CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA209899Orig1s001

Trade Name:	**Zeposia, Capsule**
Generic or Proper Name:	(Ozanimod Hydrochloride)
Sponsor:	**Celgene Intl.**
Approval Date:	May 27, 2021
Indication:	Zeposia is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. Moderately to severe active ulcerative colitis (UC) in adults.

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA209899Orig1s001

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology** • **Clinical Microbiology/Virology**	**X**
Product Quality Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA209899Orig1s001

APPROVAL LETTER

NDA 209899/S-001

SUPPLEMENT APPROVAL

Celgene International II Sàrl
Attention: Petra Pavlickova, PhD, RAC
Associate Director, Regulatory Affairs
3033 Science Park Road, Suite 300
San Diego, CA 92121

Dear Dr. Pavlickova:

Please refer to your supplemental new drug application (sNDA) dated and received November 30, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zeposia (ozanimod) capsules.

This Prior Approval supplemental new drug application provides for the use of Zeposia (ozanimod) for the treatment of moderately to severely active ulcerative colitis in adult patients.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

We acknowledge your November 30, 2020, submission containing final printed carton and container labeling.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes from the use of Zeposia (Ozanimod) during pregnancy.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4066-1 An international, prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of females exposed to ZEPOSIA (ozanimod) during pregnancy with women exposed to any other ulcerative colitis therapy during pregnancy and an unexposed comparator population. External disease matched comparators and use of existing disease registries can be considered. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. This study can be conducted as part of the ongoing study under NDA 209899 PMR 3809-3.

The timetable you submitted on May 26, 2021 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2021
Final Protocol Submission:	06/2022
Interim Report #1 Submission:	06/2025
Interim Report #2 Submission:	06/2028
Study Completion:	06/2032
Final Study Report:	06/2033

4066-2 A pregnancy outcomes study using a different study design than provided for in PMR 4066-1 (for example, a retrospective cohort study using claims or electronic medical record data) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in females exposed to ZEPOSIA (ozanimod) during pregnancy compared to an unexposed control population. This study can be conducted as part of the ongoing study under NDA 209899 PMR 3809-4.

The timetable you submitted on May 26, 2021 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2021
Final Protocol Submission:	06/2022
Interim Report #1 Submission:	06/2025
Interim Report #2 Submission:	06/2028
Study Completion:	06/2032
Final Study Report:	06/2033

4066-3 A lactation study (milk only) in lactating women who have received therapeutic doses of ZEPOSIA (ozanimod) using a validated assay to assess concentrations of ZEPOSIA (ozanimod) and its major metabolites in breast milk, and effects on the breastfed infant.

The timetable you submitted on April 28, 2021 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2022
Final Protocol Submission:	09/2022
Study Completion:	09/2024
Final Study Report:	09/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 115243, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4066-4 A one year, randomized, blinded trial to evaluate the safety, efficacy, and pharmacokinetics of ZEPOSIA (ozanimod) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

The timetable you submitted on April 28, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2021
Trial Completion:	12/2025
Final Study Report:	06/2026

4066-5 A long term extension study to evaluate the long-term safety of ZEPOSIA (ozanimod) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in postmarketing commitment Study 3. This study can be conducted as part of postmarketing commitment study 4066-4.

The timetable you submitted on April 28, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2021
Trial Completion:	10/2030
Final Study Report:	04/2031

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 115243 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be

prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Jay Fajiculay, Regulatory Health Project Manager, at (301) 796-9007 or email at jay.fajiculay@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, MMSc
Director
Division of Gastroenterology
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

/s/

JESSICA J LEE
05/27/2021 12:07:54 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA209899Orig1s001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEPOSIA safely and effectively. See full prescribing information for ZEPOSIA.

ZEPOSIA® (ozanimod) capsules, for oral use
Initial U.S. Approval: 2020

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	5/2021
Dosage and Administration (2.2)	5/2021
Warnings and Precautions (5.1, 5.2, 5.3, 5.5, 5.6, 5.7)	5/2021

----------INDICATIONS AND USAGE----------

ZEPOSIA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)
- Moderately to severely active ulcerative colitis (UC) in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- Assessments are required prior to initiating ZEPOSIA. (2.1)
- Titration is required for treatment initiation. (2.2)
- The recommended maintenance dosage is 0.92 mg orally once daily. (2.2)
- If a dose is missed within the first 2 weeks of treatment, reinitiate with the titration regimen. If a dose is missed after the first 2 weeks of treatment, continue treatment as planned. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 0.23 mg, 0.46 mg, 0.92 mg ozanimod (3)

----------CONTRAINDICATIONS----------

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure. (4)
- Presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker. (4)
- Severe untreated sleep apnea. (4)
- Concomitant use of a monoamine oxidase inhibitor. (4, 7)

----------WARNINGS AND PRECAUTIONS----------

- Infections: ZEPOSIA may increase the risk of infections. Obtain a complete blood count (CBC) before initiation of treatment. Monitor for infection during treatment and for 3 months after discontinuation. Do not start ZEPOSIA in patients with active infections. (5.1)
- Bradyarrhythmia and Atrioventricular Conduction Delays: ZEPOSIA may result in transient decrease in heart rate; titration is required for treatment initiation. Check an electrocardiogram (ECG) to assess for preexisting cardiac conduction abnormalities before starting ZEPOSIA. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate. (2.1, 2.2, 5.2, 7)
- Liver Injury: Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating ZEPOSIA. (5.3)
- Fetal Risk: Women of childbearing potential should use effective contraception during treatment and for 3 months after stopping ZEPOSIA. (5.4, 8.3)
- Increased Blood Pressure (BP): Monitor BP during treatment. (5.5)
- Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated. (5.6)
- Macular Edema: A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA. Diabetes mellitus and uveitis increase the risk of macular edema; patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥4%) are:

- Multiple Sclerosis: upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension. (6.1)
- Ulcerative Colitis: liver test increased, upper respiratory infection, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Vaccination: Avoid use of live attenuated vaccines during and for up to 3 months after treatment with ZEPOSIA. (7)
- See full prescribing information for a list of clinically important drug interactions. (7)

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment: Use is not recommended. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZEPOSIA is indicated for the treatment of:

- relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
- moderately to severely active ulcerative colitis (UC) in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to First Dose of ZEPOSIA

Before initiation of treatment with ZEPOSIA, assess the following:

Complete Blood Count

Obtain a recent (i.e., within the last 6 months or after discontinuation of prior MS or UC therapy) complete blood count (CBC), including lymphocyte count *[see Warnings and Precautions (5.1)]*.

Cardiac Evaluation

Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist should be sought *[see Warnings and Precautions (5.2)]*.

Liver Function Tests

Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels *[see Warnings and Precautions (5.3)]*.

Ophthalmic Assessment

In patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula *[see Warnings and Precautions (5.7)]*.

Current or Prior Medications

- If patients are taking anti-neoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with ZEPOSIA *[see Warnings and Precautions (5.1) and Drug Interactions (7)]*.
- Determine if patients are taking drugs that could slow heart rate or atrioventricular conduction *[see Warnings and Precautions (5.2) and Drug Interactions (7)]*.

Vaccinations

Test patients for antibodies to varicella zoster virus (VZV) before initiating ZEPOSIA; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with ZEPOSIA *[see Warnings and Precautions (5.1) and Drug Interactions (7)]*.
If live *attenuated* vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

2.2 Recommended Dosage for Multiple Sclerosis and Ulcerative Colitis

Initiate ZEPOSIA with a 7-day titration, as shown in Table 1 *[see Warnings and Precautions (5.2)]*. After initial titration, the recommended dosage of ZEPOSIA is 0.92 mg taken orally once daily starting on Day 8.

Swallow ZEPOSIA capsules whole, with or without food *[see Clinical Pharmacology (12.3)]*.

Table 1: Dose Titration Regimen

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

2.3 Reinitiation of ZEPOSIA after Treatment Interruption

If a dose of ZEPOSIA is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen *[see Dosage and Administration (2.2)]*.

If a dose of ZEPOSIA is missed after the first 2 weeks of treatment, continue with the treatment as planned.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 0.23 mg ozanimod: light grey opaque body/light grey opaque cap imprinted with black ink "OZA" on the cap and "0.23 mg" on the body
- 0.46 mg ozanimod: light grey opaque body/orange opaque cap imprinted with black ink "OZA" on the cap and "0.46 mg" on the body
- 0.92 mg ozanimod: orange opaque body/orange opaque cap imprinted with black ink "OZA" on the cap and "0.92 mg" on the body

4 CONTRAINDICATIONS

ZEPOSIA is contraindicated in patients who:

- In the last 6 months, have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure *[see Warnings and Precautions (5.2)]*
- Have the presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker *[see Warnings and Precautions (5.2)]*
- Have severe untreated sleep apnea *[see Warnings and Precautions (5.2)]*
- Are taking a monoamine oxidase (MAO) inhibitor *[see Drug Interactions (7)]*

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Risk of Infections

ZEPOSIA causes a mean reduction in peripheral blood lymphocyte count to approximately 45% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues *[see Clinical Pharmacology (12.2)]*. ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA.

Obtain a recent (i.e., within 6 months or after discontinuation of prior MS or UC therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA.

Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved.

In MS Study 1 and Study 2, the overall rate of infections and rate of serious infections in patients treated with ZEPOSIA were similar to that in patients who received interferon (IFN) beta-1a (35% vs. 34% and 1% vs. 0.8%, respectively). In UC Study 1 and Study 3, the overall rate of infections and rate of serious infections in patients treated with ZEPOSIA were similar to that in patients who received placebo (9.9% vs. 10.7% and 0.8% vs. 0.4%, respectively). In UC Study 2, the overall rate of infections in patients treated with ZEPOSIA was higher than in patients treated with placebo (23% vs. 12%) and the rate of serious infections was similar (0.9% vs. 1.8%).

ZEPOSIA increased the risk of viral upper respiratory tract infections, urinary tract infections, and herpes infections *[see Adverse Reactions (6.1)]*.

The proportion of patients treated with ZEPOSIA who experienced lymphocyte counts less than 0.2 x 10^9/L was 3.3% in MS Study 1

and Study 2. The proportion of patients treated with ZEPOSIA with lymphocyte counts less than 0.2 x 10^9/L was 2% in UC Study 1 and Study 3 and 2.3% in UC Study 2. These values generally returned to greater than 0.2 x 10^9/L while patients remained on treatment with ZEPOSIA. After discontinuing ZEPOSIA 0.92 mg, the median time for peripheral blood lymphocytes to return to the normal range was approximately 30 days, with approximately 80% to 90% of patients in the normal range within 3 months *[see Clinical Pharmacology (12.2)]*.

Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection.

Because the elimination of ZEPOSIA after discontinuation may take up to 3 months, continue monitoring for infections throughout this period.

Herpes Viral Infection

Cases of localized herpes virus infection (e.g., herpes zoster and herpes simplex) were seen in clinical trials of ZEPOSIA.

In MS Study 1 and Study 2, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with ZEPOSIA 0.92 mg and in 0.2% of patients who received IFN beta-1a.

In UC Study 1 and Study 3, herpes zoster was reported in 0.4% of patients who received ZEPOSIA and none in patients who received placebo. In UC Study 2, herpes zoster was reported in 2.2% of patients who received ZEPOSIA and 0.4% of patients who received placebo. None were serious or disseminated.

Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA *(see Vaccinations below).*

Cryptococcal Infection

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with S1P receptor modulators. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. ZEPOSIA treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

PML has been reported in patients treated with S1P receptor modulators and other multiple sclerosis (MS) and UC therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with ZEPOSIA should be suspended until PML has been excluded by an appropriate diagnostic evaluation.

If PML is confirmed, treatment with ZEPOSIA should be discontinued.

Prior and Concomitant Treatment with Anti-Neoplastic, Non-Corticosteroid Immunosuppressive, or Immune-modulating Therapies

In the MS and UC clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with anti-neoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for the treatment of MS and UC. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. In UC studies, concomitant use of corticosteroids was allowed and did not appear to influence the safety or efficacy of ZEPOSIA *[see Clinical Studies (14.2)]*.

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects during such therapy. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

Vaccinations

Patients without a healthcare professional-confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative

patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA, following which initiation of treatment with ZEPOSIA should be postponed for 4 weeks to allow the full effect of vaccination to occur.

No clinical data are available on the efficacy and safety of vaccinations in patients taking ZEPOSIA. Vaccinations may be less effective if administered during ZEPOSIA treatment.

If live *attenuated* vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA. Avoid the use of live *attenuated* vaccines during and for 3 months after treatment with ZEPOSIA.

5.2 Bradyarrhythmia and Atrioventricular Conduction Delays

Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)]*.

ZEPOSIA was not studied in patients who had:

- A myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization within the last 6 months
- New York Heart Association Class III / IV heart failure
- Cardiac conduction or rhythm disorders, including sick sinus syndrome, significant QT prolongation (QTcF > 450 msec in males, > 470 msec in females), risk factors for QT prolongation, or other conduction abnormalities or cardiac condition that in the opinion of the treating investigator could jeopardize the patient's health
- Other pre-existing stable cardiac conditions without clearance from a cardiologist
- Severe untreated sleep apnea
- A resting heart rate less than 55 beats per minute (bpm) at baseline

Reduction in Heart Rate

Initiation of ZEPOSIA may result in a transient decrease in heart rate. After the initial dose of ZEPOSIA 0.23 mg, the greatest mean decrease from baseline in heart rate occurred at Hour 5 on Day 1 (decrease of 1.2 bpm in MS Study 1 and Study 2, and 0.7 bpm in UC Study 1 and Study 3), returning to near baseline at Hour 6. With continued up-titration, the maximal heart rate effect of ozanimod occurred on Day 8. The utility of performing first-dose cardiac monitoring when initiating ZEPOSIA in patients with characteristics similar to those studied in the clinical trials of ZEPOSIA is unclear. Heart rates below 40 bpm were not observed. Initiation of ZEPOSIA without titration may result in greater decreases in heart rate *[see Dosage and Administration (2.2)]*.

In MS Study 1 and Study 2, bradycardia was reported on the day of treatment initiation in 0.6% of patients treated with ZEPOSIA compared to no patients who received IFN beta-1a. After Day 1, the incidence of bradycardia was 0.8% in patients treated with ZEPOSIA compared to 0.7% of patients who received IFN beta-1a. In UC Study 1 and Study 3, bradycardia was reported on the day of treatment initiation in 1 patient (0.2%) treated with ZEPOSIA compared to none in patients who received placebo. After Day 1, bradycardia was reported in 1 patient (0.2%) treated with ZEPOSIA. In UC Study 2, bradycardia was not reported.

Atrioventricular Conduction Delays

Initiation of ZEPOSIA may result in transient atrioventricular conduction delays. At ZEPOSIA exposures higher than the recommended dosage without dose titration, first- and second-degree type 1 atrioventricular blocks were observed in healthy volunteers; however, in MS Study 1 and Study 2 and UC Study 1 and Study 3 with dose titration, Mobitz type 2 second- or third-degree atrioventricular blocks were not reported in patients treated with ZEPOSIA.

If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- With significant QT prolongation (QTcF > 450 msec in males, > 470 msec in females)
- With arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs

- With ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension

- With a history of with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block *[see Contraindications (4)]*

5.3 Liver Injury

Elevations of aminotransferases may occur in patients receiving ZEPOSIA.

Obtain transaminase and bilirubin levels, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA.

In MS Study 1 and Study 2, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of patients treated with ZEPOSIA 0.92 mg and 1.3% of patients who received IFN beta-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with ZEPOSIA and 3.1% of patients who received IFN beta-1a. The median time to an elevation of 3-fold the ULN was 6 months. The majority (79%) of patients continued treatment with ZEPOSIA with values returning to less than 3 times the ULN within approximately 2-4 weeks. ZEPOSIA was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate because of elevations in hepatic enzymes was 1.1% of patients with MS treated with ZEPOSIA 0.92 mg and 0.8% of patients who received IFN beta-1a.

In UC Study 1, elevations of ALT to 5-fold the ULN or greater occurred in 0.9% of patients treated with ZEPOSIA 0.92 mg and 0.5% of patients who received placebo, and in UC Study 2 elevations occurred in 0.9% of patients and no patients, respectively. In UC Study 1, elevations of ALT to 3-fold the ULN or greater occurred in 2.6% of UC patients treated with ZEPOSIA 0.92 mg and 0.5% of patients who received placebo, and in UC Study 2 elevations occurred in 2.3% of patients and no patients, respectively. In controlled and uncontrolled UC studies, the majority (96%) of patients with ALT greater than 3-fold the ULN continued treatment with ZEPOSIA with values returning to less than 3-fold the ULN within approximately 2 to 4 weeks. Overall, the discontinuation rate because of elevations in hepatic enzymes was 0.4% in patients treated with ZEPOSIA 0.92 mg, and none in patients who received placebo in the controlled UC studies.

Individuals with an AST or ALT greater than 1.5 times ULN were excluded from MS Study 1 and Study 2 and greater than 2 times the ULN for UC Study 1 and Study 3. There are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA. Use of ZEPOSIA in patients with hepatic impairment is not recommended *[see Use in Specific Populations (8.6)]*.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked, and ZEPOSIA should be discontinued if significant liver injury is confirmed.

5.4 Fetal Risk

There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm *[see Use in Specific Populations (8.1)]*. Because it takes approximately 3 months to eliminate ZEPOSIA from the body, women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA *[see Use in Specific Populations (8.3)]*.

5.5 Increased Blood Pressure

In MS Study 1 and Study 2, patients treated with ZEPOSIA had an average increase of approximately 1 to 2 mm Hg in systolic pressure over patients who received IFN beta-1a, and no effect on diastolic pressure. The increase in systolic pressure was first detected after approximately 3 months of treatment and persisted throughout treatment. Hypertension was reported as an adverse reaction in 3.9% of patients treated with ZEPOSIA 0.92 mg and in 2.1% of patients who received IFN beta-1a. Two patients treated with ZEPOSIA in MS Study 1 and one patient treated with interferon (IFN) beta-1a in Study 2 experienced a hypertensive crisis that was not clearly influenced by a concomitant medication.

The mean increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in UC patients treated with ZEPOSIA is similar to patients with MS. In UC Study 1 and Study 3, the average increase from baseline in SBP was 3.7 mm Hg in patients treated with ZEPOSIA and 2.3 mm Hg in patients treated with placebo. In UC Study 2, the average increase from baseline in SBP was 5.1 mm Hg in patients treated with ZEPOSIA and 1.5 mm Hg in patients treated with placebo. There was no effect on DBP.

Hypertension was reported as an adverse reaction in 1.2% of patients treated with ZEPOSIA 0.92 mg and none in patients treated with placebo in UC Study 1 and Study 3, and in 2.2% and 2.2% of patients in UC Study 2, respectively. Hypertensive crisis was reported in two patients receiving ZEPOSIA and one patient receiving placebo.

Blood pressure should be monitored during treatment with ZEPOSIA and managed appropriately.

Certain foods that may contain very high amounts (i.e., more than 150 mg) of tyramine could cause severe hypertension because of potential tyramine interaction in patients taking ZEPOSIA, even at the recommended doses. Because of an increased sensitivity to tyramine, patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

5.6 Respiratory Effects

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV_1) were observed in MS patients treated with ZEPOSIA as early as 3 months after treatment initiation. In the MS pooled analyses of Study 1 and Study 2, the decline in absolute FEV_1 from baseline in patients treated with ZEPOSIA compared to patients who received IFN beta-1a was 60 mL (95% CI: -100, -20) at 12 months. The mean difference in percent predicted FEV_1 at 12 months between patients treated with ZEPOSIA and patients who received IFN beta-1a was 1.9% (95% CI: -2.9, -0.8). Dose-dependent reductions in forced vital capacity (FVC) (absolute value and %-predicted) were also seen at Month 3 in pooled analyses comparing patients treated with ZEPOSIA to patients who received IFN beta-1a [60 mL, 95% CI (-110, -10); 1.4%, 95% CI: (-2.6, -0.2)], though significant reductions were not seen at other timepoints. There is insufficient information to determine the reversibility of the decrease in FEV_1 or FVC after drug discontinuation. One patient in MS Study 1 discontinued ZEPOSIA because of dyspnea.

In UC Study 1 the mean difference in decline in absolute FEV_1 from baseline in patients treated with ZEPOSIA compared to patients who received placebo was 22 mL (95% CI: -84, 39) at 10 weeks. The mean difference in percent predicted normal (PPN) FEV_1 at 10 weeks between patients treated with ZEPOSIA compared to those who received placebo was 0.8% (95% CI: -2.6, 1.0). The difference in reductions in FVC (absolute value and %-predicted) seen at Week 10 in UC Study 1, comparing patients who were treated with ZEPOSIA to those who received placebo was 44 mL, 95% CI (-114, 26); 0.5%, 95% CI (-2.3, 1.2), respectively. There is insufficient information to determine the reversibility of observed decreases in FEV_1 or FVC after discontinuation of ZEPOSIA, or whether changes could be progressive with continued use.

Spirometric evaluation of respiratory function should be performed during therapy with ZEPOSIA, if clinically indicated.

5.7 Macular Edema

Sphingosine 1-phosphate (S1P) receptor modulators, including ZEPOSIA, have been associated with an increased risk of macular edema.

In MS Study 1 and Study 2, macular edema was observed in 0.3% of patients treated with ZEPOSIA and in 0.3% of patients who received IFN beta-1a. Macular edema was reported in a total of 1 (0.2%) patient in UC Study 1 and Study 3, and in 1 (0.4%) patient in UC Study 2 treated with ZEPOSIA, and in no patients who received placebo.

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking ZEPOSIA.

Continuation of ZEPOSIA therapy in patients with macular edema has not been evaluated. A decision on whether or not ZEPOSIA should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus
Patients with a history of uveitis and patients with a history of diabetes mellitus are at increased risk of macular edema during ZEPOSIA therapy. The incidence of macular edema is also increased in patients with a history of uveitis. In addition to the examination of the fundus, including the macula, prior to treatment, patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

5.8 Posterior Reversible Encephalopathy Syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. In MS controlled clinical trials with ZEPOSIA, one case of PRES was reported. Should a ZEPOSIA-treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination

and should consider an MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued.

5.9 Unintended Additive Immunosuppressive Effects from Prior Treatment with Immunosuppressive or Immune-Modulating Drugs

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation, when initiating ZEPOSIA.

Initiating treatment with ZEPOSIA after treatment with alemtuzumab is not recommended *[see Drug Interactions (7)]*.

5.10 Severe Increase in Multiple Sclerosis Disability after Stopping ZEPOSIA

In MS, severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping ZEPOSIA treatment. Patients should be observed for a severe increase in disability upon ZEPOSIA discontinuation and appropriate treatment should be instituted, as required.

5.11 Immune System Effects after Stopping ZEPOSIA

After discontinuing ZEPOSIA, the median time for peripheral blood lymphocytes to return to the normal range was approximately 30 days, with approximately 80% to 90% of patients in the normal range within 3 months *[see Clinical Pharmacology (12.2)]*. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Bradyarrhythmia and Atrioventricular Conduction Delays *[see Warnings and Precautions (5.2)]*
- Liver Injury *[see Warnings and Precautions (5.3)]*
- Fetal Risk *[see Warnings and Precautions (5.4)]*
- Increased Blood Pressure *[see Warnings and Precautions (5.5)]*
- Respiratory Effects *[see Warnings and Precautions (5.6)]*
- Macular Edema *[see Warnings and Precautions (5.7)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.8)]*
- Unintended Additive Immunosuppressive Effects from Prior Treatment with Immunosuppressive or Immune-Modulating Drugs *[see Warnings and Precautions (5.9)]*
- Severe Increase in Multiple Sclerosis Disability after Stopping ZEPOSIA *[see Warnings and Precautions (5.10)]*
- Immune System Effects after Stopping ZEPOSIA *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Common Adverse Reactions

Multiple Sclerosis

The safety of ZEPOSIA was evaluated in two randomized, double-blind, active comparator-controlled clinical studies in which 882 patients received ZEPOSIA 0.92 mg *[see Clinical Studies (14.1)]*.

Table 2 lists adverse reactions that occurred in at least 2% of ZEPOSIA-treated patients and greater than comparator. The most common adverse reactions that occurred in at least 4% of ZEPOSIA-treated patients and greater than in patients who received IFN

beta-1a were upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

Table 2: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater than IFN beta-1a in Patients with Multiple Sclerosis (Pooled MS Study 1 and Study 2)[a]

Adverse Reactions	MS Studies 1 and 2	
	ZEPOSIA 0.92 mg Once Daily[e] (n=882) %	IFN beta-1a 30 mcg Intramuscularly Once Weekly (n=885) %
Upper respiratory infection[b]	26	23
Hepatic transaminase elevation[c]	10	5
Orthostatic hypotension	4	3
Urinary tract infection	4	3
Back pain	4	3
Hypertension[d]	4	2
Upper abdominal pain	2	1

[a] Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control.
[b] Includes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, viral respiratory tract infection, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis.
[c] Includes the following terms: alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, abnormal liver function test, and increased transaminases.
[d] Includes hypertension, essential hypertension, and orthostatic hypertension.
[e] ZEPOSIA was initiated with a 7-day titration *[see Dosage and Administration (2.2)]*.

Ulcerative Colitis

The safety of ZEPOSIA was evaluated in two randomized, double-blind, placebo-controlled clinical studies [UC Study 1 (induction), n=429; and UC Study 2 (maintenance), n=230] in adult patients with moderately to severely active ulcerative colitis *[see Clinical Studies (14.2)]*. Additional data from the induction period of a randomized, double-blind, placebo-controlled study (UC Study 3, NCT01647516) included 67 patients who received ZEPOSIA 0.92 mg once daily.

Common adverse reactions in UC Study 1 and Study 3 and in UC Study 2 are listed in Tables 3 and 4, respectively. The most common adverse reactions that occurred in at least 4% of ZEPOSIA-treated patients and greater than in patients who received placebo were liver test increased, upper respiratory infection, and headache.

Table 3: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater than Placebo in Patients with Ulcerative Colitis (Pooled UC Study 1 and Study 3)

Adverse Reactions	Induction Periods (UC Study 1 and Study 3)	
	ZEPOSIA 0.92 mg Once Daily (n=496)[c,d] %	Placebo (n=281) %[d]
Upper respiratory infection[a]	5	4
Liver test increased[b]	5	0
Headache	4	3
Pyrexia	3	2
Nausea	3	2
Arthralgia	3	1

[a] Includes the following terms: streptococcal pharyngitis, pharyngotonsillitis, bacterial pharyngitis, nasopharyngitis, upper respiratory tract infection, pharyngitis, sinusitis, tonsillitis, viral upper respiratory tract infection, laryngitis, acute sinusitis, catarrh, chronic sinusitis, upper respiratory tract inflammation, chronic tonsillitis, viral pharyngitis, viral sinusitis, bacterial sinusitis, bacterial upper respiratory tract infection, viral labyrinthitis, laryngeal inflammation, and pharyngeal inflammation.
[b] Includes the following terms: gamma-glutamyl transferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hyperbilirubinemia, liver function test increased, blood alkaline phosphatase increased, and increased transaminases.
[c] ZEPOSIA was initiated with a 7-day titration *[see Dosage and Administration (2.2)]*.
[d] Percentages were calculated as the sum of each individual study percentage multiplied by its Cochran-Mantel-Haenszel weight.

Table 4: Adverse Reactions with an Incidence of at Least 4% in ZEPOSIA-Treated Patients and at Least 1% Greater than Placebo in Patients with Ulcerative Colitis (UC Study 2)

Adverse Reactions	Maintenance Period (UC Study 2)	
	ZEPOSIA 0.92 mg Once Daily (n=230) %	Placebo (n=227) %
Liver test increased[a]	11	2
Headache	5	<1

[a] Includes the following terms: gamma-glutamyl transferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hyperbilirubinemia, blood bilirubin increased, liver function test increased, and blood alkaline phosphatase increased.

Other Adverse Reactions

Reduction in Heart Rate

Initiation of ZEPOSIA may result in transient decrease in heart rate in MS and UC patients *[see Warnings and Precautions (5.2)]*.

Respiratory Effects

Dose-dependent reductions in absolute FEV_1 and FVC were observed in MS and UC patients treated with ZEPOSIA *[see Warnings and Precautions (5.6)]*.

Malignancies

Malignancies, such as melanoma, basal cell carcinoma, breast cancer, seminoma, cervical carcinoma, and adenocarcinomas, including rectal adenocarcinoma, were reported with ZEPOSIA in controlled trials of MS and UC. An increased risk of cutaneous malignancies has been reported with another S1P receptor modulator.

Hypersensitivity

Hypersensitivity, including rash and urticaria, has been reported with ZEPOSIA in active-controlled MS clinical trials.

Peripheral Edema

Peripheral edema was observed in 3% of ZEPOSIA-treated patients and in 0.4% of patients who received placebo in UC Study 2.

7 DRUG INTERACTIONS

Tables 5 and 6 include drugs with clinically important drug, tyramine, and vaccine interactions when administered concomitantly with ZEPOSIA and instructions for preventing or managing them.

Table 5: Clinically Relevant Interactions Affecting Drugs, Tyramine, and Vaccines Co-administered with ZEPOSIA

Anti-Neoplastic, Immune-Modulating, or Non-Corticosteroid Immunosuppressive Therapies	
Clinical Impact:	ZEPOSIA has not been studied in combination with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies with the exception of cyclosporine, which had no pharmacokinetic interaction *[see Clinical Pharmacology (12.3)]*.
Prevention or Management:	Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration *[see Warnings and Precautions (5.1)]*. When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive immunosuppressive effects *[see Warnings and Precautions (5.9)]*. Alemtuzumab: Initiating treatment with ZEPOSIA after alemtuzumab is not recommended because of the characteristics and duration of alemtuzumab immune suppressive effects. Beta interferon or glatiramer acetate: ZEPOSIA can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.
Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate	
Clinical Impact:	ZEPOSIA has not been studied in patients taking QT prolonging drugs. Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia.
Prevention or Management:	If treatment with ZEPOSIA is considered in patients on Class Ia or Class III anti-arrhythmic drugs, advice from a cardiologist should be sought *[see Warnings and Precautions (5.2)]*. Because of the potential additive effects on heart rate, treatment with ZEPOSIA should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties *[see Warnings and Precautions (5.2)]*. If treatment initiation with ZEPOSIA is considered in patients on QT prolonging drugs, advice from a cardiologist should be sought.
Adrenergic and Serotonergic Drugs	
Clinical Impact:	Because an active metabolite of ozanimod inhibits MAO-B in vitro, there is a potential for serious adverse reactions, including hypertensive crisis with co-administration of ZEPOSIA with drugs or over-the-counter medications that can increase norepinephrine or serotonin [e.g., opioid drugs, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclics, tyramine]. Opioid Drugs Serious, sometimes fatal reactions have been precipitated with concomitant use of opioid drugs (e.g., meperidine and its derivatives, methadone, or tramadol) and MAOIs, including selective MAO-B inhibitors. Although a small number of patients treated with ZEPOSIA were concomitantly exposed to opioids, this exposure was not adequate to rule out the possibility of an adverse reaction from co-administration. Serotonergic Drugs Although a small number of patients treated with ZEPOSIA were concomitantly exposed to serotonergic medications, this exposure was not adequate to rule out the possibility of an adverse reaction from co-administration. Sympathomimetic Medications Concomitant use of ZEPOSIA with pseudoephedrine did not potentiate the effects on blood pressure *[see Clinical Pharmacology (12.2)]*. However, hypertensive crisis has occurred with administration of ZEPOSIA alone *[see Warnings and Precautions (5.5)]* and hypertensive crisis has been reported with co-administration of other selective and nonselective MAO inhibitors (e.g., rasagiline) with sympathomimetic medications.

Prevention or Management:	Co-administration of ZEPOSIA with drugs or over-the-counter medications that can increase norepinephrine or serotonin (e.g., opioid drugs, SSRIs, SNRIs, tricyclics, tyramine) is not recommended. Monitor patients for hypertension with concomitant use.
Combination Beta Blocker and Calcium Channel Blocker	
Clinical Impact:	The co-administration of ZEPOSIA with both a beta blocker and a calcium channel blocker has not been studied. However, there is a potential of additive effects on heart rate.
Prevention or Management:	Treatment with ZEPOSIA should generally not be initiated in patients who are concurrently treated with both a heart rate lowering calcium channel blocker (e.g., verapamil, diltiazem) and beta blocker *[see Warnings and Precautions (5.2)]*. If treatment initiation with ZEPOSIA is considered in patients on both a heart rate lowering calcium channel blocker and beta blocker, advice from a cardiologist should be sought.
Tyramine	
Clinical Impact:	MAO in the gastrointestinal tract and liver (primarily type A) provides protection from exogenous amines (e.g., tyramine). If tyramine were absorbed intact, it could lead to severe hypertension, including hypertensive crisis. Aged, fermented, cured, smoked, and pickled foods containing large amounts of exogenous amines (e.g., aged cheese, pickled herring) may cause release of norepinephrine resulting in a rise in blood pressure (tyramine reaction).
Prevention or Management:	Patients should be advised to avoid foods containing a large amount of tyramine while taking recommended doses of ZEPOSIA *[see Warnings and Precautions (5.5)]*.
Vaccination	
Clinical Impact:	During, and for up to three months after, discontinuation of treatment with ZEPOSIA, vaccinations may be less effective. The use of live *attenuated* vaccines may carry the risk of infection.
Prevention or Management:	Live *attenuated* vaccines should be avoided during ZEPOSIA treatment and for up to 3 months after discontinuation of treatment with ZEPOSIA *[see Warnings and Precautions (5.1)]*.

Table 6: Clinically Relevant Interactions Affecting ZEPOSIA When Co-administered with Other Drugs

Monoamine Oxidase (MAO) Inhibitors	
Clinical Impact:	Co-administration of ZEPOSIA with MAO-B inhibitors may decrease exposure of the active metabolites of ozanimod. In addition, metabolites of ozanimod may inhibit MAO *[see Clinical Pharmacology (12.3)]*. The potential for a clinical interaction with MAO inhibitors has not been studied; however, the increased risk of nonselective MAO inhibition may lead to a hypertensive crisis.
Prevention or Management:	Co-administration of ZEPOSIA with MAO inhibitors (e.g., selegiline, phenelzine, linezolid) is contraindicated. At least 14 days should elapse between discontinuation of ZEPOSIA and initiation of treatment with MAO inhibitors.
Strong CYP2C8 Inhibitors	
Clinical Impact:	Co-administration of ZEPOSIA with strong CYP2C8 inhibitors increases the exposure of the active metabolites of ozanimod *[see Clinical Pharmacology (12.3)]*, which may increase the risk of ZEPOSIA adverse reactions.
Prevention or Management:	Co-administration of ZEPOSIA with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended.
Strong CYP2C8 Inducers	
Clinical Impact:	Co-administration of ZEPOSIA with strong CYP2C8 inducers (e.g., rifampin) reduces the exposure of the major active metabolites of ozanimod *[see Clinical Pharmacology (12.3)]*, which may decrease the efficacy of ZEPOSIA.
Prevention or Management:	Co-administration of ZEPOSIA with strong CYP2C8 inducers should be avoided.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women. In animal studies, administration of ozanimod during pregnancy produced adverse effects on development, including embryolethality, an increase in fetal malformations, and neurobehavioral changes, in the absence of maternal toxicity. In rabbits, fetal blood vessel malformations occurred at clinically relevant maternal ozanimod and metabolite exposures *(see Data)*. The receptor affected by ozanimod (sphingosine1-phosphate) has been demonstrated to have an important role in embryogenesis, including vascular and neural development.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

There are no data on the presence of ozanimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Following oral administration of ozanimod, ozanimod and/or metabolites were detected in the milk of lactating rat at levels higher than those in maternal plasma.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEPOSIA and any potential adverse effects on the breastfed infant from ZEPOSIA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Before initiation of ZEPOSIA treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for contraception during treatment with ZEPOSIA *[see Use in Specific Populations (8.1)]*. Because of the time it takes to eliminate the drug from the body after stopping treatment, the potential risk to the fetus may persist and women of childbearing age should also use effective contraception for 3 months after stopping ZEPOSIA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ZEPOSIA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. No clinically significant differences in the pharmacokinetics of ozanimod and CC112273 were observed based on age *[see Clinical Pharmacology (12.3)]*. Monitor elderly patients for cardiac and hepatic adverse reactions, because of the greater frequency of reduced cardiac and hepatic function in the elderly population.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of the ozanimod major active metabolites is unknown *[see Clinical Pharmacology (12.3)]*. Use of ZEPOSIA in patients with hepatic impairment is not recommended.

