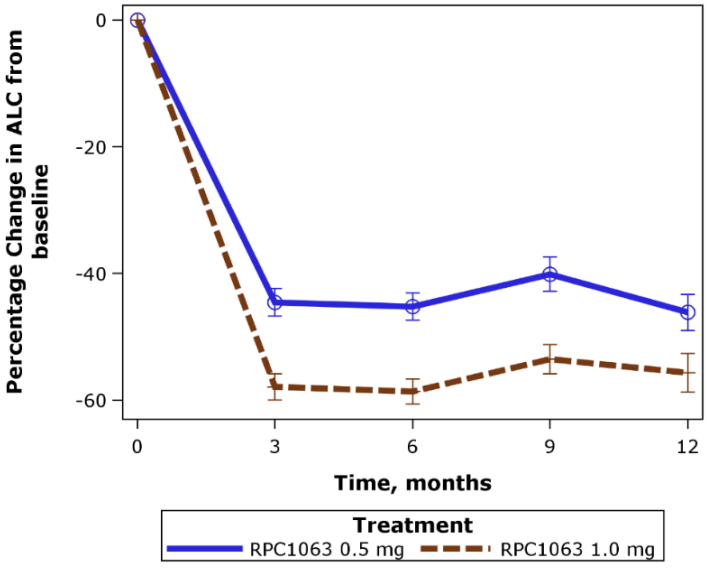
Figure 6: Percentage change in ALC from baseline versus time



Source: Reviewer's analysis

Study 301

Figure 7: Percentage change in ALC from baseline versus time



Source: Reviewer's analysis

ALC in Smokers and Nonsmokers: At the mid-cycle meeting OCP mentioned that it will request the sponsor to provide additional information for smokers and nonsmokers pertaining the PD marker, ALC as well as the clinical endpoint of ARR. More specifically, to provide the observed percent reduction in ALC from baseline for smokers and nonsmokers, and for the same groups the ARR from each of the clinical studies and for the pooled analysis of the data from these two studies. This was conveyed to the sponsor in the mid-cycle communication convey of September 10, 2019. The sponsor provided the requested information on September 24, 2019.

Tables 5 and 6 below show the percentage change in ALC from baseline between smokers and nonsmokers for the two clinical studies (201B and 301).

Table 5: Percentage change in ALC from baseline between smokers and nonsmokers (Study 201B)

Study	Dose	Smoking Status	Number of Subjects / |ALC Percent Change from Baseline (95% CI)			
			Month 3	Month 6	Month 9	Month 12
RPC01-201B	0.5 mg	Smoker	n = 43 -27.724 (-34.9151, -20.5334)	n = 36 -44.980 (-47.6546, -42.3044)	n = 35 -32.749 (-41.7258, -23.7730)	n = 34 -31.332 (-40.8722, -21.7923)
		Non-smoker	n = 340 -44.980 (-47.6546, -42.3044)	n = 334 -46.622 (-49.3923, -43.8517)	n = 329 -45.860 (-48.8816, -42.8382)	n = 317 -47.928 (-50.7084, -45.1478)
		Intermittent Smoker	n = 54 -36.178 (-42.1981, -30.1581)	n = 52 -34.889 (-41.4047, -28.3737)	n = 53 -31.077 (-38.8845, -23.2696)	n = 52 -40.529 (-45.9306, -35.1269)
	1 mg	Smoker	n = 58 -45.182 (-51.5310, -38.8328)	n = 55 -48.255 (-53.9851, -42.5253	n = 54 -48.255 (-53.9851, -42.5253)	n = 55 -48.564 (-54.4428, -42.6857)
		Non-smoker	n = 321 -54.368 (-56.9921, -51.7444)	n = 311 -55.835 (-58.4711, -53.1994)	n = 307 -53.725 (-59.8481, -47.6023)	n = 299 -59.100 (-61.3503, -56.8502)
		Intermittent Smoker	n = 52 -54.798 (-59.9105, -49.6857)	n = 52 -53.725 (-59.8481, -47.6023)	n = 51 -54.181 (-60.1500, -48.2119)	n = 50 -57.647 (-62.8220, -52.4714)

Source: Page 10 of Information Request of September 24, 2019

Table 6: Percentage change in ALC from baseline between smokers and nonsmokers (Study 301)