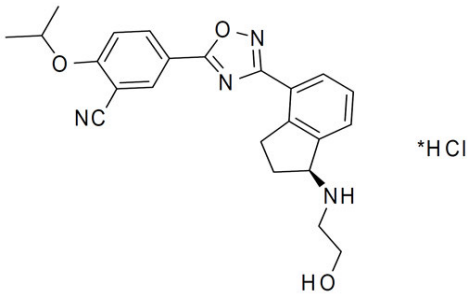
11 DESCRIPTION

ZEPOSIA contains ozanimod, a sphingosine 1-phosphate receptor modulator and is supplied as ozanimod hydrochloride (HCl).

The chemical name of ozanimod HCl is 5-(3-{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1*H*-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile, monohydrochloride.

Ozanimod HCl is a white to off-white solid that is freely soluble in water and alcohol with a molecular weight of 440.92 g/mol.

The chemical structure is:



ZEPOSIA capsules are provided as hard gelatin capsules for oral administration, containing 0.23, 0.46, or 0.92 mg of ozanimod (equivalent to 0.25, 0.5, and 1 mg ozanimod HCl, respectively). ZEPOSIA capsules consist of the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The capsule shell, imprinted with black ink, contains the following inactive ingredients: black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Ozanimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. Ozanimod has minimal or no activity on $S1P_2$, $S1P_3$, and $S1P_4$. The mechanism by which ozanimod exerts therapeutic effects in multiple sclerosis and ulcerative colitis is unknown but may involve the reduction of lymphocyte migration into the central nervous system and intestine.

12.2 Pharmacodynamics

Reduction in Blood Lymphocyte Counts

In active-controlled MS and controlled UC clinical trials, mean lymphocyte counts decreased to approximately 45% of baseline at 3 months (approximate mean blood lymphocyte counts 0.8 x 10^9/L), and low lymphocyte counts were maintained during treatment with ZEPOSIA *[see Warnings and Precautions (5.1)]*.

After discontinuing ZEPOSIA 0.92 mg, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients in the normal range within 3 months.

Reduction in Heart Rate

ZEPOSIA may cause a transient decrease in heart rate on initiation of dosing *[see Warnings and Precautions (5.2)]*. An up-titration schedule of ZEPOSIA 0.23 mg followed by doses of 0.46 mg, and 0.92 mg attenuates the magnitude of heart rate reductions *[see Dosage and Administration (2.2)]*.

Drug Interaction Studies

Sympathomimetic Agents

No clinically significant differences in heart rate or blood pressure was observed when ZEPOSIA 1.84 mg daily (two times the recommended dosage) for 28 days was co-administered with a single dose of 60 mg pseudoephedrine (a sympathomimetic agent) compared to pseudoephedrine alone *[see Drug Interactions (7)]*.

Beta Blocker or Calcium Channel Blocker

The effect of co-administration of the maintenance dosage of ZEPOSIA, propranolol, or diltiazem, or administration with both a beta blocker and a calcium channel blocker taken together has not been studied *[see Drug Interactions (7)]*.

Pulmonary Function

Dose-dependent reductions in FEV_1 and FVC were observed in patients treated with ZEPOSIA *[see Warnings and Precautions (5.6)]*.

Cardiac Electrophysiology

Following a 14-day titration regimen of once daily doses of ozanimod 0.23 mg for 4 days, 0.46 mg for 3 days, 0.92 mg for 3 days, and 1.84 mg (2 times the maximum approved recommended dose) for 4 days in healthy subjects, ZEPOSIA did not prolong the QTc interval to any clinically relevant extent *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

The steady state exposure parameters of ozanimod and its major active metabolite, CC112273 are summarized in Table 7. Population pharmacokinetic analysis indicated no meaningful differences in these pharmacokinetic parameters in patients with relapsing MS or UC.

Table 7: Exposure Parameters of Ozanimod and its Major Metabolite[a]

Parameters	Ozanimod	CC112273
$C_{max,ss}$	0.244 ng/mL (31.8%)	6.98 ng/mL (42.7%)
$AUC_{tau,ss}$	4.46 ng*h/mL (31.8%)	143.77 ng*h/mL (39.2%)
Dose Proportionality	The C_{max} and AUC increases proportionally over the ozanimod dose range from 0.46 mg to 0.92 mg.	
Time to Steady State	102 hours (28.2%)[b]	45 days (45%)
Accumulation Ratio	2.40 (21.1%)[b]	16 (101%)

[a] Mean [coefficient of variation (CV%)] following ozanimod 0.92 mg once daily dose in relapsing MS patients, unless otherwise specified.
[b] In healthy subjects.
$C_{max,ss}$ = maximum observed plasma concentration at steady state, $AUC_{tau,ss}$ = area under the plasma concentration-time curve during a dosage interval at steady state.

Absorption

The T_{max} of ozanimod is approximately 6 to 8 hours.

Effect of Food

No clinically significant differences in the C_{max} and AUC of ozanimod were observed following administration of ZEPOSIA with either a high-fat, high-calorie meal (1000 calories, 50% fat) or a low-fat, low-calorie meal (300 calories, 10% fat) compared to fasted conditions *[see Dosage and Administration (2.2)]*.

Distribution

The mean (CV%) apparent volume of distribution of ozanimod (Vz/F) is 5590 L (27%). Human plasma proteins binding of ozanimod, CC112273 and CC1084037 is approximately 98.2%, 99.8%, and 99.3%, respectively.

Elimination

The mean (CV%) plasma half-life (t1/2) of ozanimod is approximately 21 hours (15%). The mean (CV%) effective half-life (t1/2) of CC112273 and its direct interconverting metabolite CC1084037 was approximately 11 days (104%) in relapsing MS patients. The mean (CV%) apparent oral clearance for ozanimod was approximately 192 L/h (37%).

Metabolism

Ozanimod is metabolized by multiple enzymes to form circulating major active metabolites (e.g., CC112273 and CC1084037) and minor active metabolites (e.g., RP101988, RP101075, and RP112509) with similar activity and selectivity for $S1P_1$ and $S1P_5$. Ozanimod is metabolized by ALDH/ADH to form carboxylate metabolite RP101988 and by CYP3A4 to form RP101075. RP101075 is then metabolized either by NAT-2 to form a minor active metabolite RP101442 or by MAO-B to form CC112273. CC112273 is then metabolized by CYP2C8 to form RP112509 or reduced to form CC1084037. CC1084037 is metabolized by AKR 1C1/1C2 and/or 3β- and 11β-HSD to form CC112273. The interconversion between CC112273 and CC1084037 favors CC112273. Approximately 94% of circulating total active drug exposure is represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%), in humans.

Excretion

Following a single oral dose of radiolabeled ozanimod 0.92 mg, approximately 26% of the radioactivity was recovered in urine and 37% in feces, primarily composed of inactive metabolites.

Specific Populations

Geriatric Patients

Population pharmacokinetic analyses showed that steady state exposure (AUC) of CC112273 in UC patients over 65 years of age was approximately 3% to 4% greater than patients 45 to 65 years of age and 27% greater than adult patients under 45 years of age. There is no meaningful difference in the pharmacokinetics in elderly patients with UC *[see Use in Specific Populations (8.5)]*.

Male and Female Patients

No clinically significant differences in the pharmacokinetics of ozanimod and CC112273 were observed based on sex or weight.

Racial or Ethnic Groups

In a dedicated Japanese PK bridging study, following repeated dosing of 0.96 mg ZEPOSIA, ozanimod exposures (C_{max} and AUC_{tau}) were unchanged and CC112273 exposures (C_{max} and AUC_{tau}) were approximately 28% and 43% higher, respectively, in Japanese subjects (N=10) compared to Caucasian subjects (N=12). These differences are not considered clinically meaningful.

Patients with Renal Impairment

In a dedicated renal impairment trial, following a single oral dose of 0.23 mg ZEPOSIA, exposures (AUC_{last}) for ozanimod and CC112273 were approximately 27% higher and 23% lower, respectively, in subjects with end stage renal disease (N=8) compared to subjects with normal renal function (N=8). Based on this trial, renal impairment has no clinically important effects on pharmacokinetics of ozanimod or CC112273.

Smokers

Population PK analyses showed that CC112273 steady-state exposure (AUC) was approximately 50% lower in smokers than in nonsmokers, although for smokers this reduction in exposure did not result in meaningful differences in absolute lymphocyte count (ALC) reduction or an apparent impact on clinical efficacy.

Drug Interaction Studies

Clinical Studies

Strong CYP3A and P-gp Inhibitors

No clinically significant differences in the pharmacokinetics of ozanimod and its major active metabolites CC112273 and CC1084037 were observed when co-administered with itraconazole (P-gp and strong CYP3A inhibitor).

Strong CYP2C8 Inhibitors

Co-administration of ozanimod with gemfibrozil (a strong CYP2C8 inhibitor) increased exposure (AUC) of active metabolites CC112273 and CC1084037 by approximately 47% and 69%, respectively, with no change in the AUC of ozanimod *[see Drug Interactions (7)]*.

BCRP Inhibitors

Co-administration of ozanimod with cyclosporine (BCRP inhibitor) had no effect on the exposure of ozanimod or the major active metabolites CC112273 and CC1084037.

Strong CYP2C8 Inducers

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 effect on CC112273 and CC1084037 is primarily caused by induction of CYP2C8 *[see Drug Interactions (7)]*.

Prednisone and Prednisolone

Population pharmacokinetic analyses showed that concomitant administration of prednisone or prednisolone in patients with UC did not alter the apparent clearance of the predominant active metabolite CC112273. The impact of prednisone or prednisolone on the pharmacokinetics of CC1084037 is unknown.

Monoamine Oxidase Inhibitors

No clinical studies evaluating the drug interaction potential of ozanimod with MAO inhibitors have been conducted *[see Drug Interaction (7)]*.

Oral Contraceptives

No clinically significant differences in the pharmacokinetic of oral contraceptive containing ethinyl estradiol and norethindrone were observed when co-administered with ozanimod.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes

Ozanimod, CC112273, CC1084037, and other metabolites do not inhibit CYPs 1A2, 2B6, 2C19, 2C8, 2C9, 2D6, and 3A, and do not induce CYPs 1A2, 2B6, and 3A.

In vitro, CC112273 and CC1084037 inhibited MAO-B (IC_{50} values of 5.72 nM and 58 nM, respectively) with more than 1000-fold selectivity over monoamine oxidase A (MAO-A).

Transporter Systems

Ozanimod, CC112273, CC1084037, and other metabolites do not inhibit P-gp, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, or MATE2-K. CC112273 and CC1084037 do not inhibit BCRP at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral administration of ozanimod (0, 8, 25, or 80 mg/kg/day) to Tg rasH2 mice for 26-weeks resulted in an increase in hemangioma and hemangiosarcoma (combined) in males and females at the mid and high doses tested.

Oral administration of ozanimod (0, 0.2, 0.7, or 2 mg/kg/day) to rats for 2 years resulted in no increase in tumors. At the highest dose tested (2 mg/kg/day), plasma exposure (AUC) for ozanimod was approximately 100 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Mutagenesis

Ozanimod was negative in a battery of in vitro (Ames, mouse lymphoma tk) and in vivo (rat micronucleus) assays. Metabolite CC112273 was negative in in vitro (Ames, chromosomal aberration in mammalian cell) assays. Metabolite CC1084037 was negative in an Ames assay, and positive in an in vitro chromosomal aberration assay in human (TK6) cells but negative in an in vivo rat micronucleus/comet assay.

Impairment of Fertility

Oral administration of ozanimod (0, 0.2, 2, or 30 mg/kg/day) to male and female rats prior to and during mating and continuing through gestation day 7 resulted in no adverse effects on fertility. At the highest dose tested (30 mg/kg/day), plasma ozanimod exposure (AUC) was approximately 1600 times that in humans at the maximum recommended human dose (MRHD) (0.92 mg/day); plasma AUCs for metabolites, CC112273 and CC1084037, at 30 mg/kg/day were 13 and 3 times, respectively, those in humans at the MRHD.

14 CLINICAL STUDIES

14.1 Multiple Sclerosis

The efficacy of ZEPOSIA was demonstrated in 2 randomized, double-blind, double-dummy, parallel-group, active comparator-controlled clinical trials of similar design, in patients with relapsing forms of MS [Study 1 (NCT02294058) and Study 2 (NCT02047734)]. Patients in Study 1 were treated until the last enrolled patient completed 1 year of treatment. Patients in Study 2 were treated for 24 months. Both studies included patients who had experienced at least 1 relapse within the prior year, or 1 relapse within the prior 2 years with evidence of at least a gadolinium-enhancing (GdE) lesion in the prior year, and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.0 at baseline. Patients with primary progressive MS were excluded.

Patients were randomized to receive either ZEPOSIA 0.92 mg given orally once daily, beginning with a dosage titration *[see Dosage and Administration (2.2)]*, or interferon (IFN) beta-1a, the active comparator, 30 mcg given intramuscularly once weekly. Neurological evaluations were performed at baseline, every 3 months, and at the time of a suspected relapse. Brain MRI scans were performed at baseline, 6 months (Study 1), 1 year (Studies 1 and 2), and 2 years (Study 2).

The primary endpoint of both Study 1 and Study 2 was the annualized relapse rate (ARR) over the treatment period (Study 1) and 24 months (Study 2). Additional outcome measures included: 1) the number of new or enlarging MRI T2 hyperintense lesions over 12 and 24 months, 2) the number of MRI T1 Gadolinium-enhancing (Gd+) lesions at 12 and 24 months, and 3) the time to confirmed disability progression, defined as at least a 1-point increase from baseline EDSS confirmed after 3 months and after 6 months. Confirmed disability progression was evaluated in a pooled analysis of Studies 1 and 2.

In Study 1, a total of 895 patients were randomized to receive ZEPOSIA (n=447) or IFN beta-1a (n=448); of these patients, 94% who received ZEPOSIA and 92% who received IFN beta-1a completed the study. The mean age was 35.4 years, 99.8% were White, and 65% were female. The mean time since MS symptom-onset was 6.9 years, and the median EDSS score at baseline was 2.5; 31% had been treated with a non-steroid therapy for MS. At baseline, the mean number of relapses in the prior year was 1.3 and 48% of patients had one or more T1 Gd-enhancing lesions (mean 1.8) on their baseline MRI scan.

In Study 2, a total of 874 patients were randomized to receive ZEPOSIA (n=433) or IFN beta-1a (n=441); of these patients, 90% who received ZEPOSIA and 85% who received IFN beta-1a completed the study. The mean age was 35.6 years, 98% were White, and 68% were female. The mean time since MS symptom onset was 6.6 years, and the median EDSS score at baseline was 2.5; 29% of patients had been treated with a non-steroid therapy for MS. At baseline, the mean number of relapses in the prior year was 1.3 and 43% of patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The ARR was statistically significantly lower in patients treated with ZEPOSIA 0.92 mg than in patients who received IFN beta-1a 30 mcg IM. The number of new or enlarging T2 lesions and the number of GdE lesions were statistically significantly lower in patients treated with ZEPOSIA 0.92 mg than in patients who received IFN beta-1a.

There was no statistically significant difference in the three-month and six-month confirmed disability progression between ZEPOSIA and IFN beta-1a-treated patients over 2 years.

The results for Study 1 and Study 2 are shown in Table 8.

Table 8: Clinical and MRI Endpoints from MS Study 1 and Study 2

Endpoints	Study 1		Study 2	
	ZEPOSIA 0.92 mg (n=447) %	IFN beta-1a 30 mcg (n=448) %	ZEPOSIA 0.92 mg (n=433) %	IFN beta-1a 30 mcg (n=441) %
Clinical Endpoints				
Annualized Relapse Rate (Primary Endpoint)	0.181[a]	0.350[a]	0.172	0.276
Relative Reduction	48% (p<0.0001)		38% (p<0.0001)	
Percentage of patients without relapse[b]	78%	66%	76%	64%
Proportion of Patients with 3-Month Confirmed Disability Progression[c,d]	7.6% ZEPOSIA vs. 7.8% IFN beta-1a			
Hazard Ratio	0.95 (p=0.77)[e]			
MRI Endpoints				
Mean number of new or enlarging T2 hyperintense lesions per MRI[f]	1.47	2.84	1.84	3.18
Relative Reduction	48% (p<0.0001)		42% (p<0.0001)	
Mean number of T1 Gd-enhancing lesions[g]	0.16	0.43	0.18	0.37
Relative Reduction	63% (p<0.0001)		53% (p=0.0006)	

[a] Through the treatment period (mean duration 13.6 months).
[b] Over treatment period for Study 1 and over 24 months for Study 2.
[c] Disability progression defined as 1-point increase in Expanded Disability Status Scale (EDSS) confirmed 3 months or 6 months later.
[d] Prospective planned pooled analysis of Studies 1 and 2.
[e] Not statistically significant.
[f] Over 12 months for Study 1 and over 24 months for Study 2.
[g] At 12 months for Study 1 and at 24 months for Study 2.

A similar effect of ZEPOSIA on the ARR compared to IFN beta-1a was observed in exploratory subgroups defined by sex, age, prior non-steroid therapy for MS, and baseline disease activity.

14.2 Ulcerative Colitis

The efficacy and safety of ZEPOSIA were evaluated in two multicenter, randomized, double-blind, placebo-controlled clinical studies [UC Study 1 (induction) and UC Study 2 (maintenance) (NCT02435992)] in adult patients with moderately to severely active ulcerative colitis.

UC Study 1

In UC Study 1, a total of 645 patients were randomized 2:1 to either ZEPOSIA 0.92 mg given orally once daily or placebo for 10 weeks, beginning with a dosage titration *[see Dosage and Administration (2.2)]*. The trial included adult patients with moderately to severely active UC who had an inadequate response or were intolerant to any of the following: oral aminosalicylates, corticosteroids, immunomodulators (e.g., 6-mercaptopurine and azathioprine), or a biologic (e.g., TNF blocker and/or vedolizumab). Patients were required to be on stable doses of oral aminosalicylates and/or corticosteroids (prednisone daily dose up to 20 mg equivalent or budesonide extended-release tablets) prior to enrollment. Seventy-one percent of patients were receiving mesalamine, 13% sulfasalazine, and 33% oral corticosteroids. A total of 30% of patients had previously failed or were intolerant to TNF blockers. Of these patients, 63% received at least two biologics including TNF blockers.

The disease activity was assessed by the Mayo score (0 to 12) which consists of four subscores (0 to 3 for each subscore): stool frequency, rectal bleeding, findings on centrally-read endoscopy, and physician global assessment. An endoscopy subscore of 2 was defined by marked erythema, lack of vascular pattern, friability, and erosions; an endoscopy subscore of 3 was defined by spontaneous bleeding and ulceration. Enrolled patients had Mayo scores between 6 to 12; at baseline, patients had a median Mayo score of 9, with 86% of patients having moderate disease (Mayo score 6-10), and 14% having severe disease (Mayo score 11-12).

Concomitant immunomodulators or biologic therapies were not permitted.

The primary endpoint was clinical remission at Week 10, defined using a 3-component Mayo score without the physician global assessment: rectal bleeding subscore = 0, stool frequency subscore = 0 or 1 (and a decrease of ≥ 1 point from the baseline stool

frequency subscore), and endoscopy subscore = 0 or 1 (an endoscopy subscore of 0 defined as normal or inactive disease, and an endoscopy subscore of 1 defined as presence of erythema, decreased vascular pattern and no friability).

The secondary endpoints were clinical response, endoscopic improvement, and endoscopic-histologic mucosal improvement. Clinical response (reduction from baseline in the 3-component Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1), endoscopic improvement (Mayo endoscopy subscore of 0 or 1), and endoscopic-histologic mucosal improvement [combined endoscopic improvement and histologic improvement of colonic tissue (no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue, i.e., Geboes < 2.0)].

A significantly greater proportion of patients treated with ZEPOSIA achieved clinical remission, clinical response, endoscopic improvement, and endoscopic-histologic mucosal improvement compared to placebo at Week 10 (see Table 9).

Table 9: Proportion of Patients Meeting Efficacy Endpoints in the Induction Period at Week 10 in UC Study 1

Endpoint	ZEPOSIA 0.92 mg Once Daily[a] (N=429)		Placebo (N=216)		Treatment Difference[b] (95% CI)
	n	%	n	%	
Clinical remission[c]	**79**	**18%**	**13**	**6%**	**12% (8%, 17%)[g]**
Without prior TNF blocker exposure	66/299	22%	10/151	7%	
Prior TNF blocker exposure	13/130	10%	3/65	5%	
Clinical response[d]	**205**	**48%**	**56**	**26%**	**22% (14%, 29%)[g]**
Without prior TNF blocker exposure	157/299	53%	44/151	29%	
Prior TNF blocker exposure	48/130	37%	12/65	19%	
Endoscopic improvement[e]	**117**	**27%**	**25**	**12%**	**16% (10%, 22%)[g]**
Without prior TNF blocker exposure	97/299	32%	18/151	12%	
Prior TNF blocker exposure	20/130	15%	7/65	11%	
Endoscopic-histologic mucosal improvement[f]	**54**	**13%**	**8**	**4%**	**9% (5%, 13%)[h]**
Without prior TNF blocker exposure	47/299	16%	6/151	4%	
Prior TNF blocker exposure	7/130	5%	2/65	3%	

CI = confidence interval; TNF = tumor necrosis factor.

[a] ZEPOSIA was initiated with a 7-day titration *[see Dosage and Administration (2.2)]*.

[b] Treatment difference (adjusted for stratification factors of prior anti-TNF exposure and corticosteroid use at baseline).

[c] Clinical remission is defined as: rectal bleeding subscore = 0, stool frequency subscore = 0 or 1 (and a decrease from baseline in the stool frequency subscore of ≥ 1 point), and endoscopy subscore = 0 or 1 without friability.

[d] Clinical response is defined as a reduction from baseline in the 3-component Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1.

[e] Endoscopic improvement is defined as a Mayo endoscopy subscore of 0 or 1 without friability.

[f] Endoscopic-histologic mucosal improvement is defined as both Mayo endoscopic subscore of 0 or 1 without friability and histologic improvement of colonic tissue (defined as no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue, i.e., Geboes <2.0).

[g] $p<0.0001$.

[h] $p<0.001$.

The relationship of endoscopic-histologic mucosal improvement, as defined in UC Study 1, at Week 10 to disease progression and long term outcomes was not evaluated during UC Study 1.

Rectal Bleeding Subscore and Stool Frequency Subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 (i.e., 1 week after completing the required 7-day dosage titration) in patients treated with ZEPOSIA.

UC Study 2

In UC Study 2, a total of 457 patients who received ZEPOSIA in either UC Study 1 or in an open-label arm and achieved clinical response at Week 10 were re-randomized 1:1 and were treated with either ZEPOSIA 0.92 mg (n=230) or placebo (n=227) for 42 weeks (UC Study 2), for a total of 52 weeks of treatment.

Patients were permitted to be on stable doses of oral aminosalicylates. Corticosteroid tapering was required upon entering this study for patients who were receiving corticosteroids during the induction period. Concomitant oral immunomodulators or biologic therapies were not permitted. At study entry, 35% of patients were in clinical remission; 29% of patients were on corticosteroids; and 31% of patients had an inadequate response, loss of response, or intolerance to TNF blockers.

The primary endpoint was the proportion of patients in clinical remission at Week 52. The secondary endpoints at Week 52 were the proportion of patients with clinical response, endoscopic improvement, endoscopic-histologic mucosal improvement, corticosteroid-free clinical remission, and maintenance of clinical remission at Week 52 among patients who achieved clinical remission at Week 10 in UC Study 1.

The results of the efficacy endpoints in the maintenance period are shown in Table 10.

Table 10: Proportion of Patients Meeting Efficacy Endpoints in the Maintenance Period at Week 52 in UC Study 2

Endpoint	ZEPOSIA 0.92 mg Once Daily[a] (N=230)		Placebo (N=227)		Treatment Difference[b] (95% CI)
	n	%	n	%	
Clinical remission[c]	**85**	**37%**	**42**	**19%**	**19% (11%, 26%)[i]**
Without prior TNF blocker exposure	63/154	41%	35/158	22%	
Prior TNF blocker exposure	22/76	29%	7/69	10%	
Clinical response[d]	**138**	**60%**	**93**	**41%**	**19% (10%, 28%)[i]**
Without prior TNF blocker exposure	96/154	62%	76/158	48%	
Prior TNF blocker exposure	42/76	55%	17/69	25%	
Endoscopic improvement[e]	**105**	**46%**	**60**	**26%**	**19% (11%, 28%)[j]**
Without prior TNF blocker exposure	77/154	50%	48/158	30%	
Prior TNF blocker exposure	28/76	37%	12/69	17%	
Maintenance of clinical remission at Week 52 in the subset of patients in remission at Week 10[f]	**41/79**	**52%**	**22/75**	**29%**	**24% (9%, 39%)[k]**
Without prior TNF blocker exposure	37/64	58%	19/58	33%	
Prior TNF blocker exposure	4/15	27%	3/17	18%	
Corticosteroid-free clinical remission[g]	**73**	**32%**	**38**	**17%**	**15% (8%, 23%)[j]**
Without prior TNF blocker exposure	55/154	36%	31/158	20%	
Prior TNF blocker exposure	18/76	24%	7/69	10%	
Endoscopic-histologic mucosal improvement[h]	**68**	**30%**	**32**	**14%**	**16% (8%, 23%)[j]**
Without prior TNF blocker exposure	51/154	33%	28/158	18%	
Prior TNF blocker exposure	17/76	22%	4/69	6%	

CI = confidence interval; TNF = tumor necrosis factor.

[a] ZEPOSIA was initiated with a 7-day titration *[see Dosage and Administration (2.2)]*.

[b] Treatment difference (adjusted for stratification factors of clinical remission and concomitant corticosteroid use at Week 10).

[c] Clinical remission is defined as: rectal bleeding subscore = 0, stool frequency subscore = 0 or 1 (and a decrease from baseline in the stool frequency subscore of ≥ 1 point), and endoscopy subscore = 0 or 1 without friability.

[d] Clinical response is defined as a reduction from baseline in the 3-component Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1.

[e] Endoscopic improvement is defined as a Mayo endoscopy subscore of 0 or 1 without friability.

[f] Maintenance of remission is defined as clinical remission at Week 52 in the subset of patients in clinical remission at Week 10.

[g] Corticosteroid-free remission is defined as clinical remission at Week 52 while off corticosteroids for ≥ 12 weeks.

[h] Endoscopic-histologic mucosal improvement is defined as both Mayo endoscopic score of 0 or 1 without friability and histologic improvement of colonic tissue (defined as no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue, i.e., Geboes <2.0).

[i] $p<0.0001$.

[j] $p<0.001$.

[k] $p=0.0025$.

The relationship of endoscopic-histologic mucosal improvement, as defined in UC Study 2, at Week 52 to disease progression and long term outcomes was not evaluated during UC Study 2.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZEPOSIA is available as capsules in the following dosage strengths:

- 0.23 mg ozanimod: light grey opaque body/light grey opaque cap imprinted with black ink “OZA” on the cap and “0.23 mg” on the body

- 0.46 mg ozanimod: light grey opaque body/orange opaque cap imprinted with black ink “OZA” on the cap and “0.46 mg” on the body
- 0.92 mg ozanimod: orange opaque body/orange opaque cap imprinted with black ink “OZA” on the cap and “0.92 mg” on the body

Capsules are supplied in the following strengths and package configurations:

Package configuration	Tablet strength	NDC number
Bottles of 30	0.92 mg ozanimod	59572-820-30
7-Day Starter Pack	7-capsule starter pack containing: (4) 0.23 mg ozanimod capsules and (3) 0.46 ozanimod mg capsules	59572-810-07
Starter Kit (7-Day Starter Pack and 0.92 mg 30-count Bottle)	37-capsule starter kit including: one 7-capsule starter pack containing: (4) 0.23 mg ozanimod capsules and (3) 0.46 mg ozanimod capsules and one bottle containing: (30) 0.92 mg ozanimod capsules	59572-890-91 59572-890-07 59572-890-30

16.2 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Infections

Inform patients that they may be more likely to get infections, some of which could be life-threatening, when taking ZEPOSIA and for 3 months after stopping it, and that they should contact their healthcare provider if they develop symptoms of infection *[see Warnings and Precautions (5.1)]*. Inform patients that prior or concomitant use of drugs that suppress the immune system may increase the risk of infection. Advise patients that some vaccines containing live virus (live attenuated vaccines) should be avoided during treatment with ZEPOSIA. Advise patients that if immunizations are planned, they should be administered at least 1 month prior to initiation of ZEPOSIA. Inform patients that the use of live *attenuated* vaccines should be avoided during and for 3 months after treatment with ZEPOSIA.

Cardiac Effects

Advise patients that initiation of ZEPOSIA treatment may result in a transient decrease in heart rate. Inform patients that to reduce this effect, dose titration is required. Advise patients that the dose titration is also required if a dose is missed for 1 day or more during the first 14 days of treatment *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.2)]*.

Liver Injury

Inform patients that ZEPOSIA may increase liver enzymes. Advise patients that they should contact their healthcare provider if they have any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine *[see Warnings and Precautions (5.3)]*.

Pregnancy and Fetal Risk

Inform patients that, based on animal studies, ZEPOSIA may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing potential of the need for effective contraception during treatment with ZEPOSIA and for 3 months after stopping ZEPOSIA. Advise a female patient to immediately inform her healthcare provider if she is pregnant or planning to become pregnant *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.3)]*.

Respiratory Effects

Advise patients that they should contact their healthcare provider if they experience new onset or worsening dyspnea *[see Warnings and Precautions (5.6)]*.

Macular Edema

Advise patients that ZEPOSIA may cause macular edema, and that they should contact their healthcare provider if they experience any changes in their vision. Inform patient with diabetes mellitus or a history of uveitis that their risk of macular edema may be increased *[see Warnings and Precautions (5.7)]*.

Posterior Reversible Encephalopathy Syndrome

Advise patients to immediately report to their healthcare provide any symptoms involving sudden onset of severe headache, altered mental status, visual disturbances, or seizure. Inform patients that delayed treatment could lead to permanent neurological consequences *[see Warnings and Precautions (5.8)]*.

Severe Increase in Multiple Sclerosis Disability after Stopping ZEPOSIA

Inform patients with multiple sclerosis that severe increase in disability has been reported after discontinuation of a S1P receptor modulator like ZEPOSIA. Advise patients to contact their physician if they develop worsening symptoms of MS following discontinuation of ZEPOSIA *[see Warnings and Precautions (5.10)]*.

Immune System Effects after Stopping ZEPOSIA

Advise patients that ZEPOSIA continues to have effects, such as lowering effects on peripheral lymphocyte count, for up to 3 months after the last dose *[see Warnings and Precautions (5.11)]*.

Manufactured for: Celgene Corporation
Summit, NJ 07901

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ZEPPI/ZEPMG.003

MEDICATION GUIDE

ZEPOSIA® (zeh-poe'-see-ah)
(ozanimod)
capsules, for oral use

Read this Medication Guide before you start taking ZEPOSIA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ZEPOSIA?
ZEPOSIA may cause serious side effects, including:

1. **Infections.** ZEPOSIA can increase your risk of serious infections that can be life-threatening and cause death. ZEPOSIA lowers the number of white blood cells (lymphocytes) in your blood. This will usually go back to normal within 3 months of stopping treatment. Your healthcare provider may do a blood test of your white blood cells before you start taking ZEPOSIA.

   Call your healthcare provider right away if you have any of the following symptoms of an infection during treatment with ZEPOSIA and for 3 months after your last dose of ZEPOSIA:

   - fever
   - feeling very tired
   - flu-like symptoms
   - cough
   - painful and frequent urination (signs of a urinary tract infection)
   - rash
   - headache with fever, neck stiffness, sensitivity to light, nausea or confusion (these may be symptoms of meningitis, an infection of the lining around your brain and spine)

   Your healthcare provider may delay starting or may stop your ZEPOSIA treatment if you have an infection.

2. **Slow heart rate (also known as bradyarrhythmia) when you start taking ZEPOSIA.** ZEPOSIA may cause your heart rate to temporarily slow down, especially during the first 8 days that you take ZEPOSIA. You will have a test to check the electrical activity of your heart called an electrocardiogram (ECG) before you take your first dose of ZEPOSIA. Call your healthcare provider if you experience the following symptoms of slow heart rate:

   - dizziness
   - lightheadedness
   - feeling like your heart is beating slowly or skipping beats
   - shortness of breath
   - confusion
   - chest pain
   - tiredness

   Follow directions from your healthcare provider when starting ZEPOSIA and when you miss a dose. See **"How should I take ZEPOSIA?".**

See "**What are possible side effects of ZEPOSIA?**" for more information about side effects.

What is ZEPOSIA?

ZEPOSIA is a prescription medicine used to treat:

- adults with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.
- adults with moderately to severely active ulcerative colitis.

It is not known if ZEPOSIA is safe and effective in children.

Do not take ZEPOSIA if you:

- have had a heart attack, chest pain (unstable angina), stroke or mini-stroke (transient ischemic attack or TIA), or certain types of heart failure in the last 6 months.
- have or have had a history of certain types of an irregular or abnormal heartbeat (arrhythmia) that is not corrected by a pacemaker.
- have untreated, severe breathing problems during your sleep (sleep apnea).
- take certain medicines called monoamine oxidase (MAO) inhibitors (such as selegiline, phenelzine, linezolid).

Talk to your healthcare provider before taking ZEPOSIA if you have any of these conditions or do not know if you have any of these conditions.

Before taking ZEPOSIA, tell your healthcare provider about all of your medical conditions, including if you:

- have a fever or infection, or you are unable to fight infections due to a disease, or take or have taken medicines that lower your immune system.

- received a vaccine in the past 30 days or are scheduled to receive a vaccine. ZEPOSIA may cause vaccines to be less effective.
- Before you start treatment with ZEPOSIA, your healthcare provider may give you a chicken pox (Varicella Zoster Virus) vaccine if you have not had one before.
- have had chickenpox or have received the vaccine for chickenpox. Your healthcare provider may do a blood test for the chickenpox virus. You may need to get the full course of the vaccine for chickenpox and then wait 1 month before you start taking ZEPOSIA.
- have a slow heart rate.
- have an irregular or abnormal heartbeat (arrhythmia).
- have a history of a stroke.
- have heart problems, including a heart attack or chest pain.
- have high blood pressure.
- have liver problems.
- have breathing problems, including during your sleep.
- have eye problems, especially an inflammation of the eye called uveitis.
- have diabetes.
- are pregnant or plan to become pregnant. ZEPOSIA may harm your unborn baby. Talk with your healthcare provider if you are pregnant or plan to become pregnant. If you are a female who can become pregnant, you should use effective birth control during your treatment with ZEPOSIA and for 3 months after you stop taking ZEPOSIA. Talk with your healthcare provider about what birth control method is right for you during this time. Tell your healthcare provider right away if you become pregnant while taking ZEPOSIA or if you become pregnant within 3 months after you stop taking ZEPOSIA.
- are breastfeeding or plan to breastfeed. It is not known if ZEPOSIA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ZEPOSIA.

Tell your healthcare provider about all the medicines you take or have recently taken, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using ZEPOSIA with other medicines can cause serious side effects. Especially tell your healthcare provider if you take or have taken:

- medicines that affect your immune system, such as alemtuzumab
- medicines to control your heart rhythm (antiarrhythmics), or heart beat
- CYP2C8 inducers such as rifampin
- CYP2C8 inhibitors such as gemfibrozil (medicine to treat high fat in your blood)
- opioids (pain medicine)
- medicines to treat depression
- medicines to treat Parkinson's disease
- medicines to control your heart rate and blood pressure (beta blocker medicines and calcium channel blocker medicines)

You should not receive **live** vaccines during treatment with ZEPOSIA, for at least 1 month before taking ZEPOSIA and for 3 months after you stop taking ZEPOSIA. Vaccines may not work as well when given during treatment with ZEPOSIA.

Talk with your healthcare provider if you are not sure if you take any of these medicines.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ZEPOSIA?

You will receive a 7-day starter pack. You must start ZEPOSIA by slowly increasing doses over the first week. Follow the dose schedule in the table below. This may reduce the risk of slowing of the heart rate.

Days 1-4	Take 0.23 mg (capsule in light grey color) 1 time a day
Days 5-7	Take 0.46 mg (capsule in half-light grey and half-orange color) 1 time a day
Days 8 and thereafter	Take 0.92 mg (capsule in orange color) 1 time a day

- Take ZEPOSIA exactly as your healthcare provider tells you to take it.
- Take ZEPOSIA 1 time each day.

- Swallow ZEPOSIA capsules whole.
- Take ZEPOSIA with or without food.
- Avoid certain foods that are high (over 150 mg) in tyramine such as aged, fermented, cured, smoked and pickled foods. Eating these foods while taking ZEPOSIA may increase your blood pressure.
- Do not stop taking ZEPOSIA without talking with your healthcare provider first.
- Do not skip a dose.
- Start taking ZEPOSIA with a 7-day starter pack.
- If you miss 1 or more days of your ZEPOSIA dose during the first 14 days of treatment, talk to your healthcare provider. You will need to begin with another ZEPOSIA 7-day starter pack.
- If you miss a dose of ZEPOSIA after the first 14 days of treatment, take the next scheduled dose the following day.

What are the possible side effects of ZEPOSIA?

ZEPOSIA may cause serious side effects, including:

- See **"What is the most important information I should know about ZEPOSIA?"**
- **liver problems.** ZEPOSIA may cause liver problems. Your healthcare provider will do blood tests to check your liver before you start taking ZEPOSIA. Call your healthcare provider right away if you have any of the following symptoms:
  - unexplained nausea
  - vomiting
  - stomach area (abdominal) pain
  - tiredness
  - loss of appetite
  - yellowing of the whites of your eyes or skin
  - dark colored urine
- **increased blood pressure.** Your healthcare provider should check your blood pressure during treatment with ZEPOSIA. A sudden, severe increase in blood pressure (hypertensive crisis) can happen when you eat certain foods that contain high levels of tyramine. See "**How should I take ZEPOSIA?**" section for more information.
- **breathing problems.** Some people who take ZEPOSIA have shortness of breath. Call your healthcare provider right away if you have new or worsening breathing problems.
- **a problem with your vision called macular edema.** Your risk for macular edema is higher if you have diabetes or have had an inflammation of your eye called uveitis. Your healthcare provider should test your vision before you start taking ZEPOSIA if you are at higher risk for macular edema or at any time you notice vision changes during treatment with ZEPOSIA. Call your healthcare provider right away if you have any of the following symptoms:
  - blurriness or shadows in the center of your vision
  - sensitivity to light
  - a blind spot in the center of your vision
  - unusually colored vision
- **swelling and narrowing of blood vessels in your brain**. A condition called PRES (Posterior Reversible Encephalopathy Syndrome) is a rare condition that has happened with ZEPOSIA and with drugs in the same class. Symptoms of PRES usually get better when you stop taking ZEPOSIA. If left untreated, it may lead to a stroke. Your healthcare provider will do a test if you have any symptoms of PRES. Call your healthcare provider right away if you have any of the following symptoms:
  - sudden severe headache
  - sudden confusion
  - sudden loss of vision or other changes in your vision
  - seizure
- **severe worsening of multiple sclerosis (MS) after stopping ZEPOSIA.** When ZEPOSIA is stopped, symptoms of MS may return and become worse compared to before or during treatment. Always talk to your healthcare provider before you stop taking ZEPOSIA for any reason. Tell your healthcare provider if you have worsening symptoms of MS after stopping ZEPOSIA.

The most common side effects of ZEPOSIA can include:

- upper respiratory tract infections
- elevated liver enzymes
- low blood pressure when you stand up (orthostatic hypotension)
- painful and frequent urination (signs of urinary tract infection)
- back pain
- high blood pressure
- headache

These are not all of the possible side effects of ZEPOSIA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZEPOSIA?

- Store ZEPOSIA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ZEPOSIA and all medicines out of the reach of children.

General information about the safe and effective use of ZEPOSIA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take ZEPOSIA for conditions for which it was not prescribed. Do not give ZEPOSIA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about ZEPOSIA that is written for health professionals.

What are the ingredients in ZEPOSIA?

Active ingredient: ozanimod

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The capsule shell contains: black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide.

Manufactured for: Celgene Corporation, Summit, NJ 07901

ZEPOSIA® is a registered trademark of Celgene Corporation.

This Medication Guide has been approved by the U.S. Food and Drug Administra ion. Approved: 5/2021

ZEPMG.003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA209899Orig1s001

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA Efficacy Supplement
Application Number(s)	209899
Priority or Standard	Priority (Rare Pediatric Disease Priority Review Voucher)
Submit Date(s)	11/30/2020
Received Date(s)	11/30/2020
PDUFA Goal Date	5/30/2021
Division/Office	Division of Gastroenterology
Review Completion Date	5/25/2021
Established/Proper Name	Ozanimod HCl (RPC1063)
(Proposed) Trade Name	ZEPOSIA
Pharmacologic Class	Sphingosine 1-Phosphate receptor modulator
Code name	RPC1063
Applicant	Celgene
Doseage form	Capsules
Applicant proposed Dosing Regimen	Days 1-4: 0.23 mg once daily Days 5-7: 0.46 mg once daily Day 8 and thereafter: 0.92 mg once daily
Applicant Proposed Indication(s)/Population(s)	Moderately to severely active ulcerative colitis (UC) in adults
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	78712000 |Moderate chronic ulcerative colitis (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Moderately to severely active ulcerative colitis (UC) in adults
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	78712000 |Moderate chronic ulcerative colitis (disorder)|
Recommended Dosing Regimen	Days 1-4: 0.23 mg once daily Days 5-7: 0.46 mg once daily Day 8 and thereafter: 0.92 mg once daily

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jay Fajiculay, PharmD; Kelly Richards, RN, MSN
Nonclinical Reviewer	Dinesh Gautam, PhD
Nonclinical Team Leader	Sushanta Chakder, PhD, RPh
Office of Clinical Pharmacology Reviewer(s)	Shen Li, PhD
Office of Clinical Pharmacology Team Leader(s)	Lian Ma, PhD, Insook Kim, PhD
Clinical Reviewer	Arushi deFonseka, MD
Clinical Team Leader	Tara Altepeter, MD
Statistical Reviewer	Sara Jimenez, PhD
Statistical Team Leader	David Petullo, MS
Cross-Disciplinary Team Leader	Tara Altepeter, MD
Division Director (DG)	Jessica J. Lee, MD

Additional Reviewers of Application

OPQ	Le Zhang, Ph.D.; David Lewis, Ph.D.
Microbiology	N/A
OPDP	Adewale Adeleye, PharmD, MBA; Kathleen Klemm
OSI	Zana Marks, MD, MPH, Min Lu, MD, MPH
OSE/DEPI	Catherine Lerro, PhD, MPH; Sukhminder Sandu, Ph.D., M.P.H., M.S
OSE/DMEPA	Sherly Abraham, RPh; Idalia Rychlik, PharmD

OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management
DG = Division of Gastroenterology

Unireview Section Signature Page

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology/ Pharmacometrics Reviewer	Shen Li, Ph.D.	OTS/OCP/DIIP	Sections: 6, 15.3	**Select one:** _X_ Authored ___ Approved
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Clinical Pharmacology Team Leader	Insook Kim, Ph.D.	OTS/OCP/DIIP	Sections: 6, 15.3	**Select one:** __ Authored _X_ Approved
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Non-Clinical Reviewer	Dinesh Gautam, Ph.D.	OND/OII/DPTII	Section: 5	**Select one:** _X_ Authored ___ Approved
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Non-Clinical Team Leader	Sushanta Chakder, Ph.D., R.Ph.	OND/OII/DPTII	Section: 5	**Select one:** __ Authored _X_ Approved
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Statistical Team Leader	David Petullo, M.S.	OB/DBIII	Sections: 1.2, 1.3, 8, 15.5	**Select one:** __ Authored _X_ Approved
	Signature: David M. Petullo -S Digitally signed by David M. Petullo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300376368, cn=David M. Petullo -S Date: 2021.05.24 09:02:23 -04'00'			
Associate Director	Mahboob Sobhan, Ph.D.	OB/DBIII	Sections: 1.2, 1.3, 8, 15.5	**Select one:** ___ Authored _X_ Approved
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CMC Reviewer	Le Zhang, Ph.D.	OPQ/OLDP/DPMAI/PMB2	Section: 4.2	**Select one:** _X_ Authored ___ Approved
	Signature: Le Zhang -S Digitally signed by Le Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Le Zhang -S, 0.9.2342.19200300.100.1.1=2002240176 Date: 2021.05.21 13:18:31 -04'00'			
CMC Branch 2 Chief	David Lewis, Ph.D.	OPQ/OLDP/DPMAI	Section: 4.2	**Select one:** ___ Authored _X_ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Arushi deFonseka, M.D.	OII/DG	Sections: 1.1, 1.4, 2, 3, 7, 8.2, 8.3, 8.4, 10, 12, 15.4	**Select one:** _X_ Authored __Approved
	Signature: Arushi M. Defonseka -S Digitally signed by Arushi M. Defonseka -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2003115843, cn=Arushi M. Defonseka -S Date: 2021.05.24 17:34:42 -04'00'			
Clinical Team Leader/CDTL	Tara Altepeter, M.D.	OII/DG	Authored:1.2, 1.3, 4, 9, 11, 3, 15.4 Approved: all sections	**Select one:** _X_ Authored _X_ Approved
	Signature: Tara Altepeter -S Digitally signed by Tara Altepeter -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tara Altepeter -S, 0.9.2342.19200300.100.1.1=2001813963 Date: 2021.05.24 09:16:12 -04'00'			
Division Director	Jessica Lee, M.D., M.M.Sc.	OII/DG	Authored: Section 14 Approved: all sections	**Select one:** _X_ Authored _X_ Approved
	Signature: Jessica J. Lee -S Digitally signed by Jessica J. Lee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica J. Lee -S, 0.9.2342.19200300.100.1.1=2000596373 Date: 2021.05.24 18:32:53 -04'00'			

Glossary

ADME	absorption, distribution, metabolism, excretion
ADH	alcohol dehydrogenase
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALDH	aldehyde dehydrogenase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BLA	biologics license application
CFR	Code of Federal Regulations
CL/F	oral clearance
CHO	Chinese hamster ovary
CMC	chemistry, manufacturing, and controls
CSR	clinical study report
CV	coefficient of variation
DDI	drug-drug interaction
DLCO	diffusing capacity of the lungs for carbon monoxide
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
FDA	Food and Drug Administration
FEV1	forced expiratory volume
FVC	forced vital capacity
GIRK	G-protein coupled inwardly rectifying potassium
HR	hazard ratio
IBD	inflammatory bowel disease
IND	investigational new drug
ISS	integrated summary of safety
ITT	intent-to-treat
MAO	monoamine oxidase
MI	multiple imputation
mITT	modified intent to treat
NDA	new drug application
NRI	non-responder imputation
OLE	open-label extension
OLP	open-label period
PD	pharmacodynamics
PK	pharmacokinetics

PMR	postmarketing requirement
PopPK	population pharmacokinetic
PREA	Pediatric Research Equity Act
PY	patient-years
QD	once daily
RMS	relapsing forms of multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SCID	severe combined immunodeficiency
SFS	stool frequency subscore
sNDA	supplementary new drug application
SFS	stool frequency subscore
TEAE	treatment-emergent adverse event
TNBS	2,4,6-trinitrobenzene sulfonic acid
TNF	tumor necrosis factor
TPA	tipping point analysis
UC	ulcerative colitis
ULN	upper limit of normal

1. Executive Summary

1.1. Product Introduction

Ozanimod is an orally bioavailable bi-aryl oxadiazole small molecule that acts as a sphingosine-1-phosphate (S1P) receptor modulator, with 10-fold more selectivity for S1P receptor 1 (SIP1) relative to S1P receptor 5 (S1P5). Ozanimod is extensively metabolized in humans to form a number of circulating active metabolites including two major active metabolites, CC112273 and CC1084037. Approximately 94% of circulating total active drug exposure is represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%).

S1P signaling is involved in multiple immune functions. S1P modulators have the potential to treat immune-mediated diseases such as inflammatory bowel disease (IBD). The mechanism by which ozanimod exerts therapeutic effects is not fully elucidated, but may involve lymphocyte retention in lymphoid tissues and the reduction of lymphocyte migration to sites of inflammation including the central nervous system and intestine. As ulcerative colitis (UC) is an immune-mediated inflammatory disease, the retention of lymphocytes in the lymphoid tissue has the potential to prevent recruitment of additional inflammatory cells, local release of proinflammatory cytokines, and ongoing damage to the colonic mucosa. Reduction of this inflammatory response may allow a decrease in disease activity and subsequent healing of the mucosa.

Ozanimod is approved in the United States (US), Europe, and other countries as a treatment for relapsing forms of multiple sclerosis (MS). The Applicant is proposing to expand the indication to include treatment of moderately to severely active UC in adults. The proposed dosing of ozanimod is 0.92 mg taken orally once daily after a seven day titration consisting of 0.23 mg once daily (on days 1-4), followed by 0.46 mg once daily (on days 5-7). Ozanimod 0.92 mg is equivalent to 1 mg of ozanimod HCl (the protocol and data submitted by the Applicant refer to 1 mg ozanimod HCl; these terms may be used interchangeably within this review).

1.2. Conclusions of the Substantial Evidence of Effectiveness

The data submitted in the supplementary New Drug Application (sNDA) establish a clinical benefit of ozanimod in adult patients with moderately to severely active UC. The submission included a single, large, adequate and well-controlled trial that included a 10-week induction period and a 42-week maintenance period, for a total controlled study duration of 52 weeks (Study RPC01-3101, also refered to as Study 3101 within the review). The induction period data were utilized to demonstrate clinical benefit at Week 10, and the maintenance period data were utilized to demonstrate efficacy at Week 52. The approach to utilize a single phase 3 trial was discussed with the Division in advance. The Applicant chose to conduct a single, large, multicenter, global study which was approximately double the size of typical induction trials

submitted for UC products, with the understanding that results would be required to be statistically significant and highly persuasive in order to support approval.

The primary endpoint was the proportion of patients achieving clinical remission, which was determined using the modified (3-component) Mayo score and defined, consistent with the Division's current recommendations, as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1 (a decrease of at least 1 from baseline), and an endoscopy subscore of 0 or 1, where a score of 1 did not include friability. Results from the induction period indicated that ozanimod 0.92 mg resulted in a greater percentage of patients in remission at Week 10, as compared to placebo (18% versus 6%). Results from the maintenance period indicated that treatment with ozanimod 0.92 mg was also superior to placebo in achieving remission at Week 52 (37% versus 19%). The results from sensitivity analyses conducted to evaluate the impact of missing data were consistent with the results from the primary endpoint analyses.

Results of the analyses for the multiplicity-controlled secondary endpoints were statistically significant and supported the primary endpoints, and included the following: for induction, clinical response at Week 10, endoscopic improvement at Week 10, and endoscopic-histologic improvement at Week 10; for maintenance, clinical response at Week 52, endoscopic improvement at Week 52, endoscopic-histologic improvement at Week 52, corticosteroid-free remission at Week 52, and maintenance of clinical remission at Week 52 among patients who achieved clinical remission at Week 10.

The results from the analyses of the primary and multiplicity-controlled secondary endpoints were highly statistically persuasive and provided substantial evidence of efficacy for ozanimod in treating patients with moderately to severely active UC. Thus, the Applicant has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126 to support approval of ozanimod for the proposed indication.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ozanimod provides a novel mechanism of action in the treatment of moderately to severely active UC. The benefits of treatment are evident in the results of Study PRC01-3101, a single, large, adequate and well-controlled phase 3 trial (which included both an induction period and a maintenance period) conducted in support of this application. In the placebo-controlled induction period, ozanimod 0.92 mg for 10 weeks was superior to placebo in inducing clinical remission (18% versus 6%). In the randomized, double-blind, placebo-controlled maintenance period (which re-randomized patients in clinical response after induction treatment), ozanimod was superior to placebo in achieving clinical remission at Week 52 (37% versus 19%), as well as clinical response (60% versus 41%), endoscopic improvement (46% versus 26%), and corticosteroid-free remission at Week 52 (32% versus 17%). In addition, ozanimod was superior to placebo in maintaining clinical remission, as assessed by the proportion of patients in clinical remission at Week 52, out of those who achieved remission at Week 10 (52% versus 29%). Additionally, the Applicant assessed histologic improvement, and ozanimod demonstrated a benefit over placebo in attaining histologic-endoscopic improvement at both Week 10 (13% versus 4%) and at Week 52 (30% versus 14%). Results from sensitivity analyses, which were conducted to assess the impact of missing data, were consistent with primary analysis results for clinical remission and clinical response.

Risks of ozanimod were characterized in the safety database in the UC population. Overall, the safety profile as demonstrated in these trials was generally consistent with the known adverse event profile for S1P receptor modulators (of which several are approved for relapsing MS). The most common adverse reactions observed in UC patients treated with ozanimod included: upper respiratory tract infection (5%), increased liver function test (5%), headache (4%), and pyrexia (3%) during induction. During maintenance, the most common adverse reactions included increased liver function test (11%), headache (5%), peripheral edema (3%), herpes zoster (2%), gastroenteritis (2%), and respiratory tract infection (respiratory syncytial virus) (2%).

The Applicant assessed several adverse events of special interest (AESIs) relevant to this drug class. Some of these risks (serious infection, herpes zoster, hepatoxicity) are shared across multiple drugs used to treat UC. However, other risks (notably bradycardia and other arrhythmias, macular edema, respiratory effects) are unique to this drug class. The labeling is considered adequate to communicate these serious risks and provide appropriate risk mitigation. Because the drug has been on the market for a relatively short time (initial approval for MS in March 2020), the full extent of the potential for liver injury may not be known. Expedited reporting of liver injury cases will be requested as part of enhanced pharmacovigilance. Further, the potential for

ozanimod to result in additional adverse events with longer latency (in particular malignancy) cannot be fully characterized with the available follow-up data. Within the submitted data, a signal for malignancy was not identified; however, additional enhanced pharmacovigilance will be conducted to further evaluate this potential risk over time.

Despite these uncertainties, the overall benefit-risk profile of ozanimod is generally acceptable and supports approval of this agent to provide a new and novel mechanism of action for the treatment of patients with moderately to severely active UC.

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1.4. Patient Experience Data

Table 1. Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		3-component Mayo score includes patient and clinician reported outcomes
		X	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data were not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disorder that involves the colonic surface mucosa, including the infiltration of neutrophils and other inflammatory cells into the epithelium and submucosa of the colon. The etiology of UC is multifactorial, but likely includes a dysregulated mucosal immune response against commensal non-pathogenic bacteria of the colon, resulting in bowel inflammation. Onset of disease most commonly occurs between 15 and 40 years of age. Prevalence estimates per 100,000 persons in North America range from 139.8 (Quebec, Canada) to 286.3 (Minnesota, USA), while in Europe they range from 2.42 (Romania, 2003) to 505 (Norway, 1991-94), including 412 in Germany (2010), 340 in Hungary (2013), and 90.8 in the UK (1989). Globally, the prevalence of UC continues to rise, particularly in North America and Europe, and is expected to increase in newly industrialized countries in Africa, Asia, and South America (Ng et al. 2017).

The clinical course of UC is characterized by a lifelong course of remissions and exacerbations. Patients with UC suffer from recurrent episodes of diarrhea, rectal bleeding, weight loss, abdominal pain, fever, and are at an increased risk of perforated bowel, toxic megacolon, and colorectal cancer. The estimated risk of colorectal cancer is approximately 2% after 10 years, 5% to 10% after 20 years, and 12% to 30% after 30 to 35 years of UC (Bernstein et al. 2001; Eaden et al. 2001; Feuerstein and Cheifetz 2014).

Patients have a 10% cumulative risk of colectomy 5 years after diagnosis, and 15% at 10 years after diagosis (Fumery et al. 2018). However, with colectomy, there is a 50% risk of continued inflammation in the residual intestinal pouch (pouchitis); after 10 years, approximately 12% of patients experience pouch failure and require conversion to a permanent ileostomy (Zezos and Saibil 2015; Mark-Christensen et al. 2018). Surgical complications of proctocolectomy with ileostomy include stenosis, prolapse, and other abdominal/pelvic sequelae including small bowel obstruction, fistula, infection, persistent pain, unhealed perineal wound, sexual and bladder dysfunction, and infertility (Ross et al. 2014).

Patients with UC may also experience extra-intestinal manifestations including primary sclerosing cholangitis or eye, joint, or skin manifestations (Guidance 2018). Improved intestinal disease activity in UC is associated with an improvement in extra-intestinal manifestations (Vavricka et al. 2015).

2.2. Analysis of Current Treatment Options

The goals of UC treatment include reducing signs and symptoms, reducing long-term corticosteroid use, decreasing mucosal inflammation, reducing colon cancer risk, and improving patient quality of life. For the treatment of mildly to moderately active UC, oral aminosalicylates, topical 5-aminosalicylic acid (5-ASA) such as mesalamine suppository and

enemas, or topical steroids may be used. Topical medications are first-line treatment for distal colitis in those who are willing to use rectal therapy. Oral corticosteroids, such as budesonide or oral prednisone, may be required in patients who are refractory to topical therapies or who are systemically ill and require more rapid treatment. Mesalamines and budesonide are FDA-approved treatments for mildly to moderately active UC. Immunomodulators, such as azathioprine and 6-mercaptopurine, can be considered for patients unresponsive to or dependent on oral corticosteroids and for those experiencing disease relapse on aminosalicylates, but these are used off-label.

The currently approved systemic therapies for the treatment of moderately to severely active UC are summarized in Table 2 below.

Table 2. Approved Therapies for Moderately to Severely Active UC

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Infliximab (Remicade®) BLA 103772 Infliximab Biosimilars: Avsola® (Infliximab-AXXQ) BLA 761086 Inflectra® (Infliximab-DYYB) BLA 125544 Ixifi® (Infliximab-QBTX) BLA 761072 Renflexis® (Infliximab-ABDA) BLA 761054	Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use	Intravenous (IV) 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	69% and 62% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved clinical response at week 8 39% and 32% of patients taking infliximab 5 mg/kg and 10 mg/kg, respectively, achieved clinical remission at week 8 35% and 34% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved clinical remission at week 54 62% and 59% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved mucosal healing at week 8 45% and 47% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved mucosal healing at week 54	Boxed Warning Serious infections (including tuberculosis, bacterial sepsis, invasive fungal infections [such as histoplasmosis], and opportunistic infections), malignancies (including lymphoma, hepatosplenic T-Cell lymphoma [HSTCL], melanoma), hepatitis B virus reactivation, hepatotoxicity, hypersensitivity (serious infusion reactions including anaphylaxis or serum sickness-like reactions), cytopenias, demyelinating disease, heart failure, lupus-like syndrome. Most common adverse reactions: infections (e.g., upper respiratory, sinusitis, pharyngitis), infusion-related reactions, headache, and abdominal pain.

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Adalimumab (Humira®) BLA 125057 Adalimumab Biosimilars: Abrilada® (Adalimumab-AFZB) BLA 761118 Amjevita® (Adalimumab-ATTO) BLA 761024 Cyltezo® (Adalimumab-ADBM) BLA 761058 Hadlima® (Adalimumab-BWWD) BLA 761059 Hulio® (Adalimumab-FKJP) BLA 761154 Hyrimoz® (Adalimumab-ADAZ) BLA 761071	Inducing and sustaining clinical remission in adult patients with moderately to severely active UC who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6 mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blocker.	SQ • Initial dose (Day 1): 160 mg • Second dose two weeks later (Day 15): 80 mg • Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.	Study I: 18.5% of patients receiving adalimumab 160/80 mg achieved clinical remission at week 8 Study II: 16.5% of patients receiving adalimumab 160/80 mg achieved clinical remission at week 8. 8.5% of patients receiving adalimumab 160/80 mg achieved sustained clinical remission (clinical remission at both weeks 8 and 52).	Boxed Warning Serious infections including tuberculosis [TB], bacterial sepsis, invasive fungal infections, and opportunistic infections, malignancies (including lymphoma, HSTCL, leukemia, NMSC), anaphylaxis or serious allergic reactions, hepatitis B virus reactivation, demyelinating disease, cytopenias/pancytopenia, heart failure, lupus-like syndrome. Most common adverse reactions: infections (upper respiratory, sinusitis), injection site reactions, headache and rash.

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Golimumab (Simponi®) BLA 125289	Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroid, azathioprine, or 6-mercaptopurine for: 1. inducing and maintaining clinical response 2. improving endoscopic appearance of the mucosa during induction 3. inducing clinical remission 4. achieving and sustaining clinical remission in induction responders	SQ 200 mg initially administered by subcutaneous injection at week 0, followed by 100 mg at week 2 and then 100 mg every 4 weeks	Study I: 51% of patients receiving golimumab 200/100 mg achieved clinical response at week 6 18% of patients achieved clinical remission at week 6 42% of patients achieved improvement in endoscopic appearance of the mucosa at week 6 Study II: 50% of patients receiving golimumab 100 mg achieved clinical response through week 54 28% of patients achieved clinical remission at both week 30 and week 54	Boxed Warning Serious infections including TB, invasive fungal infections, hepatitis B reactivation, malignancies (including lymphoma, melanoma, and Merkel cell carcinoma), congestive heart failure, demyelinating disorders, hematologic cytopenias, Lupus-like syndrome, hypersensitivity reactions. Most common adverse reactions: upper respiratory tract infection, nasopharyngitis, and injection site reactions.
Vedolizumab (Entyvio®) BLA 125476	Adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant	IV 300 mg infused intravenously over approximately 30 minutes at zero, two and	Study I: 47% of patients achieved clinical response at week 6	Serious infections including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, cytomegaloviral colitis.

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
	to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids	six weeks, then every eight weeks thereafter	17% of patients achieved clinical remission at week 6 Study II: 42% of patients achieved clinical remission at week 52 57% of patients achieved clinical response at both weeks 6 and 52 52% of patients achieved improvement of endoscopic appearance of the mucosa at week 52	Most common adverse reactions: nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection.
Tofacitinib (Xeljanz®/ Xeljanz XR™) NDA-203214/ NDA-208246	Adult patients with moderately to severely active UC, who have had an inadequate response or who are intolerant to TNF blockers. Use in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.	Xeljanz: 10 mg twice daily for at least 8 weeks for a maximum of 16 weeks; then 5 or 10 mg twice daily. Xeljanz XR: 22 mg once daily for at least 8 weeks for a maximum of 16 weeks, then 11 mg once daily.	Study I: 60% of patients achieved clinical response at week 8 7% of patients achieved normalization of endoscopic appearance of the mucosa at week 8 Study II: 55% of patients achieved clinical response at week 8 7% of patients achieved normalization	BOXED WARNING Avoid use during an active serious infection (e.g.,TB, viral reactivation), including localized infections. Thrombosis (including pulmonary, deep venous and arterial), gastrointestinal perforations, lymphoma and other malignancies, lymphopenia, neutropenia, anemia, abnormal liver enzymes, dyslipidemia, and hypersensitivity reactions.

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			of endoscopic appearance of the mucosa at week 8 Study III: 52% and 62% taking 5 mg twice daily and 10 mg twice daily respectively achieved maintenance of clinical response at both baseline and week 52 46% and 56% taking 5 mg twice daily and 10 mg twice daily respectively achieved maintenance of clinical remission at week 52 15% and 17% taking 5 mg twice daily and 10 mg twice daily respectively achieved normalization of endoscopic appearance at week 52	
Ustekinumab (Stelara®) BLA-761044	Adult patients with moderately to severely active UC.	(b) (4) 90 mg subcutaneous injection every 8 weeks	Study I: 58% of patients achieved clinical response at 8 weeks 19% of patients achieved clinical remission at 8 weeks	Serious infections such as gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis. Malignancies, hypersensitivity reactions, reversible posterior leukoencephalopathy syndrome, and noninfectious pneumonia

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			25% of patients achieved endoscopic improvement at 8 weeks 17% of patients achieved histologic-endoscopic mucosal improvement at 8 weeks Study II: 74% of patients achieved maintenance of clinical response at 44 weeks 66% of patients who achieved clinical remission 8 weeks after induction achieved maintenance of clinical remission at 44 weeks 47% of patients achieved endoscopic improvement at 44 weeks	

Source: Reviewer's table – data from drugs@fda and purplebooksearch@fda, last accessed on April 26, 2021
Abbreviations: TNF = tumor necrosis factor; UC = ulcerative colitis

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The original New Drug Application (NDA) 209899 for ozanimod was submitted on March 25, 2019, and approved on March 25, 2020, for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults. Of note, the initial submission of this NDA resulted in a Refuse to File action on February 23, 2018, because a major active metabolite (RP112273) had not been adequately characterized. The development for UC was conducted under the investigational new drug (IND) 115243. (b) (4).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant met with the Division of Gastroenterology and Inborn Errors Products (now Division of Gastroenterology) during the course of the UC development program. Key recommendations and points of discussion are summarized below.

<u>July 10, 2012 (Pre-IND meeting):</u>
Key points are summarized as follows:

- The FDA provided general advice on a clinical development program usually recommended for demonstration of efficacy in UC (i.e., two adequate, well-controlled induction studies and a single maintenance study). The FDA advised that if only a single induction study was planned, a smaller significance level should be used; furthermore, study results should be internally consistent and homogenous across endpoints, subgroups, etc.
- The FDA also recommended that the design and analysis of the phase 2 study be consistent with a confirmatory study to allow the study to be considered supportive of a single phase 3 efficacy study.
- The FDA agreed with the proposed patient population for the phase 2 study and provided preliminary advice on design of the phase 3 study.

<u>August 1, 2012 (IND submission):</u>

- IND submitted to the Division of Gastroenterology and Inborn Errors Products for ozanimod for the treatment of moderately to severely active UC with a phase 2 study RPC01-202 original protocol.
- The FDA issued a “Study May Proceed” letter on September 14, 2012.

<u>December 10, 2014 (Type B EOP2 meeting):</u>
Key points (provided in meeting minutes dated January 9, 2015) are summarized as follows:

- The FDA advised that the extent to which the phase 2 trial can support a single phase 3 trial to demonstrate efficacy for induction of remission in UC cannot be determined until the final review.
- The FDA recommended that a post hoc analysis for the RPC01-202 study be performed using the same primary endpoint agreed to for the phase 3 RPC01-3101 study.
- The FDA also recommended that a 3-component Mayo score be used in the RPC01-3101 primary endpoints evaluation. Additional recommendations and agreements on primary and secondary endpoint definitions, sample size, statistical analyses, and methodology for the phase 3 study RPC01-3101 were provided.
- Finally, the FDA recommended that in the pivotal phase 3 study, RPC01-3101, placebo and active treatment responders be re-randomized prior to entering maintenance period of the study.

February 25, 2015 (Type C guidance meeting):

The key feedback provided to the Applicant is as follows:

- The FDA recommended including screening at baseline, 3 and 6 months, end of study, and yearly pulmonary function testing (forced expiratory volume (FEV1), forced vital capacity (FVC), DLCO). The FDA discussed that pulmonary abnormalities are considered to be a class effect with S1P receptor modulators and therefore accumulating pulmonary safety data in the phase 3 trials for UC would be necessary to inform labeling.
- The FDA recommended a total duration of treatment for patients in the phase 3 study of 52 weeks.
- The FDA also recommended that the potential reproductive risks of ozanimod be clearly described and that an effective birth control recommendation for women of child-bearing potential be included in the informed consent forms.
- The FDA asked that reasons for deferring required assessments for pediatric patients be provided along with a description of the planned and ongoing pediatric studies, and evidence that the studies are being conducted or will be conducted with due diligence and at earliest possible time.

June 1, 2015 (Statistical Analysis Plan submission):

- The Applicant submitted the original induction period statistical analysis plan (SAP) v1.0 and maintenance period SAP v1.0 for protocol RPC01-3101.
- In response, on August 18, 2015, the FDA issued an advice letter asking that any missing primary endpoint assessments be deemed treatment failure/non-responder for the primary analyses. The FDA also requested that the Applicant adjust for cohort effects in the primary analysis and assess the regional/country effects.

December 29, 2015 (Orphan-drug designation granted)

July 28, 2017 (Initial Pediatric Study Plan issued)

February 21, 2018 (Type C meeting on pediatric development)
Key topics of discussion included:

- FDA and the Applicant agreed to limit adolescent patients enrolled in the adult study RPC01-3101 study to those weighing ≥45 kg, until additional data are available.
- The Applicant proposed use of a separate cohort 3 for adolescents (using open-label induction, followed by a randomized maintenance period separate from the adults).
- FDA disagreed and recommended that the Applicant utilize the same study design (including placebo control) for adolescent patients who would be enrolled, but incorporate additional early escape criteria to reduce the length of time that adolescents would go untreated with active disease.
- The Applicant noted that because the adult program was 80% enrolled at this time, enrolling an adequate number of adolescents may not be practical, and agreed to evaluated alternate strategies for pediatric development and continue to work with the Division to reach agreement on an acceptable plan.

January 4, 2019 (Protocol RPC01-3101 Amendment #6 and RPC01-3102 Amendment #6):

- Added an additional cohort (cohort 3) which would enroll up to 150 adolescents (12 to <18 years of age) into RPC01-3101, randomized in a 2:1 ratio to receive ozanimod or placebo.
- Adolescent data would be analyzed separately from the main study population.

February 4, 2019 (Type C guidance written response only):

- FDA provided advice on the draft SAP regarding planned subgroup analyses and the proposed diary scoring algorithm.

June 25, 2019: Final induction period SAP (v4.0) was submitted.

March 20, 2020: Final maintenance period SAP (v4.1) was submitted.

November 4, 2019 (Type C guidance written response only):

- FDA acknowledged enrollment challenges the Applicant experienced with the proposal to enroll adolescents into study RPC01-3101 and agreed with the Applicant's proposal to stop enrollment.
- FDA provided recommendations on the planned single pediatric phase 2/3 clinical study design which will enroll pediatric patients 2 to <18 years of age.

February 20, 2020 (Pre-sNDA meeting):
The key feedback issued to the Applicant is as follows:

- The FDA recommended that for safety comparisons of the ozanimod 1-mg dose to placebo, patients who received the ozanimod 1-mg dose be pooled in the induction portion of the phase 2 controlled study RPC01-202 and cohort 1 of the phase 3 controlled study RPC01-3101. The FDA also recommended that patients who received placebo treatment in the induction periods of the two studies be separately pooled.