Study	Dose	Smoking Status	Number of Subjects / ALC Percent Change from Baseline (95% CI)			
			Month 3	Month 6	Month 9	Month 12
RPC01-301	0.5 mg	Smoker	N = 74 -34.775 (-39.3537, -30.1976)	N = 72 -35.304 (-40.5964, -30.0107)	N = 71 -26.584 (-33.8989, -19.2693)	N = 70 -35.568 (-41.0140, -30.1228)
		Non-smoker	N = 340 -47.261 (-49.5724, -44.9503)	N = 336 -47.953 (-50.2755, -45.6304)	N = 330 -43.905 (-46.6927, -41.1169)	N = 323 -49.022 (-51.4942, -46.5493)
		Intermittent Smoker	N = 34 -33.636 (-44.9635, -22.3092)	N = 35 -38.956 (-47.5940, -30.3210)	N = 35 -31.516 (-44.2582, -18.7739)	N = 35 -38.204 (-49.0445, -27.3639)
	1 mg	Smoker	N = 58 -48.798 (-56.5194, -41.0773)	N = 60 -49.112 (-55.8008, -42.4231)	N = 60 -45.637 (-53.7428, -37.5312)	N = 59 -48.959 (-57.1296, -40.7893)
		Non-smoker	N = 337 -58.852 (-61.0328, -56.6706)	N = 335 -60.361 (-62.5535, -58.1688)	N = 329 -54.768 (-57.4298, -52.1058)	N = 323 -59.606 (-62.0896, -57.1225)
		Intermittent Smoker	N = 42 -59.263 (-63.7226, -54.8036)	N = 43 -55.187 (-60.922, -49.3821)	N = 42 -48.562 (-55.3447, -41.7787)	N = 41 -50.377 (-58.4513, -42.3036)

Source: Page 11 of Information Request of September 24, 2019

In both studies (201B and 301) the percentage change (reduction) in ALC from baseline within each respective group (smokers or nonsmokers) was very similar. Furthermore, the magnitude of ALC reduction was consistent within each respective group (i.e., smokers or nonsmokers) throughout the 12 month period. As an example, with 1 mg as the treatment group the mean percent reduction in ALC from baseline observed through month 12 for nonsmokers was 54-59% compared to smokers (45-49%). For the 0.5 mg treatment group the mean percent reduction in ALC from baseline observed through month 12 for nonsmokers was 44-49% versus 27-35% for smokers.

It is seen that in both clinical studies and for each of the doses (0.5 mg and 1 mg) the percentage change in ALC reduction from baseline is greater in nonsmokers than in smokers. It is seen that a 1 mg dose in smokers is comparable to a 0.5 mg dose in nonsmokers; this is seen in both clinical studies.

Intermittent smokers: Intermittent smokers showed ALC reduction from baseline values that were within the ALC reduction from baseline values seen for smokers and nonsmokers.

Direct Comparison: In a *direct* comparison ('head to head') between smokers and nonsmokers, the overall difference, Δ, (taking into account both 0.5 mg and 1 mg doses) in ALC reduction between these two groups is 24 %. Individually, 1 mg shows less of a difference, Δ, (16%) between the two groups than the 0.5 mg group (31%), again in a direct comparison between smokers and nonsmokers.

This (direct comparison) PD difference for ALC between smokers and nonsmokers will show that the Adjusted Annualized Relapse Rate (ARR) which is the clinical endpoint, is unaffected by PD, namely ALC reduction. The next section will discuss ARR.

D) Clinical Efficacy Endpoint Adjusted Annualized Relapse Rate (ARR) in Smokers and Nonsmokers:

a) Study 201B (24 month study): Between smokers and nonsmokers there was a lower ARR in nonsmokers than smokers for the 0.5 mg group (0.198 (95% CI, 0.166, 0.235) versus 0.279 (95% CI, 0.180, 0.432); a 40 % difference) but was lower in smokers than nonsmokers for the 1 mg group (0.163 (95% CI, 0.103, 0.259 versus 0.188; (95% CI, 0.157, 0.226); a 13 % difference). There is an overlap in confidence intervals between smokers and nonsmokers. The nonsmoker group is the reference in these comparisons (see Table 7 below).

Intermittent smokers: For the 0.5 mg dose the ARR value for this group was higher (0.380, 95% CI, 0.278, 0.520) than smokers and nonsmokers but for the 1mg dose it was lower (0.099, 95% CI, 0.053, 0.184) than smokers and nonsmokers.

Difference between groups was calculated as: (|smoker – nonsmoker|) / nonsmoker (reference).

Table 7: Annualized Relapse Rate by Smoking Status in Study 201B

Smoking Status	Parameter	IFN β-1a 30 µg N = 441	Ozanimod 0.5 mg N = 439	Ozanimod 1 mg N = 433
Smokers	n	67	43	59
	Total number of relapses	35	20	18
	Unadjusted ARR	0.30	0.28	0.17
	Adjusted ARR (95% CI)[a]	0.295 (0.212, 0.411)	0.279 (0.180, 0.432)	0.163 (0.103, 0.259)
	Rate Ratio (vs IFN β-1a) (95% CI)[a]	N/A	0.944 (0.545, 1.635)	0.552 (0.313, 0.974)
	p-value[a]		0.8361	0.0404
Non-smokers	n	337	342	322
	Total number of relapses	179	127	115
	Unadjusted ARR	0.29	0.20	0.19
	Adjusted ARR (95% CI)[a]	0.286 (0.247, 0.331)	0.198 (0.166, 0.235)	0.188 (0.157, 0.226)
	Rate Ratio (vs IFN β-1a) (95% CI)[a]	N/A	0.690 (0.550, 0.867)	0.658 (0.521, 0.832)
	p-value[a]		0.0014	0.0005
Intermittent Smokers	n	37	54	52
	Total number of relapses	22	39	10
	Unadjusted ARR	0.31	0.38	0.10
	Adjusted ARR (95% CI)[a]	0.305 (0.201, 0.463)	0.380 (0.278, 0.520)	0.099 (0.053, 0.184)
	Rate Ratio (vs IFN β-1a) (95% CI)[a]	N/A	1.245 (0.738, 2.099)	0.324 (0.153, 0.684)
	p-value[a]		0.4113	0.0031

Source: Page 12 of Information Request of September 24, 2019

b) Study 301 (12 month study): Both treatments groups of 0.5 mg and 1 mg showed that smokers had a lower ARR compared to nonsmokers. ARR with 0.5 mg dose is 0.227 in smokers (95% CI, 0.145, 0.356 versus 0.260 in nonsmokers (95% CI, 0.214, 0.316); a 12 % difference. With the 1 mg dose the values are 0.159 in smokers (95% CI, 0.088, 0.286) versus 0.191 in nonsmokers (95% CI, 0.152, 0.239); a 16 % difference. The nonsmoker group is the reference in these comparisons (see Table 8 below).

Intermittent smokers: For the 0.5 mg dose the ARR value for this group was lower (0.119, 95% CI, 0.050, 0.286) than smokers and nonsmokers but for the 1mg dose it was higher (0.222, 95% CI, 0.123, 0.402) than smokers and nonsmokers.

Table 8: Annualized Relapse Rate by Smoking Status in Study 301

Smoking Status	Parameter	IFN β-1a 30 µg N = 448	Ozanimod 0.5 mg N = 451	Ozanimod 1 mg N = 447
Smokers	n	61	74	60
	Total number of relapses	26	19	11
	Unadjusted ARR	0.38	0.23	0.16
	Adjusted ARR (95% CI)[a]	0.372 (0.253, 0.546)	0.227 (0.145, 0.356)	0.159 (0.088, 0.286)
	Rate Ratio (vs IFN β-1a) (95% CI)[a]	N/A	0.610 (0.338, 1.102)	0.427 (0.211, 0.863)
	p-value[a]		0.1014	0.0178
Non-smokers	n	343	342	344
	Total number of relapses	138	101	75
	Unadjusted ARR	0.36	0.26	0.19
	Adjusted ARR (95% CI)[a]	0.354 (0.300, 0.419)	0.260 (0.214, 0.316)	0.191 (0.152, 0.239)
	Rate Ratio (vs IFN β-1a) (95% CI)[a]	N/A	0.734 (0.568, 0.948)	0.538 (0.406, 0.713)
	p-value[a]		0.0180	< 0.0001
Intermittent Smokers	n	44	35	43
	Total number of relapses	20	5	11
	Unadjusted ARR	0.41	0.12	0.22
	Adjusted ARR (95% CI)[a]	0.404 (0.261, 0.627)	0.119 (0.050, 0.286)	0.222 (0.123, 0.402)
	Rate Ratio (vs IFN β-1a) (95% CI)[a]	N/A	0.294 (0.110, 0.784)	0.550 (0.264, 1.148)
	p-value[a]		0.0144	0.1112

Source: Page 13 of Information Request of September 24, 2019

c) Pooled Data from Study 201B and 301: When data from the two studies are pooled then nonsmokers show a lower ARR than smokers for the 0.5 mg dose (0.224 (95% CI, 0.197, 0.256) versus 0.249 (95% CI, 0.182, 0.341); an 11 % difference) while the 1 mg dose shows that smokers have a lower ARR than nonsmokers (0.163 (95% CI, 0.144, 0.235) versus 0.192 (95% CI, 0.166, 0.221); a 15 % difference). The nonsmoker group is the reference in these comparisons (see Table 9 below).

Intermittent smokers: For the 0.5 mg dose the ARR value for this group was higher (0.312, 95% CI, 0.232, 0.420) than smokers and nonsmokers but for the 1mg dose it was lower (0.142, 95% CI, 0.093, 0.219) than smokers and nonsmokers.