- Regarding safety comparisons in the maintenance period, the FDA recommended that only patients who were re-randomized into the maintenance period of study RPC01-3101 be included. The FDA also recommended that the maintenance period of the phase 2 study RPC01-202 not be pooled with study RPC01-3101 due to differences in study design (i.e., lack of re-randomization at the start of the maintenance period of the phase 2 study).
- The FDA recommended that Pool D (All Controlled and Uncontrolled Ozanimod [UC, (b) (4) and MS] Studies Pool) and Pool G (All Controlled and Uncontrolled Ozanimod UC Studies Pool) be revised to include only patients who received ozanimod 1 mg or placebo.
- The FDA recommended that adverse event occurrences during the placebo dosing period in the maintenance period of study RPC01-3101 in pools D and G be included in safety analyses.
- The FDA recommended that given the long half-life of active metabolites of ozanimod, as well as potential for adverse events of long latency to occur even after study drug discontinuation, adverse events and laboratory data be submitted for all safety data up to 90 days post-treatment.
- The FDA recommended that exposure-adjusted incidence rates (EAIRs) be provided, in addition to raw cumulative incidence proportions, to account for the differing follow-up times between treatment arms in some analyses.
- The FDA recommended that in addition to the proposed Sponsor-designated events of interest, the preferred terms related to the following conditions be included:
    - Progressive multifocal leukoencephalopathy, as a class effect of S1P modulators
    - Posterior reversible encephalopathy syndrome
    - Hypotension (e.g., dizziness, light-headedness, fainting, syncope), outside of temporal association to documented potential instances of bradycardia events.
- The FDA recommended that in addition to first dose administration experience (under Section 7.9 of the Integrated Summary of Safety [ISS] SAP), analyses of cardiac safety within the first 30 days of treatment (for example, at Day 8 when achieving full dose) be provided. The FDA also asked that results of any Holter monitoring be included.
- The FDA recommended that regarding hematology (under Section 7.5.2 of ISS SAP) evaluations, a category for WBC greater than 15,000 and a category for WBC less than 500 cells/µL be included, in addition to the proposed categories of WBC greater than 20,000 cells/µL and WBC less than 3000, 2000, and 1000 cells/µL.
- The FDA advised that comparative analyses for adverse events leading to discontinuation, severe adverse events, serious infection, opportunistic infection, malignancy, and other Sponsor-designated events of interest should be included.
- The FDA recommended that for Sponsor-designated events of interest (including the additional outcomes recommended above) additional model-based analyses that utilize all safety data from the integrated phase 2 and 3 studies (including open-label extension [OLE] data) and that appropriately account for the study designs be performed.
- The FDA requested that the Applicant's NDA submission fulfill minimum International Conference on Harmonisation E1 guidance requirements for long-term treatment exposure. In addition, the FDA requested that updated tables, figures, and listings for the open-label

RPC01-3102 study be provided. The FDA requested that an interim report of the phase 2/3 Japanese study RPC01-3103 safety results in the 4-month safety update be included.

- The FDA requested the inclusion of primary endpoint results using the following, currently recommended definition of clinical remission:
    - Stool frequency subscore = 0 or 1 (without a requirement of a decrease of ≥ 1 from the baseline stool frequency subscore)
    - Rectal bleeding subscore = 0
    - Endoscopy subscore = 0 or 1 (modified to exclude friability) on Mayo score; or 0 on the Ulcerative Colitis Disease Activity Index.

Furthermore, the FDA recommended exploration of the proportion of patients in clinical remission who had a stool frequency score of 0 versus 1. While a stool frequency subscore of 0 or 1 is allowable for individual patients, a score of 1 in a significant number of patients may not be considered adequate evidence of stool normalization.

<u>September 9, 2020 (Type C guidance written responses only):</u>
Key feedback provided to the Applicant is as follows:

- In addition to Studies RPC01-3101 and RPC01-202, the FDA recommended submission of interim results and datasets from the ongoing, phase 3, OLE study (RPC01-3102) to support the long-term safety of ozanimod treatment in adult patients with moderately to severely active UC.
- The FDA recommended that bioresearch monitoring program information be provided for all major trials, including the phase 2 RPC01-202 and phase 3 RPC01-3101 studies, that are intended to support the safety and efficacy of the application.

<u>August 28, 2020 (Notification of intent to submit an application with a rare pediatric disease priority review voucher):</u>

- In response to a request from the FDA (made on September 1, 2020), additional information to support redemption of the priority review voucher was submitted on September 4, 2020.

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

4.1. Office of Scientific Investigations (OSI)

Site inspections were not requested for this sNDA. The number of patients per site was well distributed (ranging between 1- 31 patients per site) and there was no single site driving efficacy or safety results.

4.2. Product Quality

The Applicant proposes to use the same formulation for UC that was recently approved for MS. There was no new chemistry, manufacturing, and controls (CMC) information submitted with this application. A request for categorial exclusion/ environmental assessment was submitted and was deemed acceptable by the CMC reviewer (Dr. Le Zhang, 4/7/2021). No changes to the CMC sections of the label were proposed.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Ozanimod (RPC1063) is a sphingosine 1-phosphate (S1P) receptor agonist, which binds with high affinity to human S1P receptors 1 and 5. Ozanimod is currently approved for the treatment of relapsing forms of multiple sclerosis (MS) in adult patients. In the current supplement (S-001), the Applicant is seeking approval of ozanimod for the treatment of ulcerative colitis (UC).

The nonclinical studies (primary, secondary, and safety pharmacology studies, PK, repeated dose toxicity, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology) were submitted previously under the original NDA for the MS indication, and reviewed by Christopher D. Toscano, Ph.D. (March 10, 2020). In the current supplement, the Applicant submitted several in vitro and in vivo pharmacology studies with ozanimod, relevant to the UC indication along with a summary of the previously submitted nonclinical studies

Activating the lymphocytic S1P receptors causes an inhibition of the release of T-cells and B-cells from peripheral lymphoid organs, causing a subsequent decrease in the available pool of autoreactive circulating lymphocytes. Ozanimod induced leukopenia in each nonclinical species studied. In a rat model of 2,4,6-trinitrobenzene sulfonic acid- (TNBS)-induced colitis, treatment with ozanimod improved overall colonic disease score, bowel function, body weight, and animal behavior. The in vivo efficacy of ozanimod was also assessed in the naïve T-cell adoptive transfer in severe combined immunodeficiency (SCID) mice. In this mouse model, oral administration of ozanimod showed significant improvement in colon health with an improvement in histological scores of inflammation, gland loss, hyperplasia, neutrophil score, and mucosal thickness.

Ozanimod (RPC1063) is extensively metabolized, and the three metabolites, CC112273, CC1084037, and RP101124, are considered to be major human metabolites. The parent and the major human metabolites, with the exception of RP101124, are S1P1 and S1P5 receptor agonists.

In repeat dose toxicity studies, the spleen, thymus, and lung were the target organs of ozanimod toxicity in both rats and monkeys. Ozanimod and its major human metabolites (except for CC1084037) were negative in a battery of genotoxicity assays. Metabolite CC1084037 was positive in the in vitro chromosomal assay in human TK6 cells. However, it was negative in the Ames assay and in the in vivo rat micronucleus/comet assay. In a 6-month carcinogenicity study in transgenic mice, ozanimod increased the combined incidence of hemangioma and hemangiosarcoma. No drug-related increase in neoplasms was observed in the two-year carcinogenicity study in rats.

In the embryofetal developmental studies in rats and rabbits, embryonic lethality, and adverse developmental effects (e.g., incomplete skeletal ossification, malpositioned vertebrae, malformed or absent arteries, anasarca, malpositioned testes, and cleft palate) were observed.

5.2. Referenced NDAs, BLAs, and DMFs

- INDs: 115,243 (ulcerative colitis), (b) (4) 109,159 (multiple sclerosis)
- NDA: 209-899 (multiple sclerosis)

5.3. Pharmacology

The in vitro binding study was conducted to understand whether ozanimod and its metabolites bind to the same binding site within S1P1 and S1P5 receptors for the overall pharmacological effects of the drug. The in vitro binding affinity of ozanimod and its downstream metabolites was measured in membranes prepared from Chinese hamster ovary (CHO) cells stably expressing recombinant human cloned S1P1 and S1P5.

The binding affinities of ozanimod and its metabolites are shown in Table 3 below.

Table 3. Human Sphingosine-1-Phosphate Receptor 1 and 5 Radioligand Binding of Ozanimod and its Eight Major Circulating Metabolites

Compound	Human $S1P_1$	Human $S1P_5$
	K_i (nM)	K_i (nM)
S1P	6.07 ± 0.71	5.36 ± 1.18
Ozanimod	0.29 ± 0.04	5.54 ± 0.35
CC112273	**0.29 ± 0.08**	19.31 ± 1.11
CC1084037	**0.11 ± 0.03**	**1.99 ± 0.13**
RP101124	**NR**	**NR**
RP101075	0.16 ± 0.02	3.21 ± 0.80
RP101988	0.30 ± 0.05	22.56 ± 4.25
RP101442	0.50 ± 0.05	26.36 ± 1.36
RP112289	0.35 ± 0.07	8.55 ± 2.18
RP112509	0.93 ± 0.24	39.04 ± 3.36

Source: Applicant's table: Study Report RP-PH-018
Abbreviations: IC_{50} = concentration at which 50% of the [3H]-ozanimod was displaced; Ki = inhibition constant, the concentration of competing ligand that occupies 50% of the receptors if no radioligand were present (calculated from the K_D using the Cheng-Prusoff equation); S1P = Sphingosine-1-phosphate; SIP1 or SIP5 = Sphingosine-1-phosphate receptor 1 or 5; NR = no response
Data are expressed as mean and standard error, N = 3 to 4 independent experiments. Bold = major human metabolite data.

In conclusion, ozanimod and its active metabolites CC112273, CC1084037, RP101075, RP101988, RP101442, RP112289, and RP112509 competed with [3H]-ozanimod to bind to human S1P1 and human S1P5 receptors. The functionally inactive metabolite, RP101124, did not compete with [3H]-ozanimod binding to S1P1 or S1P5 receptors.

Ozanimod and Metabolites CC112273, CC1084037, RP101124, RP101075, RP101988, RP101442, RP112289, and RP112509: In Vitro Potency and Selectivity across Cynomolgus Monkey Sphingosine-1-Phosphate Receptors 1 through 5 and Rat Sphingosine 1 Phosphate Receptor 5 (Study # RP-PH-019):

The in vitro binding study was conducted to determine the potency and intrinsic activity of ozanimod and its metabolites (CC112273, CC1084037, RP101124, RP101075, RP101988, RP101442, RP112289, and RP112509) at recombinant S1P receptors (S1P1, S1P2, S1P3, S1P4, and S1P5) cloned from cynomolgus monkey, and S1P5 receptors cloned from rat.

Ozanimod and its metabolites showed robust binding in membranes prepared from CHO cells expressing cyno S1P1 and S1P5 receptors. Ozanimod displayed EC50 of 1.29 ± 0.05nM and 23.55 ± 0.49nM for monkey S1P1 and S1P5, respectively, and relative intrinsic activities of 93.3± 0.7% and 99.0 ± 3.3% of the S1P response at S1P1 and S1P5, respectively. Ozanimod did not display significant activity at the cyno S1P2, S1P3, or S1P4 receptors. The metabolites displayed a profile similar to ozanimod. CC1084037 was the most potent with an EC50 of 0.23 ± 0.01 nM for S1P1 and 6.93 ± 0.16 nM for S1P5. The least potent metabolite was RP-112509 with an EC50 of 17.27 ± 1.02 nM for S1P1 and 86.40 ± 7.26 nM for S1P5. Relative intrinsic activities of the metabolites were also similar for cyno S1P1 and were generally > 80% of the S1P response, except for RP112289, which displayed the slightly lower intrinsic activity of 61.1± 5.3%. Like

ozanimod, the metabolites also displayed weak to no activity at cyno S1P2-4. At cyno S1P3, only CC1084037 yielded a concentration response curve with an EC50 value of 423.0 ± 248 nM and with a very low intrinsic activity, 10.4 ± 1.4% of that of S1P. Metabolites RP101075 and RP101988 had low intrinsic activity at S1P3 yielding low maximal responses and only at the top 10 µM concentration tested, of 25.1 ± 1.6% and 25.6 ± 1.7%, respectively. At cyno S1P4, CC1084037, CC112273, and RP101988 had an EC50s of 729 ± 123 nM, 1,747 ± 420 nM, and 2,195 ± 114 nM with low intrinsic activity as maximal responses were only 21.8 ± 0.9%, 12.8 ± 4.6%, and 21.3 ± 2.7% of the maximal S1P response, respectively.

In rats, ozanimod had an EC50 of >1,111 nM for S1P5. since the concentration response curve did not elicit a clearly defined maximal response. The intrinsic activity of ozanimod at 10 µM, the highest concentration tested, was 78.9 ± 2.6% of the S1P response, showing that despite its weaker potency, it was still able to produce a robust agonist response. CC112273 and CC1084037 showed potencies of 200.80 ± 32.95 nM and 205.47 ± 11.05 nM, respectively, and relative intrinsic activities of 11.1 ± 1.9% and 70.3 ± 1.4%, respectively, at rat S1P5. The receptor binding data for rat are shown in Table 4 below.

Table 4. Rat Sphingosince-1-phosphate Receptor 5 Binding Data

Compound	Rat $S1P_5$	
	EC_{50} (nM)	**IA**
S1P	180.78 ± 28.10	100
Ozanimod	>1,111	*78.9 ± 2.6*
CC112273	**200.20 ± 32.95**	**11.1 ± 1.9**
CC1084037	**205.47 ± 11.05**	**70.3 ± 21.4**
RP101124	**>10,000**	**NR**
RP101075	818.75 ± 86.51	76.4 ± 7.0
RP101988	>3,333	*52.0 ± 2.6*
RP101442	239.90 ± 6.86	8.7 ± 1.0
RP112289	>10,000	NR
RP112509	>10,000	NR

EC_{50} = concentration at which 50% of maximal activity is observed; IA = intrinsic activity; NR = no response (Mean %Emax < 10%, where Emax is the maximal response achieved relative to the internal positive control, sphingosine-1-phosphate); S1P = sphingosine-1-phosphate; $S1P_5$ = sphingosine-1-phosphate receptor 5. Data are expressed as mean and standard error, N = 3 to 5 independent experiments.
Italic = response achieved at the top test compound concentration of 10,000 nM.
Bold = major human metabolites data.

Source: Applicant's submission; Study # RP-PH-019

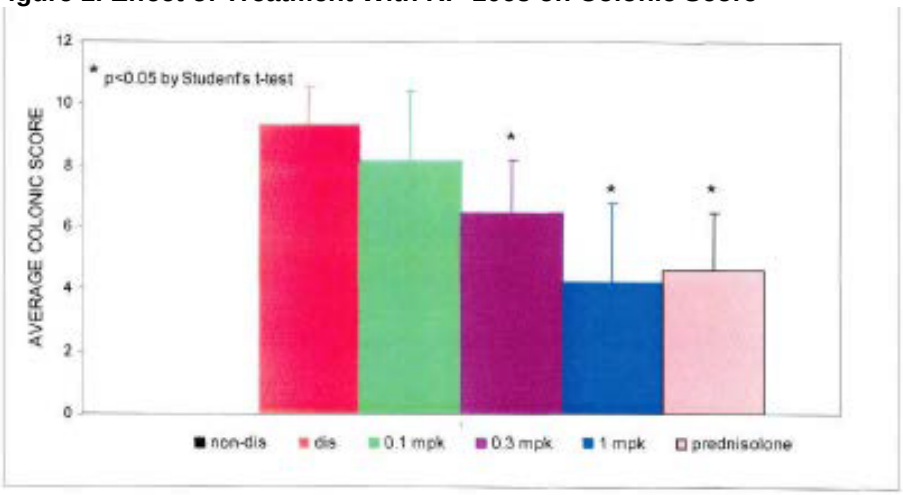
Anti-Inflammatory Activity Of Test Compounds In A Therapeutic Rat Model Of Inflammatory Bowel Disease (Study # IBD-RPI-10 and IBD-RPI-11):

The anti-inflammatory activity of ozanimod was assessed in TNBS (2,4,6-Trinitrobenzenesulfonic Acid)-induced colitis in male Sprague Dawley rats. Ozanimod at 0.1, 0.3, or 1 mg/kg, or prednisolone 10 mg/kg (positive control) was administered orally once daily for 7

days. Approximately 24 hours after the final dose, rats were terminated, and the colons resected. Colon contents were removed, and colon length, weight, and wall thickness were measured.

The TNBS vehicle-treated group had 18% weight loss over the course of the study. This weight loss was dose-dependently less in the ozanimod-treated groups and was statistically significant at the 1 mg/kg dose. In contrast, body weight loss in the prednisolone-treated group was not different from the vehicle control. A dose-dependent inhibition of the IBD parameters by ozanimod was observed in rats. A 54% inhibition of total colon disease score was calculated at the highest dose. Furthermore, there was a return to normal bowel function and improved animal health and behavior by Day 3. Figure 1 below provided by the Applicant shows the colonic score in rats.

Figure 1. Effect of Treatment With RP-1063 on Colonic Score



Source: Applicant's submission; Study # IBD-RPI-10

The efficacy of ozanimod at 1 mg/kg was replicated in IBD-RPI-11, an additional rat TNBS study. In this study, the overall colonic disease score was improved up to 50%, bowel function returned to normal, and body weight and animal behavior improved significantly in the treated group, compared to the controls.

Effects of RPC1063 on CD4+ Inflammatory Bowel Disease in Female SCID Mice (Studies # MCD4/RPC-1, MCD4/RPT-3 and MCD4/RPT-4):

Colonic inflammation was induced after intraperitoneal injection of naïve CD4+CD45RBhigh T lymphocytes from donor mice (female BALB/c mice) to SCID female mice. The mice were randomized into groups of N = 10 based on body weight loss relative to day 0. Mice were administered orally either vehicle or ozanimod (1.2 mg/kg) on study day 21 and continued for 21 consecutive days thereafter. For the positive controls, cyclosporine A (50 mg/kg) was administered orally and hamster anti-mouse tumor necrosis factor (TNF) antibody (300 µg per

mouse) was administered once-weekly, intraperitoneally. Mice were assessed every other day for body weight and clinical observations. Approximately 24 hours after final dose administration, blood samples were collected by cardiac puncture (for the measurement of circulating lymphocyte numbers) and colons were resected for the measurement of length and wet weight. Colons were then dissected into distal and proximal portions and fixed in formalin prior to histopathological assessment (Study # MCD4/RPC-1).

The results showed that the colon density was significantly reduced (71%) in ozanimod-treated mice, compared to vehicle control. Twenty four hours after the final dose, mice treated with ozanimod exhibited decreased numbers of circulating lymphocytes that were similar to cyclosporine and TNF-α positive controls. In the colon, histological scores of inflammation, gland loss, hyperplasia, neutrophil score, and mucosal thickness were significantly attenuated by ozanimod administration. Ozanimod-treated mice also showed reduced distal colon mucosal thickness similar to cyclosporine and TNF-α positive controls.

A similar study (Study # MCD4/RPT-3) was conducted in SCID mice to observe dose-response effects of ozanimod. In this study, SCID mice were administered ozanimod orally at the doses of 0.3, 0.6, and 1.2 mg/kg. The severity of the disease was greater in this study compared to a previous study (Study # MCD4/RPC-1). Colon weight/length ratios were significantly reduced in normal in mice treated with 1.2 mg/kg ozanimod. Erosion of the distal colon was significantly reduced at all dose levels, and mucosal thickness was significantly reduced in mice treated with 0.3 mg/kg (total colon and distal colon) or 1.2 mg/kg (distal colon) ozanimod. Mice treated with ozanimod had significantly reduced colon IL-10 and IL-1β levels when compared to vehicle control. Mice in the high dose (1.2 mg/kg) group also had significantly reduced IL-6 and TNF-α.

In a similar study (MCD4/RPT-4) in SCID mice, 1.2 mg/kg ozanimod did not show any beneficial effects on body weight loss, colon length, colon weight, and colon weight-length ratio. The Applicant considered this study as unsuccessful, because of the lack of a statistically significant protection by the positive control cyclosporine, and that the study conditions were different (mice from a different vendor, 49- versus 42-day duration, etc.).

5.4. ADME/PK

No new ADME/PK data were submitted in the current supplement.

5.5. Toxicology

No new toxicology studies were submitted. Repeated dose toxicity, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology studies were submitted previously under the original NDA, and were reviewed by Christopher D. Toscano, Ph.D.

6. Clinical Pharmacology

6.1. Executive Summary

Ozanimod is a sphingosine 1-phosphate receptor modulator. ZEPOSIA (ozanimod oral capsules, 0.23 mg, 0.46 mg, and 0.92 mg) was originally approved on March 25, 2020 under the same NDA as for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

In this efficacy supplement (S-001), the Applicant proposed to add a new indication for the treatment of moderately to severely active ulcerative colitis (UC) in adults. In support of this application, the Applicant submitted clinical data from one phase 2 trial RPC01-202 and one phase 3 trial RPC01-3101 in patients with moderately to severely active UC. In addition, the Applicant also provided a population pharmacokinetic (PopPK) report, CLG-Certara-UC-358-1, and pharmacokinetics/pharmacodynamics (PK/PD), exposure-response (E-R) analysis report, CLG-Certara-UC-358-2 evaluating E-R relationships using pooled PK, PD, and efficacy data. The Applicant also submitted a phase 1 drug-drug interaction (DDI) study report RPC-1063-CP-001 to evaluate the effect of cyclosporine on the PK of ozanimod and major active metabolites in healthy subjects and a phase 1 extension study report RPC01-1915 in healthy subjects.

The key clinical pharmacology review questions focused on the appropriateness of the general dosing instructions, dosage for specific patient populations, DDI, as well as population PK and E-R analyses.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed this submission and found it acceptable for approval from a clinical pharmacology standpoint.

6.1.2. Key Review Issues

Key review issues with specific recommendations and comments are summarized in Table 5 below:

Table 5. Review Issues and Recommendations

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	The effectiveness of ozanimod was supported by the efficacy results from the phase 3 trial RPC01-3101. A greater proportion of patients treated with ozanimod 0.92 mg QD achieved clinical remission at Week 10 and clinical remission at Week 52 (the primary efficacy endpoints for induction and maintenance periods), compared to placebo.
General dosing instructions	The proposed oral dosage at 0.92 mg QD, following an initial 7-day dose titration, for adult patients with moderately to severely active UC is acceptable.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Use of ozanimod in patients with hepatic impairment is not recommended since the effect of hepatic impairment on the PK of ozanimod's major active metabolites is unknown. PMR 3809-6 to assess the effect of hepatic impairment on the PK of ozanimod and its major metabolites was issued in the original NDA approval. Based on dedicated DDI studies in the original NDA submission: Co-administration of ZEPOSIA with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended. Co-administration of ZEPOSIA with strong CYP2C8 inducers should be avoided. No dosage adjustment is recommended based on other intrinsic or extrinsic factors. These recommendations are consistent with the original approval.
Bridge between the "to-be-marketed" and clinical trial formulations	The "to-be-marketed" formulation (0.23, 0.46, and 0.92 mg of ozanimod in hard gelatin capsules) for the UC indication is identical to the approved marketed formulation for the MS indication. The clinical trial formulation used in the UC program was identical to the clinical trial formulation for the MS program. The formulations were bridged in the original NDA.

Source: Reviewer's table
Abbreviations: UC = Ulcerative colitis; PMR = postmarketing requirement; DDI = drug-drug interaction; NDA = New Drug Application; PK = pharmacokinetics

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology

Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Ozanimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. However, the relevance of reduction of lymphocytes in peripheral blood to therapeutic effectiveness is not fully known.

Clinical Pharmacokinetics

Clinical pharmacokinetics of ozanimod have been characterized in the original NDA 209899 for the MS indication (refer to the Office of Clinical Pharmacology Review in DARRTS, dated December 9, 2019) and briefly summarized below.

Absorption

Following oral administration, the Tmax of ozanimod is approximately 6-8 hours. The Cmax and area under the curve (AUC) for ozanimod and its major active metabolite CC112273 increase proportionally over the ozanimod dose range from 0.46 mg to 0.92 mg. Steady-state concentrations are achieved in approximately 102 hours and 45 days for ozanimod and CC112273, respectively, with accumulation ratios of 2.4 and 16 after once-daily administration, respectively.

Food effect

No clinically significant differences in the Cmax and AUC of ozanimod were observed following administration of ozanimod with a high-fat, high-calorie meal.

Distribution

The mean (CV%) apparent volume of distribution of ozanimod (Vz/F) is 5590 L (27%). Human plasma proteins binding of ozanimod, CC112273 and CC1084037 is approximately 98.2%, 99.8%, and 99.3%, respectively.

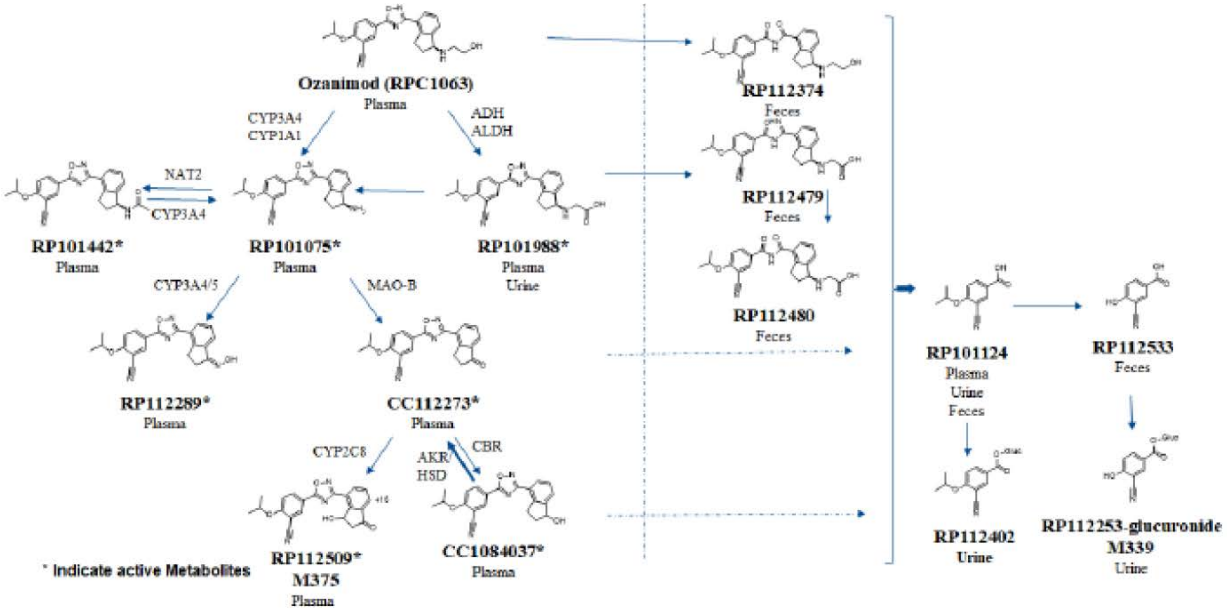
Elimination

The mean (CV%) plasma t1/2 of ozanimod is approximately 21 hours (15%). The mean (CV%) effective t1/2 of CC112273 and its direct interconverting metabolite CC1084037 was approximately 11 days (104%) in relapsing MS patients.

Metabolism

Ozanimod is metabolized by multiple enzymes to form circulating major active metabolites (e.g., CC112273 and CC1084037) and minor active metabolites (e.g., RP101988, RP101075, and RP101509) with similar activity and selectivity for S1P1 and S1P5. Ozanimod is metabolized by aldehyde dehydrogenase (ALDH)/ alcohol dehydrogenase (ADH) to form carboxylate metabolite RP101988 and by CYP3A4 to form RP101075. RP101075 is then metabolized either by N-acetyltransferase 2 (NAT-2) to form RP101442 or by monoamine oxidase B (MAO-B) to form CC112273. CC112273 is then metabolized by CYP2C8 to form RP101509 or reduced to form CC1084037. CC1084037 is metabolized by aldo-keto reductase (AKR) 1C1/1C2 and/or 3β-and 11β-hydroxysteroid dehydrogenase (HSD) to form CC112273. The interconversion between CC112273 and CC1084037 favors CC112273. Approximately 94% of circulating total active drug exposure is represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%), in humans.

Figure 2. Metabolic Pathways for Ozanimod and Metabolites in Human



Source: Metabolite identification data from Report RPC01-1909

Excretion

Following a single oral dose of radiolabeled ozanimod 0.92 mg, approximately 26% of the radioactivity was recovered in urine and 37 % in feces over 504 hours (21 days), primarily composed of inactive metabolites.

PK in Patients with Ulcerative Colitis

In the current submission, PK of ozanimod and its major circulating active metabolite CC112273 were characterized in patients with UC by population PK analysis using sparse PK samples collected in phase 2 trial RPC01-202 and phase 3 trial RPC01-3101.

Overall, the PopPK model estimated mean apparent total clearance of ozanimod from plasma after oral administration (CL/F) was 175 L/h, mean apparent central volume of distribution (Vc/F) was 209 L, and the terminal elimination half-life (t1/2) was 39.1 hours in patients with UC. For CC112273, mean CL/F was estimated to be 15.8 L/h, mean Vc/F was 1490 L, and the terminal t1/2 was 424 hours in patients with UC.

Of note, PopPK estimates that patients with UC have slightly greater (within 15%) mean ozanimod Cmax,ss and AUCss compared to healthy subjects, but similar mean Cmax,ss and AUCss compared to patients with MS, following 0.92 mg QD dosing.

Meanwhile, patients with UC are estimated to have mean CC112273 Cmax,ss and AUCss similar to healthy subjects, but slightly greater (within 20%) mean Cmax,ss and AUCss compared to patients with MS, following 0.92 mg QD dosing.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant has proposed a dosage of 0.92 mg QD, following an initial 7-day dose titration, in adult patients with moderate to severe UC.

The proposed dosing regimen is supported by the efficacy and safety data from phase 3 trial RPC01-3101. A greater proportion of patients treated with ozanimod 0.92 mg QD achieved clinical remission at Week 10 compared to placebo (18% versus 6%) during the induction phase. For the maintenance phase, similarly, a greater proportion of patients re-randomized to ozanimod (i.e., ozanimod 0.92 mg – ozanimod 0.92 mg treatment group), compared to patients re-randomized to placebo (i.e., ozanimod 0.92 mg – placebo treatment group) achieved clinical remission (37% versus 19%). Results were statistically significant. The proposed dose is the same as the approved dose for patients with MS.

See Section 8 Statistical and Clinical and Evaluation of this multi-discipline review for the related efficacy and safety data.

Therapeutic Individualization

Renal impairment
No dose adjustment is needed in patients with renal impairment. Based on a dedicated renal impairment study in the original NDA submission, renal impairment has no clinically important effects on the PK of ozanimod or CC112273. Thus, the current labeling regarding subjects with renal impairment is appropriate and no change is needed.

Hepatic impairment
The effect of hepatic impairment on the PK of ozanimod and its major active metabolites is unknown, and therefore the use of ZEPOSIA in patients with hepatic impairment is not recommended per the current labeling. Of note, at the time of original NDA approval, postmarketing requirement (PMR) 3809-6 was issued to conduct a dedicated hepatic impairment study to assess the effect of hepatic impairment on the PK of ozanimod and its major metabolites. This study is expected to be completed by February 2022. Thus, the labeling regarding subjects with hepatic impairment will be updated upon the completion of the PMR study.

Drug-drug interactions
Based on dedicated DDI studies in the original NDA submission, the current label includes the following:

- Strong CYP2C8 Inhibitors: The exposure of the active metabolites of ozanimod increased when ZEPOSIA was co-administered with strong CYP2C8 inhibitors. Therefore, co-administration of ZEPOSIA with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended.

- Breast cancer resistance protein (BCRP) Inhibitor: The exposure of the active metabolites of ozanimod increased when ZEPOSIA was co-administered with BCRP inhibitors. Therefore, co-administration of ZEPOSIA with inhibitors of BCRP (e.g., cyclosporine, eltrombopag) is not recommended.
    - Of note, the Applicant submitted the results from a new drug interaction study (RPC-1063-CP-001) with cyclosporine in this submission that evaluated the effects of cyclosporine on the PK of ozanimod and its major active metabolites in healthy subjects, and thus, a labeling update is recommended based on the new data.

- Strong CYP2C8 Inducers: Co-administration of ZEPOSIA with strong CYP2C8 inducers (e.g., rifampin) reduces the exposure of the major active metabolites of ozanimod. Therefore, co-administration of ZEPOSIA with strong CYP2C8 inducers should be avoided.

- Monoamine Oxidase Inhibitors: No clinical studies evaluating the drug interaction potential of ozanimod with MAO inhibitors have been conducted. Therefore, co-administration of ZEPOSIA with MAO inhibitors (e.g., selegiline, phenelzine, linezolid) is contraindicated.

DDI study with cyclosporine

Co-administration of a single dose of cyclosporine 600 mg with a single dose of ozanimod 0.46 mg had no effect on the Cmax of ozanimod and resulted in an increase of 19% in mean ozanimod AUC_{inf}. Cyclosporine had no effect on the AUClast of CC112273 and decreased the mean Cmax of CC112273 by approximately 14%. Cyclosporine had no effect on the Cmax of CC1084037 and increased the mean AUC_{last} of CC1084037 by approximately 11%. Consistent with previous findings, cyclosporine significantly increased Cmax and AUClast for RP101988 (a minor active metabolite) by 96% and 75%, respectively.

Considering that approximately 94% of circulating total active drug exposure is represented by ozanimod and its major metabolite (CC112273 and CC1084037) in humans, and RP101988 and RP101075 together contribute to the less than 6% of circulating total active drug exposure, this increased exposure (approximately two-fold) for the two minor active metabolites, RP101988 and RP101075, is not considered clinically meaningful. Thus, we agree with the Applicant's proposal that no dosing adjustment is necessary when ozanimod is co-administered with cyclosporine and have updated the labeling accordingly.

Refer to Section 6.3.2 for additional discussion.

Effect of CYP2C8 inhibitors on PK

The effect of co-administration of CYP2C8 inhibitors on PopPK-estimated post hoc exposure estimates (Cmax,ss and AUCss for ozanimod 0.92 mg) based on data from a previously conducted dedicated DDI study RPC01-1912 in healthy subjects (reviewed in the original NDA) was also explored. Based on PopPK analysis, the geometric mean of individual estimates of exposure parameters for CC112273 was higher in subjects who had concomitant intake of CYP2C8 inhibitors compared to subjects who received ozanimod alone. Of note, in the original

NDA, data from this dedicated DDI study RPC01-1912 indicated that 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.

In this submission, the Applicant proposed to revise the labeling to state that (b) (4) instead of "co-administration of ZEPOSIA with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended" as stated in the current labeling. From a clinical pharmacology perspective, given that the current labeling regarding strong CYP2C8 inhibitors is based on the PK results from the previously conducted and reviewed dedicated DDI study RPC01-1912 and no new safety data in patients with concomitant use of CYP2C8 inhibitors are provided, we do not agree with the Applicant's proposal. Thus, no change regarding coadministration of ozanimod with strong CYP2C8 inhibitors is recommended.

Smoking status

Population PK analyses showed that the steady-state exposure (AUC) for the major active metabolite, CC112273, was approximately 44.5% lower in smokers than in nonsmokers. However, a similar pharmacodynamic response with median steady state reduction in absolute lymphocyte count (ALC) of 58% in nonsmokers and 54.3% in smokers with UC, was observed. Additionally, the E-R analyses for efficacy suggested that smoking was associated with a numeric, but not statistically significant reduction in the odds ratio for clinical remission in induction phase and associated with a numeric, but not significant improvement in the odds ratio for clinical remission in the maintenance phase. As such, no dose adjustment is needed for smokers. Refer to Section 6.3.2 for additional discussion.

Outstanding Issues

There are no outstanding issues that would preclude the approval of ZEPOSIA for the currently proposed indication in patients with moderately to severely and active UC from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

In the current submission, PK of ozanimod in patients with UC were characterized by population PK analysis using sparse PK samples collected in phase 2 trial RPC01-202 and phase 3 trial RPC01-3101.

Mean ozanimod and CC112273 PK parameters in patients with UC estimated using PopPK analysis are summarized in Table 6 below.

Table 6. Mean (SD) Pharmacokinetic Parameters for Ozanimod and the Major Active Metabolite, CC112273 in Adult Patients With UC Following Ozanimod 0.92 mg QD Based on Population PK Analyses

PK Parameter	Ozanimod	CC112273
CL/F (L/hr)	175 (43.7)	15.8 (21.7)
Vc/F (L)	209 (254)	1490 (1150)
t1/2 (h)	39.1 (0.906)	424 (262)
AUCT,ss (ng*hr/mL)	5.57 (1.35)	86.3 (55.3)
Cmax,ss (ng/mL)	0.307 (0.075)	3.67 (2.31)

Source: Data combined from the phase 2 trial RPC01-202 and phase 3 trial RPC01-3101 in patients with UC.
Abbreviations: SD = standard deviation; UC = ulcerative colitis; QD = once daily; PK = pharmacokinetics; AUCT,ss = area under the concentration time curve during one dosing interval at steady state; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; Cmax,ss = maximum observed drug concentration during a dosing interval at steady state; t1/2 = half-life of elimination phase; V/F = apparent total volume of distribution
Note: PK parameters were estimated based on individual post hoc estimates.
Mean AUCss and Cmax,ss for CC112273 were converted from nmol/L to ng/mL using the molecular weight of CC112273 of 359.39.

Based on PopPK analysis, patients with UC have slightly greater (within 15%) mean ozanimod Cmax,ss and AUCss compared to healthy subjects, but similar mean Cmax,ss and AUCss compared to patients with MS, following 0.92 mg QD dosing. Meanwhile, PopPK analysis suggests that patients with UC are estimated to have similar mean CC112273 Cmax,ss and AUCss to healthy subjects, but slightly greater (within 20%) mean Cmax,ss and AUCss compared to patients with MS, following 0.92 mg QD dosing. Refer to Section 15.3.2 for more information.

Fecal calprotectin

In phase 3 trial RPC01-3101, reductions from baseline in fecal calprotectin at Week 10 (median change of -387 µg/g) and at Week 52 (median change of -812 µg/g) were observed following ozanimod 0.92 mg QD administration. However, relatively large variabilities in changes from baseline values were also observed, as the decreases from baseline ranged from -40515 µg/g to 47690 µg/g at Week 10 and from -27587 µg/g to 14772 µg/g at Week 52. As such, the small reductions of 387 µg/g may not represent clinically significant changes. (b) (4)

[redacted]

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of effectiveness of 0.92 mg ozanimod QD was supported by a significantly higher proportion of patients achieving clinical remission at Week 10 and a higher proportion of patients maintaining clinical remission at Week 52 compared to placebo in the placebo-controlled phase 3 trial (18.4% versus 6% during the induction phase and 37% versus 18.5% during the maintenance phase). See Section 8 of this multi-disciplinary review for the related efficacy data.

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

Yes. The proposed oral dosage at 0.92 mg QD for the general adult patient population is appropriate.

In a phase 2 dose-ranging trial, following a 7-day dose titration, ozanimod at 0.46 mg and 0.92 mg QD, or placebo, were studied in patients with moderately to severely active UC. Both doses showed numerically better efficacy than placebo based on clinical remission for the induction and maintenance treatment. While the study was not powered to compare between doses, there was a dose-dependent increase in the proportion of patients who achieved clinical remission between 0.46 mg and 0.92 mg. Only the 0.92-mg dose met the statistical significance for all endpoints while 0.46 mg did not reach a statistical significance for clinical remission and clinical response.

Induction

Efficacy results from this study suggested the proportion of patients in clinical remission at the end of induction period (Week 9), i.e., the primary efficacy endpoint of this phase 2 trial, for the 0.92 mg QD dosing regimen was statistically significantly greater than the proportion in the placebo group (16.4% versus 6.2%). The proportion of patients in clinical remission at Week 9 of ozanimod 0.46 mg QD group was numerically greater than the proportion in the placebo group (13.8% versus 6.2%), but this difference did not reach statistical significance.

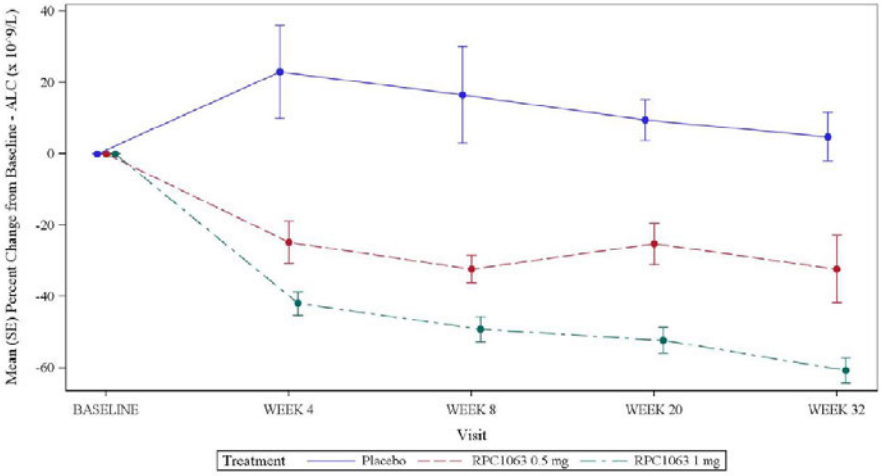
Similarly, the proportion of patients with a clinical response at Week 9, i.e., a secondary efficacy endpoint, for the 0.92 mg QD dosing regimen was statistically greater than the proportion in the placebo group (56.7% versus 36.9%), while the proportion of patients with a clinical response at Week 9 of ozanimod 0.46 mg QD group was numerically greater than the proportion in the placebo group (53.8% versus 36.9%).

Maintenance

For the maintenance period of this phase 2 trial, patients who had achieved clinical response at Week 9 continued with the treatment for an additional 24 weeks. The proportions of patients in clinical remission and with clinical response at Week 33 (secondary endpoints of this study), for the 0.92 mg QD dosing regimen were both statistically significantly greater than the proportions in the placebo group (20.9% versus 6.2% for clinical remission and 50.7% versus 20% for clinical response, respectively). For ozanimod 0.46 mg QD group, while the proportion of patients in clinical remission at Week 33 was statistically greater than the proportion in the placebo group (26.2% versus 6.2%), the proportion of patients with clinical response at Week 33 was numerically greater than the proportion in the placebo group (35.4% versus 20%); however, this difference did not reach statistical significance.

Additionally, the effects of ozanimod on ALC were assessed in this phase 2 dose-ranging trial. Reduction of circulating ALC was observed in both ozanimod dose groups at the end of the induction period (Week 9) and maintenance period (Week 33). Numerically greater reductions in ALC from baseline were observed for the 0.92-mg dose compared to the 0.46-mg dose. The mean percent changes from baseline in ALC versus time profiles are presented in Figure 3 below. It should be noted that the clinical relevance of reduction in circulating ALC with UC is not fully known yet.

Figure 3. Mean (SE) Percent Change From Baseline in Absolute Lymphocyte Count



Source: phase 2 trial RPC01-202 report, Figure 2.
Abbreviations: ALC = Absolute Lymphocytes Count; SE = standard error
Note: RPC1063 0.5 mg represents ozanimod 0.46 mg QD dose group. RPC1063 1 mg represents ozanimod 0.92 mg QD dose group.

As mentioned above, in the phase 3 trial, 0.92 mg ozanimod QD was supported by a significantly higher proportion of patients achieving clinical remission at Week 10 as well as a higher proportion of patients maintaining clinical remission at Week 52 compared to placebo treatment.

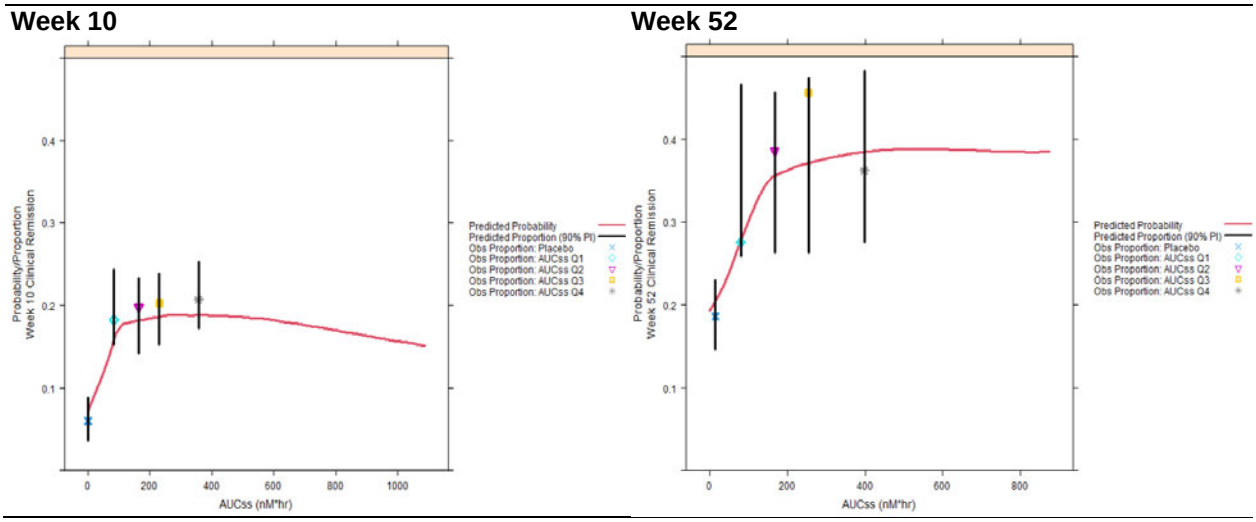
Table 7. Proportion (%) of Patients in Clinical Remission at Week 10 and Week 52 in Phase 3 Trial

	Cohort 1		Cohort 2 (open-label)
Induction (Week 10)	**Placebo (N=216)**	**0.92 mg QD (N=429)**	**0.92 mg QD (N=367)**
Patients in clinical remission, n (%)	13 (6.0)	79 (18.4)	77 (21.0)
		Re-randomized Withdrawal Patients	
Maintenance (Week 52)	**Placebo (N=69)**	**Ozanimod 0.92 mg - Placebo (N = 227)**	**Ozanimod 0.92 mg- Ozanimod 0.92 mg (N = 230)**
Patients in clinical remission, n (%)	17 (24.6)	42 (18.5)	85 (37.0)

Source: Clinical Study Report RPC01-3101, Table 18 and Table 19.
Abbreviations: QD = once daily

Meanwhile, the exposure-response relationships for the observed rates of clinical remission at Week 10 and Week 52 from phase 3 trial RPC01-3101 were also explored using population PK/PD analysis with individual PK parameter estimates for the major metabolite, CC112273, from the final PopPK model. The exposure-response relationships for proportion of clinical remission are presented in Figure 4.

Figure 4. Exposure-Response Relationship for Predicted and Observed Probability/Proportion of Clinical Remission at Week 10 and Week 52 in Phase 3 Trial in Patients with UC



Source: Clinical PK/PD Report CLG-Certara-UC-358-2, Figure 18, Figure 25.
Abbreviations: AUCss = individual estimates of CC112273 AUC at steady state; PI = prediction interval; Qn = quartile n
Red solid lines represent the predicted probability of clinical remission from the model prediction. Black vertical lines represent the 90% prediction intervals of the response rates from the model prediction across quartiles of exposure.
The observed percentage of patients achieving clinical remission are plotted as various symbols per exposure quartile.

Consistent with observed data, population PK/PD analyses suggest that there is an apparent difference in the proportion of clinical remission between the placebo- and ozanimod-treated group, with higher proportions of patients in clinical remission in the ozanimod-treated group at both Week 10 and Week 52. The proportions of patients in clinical remission at Week 10 were generally similar across the range of exposures for the 0.92 mg ozanimod dose, with a slight trend toward greater response with higher exposure. The proportions of patients in clinical remission at Week 52 appeared to be generally comparable across the range of exposures for the 0.92 mg ozanimod dose, however, with a greater variability in the predicted proportions.

Of note, the overall incidence of treatment-emergent adverse events (TEAEs) appeared to be similar between the ozanimod 0.92 mg and placebo treatment groups in the placebo-controlled induction period. The incidence of severe TEAEs, serious TEAEs, TEAEs leading to permanent discontinuation of study drug, and TEAEs leading to study withdrawal were also similar between the two treatment groups. For placebo-controlled maintenance period in phase 3 trial RPC01-3101, the incidences of severe TEAEs and TEAEs leading to temporary interruption of study drug were generally similar between the treatment groups.

Overall, the proposed dosage of 0.92 mg QD is considered appropriate for the treatment of adult patients with moderately to severely active UC based on the efficacy data in the phase 3 clinical trial.

See Section 8 of this multi-discipline review for the related efficacy and safety data.

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

No. Ozanimod is not recommended in patients with hepatic impairment. No dosage adjustment is needed based on other intrinsic factors. These recommendations are consistent with the current labeling for ozanimod.

Hepatic impairment
The effect of hepatic impairment on the PK of ozanimod and its major active metabolites is unknown. PMR 3809-6 was issued at the time of the original NDA approval to conduct a dedicated hepatic impairment study to assess the effect of hepatic impairment on the PK of ozanimod and its major metabolites. This study is expected to be completed by February 2022.

Renal impairment
Based on a dedicated renal impairment study in the original NDA submission, renal impairment does not have clinically important effects on the PK of ozanimod or CC112273.

Smoking status
Consistent with previous findings, smoking status was identified as the most influential covariate on CL/F in patients with UC from the PopPK analysis. Population PK analyses showed that CC112273 steady-state exposure (AUC) was approximately 44.5% lower in smokers than in nonsmokers; however, the decrease in ALC for the ozanimod 0.92 mg QD dose appeared to be generally similar for UC patients who are smokers and non-smokers (median reduction in ALC of 58% in nonsmokers and 54.3% in smokers).

Table 8. ALC Change From Baseline in UC Patients for Ozanimod 1 mg QD Based on Post Hoc Parameters by Smoking Status

ALC Change from Baseline (%)	Non-smoker (N=839)	Smoker (N=46)
Mean (SD)	-57.4 (14.2)	-52.7 (16.8)
Median (Min, Max)	-58.0 (-98.6, -4.36)	-54.3 (-84.5, -11.4)

Source: Clinical PK/PD Report CLG-Certara-UC-358-2, Appendix A, Table 15.
Abbreviations: ALC = absolute lymphocyte count; Max = maximum; Min = minimum; N = sample size; SD = standard deviation; UC = ulcerative colitis; QD = once daily

The clinical impact of smoking on ozanimod treatment for patients with UC is not fully known yet. Of note, there was no consistent response by smoking status based on E-R analyses. The E-R analyses for efficacy suggested that smoking was associated with a numerical, but not

significant, reduction in the odds ratio for clinical remission of approximately 30% in the induction phase and a numerical, but not significant, improvement in the odds ratio of 62% for clinical remission in the maintenance phase. However, it should be noted that the number of smokers in UC patients is too small to make any definitive conclusions. Taken together, it appears that no dose adjustment is needed for smokers based on the totality of the available data.

Patients ≥65 years of age

Population PK analyses estimated that steady state AUCss of CC112273 in UC patients over 65 years of age was approximately 3% to 4% greater than patients 45 to 65 years of age, and approximately 27% greater than adult patients under 45 years of age. These differences are not considered clinically meaningful. It should be noted the number of patients ≥65 years of age was small to make any definitive conclusions. (b) (4) Refer to Section 15.3 for additional discussion.

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

The proposed dosing instruction to administer ozanimod with or without food is appropriate based on a food effect study and the current labeling.

Based on dedicated DDI studies in the original NDA submission, current recommendations with regard to the DDIs with strong CYP2C8 inhibitors, strong CYP2C8 inducers, and monoamine oxidase inhibitors in the approved label are also applicable to and appropriate for patients with UC. Thus, no change is recommended from clinical pharmacology perspective.

In the current submission, the Applicant submitted new data from a dedicated DDI study (RPC-1063-CP-001) with cyclosporine as well as PopPK analysis using new data in patients with UC with concomitant use of prednisone or prednisolone. Details are discussed below.

DDI study with cyclosporine

In the original NDA submission, a clinical drug interaction study (RPC01-1903) was conducted to evaluate the effect of cyclosporine (an index inhibitor for BCRP, also a moderate CYP3A inhibitor, P-gp inhibitor, and OATP inhibitor) on the single-dose PK of ozanimod and its metabolites in healthy adult subjects. In that study (RPC01-1903), cyclosporine had no effect on ozanimod exposure and doubled the exposure of the minor active metabolites RP101988 and RP101075. However, the effect of cyclosporine on the major metabolites CC112273 and CC1084037 was not evaluated as these metabolites had not been identified at the time this study was conducted.

In the current submission, another clinical drug interaction study (RPC-1063-CP-001) was conducted to evaluate the effects of cyclosporine on the PK of ozanimod and its major circulating active metabolites CC112273 and CC1084037 in healthy adult subjects.

Co-administration of a single dose of cyclosporine 600 mg with a single dose of ozanimod 0.46 mg had no effect on the Cmax of ozanimod and resulted in an increase of 19% in mean ozanimod AUCinf. Cyclosporine had no effect on the AUClast of CC112273 and decreased its mean Cmax by approximately 14%. Cyclosporine also had no effect on the Cmax of CC1084037 and increased its mean AUClast by approximately 11%. Consistent with previous findings, cyclosporine significantly increased Cmax and AUClast for RP101988 (a minor active metabolite) by 96% and 75%, respectively.

Table 9. Statistical Analysis to Assess the Effect of Cyclosporine on the PK of Ozanimod and Metabolites

		Number of Subjects		Geometric LS Means			
Analyte	PK Parameter	Test	Reference	Test	Reference	Ratio of Geometric LS Means (Test to Reference)	90% CI for Geometric LS Mean Ratio of (Test to Reference)
Ozanimod	C_{max} (pg/mL)	20	20	79.0	78.31	1.008	(0.881, 1.153)
	$AUC_{0-\infty}$ (pg*h/mL)	13	16	2750	2305.7	1.193	(0.997, 1.427)
	AUC_{0-last} (pg*h/mL)	19	20	2107	1961.9	1.074	(0.916, 1.259)
CC112273	C_{max} (pg/mL)	20	20	152	176	0.865	(0.746, 1.003)
	AUC_{0-last} (pg*h/mL)	19	20	23184	22736	1.020	(0.850, 1.223)
CC1084037	C_{max} (pg/mL)	20	20	20.8	20.9	0.992	(0.865, 1.139)
	AUC_{0-last} (pg*h/mL)	18	20	3471	3129	1.109	(0.714, 1.724)
RP101988	C_{max} (pg/mL)	20	20	220	113	1.956	(1.702, 2.249)
	AUC_{0-last} (pg*h/mL)	19	20	3305	1887	1.751	(1.466, 2.093)

Source: Clinical Study Report RPC-1063-CP-001, Table 5.
Abbreviations: PK = pharmacokinetics; CI = confidence interval; LS = least squares; AUC = area under the curve
Reference indicates treatment group A, a single oral dose of ozanimod 0.46 mg.
Test indicates treatment group B, a single oral dose of ozanimod 0.46 mg plus a single oral dose of cyclosporine 600 mg.

Considering that approximately 94% of circulating total active drug exposure is represented by ozanimod and its major metabolite (CC112273 and CC1084037) in humans, and RP101988 and RP101075 together contribute to the less than 6% of circulating total active drug exposure, this increased exposure (approximately two-fold) for the two minor active metabolites, RP101988 and RP101075, is not considered clinically meaningful. Thus, no dosing adjustment is necessary when ozanimod is co-administered with cyclosporine.

Concomitant use of prednisone and prednisolone

Based on PopPK analysis, concomitant use of prednisone or prednisolone was associated with a 7.1% reduction in apparent clearance of CC112273 and a 12% reduction in apparent clearance of ozanimod. Based on these results, the impact on PK was insignificant for both CC112273 and the parent drug ozanimod.

It should be noted that the analysis was based on sparse PK data collected in UC patients with and without concomitant prednisone or prednisolone use. In addition, PopPK analysis for CC1084037 has not been conducted and the impact of prednisone or prednisolone on the exposure of CC1084037 is not yet known. We recommend that the results from the current PopPK analysis be included in the labeling.

Refer to Section 15.3 for additional discussion.

Bridge between the "to-be-marketed" and clinical trial formulations

The clinical trial formulation used in the UC program is identical to the clinical trial formulation for the MS program in the original NDA submission. The "to-be-marketed" formulation (0.23, 0.46, and 0.92 mg capsules) for the UC indication is identical to the approved marketed formulation for the MS indication. The formulations were bridged in the original NDA. Thus, no additional formulation bridging study is needed.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 10. Key Design Elements of Clinical Trials in Support of Approval

NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Study Population	Demographics
RPC01-202 Phase 2 IP and MP: 26 Dec 2012 - 10 Mar 2015 OLP: 17 May 2013 - 29 Aug 2019 No. of Centers: 57 Regions: Europe, North America, and Asia-Pacific region	Multicenter study comprising a randomized, double-blind, placebo-controlled parallel-group Core Period (IP and MP) and an OLP <u>Core Period</u>: Subjects who completed the 9-week IP and who were responders entered a 24-week MP. <u>OLP</u>: Subjects who are non-responders at Week 9 of the IP, who completed the MP, or who entered the MP and experienced disease relapse had the option to enter the OLP and receive treatment with ozanimod for up to 6 years	Eligible subjects were randomized (1:1:1) to receive 1 of 3 regimens for the IP: placebo, ozanimod 0.5 mg, or ozanimod 1 mg. All assigned treatments were QD PO <u>IP (9 weeks):</u> All subjects received an initial 7-day dose titration: -Days 1-4: ozanimod 0.25 mg or placebo; QD PO -Days 5-7: ozanimod 0.5 mg or placebo; QD PO -Day 8: ozanimod 0.5 mg, ozanimod 1 mg, or placebo; QD PO Subjects received their assigned dose starting at Day 8 and continuing for 8 weeks following the 1-week dose titration. <u>MP (24 weeks):</u>	Primary endpoint: Proportion of subjects in clinical remission at Week 9 (4-component Mayo score)	Adult subjects with moderately to severely active UC (Mayo score ≥ 6 with endoscopic subscore ≥ 2) confirmed by endoscopic and histologic evidence. <u>IP:</u> Randomized: 199 Treated: 197 Completed: 186 Discontinued: 11 <u>MP:</u> Entered: 103 Completed: 91 Discontinued: 12 <u>OLP:</u> Enrolled: 170 Completed: 14 Completed Week 56: 123 Completed Week 104: 120 Completed Week 152: 84 Completed Week 200: 71 Completed Week 248: 24 Discontinued: 156 (54 of these subjects rolled	IP: Sex: Male: 115 (58.4%) Female: 82 (41.6%) Age (yrs.): Mean (SD): 40.8 (11.82) Min, Max: 18, 73 Race: White: 182 (92.4%) Asian: 8 (4.1%) Black: 4 (2.0%) Other: 2 (1.0%)

NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Study Population	Demographics
		Subjects continued same treatment received in IP for an additional 24 weeks. OLP (Week 33 onwards): Ozanimod 1 mg QD PO		into Study RPC01-3102)	
RPC01-3101 Phase 3 IP and MP: 12 Aug 2015 – 27 Mar 2020 No. of Centers: 370 Regions: North America, Europe, Asia Pacific, South America, South Africa	Multicenter, randomized, double-blind, placebo-controlled study comprising IP and MP. IP (10 weeks): • Cohort 1 – double-blind, placebo-controlled induction with option for ozanimod responders to participate in MP • Cohort 2 – open-label, active treatment induction with option for responders to participate in MP MP (42 weeks): • Subjects in Cohort 1 or Cohort 2 who received active ozanimod and completed the IP and were in clinical response at Week 10 were re-randomized to an additional 42 weeks of double-	IP (10 weeks): Cohort 1 (blinded): Eligible subjects were randomized (2:1) to ozanimod 1 mg or placebo. All assigned treatments were QD PO Cohort 2 (open-label): Ozanimod 1 mg QD PO All subjects received an initial 7-day dose titration: • Days 1-4: ozanimod 0.25 mg or placebo; QD PO • Days 5-7: ozanimod 0.5 mg or placebo; QD PO • Day 8: ozanimod 1 mg or placebo; QD PO Subjects received their assigned dose starting at Day 8 and continuing for 9 weeks following the 1-week dose titration. MP (42 weeks): • Subjects in Cohort 1 or Cohort 2 who received active ozanimod and completed the IP and were in clinical response at Week 10 were re-	IP: Proportion of subjects in clinical remission at Week 10 (3-component Mayo score) MP: Proportion of subjects in clinical remission at Week 52 (3-component Mayo score)	Adult subjects with moderately to severely active UC IP: Cohort 1: Randomized: 645 Completed: 593 Discontinued: 52 Cohort 2: Enrolled: 367 Completed: 324 Discontinued: 43 MP (Active Responders): Randomized: 457 Completed: 308 Discontinued: 149 MP (Placebo): Entered: 69 Completed: 45 Discontinued: 24	IP Cohort 1 Sex: Male: 388 (60.2%) Female: 257 (39.8%) Age (yrs.): Mean (SD): 41.6 (13.56) Min, Max: 18, 74 Race: White: 562 (87.1%) Black: 18 (2.8%) Asian: 53 (8.2%) Other: 12 (1.9%) IP Cohort 2 Sex: Male: 214 (58.3%) Female: 153 (41.7%) Age (yrs.): Mean (SD): 42.1 (13.72) Min, Max: 18, 74 Race: White: 336 (91.6%) Black: 10 (2.7%) Asian: 12 (3.3%) Other: 9 (2.5%)

NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Study Population	Demographics
	blind, placebo-controlled maintenance. • Subjects in Cohort 1 who received placebo and showed a clinical response at Week 10 continued to receive placebo. Subjects who completed the IP and were non-responders at Week 10, who completed the MP, or who experienced disease relapse during the MP had the option to enter the OLE Study RPC01-3102.	randomized to receive either ozanimod 1 mg QD PO or matching placebo QD PO Subjects in Cohort 1 who received placebo and showed a clinical response at Week 10 continued to receive placebo.			

NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Study Population	Demographics
RPC01-3102 Phase 3 safety (OLE) 02 Dec 2015 - ongoing (data cutoff 31 Mar 2020) No. of Centers: 229 Regions: North America, Europe, Asia Pacific, South America, South Africa	Multicenter OLE study Duration of treatment: until the end of 2021, or until approval for UC is obtained in the country of the clinical site, or until the Sponsor discontinues the development program, whichever comes first	Ozanimod 1 mg QD PO Subjects entering the study from a blinded prior study will initiate therapy with 7-day dose titration: • Days 1-4: ozanimod 0.25 mg QD PO • Days 5-7: ozanimod 0.5 mg QD PO • Day 8 and beyond: ozanimod 1 mg QD PO	Long-term safety and efficacy	Subjects who previously participated in a UC trial of ozanimod (i.e., Study RPC01-3101 or completed at least 1 year of the OLP of Study RPC01-202) Subjects from 3101: Enrolled: 824 Treated: 821 Completed: 0 Completed Week 22: 587 Completed Week 46: 430 Completed Week 94: 186 Completed Week 142: 71 Discontinued: 318 Subjects from 202: Enrolled: 54 Treated: 54 Completed: Not available	Subjects from 3101 (N = 821): Sex: Male: 486 (59.2%) Female: 335 (40.8%) Age (yrs.): Mean (SD): 41.7 (13.65) Min, Max: 18, 74 Race: White: 731 (89.0%) Black: 24 (2.9%) Asian: 54 (6.6%) Other: 12 (1.5%) Subjects from 202 (N = 54): Sex: Male: 32 (59.3%) Female: 22 (40.7%) Age (yrs.): Mean (SD): 42.4 (11.55) Min, Max: 18, 64 Race: White: 48 (88.9%) Black: 1 (1.9%) Asian: 3 (5.6%) Other: 2 (3.7%)

Source: reviewer's table summarizing the contents of Applicant's submission.
Abbreviations: BL = baseline; IP = induction period; Max = maximum; Min = minimum; MP = maintenance period; No. = number; OLE = open-label extension; OLP = open-label period; PK = pharmacokinetic; PO = orally or by mouth; QD = once daily; SD = standard deviation; UC = ulcerative colitis

7.2. Review Strategy

The ozanimod clinical program supporting registration of ozanimod for the treatment of moderately to severely active UC consists of one placebo-controlled dose-ranging phase 2 study (RPC01-202), one pivotal phase 3 study (RPC01-3101) comprised of an induction period and a maintenance period, and an ongoing long-term OLE study (RPC01-3102).

The three trials are summarized as follows:

- Study RPC01-202: A phase 2, multicenter, randomized, double-blind, placebo-controlled parallel-group study to evaluate the clinical efficacy and safety of induction therapy with ozanimod for moderate to severe UC. This trial included a 9-week induction period and a 24-week maintenance period, for a total controlled study duration of 33 weeks. Study RPC01-202 also included an optional open-label period (OLP).

This study provided support for the dose selection, contributed patients to the induction period safety analyses, and provided supportive evidence of effectiveness.

- Study RPC01-3101: A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of ozanimod as induction and maintenance therapy for moderate to severe UC. This trial included a 10-week induction period and a 42-week maintenance period, for a total controlled study duration of 52 weeks.

This study provided the substantial evidence of effectiveness for both induction and maintenance periods of treatment and provides the controlled safety data for the maintenance period.

- Study RPC01-3102: A phase 3, multicenter, OLE trial of oral ozanimod as therapy for moderate to severe UC. Eligible patients completed at least Week 10 of the induction period in Study RPC01-3101 or completed at least one year of ozanimod 1 mg treatment in the Study RPC01-202 OLP. This trial is ongoing; data are presented as of the data cutoff date of 31 Mar 2020.

This study provides additional supportive long-term safety and efficacy data.

No pooling of data across studies was performed for efficacy analyses. For the evaluation of induction safety, patients who received blinded 1 mg or placebo from Study RPC01-202 were pooled with patients in cohort 1 of Study RPC01-3101 (placebo-controlled induction period) for select analyses. All UC studies were pooled for additional exposure-adjusted safety analyses as described further in the safety section that follows.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. RPC01-3101 – Trial Design

Compliance with Good Clinical Practices

The Applicant included a statement that the trial was conducted in accordance with applicable guidelines for Good Clinical Practice, or the applicable drug and data protection laws in the respective countries where the trial was conducted.

Financial Disclosure

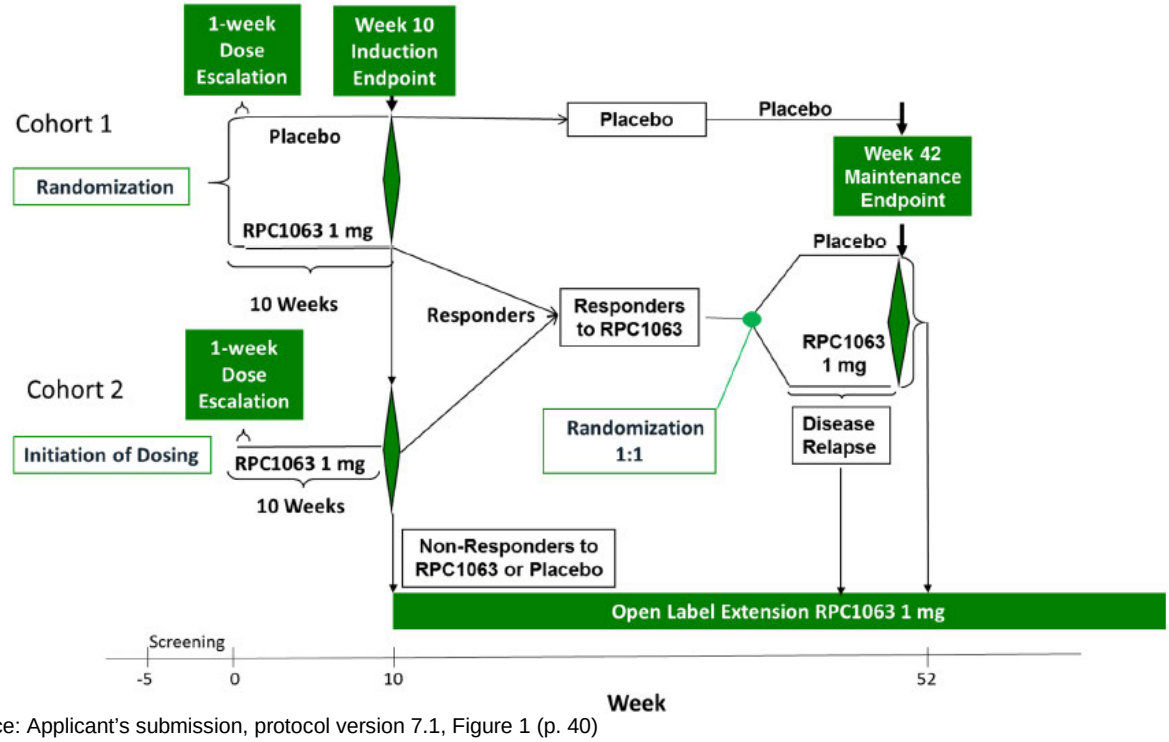
A single investigator (b) (6) had reportable financial interests. (b) (6) participated as a sub-investigator for a total of 13 patients, representing 1% of the study patients treated. Given the trial size and total number of investigators, and the potential impact of this financial arrangement is not expected to influence the trial outcome. Details are in the Appendix.

Trial Design

Study 3101 was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating ozanimod 1 mg versus placebo for the treatment of moderately to severely active UC. The trial consisted of an induction period (evaluating early efficacy at Week 10), followed by a maintenance period (evaluating efficacy at Week 52).

As shown in Figure 5. below, the induction period consisted of two cohorts of patients. Cohort 1 randomized patients 2:1 to either ozanimod 1 mg or placebo. Cohort 2, an open-label study where all patients received 1 mg of ozanimod for 10 weeks, was included to ensure an adequate number of clinical responders entered the maintenance period. At Week 10, patients underwent an efficacy evaluation (including flexible sigmoidoscopy). Patients who were in clinical response after receiving ozanimod were then re-randomized 1:1 to receive either continued treatment with ozanimod 1 mg or placebo. Placebo-treated patients who were in clinical response at Week 10 were continued on blinded placebo. Patients who were not in clinical response at Week 10 were eligible to enter the OLE trial. At Week 52, patients were re-evaluated for efficacy, including repeat sigmoidoscopy.

Figure 5. RPC01-3101 Trial Schematic for Cohort 1 and Cohort 2



Source: Applicant's submission, protocol version 7.1, Figure 1 (p. 40)

The protocol included a planned cohort 3, which was intended to include adolescent patients. However, no adolescents were enrolled in the study.

Study Population

The study included adult patients (18 to 75 years of age at screening) with a history of UC for at least 3 months prior to first dose of investigational drug. Patients had moderately to severely active UC disease (defined by complete Mayo score of 6 to 12 inclusive, with an endoscopic subscore of ≥2, a rectal bleeding subscore of ≥1, and a stool frequency subscore of ≥1). All patients had colitis extending at least ≥15 cm beyond the anal verge as determined by baseline flexible sigmoidoscopy or colonoscopy.

Patients were required to be receiving treatment with at least one of the following therapies (which was continued through induction): oral aminosalicylate stable for at least 3 weeks prior to screening, prednisone at dose ≤20 mg per day or equivalent at a stable dose for at least 2 weeks prior to screening, or budesonide extended release at a stable dose for at least 2 weeks prior to screening.

Patients were excluded if they received treatment with any of the following: prior biologic therapy within 8 weeks or 5 half-lives (whichever was less), any investigational agent within 5 half-lives, topical rectal 5-ASA or steroid within 2 weeks of screening endoscopy, anti-motility agents during screening period, or live vaccine within 4 weeks prior to randomization.