Table 9: Pooled Data from Study 201B and 301

Smoking Status	Parameter	IFN β-1a 30 µg N = 889	Ozanimod 0.5 mg N = 890	Ozanimod 1 mg N = 880
Smokers	n	128	117	119
	Total number of relapses	61	39	29
	Unadjusted ARR	0.33	0.25	0.16
	Adjusted ARR (95% CI)[a]	0.329 (0.256, 0.423)	0.249 (0.182, 0.341)	0.163 (0.114, 0.235)
	Rate Ratio (vs IFN β-1a) (95% CI)[a]	N/A	0.757 (0.506, 1.131)	0.497 (0.320, 0.774)
	p-value[a]		0.1742	0.0019
Non-smokers	n	680	684	666
	Total number of relapses	317	228	190
	Unadjusted ARR	0.32	0.22	0.19
	Adjusted ARR (95% CI)[a]	0.317 (0.283, 0.354)	0.224 (0.197, 0.256)	0.192 (0.166, 0.221)
	Rate Ratio (vs IFN β-1a) (95% CI)[a]	N/A	0.709 (0.598, 0.840)	0.605 (0.506, 0.725)
	p-value[a]		< 0.0001	< 0.0001
Intermittent Smokers	n	81	89	95
	Total number of relapses	42	44	21
	Unadjusted ARR	0.35	0.31	0.14
	Adjusted ARR (95% CI)[a]	0.349 (0.258, 0.473)	0.312 (0.232, 0.420)	0.142 (0.093, 0.219)
	Rate Ratio (vs IFN β-1a) (95% CI)[a]	N/A	0.895 (0.586, 1.366)	0.408 (0.242, 0.689)
	p-value[a]		0.6069	0.0008

Source: Page 12 of Information Request of September 24, 2019

Dose of 0.5 mg in smokers versus Dose of 1 mg in smokers: The results for the 0.5 mg dose in Study 201B show that nonsmokers have a lower ARR than smokers (0.198 versus 0.279). In study 301 the opposite is seen for the 0.5 mg dose with smokers showing a lowering of 0.227 versus 0.260 for nonsmokers. This may be an indication of a lesser or less than optimal ARR lowering effect for smokers at the 0.5 mg dose.

In contrast to the 0.5 mg dose, the 1 mg dose shows a consistent pattern for smokers where in both studies (201B and 301) smokers show lower ARR values compared to nonsmokers (0.163

smokers versus 0.188 nonsmokers in Study 201B, and 0.159 for smokers versus 0.191 for nonsmokers in Study 301).

Intermittent smokers: For either dose, 0.5 mg or 1 mg, the ARR results for intermittent smokers are in opposite directions (either higher or lower when compared to smokers and nonsmokers) for the two studies (201B and 301). It is important to note though that the 1 mg dose showed lower ARR results for intermittent smokers compared to either smokers or nonsmokers on two out of three sets of analyses, namely study 201B and for the pooled analysis. The 0.5 mg dose, in contrast, shows higher ARR values on two out of the three occasions for intermittent smokers compared to either smokers or nonsmokers. Therefore, dosing with 1 mg seems also appropriate for intermittent smokers.

Reviewer's Overall Comment:

Smokers have about 55 % lower concentrations of the major active metabolite -73, than nonsmokers (PK). Lower concentrations of metabolite -73 result in about 24 % less mean reduction in absolute lymphocyte count, ALC (PD), in smokers than nonsmokers. From a PD standpoint it is seen that a 1 mg dose in smokers is comparable for ALC to a 0.5 mg dose in nonsmokers and this is seen in both the clinical studies. For the clinical endpoint of ARR, the 0.5 mg dose shows results in opposite directions for smokers in the two clinical studies for the outcome of the ARR lowering effect at this dose level (i.e., 0.5 mg) for the smoking group. The 1 mg dose, where in both studies the ARR is consistently lower in smokers than in nonsmokers, provides a clear indication that smokers can, and should, be dosed at the 1 mg dose level. Further, the 1 mg dose appears appropriate for the intermittent smoking group as two out of three clinical occasions favor its ARR lowering effect. Therefore, the 1 mg dose appears to be optimal for smokers, nonsmokers and intermittent smokers. Thus, neither the reduced exposure of metabolite -73 (PK) nor the lesser ALC reduction (PD) among smokers translates into any lesser of a clinical effect in smokers compared to nonsmokers when given the 1 mg dose. Therefore, as far as dosing is concerned, the 1 mg dose provides sufficient exposure and response in the treatment of RMS regardless of smoking status after a 7-day dose escalation scheme has been followed in RMS patients.

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