Specific exclusion criteria related to the known safety profile of ozanimod and other drugs within the S1P receptor modulator class included the following:

- Cardiovascular: Patients were excluded if they had history (within the preceding 6 months) of myocardial infarction, unstable angina, transient ischemic attack, decompensated heart failure, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea. Additionally, patients with corrected QT interval prolongation (QTcF >450 msec for males, >470 msec for females), those with risk factors for QT prolongation (hypokalemia, hypomagnesemia, congenital long QT syndrome), and those with resting heart rate < 55bpm were excluded.
- Diabetes: Patients with a history of diabetes type 1, uncontrolled diabetes mellitus type 2 with glycosylated A1C of >9% and any patient with complication of diabetes including retinopathy or nephropathy, were excluded.
- Ocular: Patients with history of uveitis (within the last year) or macular edema were excluded.

Study Endpoints

Induction Period

The primary objective of the induction period was to demonstrate efficacy of ozanimod versus placebo on induction of clinical remission in adults.

The primary endpoint was the proportion of patients in clinical remission at Week 10 evaluated in the intent-to-treat (ITT) population. Multiplicity-controlled secondary efficacy endpoints for induction are defined in Table 11.

Clinical remission and clinical response were defined in this study using the 3-component Mayo score. The 3-component Mayo score is derived from the original Mayo Clinic Score, and consists of three subscores (rectal bleeding subscore, stool frequency subscore [SFS], and endoscopy subscore). The definition of remission is acceptable and consistent with the Division's currently recommended approach to evaluation of efficacy in UC trials. The primary analysis algorithm for Mayo score derivation was the 7-day scoring algorithm. A 14-day scoring algorithm for Mayo score derivation was utilized for supportive purposes. Details of the 3-component Mayo score appear in the Appendix, Table 68.

Table 11. Endpoint Definitions for Induction Period

Endpoint	Definition
Primary endpoint	
Clinical remission	RBS = 0, SFS ≤ 1 (and a decrease of ≥ 1 from baseline), endoscopy subscore of ≤ 1 without friability
Key secondary endpoints	
Clinical response	Reduction from baseline in the 9-point Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in RBS of ≥ 1 or an absolute RBS of ≤ 1
Endoscopic improvement	Endoscopy subscore of ≤ 1 without friability
"Mucosal healing"	Endoscopy subscore of ≤ 1 without friability and a Geboes index score of < 2.0 (no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations or granulation tissue)

Source: Reviewer's table based upon clinical study protocol, v7.1
Abbreviations: RBS = rectal bleeding subscore; SFS = stool frequency subscore

The definitions of the primary and key secondary endpoints are acceptable. There is a lack of consensus as to the best definition of "mucosal healing." Thus, while the endpoint that was assessed in the trial is considered clinically important, the term "mucosal healing" is promotional and not appropriate for inclusion in labeling. Instead, this endpoint will be described in labeling as "endoscopic-histologic mucosal improvement."

The Geboes histology index was chosen by the Applicant as the measure for the assessment of histologic changes because, based on published literature, it is reported to have high intra- and inter-rater reliability and because its content validation was established using literature review and expert opinion for the development of the index (Mosli et al. 2017b). Although several indices are available, the clinical reviewer agrees that the selection of the Geboes index is reasonable.

In the induction and maintenance periods of Study RPC01-3101, "mucosal healing " (defined as an endoscopy subscore ≤ 1 and a Geboes score of < 2.0) was a key secondary endpoint included in the statistical testing hierarchy, and "histologic remission" (defined as a Geboes score of < 2.0) was a secondary endpoint not included in the statistical testing hierarchy. Both endpoint definitions require the resolution of histologic architecture abnormalities due to UC (crypt destruction, erosions, ulcerations or granulation), the absence of infiltration of neutrophils in epithelial crypts, as well as the absence of infiltration of neutrophils and eosinophils in the lamina propria. The Applicant asserts that defining histologic remission as a Geboes score < 2.0 is supported by an expert consensus process for the development of an index for histologic grading of UC, which concluded that neutrophils in the lamina propria within a single biopsy fragment should be considered abnormal (Mosli et al. 2017a).

Pai et al. reported the correlation between residual histologic activity and clinical outcomes in a prospective study of 182 UC patients followed for a 3-year follow-up time period. Patients with histologic evidence of UC disease activity (as defined as a Geboes score ≥ 2B.1, indicative of a

mild but unequivocal increase in lamina propria neutrophils, neutrophils in the epithelium, crypt destruction, erosions, or ulceration) had increased rates of corticosteroid use, colectomy, and hospitalization over the follow-up time period. In patients with endoscopic remission, only the presence of histologic activity of Geboes score > 2B.1 was independently associated with the use of corticosteroids (odds ratio [OR] = 6.34 [95% CI: 2.20, 18.28]). Additionally, patients with endoscopic remission alone but with the presence of mucosal neutrophils continued to have higher rates of corticosteroid use over the follow-up time period (Pai et al. 2020).

An additional prospective study also demonstrated improvements in health outcomes in UC patients with low histologic activity. Bryant, et al. reported that in a cohort of 91 patients with UC followed for a median 72 months, 24% of patients had evidence of histologic inflammation despite endoscopic remission. Importantly, the authors found that only histologic remission (defined by the absence of erosions, crypt abscesses, and neutrophilic infiltration), but not endoscopic remission, was associated with a reduced risk of both corticosteroid use (hazard ratio [HR] = 0.42 [95% CI: 0.2, 0.9]) and acute severe colitis requiring hospitalization (HR = 0.21 [95% CI: 0.1, 0.7]) over the 6-year follow-up period (Bryant et al. 2016).

Recently, histologic improvement (defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue) and combined endoscopic (Mayo endoscopic subscore of 0 or 1) and histologic improvement using the components of the Geboes score were incorporated into the phase 3 ustekinumab UC program (Sands et al. 2019). The achievement of endoscopic and histologic mucosal healing after induction therapy was subsequently reported to be associated with lower disease activity (by Mayo and partial Mayo score) at the end of maintenance therapy than either histologic or endoscopic improvement alone (Li et al. 2020).

Within Study RPC01-3101, the procedures for biopsy collection and specimen handling were standardized (see Section 15.4.6). Uncertainty remains regarding the optimal location and number of biopsies to collect in patients with UC, to ensure sampling error does not negatively impact the overall histologic assessment of disease activity. Additionally, UC trials (including RPC01-3101) typically utilize a limited sigmpoidoscopy to evaluate colonic inflammation, and there is uncertainty regarding whether or not biopsies taken only from the distal colon may accurately capture the degree of histologic disease activity present throughout the entire colon, in patients with more extensive disease or pancolitis. Additional work is also ongoing to determine the definition(s) of histologic remission that is most clinically relevant, and which scoring system (such as Geboes, Nancy Histologic Index, or others) is optimal for use in clinical trials.

Despite these limitations, the clinical reviewer finds the definition used by the Applicant for endoscopic-histologic mucosal healing to be reasonable; the available published literature support that clinical benefit is associated with achieving this endpoint, which captures both resolution of the key features of UC visible on sigmoidoscopy, as well as improvement in several key histologic abnormalities that are associated with active UC. Language will be included in

the label to note that the association between endoscopic-histologic mucosal improvement and long-term outcomes / disease progression was not evaluated within Study RPC01-3101.

Maintenance Period

The primary endpoint for maintenance was the proportion of patients in clinical remission at Week 52 evaluated in the ITT population.

Multiplicity-controlled secondary endpoints for maintenance are defined in Table 12.

Table 12. Endpoint Definitions for Maintenance Period

Endpoint	Definition
Primary endpoint	
Clinical remission	Same as in Table 11
Key secondary endpoints	
Clinical response	Same as in Table 11
Endoscopic improvement	Same as in Table 11
Clinical remission at Week 52 in the subset of patients who were in clinical remission at Week 10	See above for clinical remission definition
Corticosteroid-free remission	Clinical remission at Week 52 while off corticosteroids for ≥ 12 weeks
"Mucosal healing"	Same as in Table 11
Durable clinical remission	Clinical remission at Week 10 and Week 52 in all patients who entered the maintenance period

Source: Reviewer's table based upon clinical study protocol, v7.1

Statistical Analysis Plan for Induction Period

The primary analysis population for the induction period was the ITT population, which was defined as follows for each cohort:

- Cohort 1: all randomized patients from cohort 1 who received at least 1 dose of investigational drug (RPC1063 or placebo). Cohort 1 was used to formally assess efficacy endpoints during the induction period.
- Cohort 2: all enrolled patients from cohort 2 who received at least 1 dose of investigational drug (RPC1063). Endpoint results for cohort 2 were summarized descriptively.

The safety population consisted of all patients who received at least 1 dose of investigational drug in the induction period.

Analysis for Primary Endpoint

The primary endpoint, the proportion of patients in clinical remission at Week 10, was compared between the ozanimod and placebo groups in cohort 1 with a Cochran-Mantel-Haenszel (CMH) test stratified by corticosteroid use at screening (yes or no) and prior anti-TNF therapy use (yes or no). The analysis also included a normal approximation for the 95% confidence interval (CI) for the difference in binomial clinical remission proportions between the ozanimod and placebo groups.

Analysis for Key Secondary Endpoints

The key secondary endpoints were analyzed in the same manner as the primary endpoint.

Multiple Testing Approach

The protocol specified that a closed, hierarchical testing procedure was used to control the overall type I error rate for testing multiple endpoints. The primary endpoint was to be tested at the two-sided significance level of 0.05 first. If the primary endpoint was statistically significant, the proportion of patients with a clinical response at Week 10 was to be tested at a two-sided significance level of 0.05. If that endpoint was significant, then the proportion of patients with endoscopic improvement at Week 10 was to be tested at a two-sided significance level of 0.05. This testing procedure was to continue through each of the 3 key secondary endpoints listed in Table 11 until an endpoint failed to reach statistical significance, after which all subsequent key secondary endpoints were to be considered exploratory.

Handling of Missing Data

Non-responder imputation (NRI) was the primary method specified in the protocol for handling missing binary efficacy endpoint values. With NRI, patients with missing efficacy endpoint values were treated as non-responders.

Sensitivity Analyses

Sensitivity analyses were conducted for the clinical remission primary efficacy endpoint and the clinical response key secondary endpoint in the ITT population in order to examine the departures from the assumptions regarding missing data in the Applicant's pre-specified efficacy analysis. The pre-specified method for handling missing binary efficacy endpoint values was NRI. An alternative method for handling missing data, multiple imputation (MI), takes uncertainty into account in assigning missing values and imputes values based upon observed independent variables.

The statistical reviewer's sensitivity analyses included MI for each component of the clinical remission and clinical response definitions: rectal bleeding, stool frequency, and endoscopy. Clinical remission was then assigned according to the imputed values for each of the 3 component subscores. Clinical response was also assigned according to the imputed values for each of the 3 component subscores, along with the corresponding derived Mayo score and change and percent change from baseline in Mayo score.

Non-monotone missing data for each subscore were first imputed using a missing at random assumption. Monotone missing data from the ozanimod group were then imputed under a missing not at random assumption and utilized data from the placebo group as a reference. Missing data from the placebo group were also imputed under this assumption. For each

subscore, the imputation model included the following variables: stratification factors, baseline subscore value, and subscore value at each time point (i.e., Week 10 and Week 52).

For each rectal bleeding, stool frequency, and endoscopy subscore, 50 datasets with imputed data were created. After clinical remission and clinical response were derived from the imputed values, the same analysis method specified for the clinical remission and clinical response endpoint was conducted on the imputed datasets. Since the CMH test produces a test statistic that is not normally distributed, a Wilson-Hilferty normalizing transformation was performed on the CMH test statistic in each imputed dataset (Wilson and Hilferty 1931), (Ratitch et al. 2013). Analysis results were then combined using Rubin's rule.

The Applicant conducted a tipping point analysis (TPA) for the clinical remission and clinical response endpoints using methods for a binary variable as described in (Yan et al. 2009). The TPA included all observed data and then varied the missing efficacy outcomes in both treatment groups; a responder status was assigned to some patients with missing efficacy data, and other patients were assigned as non-responders. The plausibility of the scenarios that did not result in the same conclusion as the primary analysis for the endpoint was then examined.

Protocol Amendments

Study RPC01-3101 Protocol Amendments
The original protocol (dated March 30, 2015) had 6 amendments. The majority of the changes were to clarify the original intent, or to modify safety monitoring plans as information evolved. None of the changes had a major impact on the overall study design, efficacy assessments, or negatively impacted collection of safety data. A detailed summary is included in the Appendix Section 15.4.

Statistical Analysis Plan for Maintenance Period

The primary analysis population of the maintenance period was the ITT population, which was defined as patients who achieved clinical response to ozanimod at Week 10 of induction, were re-randomized, and who received at least 1 dose of investigational drug (RPC1063 or placebo). The safety population consisted of all patients who received at least 1 dose of investigational drug in the maintenance period (which is identical to the maintenance ITT population).

Analysis for Primary Endpoint

The primary endpoint, the proportion of patients in clinical remission at Week 52, was compared between the ozanimod and placebo groups with a CMH test stratified by clinical remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no). The analysis also included a normal approximation for the 95% CI for the difference in binomial clinical remission proportions between the ozanimod and placebo groups.

Analysis for Key Secondary Endpoints

The key secondary endpoints were analyzed in the same manner as the primary endpoint.

Multiple Testing Approach

The protocol specified that a closed, hierarchical testing procedure was used to control the overall type I error rate for testing multiple endpoints. The primary endpoint was to be tested at the two-sided significance level of 0.05 first. If the primary endpoint was statistically significant, the proportion of patients with a clinical response at Week 52 was to be tested at a two-sided significance level of 0.05. If that endpoint was significant, then the proportion of patients with endoscopic improvement at Week 52 was to be tested at a two-sided significance level of 0.05. This testing procedure was to continue through each of the 6 key secondary endpoints listed in Table 12 until an endpoint failed to reach statistical significance, after which all subsequent key secondary endpoints were to be considered exploratory.

Handling of Missing Data

NRI was the primary method specified in the protocol for handling missing binary efficacy endpoint values. With NRI, patients with missing efficacy endpoint values were treated as non-responders.

Sensitivity Analyses

Sensitivity analyses for the clinical remission primary efficacy endpoint and clinical response key secondary endpoint in the maintenance period were conducted in the same manner as described in the "Sensitivity Analyses" section for the induction period.

8.1.2. RPC01-3101 Induction Period Results

Patient Disposition

Study RPC01-3101 enrolled 1012 patients, including 645 patients in cohort 1 (429 randomized to ozanimod 1 mg and 216 to placebo) and 367 patients in cohort 2 (all treated with ozanimod 1 mg). The majority of ozanimod-treated patients completed the 10-week induction period (93.5% in cohort 1 and 88.3% in cohort 2) and continued into either the maintenance period (54.3% and 61.0%, respectively) or the OLE study, RPC01-3102 (37.1% and 21.5%, respectively). Most of the placebo-treated patients in cohort 1 also completed the 10-week induction period (88.9%) and enrolled in the OLE study (55.6%), while relatively fewer placebo-treated patients continued into the maintenance period (31.9%) compared to ozanimod-treated patients.

In the cohort 1 ozanimod group, the most frequently reported reasons for study withdrawal in descending order were AEs and withdrawal by patient. In the cohort 1 placebo group, the most frequently reported reasons for study withdrawal in descending order were lack of efficacy,

withdrawal by patient, and AEs. In cohort 2, the most frequently reported reasons for study withdrawal were withdrawal by patient, AEs, and lack of efficacy.

Table 13 summarizes patient disposition by treatment group for the induction period.

Table 13. Patient Disposition for Induction Period (Randomized Patients)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429) n (%)	**Placebo (N = 216) n (%)**	**Ozanimod 1 mg (N = 367) n (%)**
Patients dosed[a]	429 (100.0)	216 (100.0)	367 (100.0)
Patients who completed induction period[b]	401 (93.5)	192 (88.9)	324 (88.3)
Completed induction Week 10, continuing into maintenance period	233 (54.3)	69 (31.9)	224 (61.0)
Completed induction Week 10, enrolled into OLE study	159 (37.1)	120 (55.6)	79 (21.5)
Completed induction Week 10, but discontinued study participation and did not enroll in OLE study	9 (2.1)	3 (1.4)	21 (5.7)
Patients discontinued from induction period[b]	28 (6.5)	24 (11.1)	43 (11.7)
Primary reason for study withdrawal[b]			
Adverse event	11 (2.6)	6 (2.8)	12 (3.3)
Withdrawal by patient	10 (2.3)	8 (3.7)	20 (5.4)
Lack of efficacy	4 (0.9)	10 (4.6)	9 (2.5)
Non-compliance with protocol/protocol deviation	2 (0.5)	0	1 (0.3)
Other	1 (0.2)	0	0
Physician decision	0	0	1 (0.3)

Source: Study RPC01-3101 CSR Table 6 (p. 92)
Abbreviations: OLE = open-label extension
[a] Percentages are based on the number of patients in the randomized population (cohort 1) or enrolled population (cohort 2).
[b] Percentages are based on the number of patients dosed.

Protocol Violations/Deviations

In cohort 1, 278 (43.1%) patients had at least 1 major protocol deviation during the induction period, including 182 (42.4%) patients in the ozanimod group and 96 (44.4%) patients in the placebo group. In the cohort 2 ozanimod group, 126 (34.3%) patients had at least 1 major protocol deviation. The most common protocol deviations in both cohorts were “study procedure”, “selection criteria not met”, and “treatment deviation.” In general, the protocol deviations varied in nature and were not considered to have any clinically significant impact on data integrity or patient safety.

Demographic Characteristics

The demographic characteristics of patients in the induction period are summarized by treatment group in Table 14. Overall, the majority of patients were male (60% and 58% in cohort 1 and cohort 2, respectively) and most were white (87% and 92% in cohot 1 and cohort 2, respectively). The mean age was approximately 42 years in both cohorts, ranging from 18 to 74 years in each cohort. The mean weight was approximately 75 kg and 76 kg in cohort 1 and cohort 2, respectively, ranging from 38 to 173 kg in cohort 1 and 38 to 156 kg in cohort 2. Demographic characteristics were generally similar among treatment groups.

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Table 14. Demographic Characteristics for Induction Period (ITT Population)

	Cohort 1		Cohort 2
Demographic Characteristic	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Sex, n (%)			
Male	245 (57.1)	143 (66.2)	214 (58.3)
Female	184 (42.9)	73 (33.8)	153 (41.7)
Age (years)			
n	429	216	367
Mean (SD)	41.4 (13.5)	41.9 (13.6)	42.1 (13.7)
Median	40.0	40.0	40.0
Min, max	18, 72	19, 74	18, 74
Age category (years), n (%)			
18-29	105 (24.5)	46 (21.3)	85 (23.2)
30-39	103 (24.0)	58 (26.9)	95 (25.9)
40-49	91 (21.2)	50 (23.1)	71 (19.3)
50-59	77 (17.9)	32 (14.8)	64 (17.4)
60-69	48 (11.2)	24 (11.1)	49 (13.4)
70-75	5 (1.2)	6 (2.8)	3 (0.8)
< 65	410 (95.6)	202 (93.5)	346 (94.3)
≥ 65	19 (4.4)	14 (6.5)	21 (5.7)
Weight (kg)			
n	429	216	366
Mean (SD)	74.4 (18.3)	75.0 (16.3)	76.4 (18.6)
Median	71.0	73.7	72.0
Min, max	38, 173	40, 126	38, 156
Race, n (%)			
White	370 (86.2)	192 (88.9)	336 (91.6)
Black or African American	14 (3.3)	4 (1.9)	10 (2.7)
Asian	36 (8.4)	17 (7.9)	12 (3.3)
Other	9 (2.1)	3 (1.4)	9 (2.5)
Ethnicity, n (%)			
Hispanic or Latino	26 (6.1)	8 (3.7)	16 (4.4)
Not Hispanic or Latino	403 (93.9)	208 (96.3)	351 (95.6)
Region, n (%)			
North America	107 (24.9)	60 (27.8)	80 (21.8)
Eastern Europe	215 (50.1)	112 (51.9)	200 (54.5)
Western Europe	62 (14.5)	21 (9.7)	60 (16.3)
Asia Pacific	62 (14.5)	21 (9.7)	60 (16.3)
South America	3 (0.7)	0	0
South Africa	6 (1.4)	3 (1.4)	0

Source: Study RPC01-3101 CSR Table 12 (p. 98), Table 14.1.5.1.2A (p. 120)
Abbreviations: ITT = intent-to-treat; SD = standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline characteristics of patients in the induction period are summarized by treatment group in Table 15. In cohorts 1 and 2, the mean time since UC diagnosis was approximately 7 and 8 years, respectively. The mean duration of UC symptoms at the beginning of the induction period was approximately 8 years in cohort 1 and 9 years in cohort 2. The mean 3-component Mayo score at baseline was 6.6 in cohort 1 and 6.8 in cohort 2. Baseline characteristics were generally similar among treatment groups.

Table 15. Baseline Characteristics for Induction Period (ITT Population)

	Cohort 1		Cohort 2
Characteristic	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)***
Age at UC symptom onset (years)			
Mean (SD)	33.7 (13.0)	34.6 (13.5)	33.7 (13.5)
Median	31.0	32.0	31.0
Min, max	10, 70	11, 70	3, 73
Age at UC diagnosis (years)			
Mean (SD)	34.6 (13.2)	35.3 (13.6)	34.5 (13.4)
Median	32.0	33.0	32.0
Min, max	10, 70	12, 70	3, 73
Years since UC symptom onset			
Mean (SD)	7.9 (7.2)	7.6 (7.1)	8.7 (7.8)
Median	5.62	5.35	6.21
Min, max	0.0, 49.1	0.5, 39.7	0.0, 41.2
Years since UC diagnosis			
Mean (SD)	6.9 (6.6)	6.8 (7.0)	7.9 (7.4)
Median	4.80	4.42	5.57
Min, max	0.2, 38.6	0.3, 38.7	0.2, 41.2
Baseline 3-component Mayo score			
Mean (SD)	6.6 (1.2)	6.6 (1.2)	6.8 (1.3)
Median	7.0	7.0	7.0
Min, max	3, 9	4, 9	4, 9
Baseline 4-component Mayo score			
Mean (SD)	8.9 (1.5)	8.9 (1.4)	9.1 (1.5)
Median	9.0	9.0	9.0
Min, max	6, 12	6, 12	6, 12
Baseline histologic assessment^, n (%)			
Grade 0	20 (4.7)	9 (4.2)	5 (1.4)
Grade 1	2 (0.5)	4 (1.9)	2 (0.5)
Grade 2	18 (4.2)	13 (6.0)	7 (1.9)
Grade 3	44 (10.3)	25 (11.6)	30 (8.2)
Grade 4	44 (10.3)	18 (8.3)	22 (6.0)
Grade 5	282 (65.7)	138 (63.9)	266 (72.5)
Histologic remission at baseline, n (%)	22 (5.1)	13 (6.0)	7 (1.9)

Source: Study RPC01-3101 CSR Table 14 (p. 102), Table 14.1.5.2.1A (p. 120)
Abbreviations: ITT = intent-to-treat; SD = standard deviation; UC = ulcerative colitis
*Age of symptom onset was missing for one patient in cohort 2.
^ Each grade includes categorical index scores of 0-0.3 (e.g. Grade 1 includes 1.1-1.3, Grade 2 includes 2.1-2.3, etc.). Percentages are based on the ITT population. Histologic remission is defined as Geboes index score < 2.0.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Patients who took less than 80% or more than 120% of investigational drug during the entire treatment period were considered non-compliant. Treatment compliance was approximately 100% across treatment groups during the induction period and approximately 98% to 99% across treatment groups during the maintenance period.

All treatments, other than ozanimod, being taken by patients at study entry or at any time during the study, including through the Safety Follow-up Visit, were documented as concomitant medications. Histories of all prior medications taken during the 30 days prior to the date of informed consent/assent and previous treatments for UC were also documented.

Common concomitant medications for patients in the induction period included medications used for endoscopy. Patients enrolling in the study were required to be treated with other concomitant therapies including aminosalicylates (e.g., mesalazine 71% of total patients; sulfasalazine 13% of total patients). The most commonly used (i.e., used by ≥ 15% of patients in any group) concomitant 5-ASA medications for patients in the induction period included mesalazine (69.5% of patients in the cohort 1 ozanimod group, 65.3% of patients in the placebo group, and 74.9% of patients in the cohort 2 ozanimod group) and sulfasalazine (15.6% of patients in the cohort 1 ozanimod group, 14.4% of patients in the placebo group, and 9.8% of patients in the cohort 2 ozanimod group). Concomitant corticosteroids for systemic use were used in 27.7% of patients in the cohort 1 ozanimod group, 32.4% of patients in the placebo group, and 33.8% of patients in the cohort 2 ozanimod group. The most commonly used corticosteroid for patients in the induction period was prednisone (16.1% of patients in the cohort 1 ozanimod group, 17.6% of patients in the placebo group, and 20.4% of patients in the cohort 2 ozanimod group). Budesonide was used concomitantly by 4.4% of patients in the cohort 1 ozanimod group, 6.0% of patients in the placebo group, and 6.3% of patients in the cohort 2 ozanimod group.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the proportion of patients in clinical remission (defined as rectal bleeding subscore = 0, SFS ≤ 1 [and a decrease of ≥ 1 from the baseline SFS], and endoscopy subscore ≤ 1 without friability) at Week 10. Results for the primary efficacy endpoint based on the ITT population are displayed in Table 16. In cohort 1, a statistically significantly higher percentage of patients in clinical remission at Week 10 were observed in the ozanimod group (18.4%) relative to the placebo group (6.0%) (p-value < 0.0001). The observed difference between the treatment groups in the percentage of patients in clinical remission was 12.4%, 95% CI: (7.5, 17.2). The cohort 2 ozanimod group had a similar rate of clinical remission (21.0%) to the cohort 1 ozanimod group. These results were confirmed by the statistical reviewer.

Table 16. Primary Efficacy Endpoint Analysis for Induction Period: Proportion of Patients in Clinical Remission at Week 10[a] (ITT Population)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Number of patients in clinical remission at Week 10, n (%)	79 (18.4)	13 (6.0)	77 (21.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.124 (0.075, 0.172)		
p-value for difference in proportions[c]	< 0.0001		

Source: Study RPC01-3101 CSR Table 18 (p. 111), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by corticosteroid use at screening and prior anti-TNF use.

An exploratory analysis of clinical remission by SFS is in Table 74 in Appendix Section 15.5.1, to ensure that results were not driven primarily by patients unable to achieve a SFS of 0.

Efficacy Results – Key Secondary Endpoints

The induction period had the following multiplicity-controlled secondary endpoints at Week 10:

- The proportion of patients with a clinical response
- The proportion of patients with endoscopic improvement
- The proportion of patients with "mucosal healing" (endoscopic-histologic mucosal improvement[1]).

In cohort 1, statistically significantly higher response proportions were observed in the ozanimod group relative to the placebo group for all the multiplicity-controlled secondary endpoints. These results were confirmed by the statistical reviewer and are presented below in Table 17 through Table 19. Results for the open-label cohort 2 patients are presented side-by-side (and were generally numerically similar to the blinded ozanimod-treated patients). Results from the secondary endpoints are consistent with, and support the benefit demonstrated on the primary efficacy endpoint.

[1]Defined by: Endoscopy subscore of ≤ 1 without friability and a Geboes index score of < 2.0 (no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations or granulation tissue)

Table 17. Clinical Response at Week 10[a] (ITT Population)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Number of patients with a clinical response at Week 10, n (%)	205 (47.8)	56 (25.9)	193 (52.6)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.219 (0.144, 0.293)		
p-value for difference in proportions[c]	< 0.0001		

Source: Study RPC01-3101 CSR Table 20 (p. 114), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by corticosteroid use at screening and prior anti-TNF use.

Table 18. Endoscopic Improvement at Week 10[a] (ITT Population)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Number of patients with endoscopic improvement at Week 10, n (%)	117 (27.3)	25 (11.6)	100 (27.2)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.157 (0.097, 0.217)		
p-value for difference in proportions[c]	< 0.0001		

Source: Study RPC01-3101 CSR Table 21 (p. 115), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by corticosteroid use at screening and prior anti-TNF use.

Table 19. "Mucosal Healing" (Endoscopic-Histologic Mucosal Improvement) at Week 10[a] (ITT Population)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Number of patients with "mucosal healing" at Week 10, n (%)	54 (12.6)	8 (3.7)	42 (11.4)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.089 (0.049, 0.129)		
p-value for difference in proportions[c]	< 0.0010		

Source: Study RPC01-3101 CSR Table 22 (p. 115), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by corticosteroid use at screening and prior anti-TNF use.

As discussed above, uncertainties remain regarding the optimal methods to evaluate endoscopic-histologic improvement. Therefore, language will be included in the label to note that the association between endoscopic-histologic mucosal improvement and long-term outcomes / disease progression was not evaluated within Study RPC01-3101.

Efficacy Results – Exploratory Endpoints

Histologic Remission

Histologic remission[2] was a secondary endpoint not included in the statistical testing hierarchy. In cohort 1, a larger proportion of ozanimod-treated patients 78/429 (18%) achieved histologic remission compared to placebo 16/216 (7%)[3] at Week 10 (CSR Table 30). This endpoint was not recommended for inclusion in labeling, as the clinical significance of achieving histologic remission without endoscopic remission is unclear. Most published literature which supports the importance of evaluation of histologic improvement focuses on patients who have achieved endoscopic remission, and the additional benefits derived from further achieving histologic remission. Additionally, at baseline, 5.4% of patients met the definition of histologic remission, despite qualifying for the trial with the presence of active disease on sigmoidoscopy and clinical signs/symptoms. This supports that there are important limitations to the approach taken in this trial of sampling two biopsies from the left colon (based on flexible sigmoidoscopy), intended to accurately represent histologic activity of the overall colon.

We further evaluated these data in the subset of patients who had both endoscopic and histologic data at Week 10, to explore how frequently histologic remission was documented in the absence of endoscopic remission (a situation that may be related to sampling error or limitations in the current evaluation of histologic findings in UC). More patients achieved endoscopic improvement alone, as compared to endoscopic improvement with histologic remission, as expected, supporting the assertion that the combination of endoscopic and histologic improvement is a more stringent endpoint. Of note, approximately 5-6% of patients in cohort 1 were reported to achieve histologic remission at Week 10, though they had active disease on endoscopy defined by endoscopic subscore of ≥2[4]. Missing data may limit the interpretation of these results, as only 87% (375/429) of patients in the ozanimod group and 81% (175/216) of patients in the placebo group had both endoscopic and histologic data at Week 10 (results in Table 20 below).

[2] Defined as no neutrophils in the epithelial crypts or lamina propria, and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue (Geboes index score < 2.0).
[3] ITT population, NRI imputation
[4] Applicant's response to Information Request, received 4/27/21; the reported percentages are calculated out of the subset of patients who had data for both the endoscopic and histologic endpoint at Week 10.

Table 20. Exploratory Analysis: Histologic Remission and Endoscopic Improvement at Week 10 (ITT Population, Patients With Both Mayo Endoscopy Subscore and Histologic Score Available)

Endpoint	Number (%) of Subjects		
	Cohort 1		Cohort 2
	Ozanimod 1 mg N = 429	Placebo N = 216	Ozanimod 1 mg N = 367
Subjects having both endoscopy and Geboes score at Week 10[a]	375	175	312
Endoscopic improvement with histologic remission (mucosal healing)[b]	54 (14.4)	8 (4.6)	42 (13.5)
Endoscopic improvement without histologic remission[c]	58 (15.5)	14 (8.0)	56 (17.9)
Histologic remission without endoscopic improvement[d]	24 (6.4)	8 (4.6)	22 (7.1)

ITT = Intent-to-Treat.
[a] Denominator used to calculate percentages.
[b] Endoscopic improvement is defined as: endoscopy subscore of ≤ 1 point without friability. Histologic remission is defined as: Geboes index score < 2.0 (no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions ulcerations or granulation tissue).
Note: Subjects with missing endoscopy subscore or Geboes index score at Week 10 are excluded from analysis.
Source: RPC01-3101 CSR Table 14.2.4.2A; Appendix A, Table 14.2.11.2A and Table 14.2.11.3A

Source: Applicant's response to Information Request, received 4/27/21
Analysis was conducted in the ITT population, using observed cases, limited to patients who had available data for both Mayo endoscopy subscore and Geboes index score at Week 10.

Sensitivity Analyses

Sensitivity analysis results for the primary endpoint in the induction period, where missing clinical remission subscore values were imputed using MI with the placebo group as a reference, are displayed in Table 77 in Appendix Section 15.5.2. In cohort 1, the percentage of patients with missing efficacy data at Week 10 ranged from 13% (ozanimod group) to 21% (placebo group). The sensitivity analysis results are consistent with the primary analysis results for clinical remission (Table 16).

Sensitivity analysis results for the clinical response endpoint in the induction period, where missing clinical response subscore values were imputed using MI with the placebo group as a reference, are displayed in Table 78 in Appendix Section 15.5.2. The sensitivity analysis results are consistent with Table 17.

The Applicant's TPA results for the induction period were also consistent with the clinical remission and clinical response endpoint results (Appendix Section 15.5.2).

Thus, sensitivity analyses for clinical remission and clinical response revealed robustness of the primary analysis results to alternative scenarios for missing data assumptions.

Data Quality and Integrity

In general, the data submitted by the Applicant to support the efficacy and safety of ozanimod for the proposed indication were acceptable.

Additional Analyses Conducted on the Individual Trial (Induction Period Cohort 1)

Pre-specified subgroup analyses of interest for cohort 1 in the induction period include analyses of the primary and key secondary endpoints by previous use of anti-TNF therapy and by concomitant corticosteroid use at baseline.

Larger response proportions were observed in the ozanimod group compared to the placebo group regardless of prior anti-TNF therapy use . Results from these analyses are displayed in Table 21.

Table 21. Induction Period Subgroup Analyses by Prior Anti-TNF Therapy[a] (ITT Population)

	Number of Patients in Cohort 1, (%)		
Endpoint Subgroup	**Ozanimod 1 mg**	**Placebo**	**Difference in Proportions (Ozanimod-Placebo), 95% CI[b]**
Clinical remission			
No prior anti-TNF	66/299 (22.1)	10/151 (6.6)	0.154 (0.092, 0.215)
Prior anti-TNF	13/130 (10.0)	3/65 (4.6)	0.054 (-0.018, 0.126)
Clinical response			
No prior anti-TNF	157/299 (52.5)	44/151 (29.1)	0.233 (0.141, 0.325)
Prior anti-TNF	48/130 (36.9)	12/65 (18.5)	0.185 (0.060, 0.310)
Endoscopic improvement			
No prior anti-TNF	97/299 (32.4)	18/151 (11.9)	0.205 (0.131, 0.279)
Prior anti-TNF	20/130 (15.4)	7/65 (10.8)	0.046 (-0.051, 0.144)
“Mucosal healing”			
No prior anti-TNF	47/299 (15.7)	6/151 (4.0)	0.117 (0.065, 0.169)
Prior anti-TNF	7/130 (5.4)	2/65 (3.1)	0.023 (-0.034, 0.080)

Source: Study RPC01-3101 CSR Table 33 (p. 124), statistical reviewer’s analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat; TNF = tumor necrosis factor
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Larger response proportions were observed in the ozanimod group compared to the placebo group regardless of concomitant corticosteroid use at baseline. Results from these analyses are displayed in Table 22.

Table 22. Induction Period Subgroup Analyses by Concomitant Corticosteroid Use at Baseline[a] (ITT Population)

	Number of Patients in Cohort 1, (%)		
Endpoint Subgroup	Ozanimod 1 mg	Placebo	Difference in Proportions (Ozanimod-Placebo), 95% CI[b]
Clinical remission			
No CS use at BL	63/286 (22.0)	11/143 (7.7)	0.143 (0.078, 0.208)
CS use at BL	16/143 (11.2)	2/73 (2.7)	0.085 (0.021, 0.149)
Clinical response			
No CS use at BL	144/286 (50.4)	42/143 (29.4)	0.209 (0.115, 0.304)
CS use at BL	61/143 (42.7)	14/73 (19.2)	0.237 (0.118, 0.357)
Endoscopic improvement			
No CS use at BL	87/286 (30.4)	17/143 (11.9)	0.185 (0.110, 0.260)
CS use at BL	30/143 (21.0)	8/73 (11.0)	0.102 (0.004, 0.199)
"Mucosal healing"			
No CS use at BL	42/286 (14.7)	6/143 (4.2)	0.105 (0.052, 0.157)
CS use at BL	12/143 (8.4)	2/73 (2.7)	0.058 (-0.001, 0.116)

Source: Study RPC01-3101 Table 14.2.1.9.1A (p. 273), Table 14.2.2.10.1A (p. 297), Table 14.2.3.3.1A (p. 314), Table 14.2.4.3.1A (p. 331), statistical reviewer's analysis
Abbreviations: BL = baseline; CI = confidence interval; CS = corticosteroid; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 81, Table 82, Table 83, and Table 84 in Appendix Section 15.5.3 contain subgroup analyses of the induction period primary endpoint by sex, age, race, and region. The subgroup analyses are limited by small patient counts, and results should be interpreted with caution. In general, the subgroup analysis results were consistent with the primary endpoint results in Table 16.

8.1.3. RPC01-3101 Maintenance Period Results

Patient Disposition

A total of 526 patients were treated during the maintenance period, including 230 who were re-randomized to ozanimod 1 mg (116 from cohort 1, 114 from cohort 2), 227 who were re-randomized from ozanimod 1 mg to placebo (117 from cohort 1, 110 from cohort 2), and 69 who continued on placebo (i.e., placebo responders from cohort 1 of the induction period). The completion rate for the maintenance period was 80.0% in patients continuously treated with ozanimod, 54.6% in patients re-randomized from ozanimod 1 mg to placebo, and 65.2% in patients continuously treated with placebo.

The most frequently reported reason for study withdrawal was disease relapse, which occurred in 77 patients re-randomized to placebo (33.9%) and 31 patients re-randomized to ozanimod

(13.5%). Out of 1012 patients who enrolled in RPC01-3101, 824 (~81%) enrolled in the RPC01-3102 OLE study.

Table 23 summarizes patient disposition by treatment group for the maintenance period.

Table 23. Patient Disposition for Maintenance Period (Randomized Patients)

		Re-randomized Patients	
	Placebo (N = 69) n (%)	**Ozanimod 1 mg – Placebo (N = 227) n (%)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230) n (%)**
Patients dosed[a]	69 (100.0)	227 (100.0)	230 (100.0)
Patients who completed maintenance period[b]	45 (65.2)	124 (54.6)	184 (80.0)
Completed maintenance Week 42, enrolled into OLE study[b]	42 (60.9)	116 (51.1)	171 (74.3)
Completed maintenance Week 42, but discontinued study participation and did not enroll in OLE study[b]	3 (4.3)	8 (3.5)	13 (5.7)
Patients discontinued from maintenance period[b]	24 (34.8)	103 (45.4)	46 (20.0)
Primary reason for study withdrawal[b]			
Maintenance disease relapse	20 (29.0)	77 (33.9)	31 (13.5)
Enrolled in OLE study	2 (2.9)	3 (1.3)	3 (1.3)
Withdrawal by patient	1 (1.4)	13 (5.7)	7 (3.0)
Other	1 (1.4)	2 (0.9)	0
Adverse event	0	5 (2.2)	2 (0.9)
Lack of efficacy	0	3 (1.3)	2 (0.9)
Non-compliance with protocol/protocol deviation	0	0	1 (0.4)

Source: Study RPC01-3101 CSR Table 7 (p. 94)
Abbreviations: OLE = open-label extension
[a] Percentages are based on the number of patients in the enrolled population.
[b] Percentages are based on the number of patients dosed.

Protocol Violations/Deviations

A total of 21 (30.4%) patients who continued on placebo, 48 (21.1%) patients who were re-randomized from ozanimod 1 mg to placebo, and 58 (25.2%) patients who continued on ozanimod had at least 1 major protocol deviation during the maintenance period. The most common protocol deviations included “study procedure”, “treatment deviation”, and “informed consent.” In general, the protocol deviations varied in nature and were not considered to have any clinically significant impact on data integrity or patient safety.

Demographic Characteristics

The demographic characteristics of patients in the maintenance period are summarized by treatment group in Table 24. Among re-randomized patients, the majority of patients were male (54% and 51% in patients randomized to placebo and ozanimod, respectively) and most were white (89% in both treatment groups). The mean age was approximately 43 years and 42 years in patients re-randomized to placebo and ozanimod, respectively, and the mean weight was approximately 75 kg in both treatment groups. Among patients who continued in the placebo group, most patients were male (67%) and white (90%) and had mean age and weight values of 44 years and 76 kg, respectively. Demographic characteristics were generally similar among treatment groups.

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Table 24. Demographic Characteristics for Maintenance Period (ITT Population)

		Re-randomized Patients	
Demographic Characteristic	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Sex, n (%)			
Male	46 (66.7)	122 (53.7)	117 (50.9)
Female	23 (33.3)	105 (46.3)	113 (49.1)
Age (years)			
N	69	227	230
Mean (SD)	44.1 (14.7)	43.0 (13.7)	42.4 (13.5)
Median	43.0	43.0	41.0
Min, max	19, 74	18, 74	18, 72
Age category (years), n (%)			
18-29	13 (18.8)	51 (22.5)	51 (22.2)
30-39	19 (27.5)	48 (21.1)	58 (25.2)
40-49	11 (15.9)	49 (21.6)	48 (20.9)
50-59	12 (17.4)	48 (21.1)	39 (17.0)
60-69	11 (15.9)	28 (12.3)	30 (13.0)
70-75	3 (4.3)	3 (1.3)	4 (1.7)
< 65	63 (91.3)	215 (94.7)	217 (94.3)
≥ 65	6 (8.7)	12 (5.3)	13 (5.7)
Weight (kg)			
N	69	227	229
Mean (SD)	76.3 (17.0)	75.4 (17.8)	74.8 (19.4)
Median	75.0	73.8	72.6
Min, max	51, 126	41, 173	38, 156
Race, n (%)			
White	62 (89.9)	202 (89.0)	205 (89.1)
Black or African American	3 (4.3)	9 (4.0)	9 (3.9)
Asian	4 (5.8)	12 (5.3)	13 (5.7)
Other	4 (5.8)	12 (5.3)	13 (5.7)
Ethnicity, n (%)			
Hispanic or Latino	1 (1.4)	13 (5.7)	9 (3.9)
Not Hispanic or Latino	68 (98.6)	214 (94.3)	221 (96.1)
Region, n (%)			
North America	13 (18.8)	49 (21.6)	56 (24.3)
Eastern Europe	49 (71.0)	136 (59.9)	121 (52.6)
Western Europe	3 (4.3)	26 (11.5)	31 (13.5)
Asia Pacific	4 (5.8)	13 (5.7)	20 (8.7)
South America	0	1 (0.4)	1 (0.4)
South Africa	0	2 (0.9)	1 (0.4)

Source: Study RPC01-3101 CSR Table 13 (p. 100), Table 14.1.4.2B (p. 910)
Abbreviations: ITT = intent-to-treat; SD = standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline characteristics of patients in the maintenance period are summarized by treatment group in Table 25. Among re-randomized patients, the mean time since UC diagnosis was approximately 7 years and 8 years in the placebo and ozanimod groups, respectively. The mean duration of UC symptoms at the beginning of the maintenance period was approximately 8 years and 9 years in patients re-randomized to placebo and ozanimod, respectively. The mean

3-component Mayo score at baseline was 6.4 and 6.7 in patients re-randomized to placebo and ozanimod, respectively. Among patients who continued in the placebo group, the mean time since UC diagnosis and the mean duration of UC symptoms at the beginning of the maintenance period were approximately 8 years, and the mean 3-component Mayo score at baseline was 6.4. Baseline characteristics were generally similar across treatment groups.

Table 25. Baseline Characteristics for Maintenance Period (ITT Population)

		Re-randomized Patients	
Characteristic	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Age at UC symptom onset (years)			
N	69	227	229
Mean (SD)	35.8 (13.3)	35.1 (13.5)	33.4 (13.0)
Median	31.0	33.0	31.0
Min, max	15, 65	5, 73	8, 64
Age at UC diagnosis (years)			
N	69	227	230
Mean (SD)	36.5 (13.7)	36.0 (13.4)	34.4 (13.0)
Median	33.0	34.0	32.0
Min, max	15, 65	5, 73	8, 66
Years since UC symptom onset			
N	69	227	230
Mean (SD)	8.5 (8.4)	8.2 (7.8)	9.2 (7.9)
Median	6.04	5.62	7.67
Min, max	0.5, 39.7	0.0, 37.6	0.0, 49.1
Years since UC diagnosis			
N	69	227	230
Mean (SD)	7.8 (8.0)	7.2 (7.2)	8.4 (7.3)
Median	5.04	4.87	6.48
Min, max	0.3, 38.7	0.2, 37.6	0.2, 38.6
Baseline 3-component Mayo score			
N	69	227	230
Mean (SD)	6.4 (1.2)	6.4 (1.2)	6.7 (1.3)
Median	7.0	7.0	7.0
Min, max	4, 9	3, 9	4, 9

Source: Study RPC01-3101 CSR Table 15 (p. 104), Table 14.1.5.1B (p. 918)
Abbreviations: ITT = intent-to-treat; SD = standard deviation; UC = ulcerative colitis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was approximately 98% to 99% across treatment groups during the maintenance period.

The most commonly used (i.e., used by ≥ 15% of patients in any group) concomitant 5-ASA medications for patients in the maintenance period included mesalazine (56.5% of patients who remained on placebo, 70.9% of patients who were re-randomized to placebo, and 73.9% of patients who remained on ozanimod) and sulfasalazine (17.4% of patients who remained on

placebo, 15.0% of patients who were re-randomized to placebo, and 12.6% of patients who remained on ozanimod). Concomitant corticosteroids for systemic use were used in 26.1% of patients who remained on placebo, 26.4% of patients re-randomized to placebo, and 31.7% of patients re-randomized to ozanimod. In total, 29% of patients (133/457) who were re-randomized in the maintenance period used corticosteroids for systemic use. The most commonly used (i.e., used by ≥ 15% of patients in any group) corticosteroid for patients in the maintenance period was prednisone (15.9% of patients who remained on placebo, 14.1% of patients who were re-randomized to placebo, and 17.0% of patients who remained on ozanimod). Budesonide was used concomitantly by 1.4% of patients who remained on placebo, 6.2% of patients re-randomized to placebo, and 4.3% of patients re-randomized to ozanimod.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the proportion of patients in clinical remission at Week 52. Results for the primary efficacy endpoint based on the ITT population are displayed in Table 26. Among re-randomized patients, a statistically significantly higher percentage of patients in clinical remission at Week 52 were observed in the ozanimod group (37.0%) relative to the placebo group (18.5%) (p-value < 0.0001). The observed difference between the treatment groups in the percentage of patients in clinical remission was 18.6%, 95% CI: (10.8, 26.4). Among 69 patients who achieved clinical response on placebo at Week 10 and continuously treated with placebo in the maintenance period, 24.6% were in clinical remission at Week 52. These results were confirmed by the statistical reviewer.

Table 26. Primary Efficacy Endpoint Analysis for Maintenance Period: Proportion of Patients in Clinical Remission at Week 52[a] (ITT Population)

		Re-randomized Patients	
	Placebo (N = 69)	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Number of patients in clinical remission at Week 52, n (%)	17 (24.6)	42 (18.5)	85 (37.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.186 (0.108, 0.264)	
p-value for difference in proportions[c]		< 0.0001	

Source: Study RPC01-3101 CSR Table 19 (p. 112), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by remission status at Week 10 and corticosteroid use at Week 10.

An exploratory analysis of clinical remission by SFS is in Table 75 in Appendix Section 15.5.1, to ensure that results were not driven primarily by patients unable to achieve a SFS of 0.

Efficacy Results – Multiplicity-Controlled Secondary Endpoints

The maintenance period had the following multiplicity-controlled secondary endpoints at Week 52:

- the proportion of patients with clinical response
- the proportion of patients with endoscopic improvement
- the proportion of patients in clinical remission at Week 52 in the subset of patients in clinical remission at Week 10
- the proportion of patients with corticosteroid-free remission
- the proportion of patients with "mucosal healing" (endoscopic-histologic mucosal improvement)
- the proportion of patients with durable clinical remission

Among re-randomized patients, statistically significantly higher response proportions were observed in the ozanimod group relative to the placebo group for all the multiplicity-controlled secondary endpoints. These results were confirmed by the statistical reviewer and are summarized in Table 27, Table 28, Table 29, Table 30, Table 31, and Table 32.

Table 27. Clinical Response at Week 52[a] (ITT Population)

		Re-randomized Patients	
	Placebo (N = 69)	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Number of patients with a clinical response at Week 52, n (%)	27 (39.1)	93 (41.0)	138 (60.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.192 (0.104, 0.280)	
p-value for difference in proportions[c]		< 0.0001	

Source: Study RPC01-3101 CSR Table 23 (p. 116), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by remission status at Week 10 and corticosteroid use at Week 10.

Table 28. Endoscopic Improvement at Week 52[a] (ITT Population)

		Re-randomized Patients	
	Placebo (N = 69)	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Number of patients with endoscopic improvement at Week 52, n (%)	20 (29.0)	60 (26.4)	105 (45.7)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.194 (0.110, 0.277)	
p-value for difference in proportions[c]		< 0.0010	

Source: Study RPC01-3101 CSR Table 24 (p. 117), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by remission status at Week 10 and corticosteroid use at Week 10.

Table 29. Clinical Remission at Week 52 in the Subset of Patients in Clinical Remission at Week 10[a] (ITT Population)

		Re-randomized Patients	
	Placebo (N = 12)	**Ozanimod 1 mg – Placebo (N = 75)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 79)**
Number of patients in clinical remission at Week 52 in the subset of patients in clinical remission at Week 10, n (%)	5 (41.7)	22 (29.3)	41 (51.9)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.239 (0.091, 0.386)	
p-value for difference in proportions[c]		0.0025	

Source: Study RPC01-3101 CSR Table 25 (p. 118), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by corticosteroid use at Week 10.

Table 30. Corticosteroid-Free Remission at Week 52[a] (ITT Population)

		Re-randomized Patients	
	Placebo (N = 69)	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Number of patients in corticosteroid-free remission at Week 52, n (%)	17 (24.6)	38 (16.7)	73 (31.7)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.152 (0.078, 0.226)	
p-value for difference in proportions[c]		< 0.0010	

Source: Study RPC01-3101 CSR Table 26 (p. 119), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by remission status at Week 10 and corticosteroid use at Week 10.

An exploratory analysis of corticosteroid-free remission among patients who entered Study RPC01-3101 with concomitant steroid use is in Table 76 in Appendix Section 15.5.1. Among re-randomized patients, larger response proportions were observed in the ozanimod group compared to the placebo group (difference in proportions = 0.095, 95% CI: [0.012, 0.177]).

Table 31. "Mucosal Healing" (Endoscopic-Histologic Musocal Improvement) at Week 52[a] (ITT Population)

		Re-randomized Patients	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Number of patients with "mucosal healing" at Week 52, n (%)	7 (10.1)	32 (14.1)	68 (29.6)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.156 (0.082, 0.229)	
p-value for difference in proportions[c]		< 0.0010	

Source: Study RPC01-3101 CSR Table 27 (p. 119), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by remission status at Week 10 and corticosteroid use at Week 10.

Table 32. Durable Clinical Remission at Week 52[a] (ITT Population)

		Re-randomized Patients	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Number of patients in durable clinical remission at Week 52, n (%)	5 (7.2)	22 (9.7)	41 (17.8)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.082 (0.028, 0.136)	
p-value for difference in proportions[c]		0.0030	

Source: Study RPC01-3101 CSR Table 28 (p. 120), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.
[c] P-value was based on CMH Chi-squared test stratified by remission status at Week 10 and corticosteroid use at Week 10.

Efficacy Results – Exploratory Endpoints

Histologic Remission

Histologic remission[5] was a secondary endpoint not included in the statistical testing hierarchy. Among re-randomized patients at Week 52, a larger proportion of ozanimod-treated patients 77/230 (34%) achieved histologic remission compared to placebo 37/227 (16%)[6] (CSR Table 35). This endpoint was not recommended for inclusion in labeling; as noted above for induction period results, the clinical significance of achieving histologic remission without endoscopic remission is unclear, and uncertainty exists regarding whether the limited sampling approach taken in this program is adequate to fully characterize histologic activity within the whole colon.

[5] Defined as no neutrophils in the epithelial crypts or lamina propria, and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue (Geboes index score < 2.0).
[6] Evaluated in the ITT population, NRI imputation

Similar to the induction period, more patients achieved endoscopic improvement alone, as compared to the endsoscopic-histologic improvement, which is a more stringent endpoint. We further evaluated these data to explore how frequently histologic remission was documented in the absence of endoscopic remission (a situation that may be related to sampling error or limitations in the current evaluation of histologic findings in UC). Results of the Applicant's analysis are shown in Table 33. The percentages are reported out of the subset of patients who had both endoscopic and histologic data at Week 52. Missing data may limit the interpretation of these results, as only 50% of patients in the ozanimod-1mg placebo group and 70% of patients in the ozanimod 1mg-ozanimod 1mg group had both endoscopic and histologic data at Week 52. The reported percentage of patients who had histologic but not endoscopic remission (out of the population of patients who had data at both timepoints) was approximately 4-6% of re-randomized patients, similar to what was observed in the induction period analysis[7].

Table 33: Exploratory Analysis: Histologic Remission and Endoscopic Improvement at Week 52 (ITT Population, Patients With Both Mayo Endoscopy Subscore and Histologic Score Available)

Endpoint	Number (%) of Subjects		
		Re-randomized Subjects	
	Placebo N = 69	Ozanimod 1 mg – Placebo N = 227	Ozanimod 1 mg – Ozanimod 1 mg N = 230
Subjects having both endoscopy and Geboes score at Week 52[a]	38	115	162
Endoscopic improvement with histologic remission (mucosal healing)[b]	7 (18.4)	32 (27.8)	68 (42.0)
Endoscopic improvement without histologic remission[c]	12 (31.6)	26 (22.6)	31 (19.1)
Histologic remission without endoscopic improvement[d]	3 (7.9)	5 (4.3)	9 (5.6)

ITT = Intent-to-Treat.
[a] Denominator used to calculate percentages.
[b] Endoscopic improvement is defined as: endoscopy subscore of ≤ 1 point without friability. Histologic remission is defined as: Geboes index score < 2.0 (no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions ulcerations or granulation tissue).
Note: Subjects with missing endoscopy subscore or Geboes index score at Week 10 are excluded from analysis.
Source: RPC01-3101 CSR Table 14.2.7.2B; Appendix A, Table 14.2.11.2B and Table 14.2.11.3B.

Source: Applicant's response to Information Request, received 4/27/21
Analysis was conducted in the ITT population, using observed cases, limited to patients who had available data for both Mayo endoscopy subscore and Geboes index score at Week 52.

Sensitivity Analyses

Sensitivity analysis results for the primary endpoint in the maintenance period, where missing clinical remission subscore values were imputed using MI with the placebo group as a reference, are displayed in Table 79 in Appendix Section 15.5.2. Among re-randomized patients, the percentage of patients with missing efficacy data at Week 52 ranged from 32% (ozanimod

[7] Applicant's response to IR received 4/27/21. Percentages are calculated out of the subset of patients who had both endoscopic and histologic data at Week 52.

group) to 52% (placebo group). The sensitivity analysis results are consistent with the primary analysis results for clinical remission (Table 26).

Sensitivity analysis results for the clinical response endpoint in the maintenance period, where missing clinical response subscore values were imputed using MI with the placebo group as a reference, are displayed in Table 80 in Appendix Section 15.5.2. There was a higher percentage of responders in the ozanimod group compared to the placebo group. Thus, sensitivity analysis results are generally consistent with the primary analysis results for clinical response.

The Applicant's TPA results for the maintenance period were generally consistent with the clinical remission and clinical response endpoint results (Appendix Section 15.5.2). Missing data scenarios that did not result in a conclusion in favor of ozanimod were not plausible.

Thus, despite the observed proportions of missing data, sensitivity analyses for clinical remission and clinical response revealed robustness of the primary analysis results to alternative scenarios for missing data assumptions.

Data Quality and Integrity

In general, the data submitted by the Applicant to support the efficacy and safety of ozanimod for the proposed indication were acceptable.

Persistence of Effect

The controlled clinical trial provide evidence of durability of response by assessing clinical remission at Week 52 among patients who achieved clinical remission at Week 10 (as described above). The extension study, which was open-label, cannot provide further controlled evidence of durability of response. Among patients who were responders at Study RPC01-3102 entry (determined based on 3-component Mayo score using 7-day scoring algorithm), 69.6% were in clinical remission at Week 46, and at Week 94 and Week 142, 65.1% and 50.0%, respectively, were in clinical remission.

Additional Analyses Conducted on the Maintenance Period

Pre-specified subgroup analyses of interest for re-randomized patients in the maintenance period include analyses of the primary and key secondary endpoints by previous use of anti-TNF therapy and by concomitant corticosteroid use at baseline.

Larger response proportions were observed in the ozanimod group compared to the placebo group regardless of prior anti-TNF therapy use. Results from these analyses are displayed in Table 34.

Table 34. Maintenance Period Subgroup Analyses by Prior Anti-TNF Therapy[a] (ITT Population)

	Number of Re-randomized Patients, (%)		
Endpoint Subgroup	**Ozanimod 1 mg**	**Placebo**	**Difference in Proportions (Ozanimod-Placebo), 95% CI[b]**
Clinical remission			
No prior anti-TNF	63/154 (40.9)	35/158 (22.2)	0.185 (0.086, 0.283)
Prior anti-TNF	22/76 (28.9)	7/69 (10.1)	0.184 (0.062, 0.306)
Clinical response			
No prior anti-TNF	96/154 (62.3)	76/158 (48.1)	0.140 (0.033, 0.248)
Prior anti-TNF	42/76 (55.3)	17/69 (24.6)	0.304 (0.158, 0.451)
Endoscopic improvement			
No prior anti-TNF	77/154 (50.0)	48/158 (30.4)	0.194 (0.089, 0.298)
Prior anti-TNF	28/76 (36.8)	12/69 (17.4)	0.189 (0.053, 0.324)
Clinical remission at Week 52 in the subset of patients in clinical remission at Week 10			
No prior anti-TNF	37/64 (57.8)	19/58 (32.8)	0.250 (0.081, 0.419)
Prior anti-TNF	4/15 (26.7)	3/17 (17.6)	0.110 (-0.151, 0.370)
Corticosteroid-free clinical remission			
No prior anti-TNF	55/154 (35.7)	31/158 (19.6)	0.161 (0.068, 0.255)
Prior anti-TNF	18/76 (23.7)	7/69 (10.1)	0.129 (0.015, 0.244)
"Mucosal healing"			
No prior anti-TNF	51/154 (33.1)	28/158 (17.7)	0.153 (0.058, 0.247)
Prior anti-TNF	17/76 (22.4)	4/69 (5.8)	0.162 (0.055, 0.270)
Durable clinical remission			
No prior anti-TNF	37/154 (24.0)	19/158 (12.0)	0.115 (0.044, 0.187)
Prior anti-TNF	4/76 (5.3)	3/69 (4.3)	0.005 (-0.059, 0.069)

Source: Study RPC01-3101 CSR Table 38 (p. 131), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat; TNF = tumor necrosis factor
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Larger response proportions were observed in the ozanimod group compared to the placebo group regardless of concomitant corticosteroid use at baseline. Results from these analyses are displayed in Table 35.

Table 35. Maintenance Period Subgroup Analyses by Concomitant Corticosteroid Use at Baseline[a] (ITT Population)

	Number of Re-randomized Patients, (%)		
Endpoint Subgroup	**Ozanimod 1 mg**	**Placebo**	**Difference in Proportions (Ozanimod-Placebo), 95% CI[b]**
Clinical remission			
No CS use at BL	68/162 (42.0)	35/162 (21.6)	0.204 (0.107, 0.301)
CS use at BL	17/68 (25.0)	7/65 (10.8)	0.142 (0.016, 0.267)
Clinical response			
No CS use at BL	105/162 (64.8)	77/162 (47.5)	0.173 (0.067, 0.279)
CS use at BL	33/68 (48.5)	16/65 (24.6)	0.238 (0.083, 0.393)
Endoscopic improvement			
No CS use at BL	85/162 (52.5)	49/162 (30.3)	0.222 (0.119, 0.326)
CS use at BL	20/68 (29.4)	11/65 (16.9)	0.124 (-0.015, 0.263)
Clinical remission at Week 52 in the subset of patients in clinical remission at Week 10			
No CS use at BL	35/64 (54.7)	19/60 (31.7)	0.234 (0.067, 0.401)
CS use at BL	6/15 (40.0)	3/15 (20.0)	0.257 (-0.051, 0.566)
Corticosteroid-free clinical remission			
No CS use at BL	66/162 (40.7)	35/162 (21.6)	0.191 (0.094, 0.288)
CS use at BL	7/68 (10.3)	3/65 (4.6)	0.057 (-0.032, 0.145)
“Mucosal healing”			
No CS use at BL	55/162 (34.0)	26/162 (16.1)	0.179 (0.088, 0.270)
CS use at BL	13/68 (19.1)	6/65 (9.2)	0.099 (-0.019, 0.216)
Durable clinical remission			
No CS use at BL	35/162 (21.6)	19/162 (11.7)	0.099 (0.030, 0.168)
CS use at BL	6/68 (8.8)	3/65 (4.6)	0.041 (-0.038, 0.120)

Source: Study RPC01-3101 Table 14.2.1.9.1B (p. 1046), Table 14.2.2.9.1B (p. 1073), Table 14.2.3.3B (p. 1092), Table 14.2.4.3B (p. 1111), Table 14.2.5.3B (p. 1129), Table 14.2.6.3B (p. 1148), Table 14.2.7.3B (p. 1167), statistical reviewer’s analysis
Abbreviations: BL = baseline; CI = confidence interval; CS = corticosteroid; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 85, Table 86, Table 87, and Table 88 in Appendix Section 15.5.3 contain subgroup analyses of the maintenance period primary endpoint by sex, age, race, and region. The subgroup analyses are limited by small patient counts, and results should be interpreted with caution. In general, the subgroup analysis results were consistent with the primary endpoint results in Table 26.

8.1.4. Conclusions on Efficacy

The efficacy of ozanimod for the treatment of moderately to severely active UC in adult patients was demonstrated in Study 3101. Study 3101 comprised both an induction period and a maintenance period; evaluation of efficacy data in both periods showed clinically meaningful, positive results with very small p-values for the primary endpoint and all multiplicity-controlled secondary endpoints. Consistent results were observed in subgroup analyses among patients with prior anti-TNF therapy use and among patients with concomitant corticosteroid use. The submitted evidence supports the conclusion that ozanimod is effective in the treatment of moderately to severely active UC in adult patients.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of ozanimod for UC focuses on data from the controlled trials (RPC01-202, RPC01-3101) and is supplemented by additional data from the open-label extension trial RPC01-3102.

The Applicant defined the integrated safety analyses cohorts and subgroups as displayed in Table 36.

Table 36. Definitions of Safety Data Pools Utilized in Integrated Safety Analyses

Data Pool	Studies in Safety Data Pools
F (Controlled UC Studies)	Induction Period analyses: RPC01-202 Induction Period (placebo and ozanimod 1 mg) and RPC01-3101 Induction Period (placebo and ozanimod 1 mg of Cohort 1) Maintenance Period analyses: RPC01-3101 Maintenance Period
G (Controlled and Uncontrolled UC Studies)	RPC01-202, RPC01-3101, RPC01-3102
D (All Controlled and Uncontrolled UC, (b) (4), and MS Studies)[a]	UC: RPC01-202, RPC01-3101, RPC01-3102 (b) (4) MS: RPC01-201A, RPC01-201B, RPC01-301, RPC01-3001, RPC01-1001

(b) (4); MS = multiple sclerosis; UC = ulcerative colitis.
[a] Data from ongoing blinded studies were not included in the safety data analysis pools.
Source: Sponsor's submission, ISS SAP Table 3 (p. 19)

Within our safety review, because the phase 2 and phase 3 induction period study designs and population enrolled were sufficiently similar, the two studies were pooled (referred to within the review as "Pool F Induction") to better assess the adverse event profile within the induction

period. Study 3101 cohort 2 patients were not pooled, given that they were treated open-label, but results are presented side-by-side with the study's controlled induction period data. The maintenance study results were evaluated separately as the study re-randomized patients who initially responded to 1 mg ozanimod only (patients achieving clinical response to blinded placebo in induction continued to receive blinded placebo in maintenance). Results during the maintenance period for patients who responded to placebo in induction and continued on blinded placebo are presented side-by-side.

Exposure-adjusted analyses for key adverse events of interest were conducted within Pool G (all UC patients), focusing on patients who received placebo or 1 mg of ozanimod. This approach was utilized to summarize and quantify the risk associated with adverse events of interest which may have occurred during the open-label extension period, as the data from RPC01-3102 provided additional long-term follow-up and longer exposure to active treatment than was observed within the phase 3 study RPC01-3101 alone.

The clinical reviewer re-coded some adverse event terms using logical groupings in order to better ascertain the safety profile of ozanimod. The listing of recoded terms appears in the Appendix (Table 70 and Table 71). Statistical methodology for integrated safety analyses is in Appendix Section 15.6.

8.2.2. Review of the Safety Database

Overall, there appears to be adequate exposure to ozanimod in the UC program for the evaluation of common AEs and safety events with short latency. However, the evaluation of rare or infrequent AEs of special interest and/or those that may occur after a long duration of ozanimod treatment and are of longer latency is limited. This limitation is reasonable given feasibility constraints, and further surveillance of known and potential serious adverse events will be conducted via enhanced pharmacovigilance.

8.2.2.1. Overall Exposure

In the UC program (Pool G all UC studies), 868 patients were exposed to ozanimod 1 mg for at least 6 months, 716 patients were exposed to ozanimod 1 mg for at least 12 months, and 322 patients were exposed to ozanimod 1 mg for at least 24 months. The exposure of UC patients to the to be marketed (1mg) dose exceeds the minimum set forth in ICH E1 and is generally consistent with the size/scope of safety database expected in UC development programs.

Table 37 below presents an overview of the number of patients and total exposure for ozanimod 1 mg and placebo treatment groups across the safety analysis pools in this submission.

Table 37. Ozanimod Exposure by Analysis Pool

Safety Pool Treatment Group	N	Mean (SD) Duration of Exposure	Total Patient-years of Exposure
Pool F induction period, weeks			
Placebo	281	10.0 (2.1)	53.9
Ozanimod 1 mg	496	10.3 (1.8)	97.5
RPC01-3101 cohort 1 induction period, weeks			
Placebo	216	10.3 (2.2)	NC
Ozanimod 1 mg	429	10.4 (1.7)	NC
RPC01-3101 maintenance period, weeks			
Placebo	69	33.4 (14.2)	NC
Ozanimod 1 mg - placebo	227	30.8 (14.8)	134.2
Ozanimod 1 mg - ozanimod 1 mg	230	37.6 (11.3)	165.5
Pool G, months			
Placebo	508	5.8 (3.9)	242.8
Ozanimod 1 mg	1158	19.3 (17.3)	1841.7
Pool D, months			
Placebo	596	5.8 (3.6)	284.0
Ozanimod 1 mg	4057	34.2 (20.3)	11610.3

Source: Adapted from 2.7.4 Summary of Clinical Safety, Table 4, p. 36
Abbreviations: NC = not calculated, SD = standard deviation

Pool F included 777 unique patients who were randomized to treatment with either placebo or ozanimod 1 mg during the induction periods of RPC01-202 and RPC01-3101 (cohort 1). Treatment exposure was similar for placebo and ozanimod 1 mg, and the mean duration of exposure was approximately 10 weeks for both treatment groups. A greater percentage of patients who received ozanimod 1 mg compared with placebo had at least 10 weeks of exposure (73.8% versus 64.1%, respectively) due to slightly higher completion rates for patients who were treated with ozanimod 1 mg compared to placebo.

In the maintenance period of Study RPC01-3101, as expected, the mean duration of exposure was longer for the 230 patients in the ozanimod 1 mg – ozanimod 1 mg treatment group compared with 227 patients in the ozanimod 1 mg – placebo treatment group (approximately 38 weeks versus 31 weeks, respectively) due to a greater percentage of patients in the ozanimod 1 mg – placebo treatment group discontinuing due to disease relapse. Treatment exposure for the 69 patients who received placebo during both RPC01-3101 induction and maintenance periods was approximately 33 weeks, although this group of patients was not included in the Pool F maintenance analyses as previously noted.

8.2.2.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The datasets were adequately organized and complete to permit review.

Categorization of Adverse Events

The severity of the AE was characterized as mild, moderate, or severe. Mild events were defined as transient, not interfering with the patient's daily activities. Moderate events were defined as those that introduced a low level of inconvenience or concern to the patient and interfered with daily activities. Severe events were defined as incapacitating and interrupting the patient's usual daily activity. Serious adverse events (SAEs) were appropriately defined consistent with 21 CFR 32.32(a) and reported as required. All SAEs that occurred within 90 days of the last dose of treatment with the investigational drug, whether or not considered related to the investigational drug, also were reported. Any SAE that was ongoing when the patient completed the trial or discontinued from the trial was followed by the Investigator until the event had resolved, stabilized, or returned to baseline status.

The causal relationship between the investigational drug and the AE was characterized as unrelated, unlikely, possible, probable, or related according to definitions outlined in the study protocol. Adverse events of special interest were those that could be a consequence of S1P1 modulation; these AEs were closely monitored during the trial and included bradycardia, heart conduction abnormalities (2nd degree and higher AV block), macular edema, malignancy, serious or opportunistic infection, pulmonary effects, and hepatic effects. Within the category of infections, TB, serious bacterial infections, systemic fungal infections, viral infections such as herpes infections (including herpes zoster and disseminated herpes simplex) and protozoan infections were specifically considered AEs of special interest. An independent DSMB for the trial performed quarterly safety reviews that started after the first patient was dosed.

Safety Assessments
Patient visits occurred at screening, Induction Week 0 (Visit I1), Induction Week 5 (Visit I2), Induction Week 10 (Visit I3), Maintenance Week 0 (Visit M1), Maintenance Week 8 (Visit M2), Maintenance Week 18 (Visit M3), Maintenance Week 30 (Visit M4), Maintenance Week 42 (Visit M5, End of Treatment), Last dose + 30 to 60 days, and Last dose + 90 days ± 10 days. Patients who discontinued the trial early had a visit at the time of Early Termination. Patients who relapsed had a Relapse Visit (as indicated) for further assessment and characterization. The detailed schedule of assessments is located in the Appendix, Table 69. Select details of the safety assessment pertinent to the AESIs are specified below:

Cardiovascular monitoring: A resting electrocardiogram (ECG) was performed to confirm patient eligibility before randomization. Electrocardiograms were performed before and 6 hours after the first dose of investigational drug administration for all patients on Induction Day 1 while the patient was in clinic. The 6 hour postdose ECG was evaluated by the treating physician, with input as needed from a local cardiologist or a central reader to confirm if extended monitoring was required. Additional ECG monitoring was performed on Days 5 and 8 if cardiac issues were identified on the prior day of dose escalation.

Additional extended monitoring was instituted (to be continued until resolution) if any of the following occurred: 1) The pulse 6 hours postdose was < 45 bpm, 2) The pulse 6 hours postdose was at the lowest value postdose and lower than any other timepoint (suggesting that the maximum PD effect on the heart had not yet occurred), unless this value was greater than or equal to baseline, 3) The ECG 6 hours postdose showed new onset second degree or higher AV block, or 4) The ECG 6 hours postdose showed a prolonged QTcF interval (> 450 msec for males, > 470 msec for females).

If postdose symptomatic bradycardia occurred, continuous ECG monitoring was initiated with observation until the symptoms resolved. If a patient required pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility was instituted, and the first dose monitoring strategy was repeated the following day (Day 2). The first dose monitoring strategy was also repeated at Day 5 or at Day 8 if any cardiac safety issues were observed on the previous Day of dose escalation. Patients were given written instruction on when to return to the clinic and a 24-hour contact phone number to call in the event of any new or warranted symptoms (e.g., chest pain, dizziness, palpitations, syncope, nausea, vomiting).

Laboratory testing: Routine blood testing including hematology, chemistries and pregnancy testing (if appropriate) occurred per the schedule of assessments.

Cut-off values requiring re-testing, or treatment interruption, were outlined for neutrophils and lymphocytes as follows. If 1) Absolute neutrophil count < 1000 cells/µL or 2) Absolute lymphocyte count < 200 cells/µL, then the labs were repeated within 7 days. If the absolute neutrophil count was confirmed below the 1000 cells/µL limit, then the patient was closely monitored for increased infection risk. If the absolute lymphocyte count was confirmed below the 200 cells/µL limit, the treatment was temporarily discontinued and Medical Monitor consulted. Labs needed to be repeated weekly until the absolute lymphocyte count > 500 cells/µL. Treatment was reinitiated at the Investigator's discretion once the absolute lymphocyte count had returned to > 500 cells/µL. Patients who had a confirmed absolute lymphocyte count below the 200 cells/µL limit and permanently discontinued from participation in the study continued to get labs every 14 days (± 3 days) after the day of Early Termination until the absolute lymphocyte count was above the lower limit of normal.

Follow-up for elevations in liver enzymes (ALT or/and AST) ≥3 times the upper limit of normal (ULN) were conducted as recommended in the Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation[8].

Macular edema: Optical coherence tomography was performed at screening, Visit I3, Visit M5, day of Early Termination (if applicable), and Last dose + 90 days ± 10 days. If there was a

[8] https://www.fda.gov/media/116737/download

suspicion of new onset macular edema, then general retinal exams, including eye history, visual acuity, and dilated ophthalmoscopy were obtained. The investigational drug was discontinued in any patient who had a confirmed diagnosis of macular edema that was of new onset since Baseline. Patients with a diagnosis of macular edema were followed up monthly and more frequently if needed based on the ophthalmologist's judgment.

Pulmonary monitoring: Pulmonary function tests including FEV1 and FVC measurements were performed per the schedule of assessments. In addition, DLCO measurements were performed where locally available. If the pulmonary function test results were not within normal range, the results were verified by a pulmonologist, and potential confounding factors identified. If the patient had a decline in PFT values, the patient was evaluated by a pulmonologist. If PFT values (FEV1 and/or FVC) declined below 50% of the predicted values, treatment was discontinued. If the patient was discontinued due to a respiratory AE, the Applicant ensured that the patient has adequate evaluations as clinically indicated by a pulmonologist (such as PFTs, chest X-ray or high resolution computed tomography, based on findings of the other exams) at the time of the AE. For patients with pulmonary nodules, lung biopsy was considered (Cryptococcus pneumonia and pulmonary TB have been reported with fingolimod). Further evaluations were conducted until resolution was confirmed or no further improvement was expected by the Investigator (based on a follow-up period of not less than 3 months).

Safety monitoring after discontinuation: For patients who discontinued the trial for any reason, every attempt was made to have the patient return to the study site in order to complete the assessments for the 30-day and 90-day Safety Follow-up Visits in addition to the End of Treatment/Early Termination Visit. The timing of the 90-day visit was based on the estimated time needed to clear the major active metabolite of RPC1063 (i.e., 5 half-lives of CC112273 and CC1084037, and accounting for variation of half-live duration in a human population).

8.3. Safety Results

8.3.1. Deaths

A total of three deaths occurred in UC patients, as follows:

The first death, patient (b) (6) occurred during the induction period of Study RPC01-3101. This patient was in cohort 2 and was a 64-year-old male with a medical history of ischemic cardiomyopathy and prolonged tobacco use, who received ozanimod 1 mg for approximately 6 weeks and terminated the study early due to severe fatigue and overall poor health. The AE of moderate-severe anemia (hemoglobin of 7.3 g/dL) recorded at the visit was attributed to the temporary worsening of UC. On Study Day (b) (6) the patient was hospitalized for acute respiratory distress syndrome due to viral pneumonia with difficulty breathing. The patient died on Study Day (b) (6) The event of acute respiratory distress syndrome was considered to be unrelated to study drug by the investigator or Applicant. The death occurred during a regional outbreak of influenza. Given that ozanimod increases the risk of serious infection and related complications, it cannot be concluded that treatment with ozanimod did not contribute to this outcome.

The second death occurred during the Study RPC01-3102 OLE period. Patient (b) (6) (RPC01-3101 ozanimod 1 mg/ozanimod 1 mg treatment group), a 57-year-old male with a PMH of myocarditis and hypertension, had an unwitnessed sudden death on Day (b) (6) of the OLE study. Concomitant medications during the OLE included lisinopril, carvedilol, mesalamine, and pregabalin. The patient's last recorded BP on Day (b) (6) of the OLE was within normal range (116/74 mm Hg) and similar to the baseline value (117/68 mm Hg). The ECG on Day (b) (6) of the OLE showed sinus rhythm, atrial premature complexes, and intraventricular conduction delay (nonspecific); normal T-wave morphology was noted. On Day (b) (6) of the OLE, an echocardiogram revealed a mildly dilated left ventricle, mildly reduced global systolic function, ejection fraction 49%, impaired relaxation, mildly dilated left atrium, borderline enlarged right atrium, mitral valve prolapse with mild mitral regurgitation, and trace tricuspid regurgitation. On Day (b) (6) of the OLE, it was reported that the patient had been found lying in the street, unresponsive, and was pronounced deceased upon arrival at the medical facility. The cause of death was unknown. No autopsy was performed. The patient had been treated with ozanimod for a total of approximately 19 months in the parent and extension studies. The Applicant considered the relationship of the event to study drug unrelated. Ozanimod is known to be associated with cardiovascular adverse events, including arrythmias. However, given the patient's underlying medical history, as well as lack of autopsy or other details surrounding his demise, a relationship to study drug cannot be determined.

The third death occurred during the OLE period of Study RP01-202. Patient (b) (6) a 43-year-old female patient with UC who received ozanimod 0.5 mg for approximately 32 weeks in Study RPC01-202 and ozanimod 1 mg for approximately 863 days in RP01-202 OLP, discontinued study drug due to adenocarcinoma. The patient died in the hospital from mucinous adenocarcinoma (of gastric, pancreatic, bilial, or endometrial [intestinal type] origin) on OLE Study Day (b) (6) The event was considered to be possibly related to study drug by the investigator but was considered unrelated to study drug by the Applicant. However, as all immunosuppressive drugs have the potential to increase the risks of malignancies, a relationship to study drug cannot be excluded.

8.3.2. Serious Adverse Events (SAEs)

Table 38 below shows SAEs by treatment arm in the induction period of Study 3101. The rate of SAEs was low, with 17/429 (4%) of patients treated with ozanimod experiencing at least one SAE, as compared to 7/216 (3%) on placebo.

Table 38. Serious Adverse Events, Induction Period, Study RPC01-3101

	Cohort 1		Cohort 2
System Organ Class Preferred Term, n (%)	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Patients with ≥ 1 serious TEAE	17 (4.0)	7 (3.2)	23 (6.3)
Gastrointestinal disorders	7 (1.6)	5 (2.3)	11 (3.0)
Ulcerative colitis	6 (1.4)	4 (1.9)	9 (2.5)
Gastritis	1 (0.2)	0	0
Diarrhea	0	1 (0.5)	0
Melena	0	0	1 (0.3)
Hemorrhoids	0	0	1 (0.3)
Blood and lymphatic system disorders	4 (0.9)	0	1 (0.3)
Anemia	4 (0.9)	0	1 (0.3)
Infections and infestations	4 (0.9)	1 (0.5)	7 (1.9)
Appendicitis	1 (0.2)	0	2 (0.5)
Gastroenteritis	0	0	2 (0.5)
Bronchitis	0	1 (0.5)	0
Urinary tract infection	0	0	1 (0.3)
Pyelonephritis	1 (0.2)	0	0
Vestibular neuronitis	1 (0.2)	0	0
Upper respiratory tract infection	1 (0.2)	0	0
Influenza	0	0	1 (0.3)
Respiratory tract infection (RSV)	0	0	1 (0.3)
Injury, poisoning	1 (0.2)	0	0
Accidental overdose	1 (0.2)	0	0
Musculoskeletal and connective tissue disorders	1 (0.2)	0	0
Arthralgia	1 (0.2)	0	0
Myalgia	1 (0.2)	0	0
Eye disorders	1 (0.2)	0	0
Photophobia	1 (0.2)	0	0
Nervous system	2 (0.5)	0	0
Headache	1 (0.2)	0	0
Ischemic stroke	1 (0.2)	0	0
Renal and urinary disorders	1 (0.2)	0	0
Nephrolithiasis	1 (0.2)	0	0
General disorders and administration site conditions	0	1 (0.5)	0
Pyrexia	0	1 (0.5)	0

Source: Reviewer's table, created based on ADAE dataset; analysis for both SOC and individual PT are patient level (each patient is counted once regardless of the number of reported events).
Abbreviations: TEAE = treatment-emergent adverse event

The most common SAE was worsened UC. The next most common SAE reported in induction was anemia (occurring in 4 (0.9%) of ozanimod-treated patients and no placebo-treated patients). However, the cases of anemia during induction were examined by the clinical reviewer and were determined to be unlikely related to ozanimod exposure, as they occurred in the setting of poorly controlled UC (assessed by CRP/fecal calprotectin levels) or noncompliance (in one instance). Further, when assessing all cases of anemia (not limited to SAEs, the rate of anemia was greater in placebo-treated patients than in ozanimod-treated patients in both Pool

F induction analysis, and Study 3101 induction period alone. Results of SAE analyses in Pool F induction were similar (details not shown); the only SAEs occurring in 2 or more patients were UC and anemia.

In the maintenance period, more patients re-randomized to placebo experienced one or more SAEs than patients who received ozanimod (8% versus 6%, respectively). Results are shown in Table 39.

Appears this way in original

Table 39. Serious Adverse Events, Maintenance Period, Study RPC01-3101

		Re-randomized Patients	
System Organ Class Preferred Term, n (%)	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Patients with ≥ 1 serious TEAE	4 (5.8)	18 (7.9)	12 (5.2)
Gastrointestinal disorders	2 (2.9)	10 (4.4)	2 (0.9)
Ulcerative colitis/proctitis	1 (1.4)	9 (4.0)	2 (0.9)
Vomiting	0	1 (0.4)	0
Infections and infestations	1 (1.4)	4 (1.8)	2 (0.9)
Appendicitis	0	3 (1.3)	0
Gastroenteritis	1 (1.4)	0	1 (0.4)
Clostridium difficile infection	0	0	1 (0.4)
Yersinia	0	1 (0.4)	0
Measles	0	1 (0.4)	0
Metabolism and nutrition disorders	1 (1.4)	0	0
Dehydration	1 (1.4)	0	0
Blood and lymphatic system disorders	0	0	1 (0.4)
Anemia	0	0	1 (0.4)
Immune system disorders	0	0	1 (0.4)
Food allergy	0	0	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (0.9)	1 (0.4)
Rectal adenocarcinoma	0	0	1 (0.4)
Breast cancer	0	1 (0.4)	0
Adenocarcinoma of colon	0	1 (0.4)	0
Cardiac disorders	0	0	1 (0.4)
Pericarditis	0	0	1 (0.4)
Eye disorders	0	0	1 (0.4)
Cataract	0	0	1 (0.4)
Vascular disorders	0	1 (0.4)	1 (0.4)
Hypertension	0	1 (0.4)	1 (0.4)
Nervous system disorders	0	0	1 (0.4)
Syncope	0	0	1 (0.4)
Injury, poisoning and procedural complications	0	0	1 (0.4)
Toxicity to various agents	0	0	1 (0.4)
Hepatobiliary disorders	0	2 (0.9)	0
Cholelithiasis	0	1 (0.4)	0
Acute cholecystitis	0	1 (0.4)	0
Renal and urinary disorders	1 (1.4)	1 (0.4)	0
Urethral stenosis	0	1 (0.4)	0
Urinary calculus	1 (1.4)	0	0

Source: Reviewer's table, created based on ADAE dataset
Abbreviations: TEAE = treatment-emergent adverse event

During the maintenance period, patients re-randomized to placebo were more likely to experience an UC flare and appendicitis. Otherwise, SAEs in ozanimod-treated patients were less and were not clustered in any particular system organ class (SOC).

8.3.3. Dropouts and/or Discontinuations Due to Adverse Events

As previously discussed, the majority of patients completed the induction period (94% on ozanimod and 90% on placebo). AEs leading to discontinuation were uncommon, occurring in approximately 3% of patients in each arm (see Table 40 below).

Table 40. Dropouts and/or Discontinuations Due to Adverse Events, Induction Period, Study 3101

	Cohort 1		Cohort 2
System Organ Class Preferred Term, n (%)	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Any TEAE leading to study drug discontinuation	14 (3.3)	7 (3.2)	14 (3.8)
Eye disorders	3 (0.7)	0	1 (0.3)
Macular edema	1 (0.2)	0	0
Retinal vasculitis	1 (0.2)	0	0
Visual impairment	1 (0.2)	0	0
Eye inflammation	0	0	1 (0.3)
Gastrointestinal disorders	3 (0.7)	6 (2.8)	6 (1.6)
Ulcerative colitis	3 (0.7)	4 (1.9)	4 (1.1)
Abdominal pain	0	0	1 (0.3)
Diarrhea	0	1 (0.5)	0
Gastric ulcer	0	1 (0.5)	0
Melena	0	0	1 (0.3)
Blood and lymphatic system disorders	2 (0.5)	0	1 (0.3)
Anemia	1 (0.2)	0	1 (0.3)
Leukopenia	1 (0.2)	0	0
Investigations	2 (0.5)	0	1 (0.3)
Liver function test increased	2 (0.5)	0	1 (0.3)
Nervous system disorders	2 (0.5)	0	0
Headache	2 (0.5)	0	0
General disorders and administration site conditions	1 (0.2)	0	0
Chest discomfort	1 (0.2)	0	0
Respiratory, thoracic, and mediastinal disorders	1 (0.2)	0	0
Dyspnea	1 (0.2)	0	0
Cardiac disorders	0	0	3 (0.8)
Angina pectoris	0	0	1 (0.3)
Bradycardia	0	0	2 (0.5)
Infections and infestations	0	0	1 (0.3)
Urinary tract infection	0	0	1 (0.3)
Psychiatric disorders	0	1 (0.5)	0
Aggression	0	1 (0.5)	0
Skin and subcutaneous tissue disorders	0	0	1 (0.3)
Rash	0	0	1 (0.3)

Source: Reviewer's table, created based on ADAE dataset
Abbreviations: TEAE = treatment-emergent adverse event

During the induction period, more patients on placebo withdrew from the study after experiencing a UC flare. Overall, discontinuations due to AEs in ozanimod-treated patients

occurred at a similar rate as in placebo-treated patients; those that occurred were generally consistent with the known safety risks (including ophthalmologic concerns, leukopenia, and increased liver function tests).

Table 41 below shows the AEs leading to discontinuation in the maintenance period.

Table 41. Dropouts and/or Discontinuations Due to Adverse Events, Maintenance Period, Study 3101

		Re-randomized Patients	
System Organ Class Preferred Term, n (%)	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Any TEAE leading to study drug discontinuation	0	6 (2.6)	3 (1.3)
Gastrointestinal disorders	0	4 (1.8)	0
Ulcerative colitis	0	4 (1.8)	0
Eye disorders	0	0	1 (0.4)
Macular edema	0	0	1 (0.4)
Investigations	0	0	1 (0.4)
Liver function test increased	0	0	1 (0.4)
Reproductive system and breast disorders	0	0	1 (0.4)
Ovarian cyst	0	0	1 (0.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	1 (0.4)	0
Breast cancer	0	1 (0.4)	0
Nervous system disorders	0	1 (0.4)	0
Seizure	0	1 (0.4)	0

Source: Reviewer's table, created based on ADAE dataset
Abbreviations: TEAE = treatment-emergent adverse event

During the maintenance period, more patients re-randomized to placebo withdrew from the study after experiencing a TEAE; the most commonly reported was UC. AEs leading to discontinuation in the ozanimod arm occurred less frequently in those re-randomized to active drug than placebo, and were not associated with any one specific SOC more than others.

8.3.4. Adverse Events of Severe Intensity

Table 42 shows the adverse event rates that were considered as severe in intensity that occurred during the induction period.

Table 42. Adverse Events of Severe Intensity, Induction Period, Study 3101

	Cohort 1		Cohort 2
System Organ Class Preferred Term, n (%)	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Any severe TEAE	14 (3.3)	4 (1.9)	14 (3.8)
Gastrointestinal disorders	6 (1.4)	4 (1.9)	6 (1.6)
Ulcerative colitis	3 (0.7)	2 (0.9)	6 (1.6)
Flatulence	1 (0.2)	0	0
Gastritis	1 (0.2)	0	0
Nausea	1 (0.2)	0	0
Abdominal pain	0	1 (0.5)	0
Colon dysplasia	0	1 (0.5)	0
Nervous system disorders	4 (0.9)	0	0
Headache	3 (0.7)	0	0
Ischaemic stroke	1 (0.2)	0	0
Blood and lymphatic system disorders	3 (0.7)	0	0
Anaemia	3 (0.7)	0	0
Eye disorders	1 (0.2)	0	0
Photophobia	1 (0.2)	0	0
Infections and infestations	1 (0.2)	0	4 (1.1)
Appendicitis	1 (0.2)	0	2 (0.5)
Gastroenteritis	0	0	1 (0.3)
Pneumonia influenza	0	0	1 (0.3)
Investigations	1 (0.2)	0	1 (0.3)
Liver function test increased	1 (0.2)	0	0
Respiratory syncytial virus test positive	0	0	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.2)	0	0
Arthralgia	1 (0.2)	0	0
Myalgia	1 (0.2)	0	0
Renal and urinary disorders	1 (0.2)	0	0
Nephrolithiasis	1 (0.2)	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0	1 (0.3)
Asthma	1 (0.2)	0	0
Acute respiratory distress syndrome	0	0	1 (0.3)
Cardiac disorders	0	0	2 (0.5)
Angina pectoris	0	0	1 (0.3)
Coronary artery stenosis	0	0	1 (0.3)
General disorders and administration site conditions	0	0	1 (0.3)
Pyrexia	0	0	1 (0.3)

Source: Reviewer's table, created based on ADAE dataset
Abbreviations: TEAE = treatment-emergent adverse event

During the induction period, more patients on ozanimod experienced a severe intensity TEAE when compared to placebo. These included UC, headache, and anemia. Severe intensity AEs in the maintenance period are summarized in Table 43.

Table 43. Adverse Events of Severe Intensity, Maintenance Period, Study 3101

		Re-randomized Patients	
System Organ Class Preferred Term, n (%)	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Any severe TEAE	1 (1.4)	9 (4.0)	9 (3.9)
Infections and infestations	0	3 (1.3)	2 (0.9)
Clostridium difficile infection	0	0	1 (0.4)
Gastroenteritis norovirus	0	0	1 (0.4)
Appendicitis	0	3 (1.3)	0
Blood and lymphatic system disorders	0	0	1 (0.4)
Anemia	0	0	1 (0.4)
Gastrointestinal disorders	1 (1.4)	4 (1.8)	1 (0.4)
Ulcerative colitis/proctitis	0	4 (1.8)	1 (0.4)
Diarroea	1 (1.4)	0	0
Enterocolitis	1 (1.4)	0	0
General disorders and administration site conditions	0	0	1 (0.4)
Edema peripheral	0	0	1 (0.4)
Injury, poisoning and procedural complications	0	0	1 (0.4)
Toxicity to various agents	0	0	1 (0.4)
Musculoskeletal and connective tissue disorders	0	0	1 (0.4)
Pain	0	0	1 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	2 (0.9)	1 (0.4)
Rectal adenocarcinoma	0	0	1 (0.4)
Adenocarcinoma of colon	0	1 (0.4)	0
Breast cancer	0	1 (0.4)	0
Nervous system disorders	0	0	1 (0.4)
Syncope	0	0	1 (0.4)
Reproductive system and breast disorders	0	0	1 (0.4)
Ovarian cyst	0	0	1 (0.4)
Renal and urinary disorders	0	1 (0.4)	0
Urethral stenosis	0	1 (0.4)	0
Urinary retention	0	1 (0.4)	0

Source: Reviewer's table, created based on ADAE dataset
Abbreviations: TEAE = treatment-emergent adverse event

During the maintenance period, more patients re-randomized to placebo experienced appendicitis and UC flare compared to those who were re-randomized to continue ozanimod. Overall the rates of severe intensity AEs were comparable between ozanimod and placebo-treated patients (~4% in each arm).

8.3.5. Most Common Treatment Emergent Adverse Events

The most common TEAEs that occurred during the induction period were assessed using Pool F, which included patients from Study 3101 and Study 202 (phase 2). Results based on recoded AE preferred terms are shown in Table 44.

Table 44. Common Adverse Events Reported In ≥2% Of Patients and With ≥1% Greater Incidence Than Placebo, Pool F Induction

			Adjusted Counts and Percentages[b]		Treatment Comparison (Ozanimod 1 mg - Placebo)	
Preferred Term (Recoded)	Placebo (N=281) n (%)[a]	Ozanimod 1 mg (N=496) n (%)[a]	Placebo (N=281) n (%)	Ozanimod 1 mg (N=496) n (%)	Adjusted Difference in Proportions	95% CI[c]
Any TEAE	102 (36.3)	188 (37.9)	70.4 (36.6)	141.0 (37.3)	0.007	(-0.064, 0.078)
Upper respiratory tract infection	10 (3.6)	26 (5.2)	6.9 (3.6)	20.5 (5.0)	0.014	(-0.015, 0.043)
Liver test increased	0	23 (4.6)	0	15.6 (4.8)	0.048	(0.029, 0.067)
Headache	8 (2.8)	20 (4.0)	4.6 (2.7)	15.0 (4.0)	0.012	(-0.013, 0.038)
Pyrexia	4 (1.4)	15 (3.0)	3.3 (1.5)	10.3 (3.1)	0.016	(-0.005, 0.038)
Nausea	5 (1.8)	14 (2.8)	2.8 (1.7)	10.1 (2.8)	0.011	(-0.010, 0.032)
Arthralgia	3 (1.1)	12 (2.4)	2.4 (1.1)	8.5 (2.5)	0.013	(-0.006, 0.032)

Source: Applicant's response to Information Request, received 4/2/21; results verified by statistical reviewer. Includes reviewer's recoded preferred terms.
Abbreviations: CI = confidence interval; TEAE = treatment-emergent adverse event
[a] Percentages obtained from simple pooling
[b] Adjusted counts and percentages in each treatment group were calculated as the sum of each individual study count and percentage multiplied by its CMH weight. Study 202 had a CMH weight of 0.187. Study 3101 had a CMH weight of 0.813.
[c] 95% CI for adjusted difference in proportions was based on the normal approximation.

TEAEs occurred in 36% of patients treated with placebo and in 38% of ozanimod-treated patients (based on simple pooling between the 2 studies). The most common AEs were upper respiratory tract infections, elevated liver enzymes, headache, pyrexia, nausea and arthralgia. The adjusted incidence proportions were utilized to inform the labeling. For all AEs in Table 44 except for liver test increased, the 95% CIs for the adjusted risk differences contain 0; therefore, for those AEs, there is insufficient evidence to suggest that the adjusted incidence proportions differ between treatment groups. Details regarding the derivation of adjusted incidence proportions and 95% CIs for the adjusted risk differences are in Appendix Section 15.6.

A similar analysis (for AEs occurring in at least 2% of patients and with at least 1% risk difference from placebo) was conducted on the data from Study 3101 cohort 1 induction only. In Table 45, a similar analysis was conducted using only the induction data from Study 3101.

Table 45. Common Adverse Events Reported In ≥2% Of Patients and With ≥1% Greater Difference Than Placebo, Induction Period, Study 3101

	Cohort 1		Cohort 2
Preferred Term (Recoded), n (%)	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Patients with ≥ 1 TEAE	172 (40.1)	82 (38.0)	146 (39.8)
Upper respiratory tract infection	25 (5.8)	8 (3.7)	22 (6.0)
Headache	19 (4.4)	5 (2.3)	12 (3.3)
Nausea	13 (3.0)	3 (1.4)	3 (0.8)
Liver test increased	19 (4.4)	0	12 (3.3)

Source: Reviewer's table, created based on ADAE dataset, utilizing reviewer's recoded preferred terms.
Abbreviations: TEAE = treatment-emergent adverse event

During the induction period, more patients on ozanimod experienced at least 1 TEAE than patients on placebo. Patients on ozanimod had an increased risk of URI, headache, nausea, and liver test abnormalities. This was consistent with the results seen using the combined induction data from Studies 3101 and 202.

Table 46 below shows a similar analysis for the maintenance period.

Table 46. Common Adverse Events Reported In ≥2% Of Patients and With ≥1% Greater Difference Than Placebo, Maintenance Period, Study 3101

		Re-randomized Patients	
	Placebo N=69	**Ozanimod 1mg-Placebo N=227**	**Ozanimod 1mg – Ozanimod 1mg N=230**
Preferred Term (Recoded), n (%)			
Liver test increased	1 (1.4)	4 (1.82)	25 (10.9)
Headache	0	1 (0.4)	11 (4.8)
Edema peripheral	0	1 (0.4)	7 (3.0)
Herpes zoster	0	1 (0.4)	5 (2.2)
Gastroenteritis	1 (1.4)	2 (0.9)	6 (2.6)
Respiratory tract infection*	1(1.4)	1 (0.4)	5 (2.2)

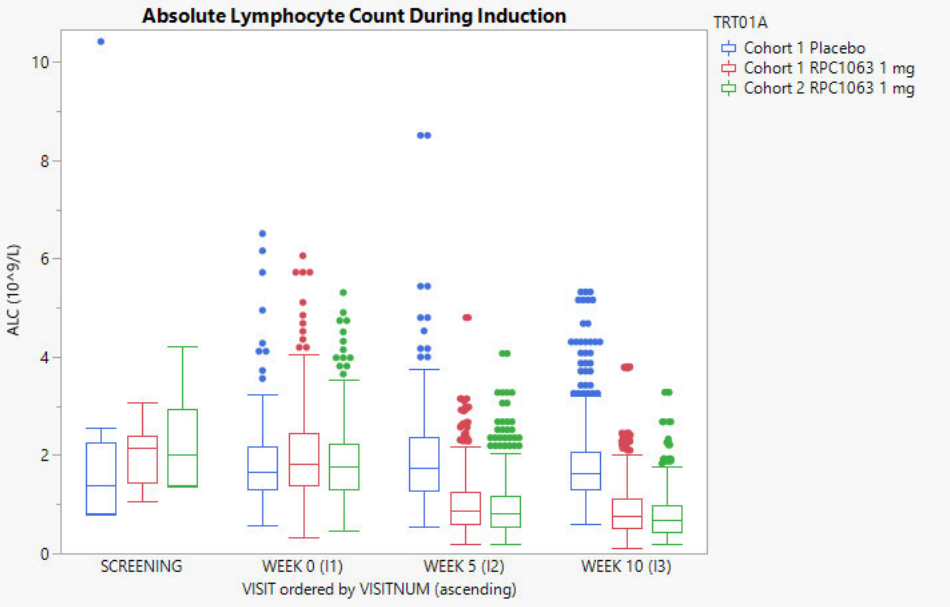
Source: Reviewer's table, created based on ADAE dataset, using reviewer's recoded preferred terms
*respiratory syncytial tract (RSV) infection test positive
Abbreviations: TEAE = treatment-emergent adverse event

During maintenance, patients re-randomized to continue ozanimod were more likely compared to patients on placebo to experience at least 1 TEAE. Patients re-randomized to placebo had a higher risk of UC flare. Patients re-randomized to continue ozanimod had a higher risk of liver enzyme abnormalities, headache, peripheral edema, herpes zoster, gastroenteritis, and respiratory syncytial virus positivity. We selected a 4% threshold for inclusion of "common" AEs in the maintenance period to inform the labeling, consistent with recent labeling of other drugs for UC with studies of similar size. Headache will be added to the terms the Applicant initially proposed. Additionally, peripheral edema will be included under "additional AEs."

8.3.6. Laboratory Findings

Hematology – Absolute Lymphocyte Count (ALC)
Ozanimod is known to cause reduction in circulating levels of lymphocytes. Within the induction period, reduction in absolute lymphocyte count (ALC) was observed in ozanimod-treated patients at Week 5 and remained relatively stable thereafter (mean % reduction from baseline was 54% at Week 10 in ozanimod-treated patients), see Figure 6. below.

Figure 6. Mean ALC Values by Visit, Induction period, RPC01-3101

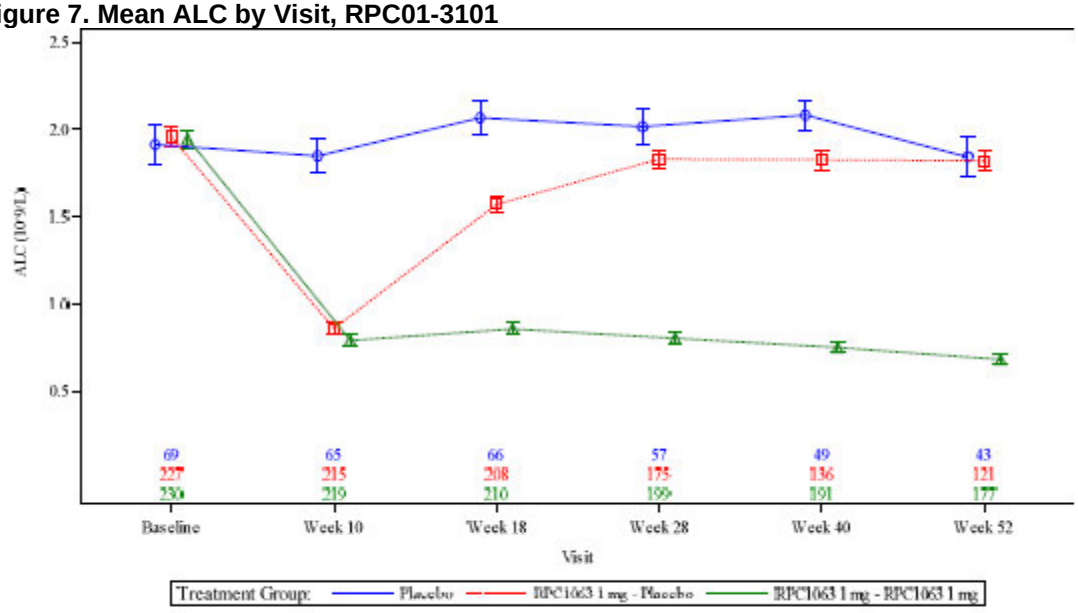


Source: Reviewer's table created from ADLB dataset

During the maintenance period, absolute lymphocyte levels remained stable over time in patients re-randomized to continue ozanimod. In patients re-randomized to placebo, values returned to normal over time. Decrease in ALC from baseline was noted to be 55% at Week 10, 13% at Week 18, and 2% by Week 28 (see Figure 7. below). Slow recovery of ALC over time (through Week 28) is expected, noting the prolonged half-life of the major active metabolite CC112273[9].

[9] Terminal t1/2 is 424 hours in UC patients.

Figure 7. Mean ALC by Visit, RPC01-3101



ALC = absolute lymphocyte count; RPC1063 = ozanimod.
Source: RPC01-3101 CSR Figure 14.3.8.1.1B

Source: Applicant's summary of clinical safety, p. 235/292.

In addition to mean values and changes from baseline, an assessment was conducted of the proportion of patients reaching clinically significant reduction in ALC. During the study, treatment was held if patients reached ALC < 0.2 x 10 cells/L until level had returned to >0.5 x10^9 cells/L. In the Pool F induction period, 111/434 patients (25.6%) in the ozanimod 1 mg treatment group who had a normal ALC value at baseline experienced reductions in ALC to < 500 x 10^6/L at a postbaseline assessment, and 6/434 patients (1.4%) reached a nadir of ALC < 200 x 10^6/L. Only 1/233 patients in the placebo group experienced a shift in ALC to < 500 x 106/L at a post-baseline assessment, and no patients in the placebo group had shifts in ALC < 200 x 106/L at any postbaseline assessment in the Pool F induction period.

No patients with an ALC < 200 x 10^6/L interrupted treatment with ozanimod 1 mg in Pool F and the induction period of Study 3101, given that none of these patients had confirmed value of ALC < 200 x10^6/L upon required repeat testing during the induction period. One patient (b) (6) with an ALC < 200 x 10^6/L interrupted treatment with ozanimod 1 mg in the Maintenance period and resumed treatment after 3 months. Two patients with initial ALC < 200 x10^6/L during induction period did later experience treatment interruption during open-label extension (day (b) (6), and (b) (6) of treatment) due to repeated occurrence of ALC < 200 x10^6/L.

During the Pool F induction period, the incidence of TEAEs of infections and infestations in the ozanimod 1 mg treatment group was comparable between those patients who had a normal ALC at baseline and experienced shifts in ALC < 500 x 10^6/L and those who did not experience a shift in ALC < 500 x 10^6/L (9.9% versus 9.3%, respectively). Similar trend was observed in analysis limited to the RPC01-3101 induction period.

In the maintenance period of Study 3101, 87/230 (38%) of ozanimod-treated patients reached an ALC nadir of < 500 x 10^6/L, compared to 4/227 (2%) in patients re-randomized to placebo. Five of 230 ozanimod-treated patients (2%) and no patients re-randomized to placebo reached a nadir of <200 x 10^6/L. Similar to the induction period, the rate of TEAEs and SAES was similar among patients who reached ALC levels of <500 x 10^6/L or <200 x 10^6/L as compared to those who did not.

Hematology- Other Parameters
Small and not clinically significant decreases in absolute neutrophil counts were observed in ozanimod-treated patients by Week 5. The total white blood cell counts showed similar trends, driven by reduction in ALC. No clinically significant changes in other hematology parameters were observed.

Chemistry
With the exception of liver enzymes, no clinically significant changes in chemistry parameters were observed.

Transaminases
In the UC program, elevations in hepatic transaminases (AST and/or ALT) occurred more frequently in ozanimod-treated patients than placebo. In the Study 3101 induction period, ALT elevation to >3X ULN occurred in 2.6% of ozanimod-treated patients, and 0.5% of placebo-treated patients. In maintenance, ALT elevation to >3X ULN occurred in 2.3% of ozanimod-treated patients and no placebo patients.

The reviewer further evaluated shifts from normal to high for AST, ALT, and bilirubin in the subset of patients who were normal at baseline, to determine if these changes were driven by patients with baseline elevation. For both AST and ALT were noted more frequently in ozanimod-treated patients than placebo-treated patients in both induction and maintenance periods (Table 47 and Table 48) and results were similar to those for the overall trial population. Clinically significant elevations in bilirubin were not detected. A detailed discussion of evaluation of hepatoxicity is included below in Section 8.3.9.5.

Table 47. Shift Table for Peak Post-baseline ALT, AST, and Total Bilirubin (Baseline Elevations Excluded), Induction Period

		Cohort 1		Cohort 2
Parameter	Criterion	Ozanimod 1mg (N=429) n (%)	Placebo (N=216) n (%)	Ozanimod 1 mg (N = 367) n (%)
ALT*		N=405	N=207	N=344
	≥ 3 x ULN	9 (2.2)	1 (0.5)	5 (1.4)
	≥ 4 x ULN	5 (1.2)	1 (0.5)	2 (0.6)
	≥ 5 x ULN	3 (0.7)	1 (0.5)	2 (0.6)
	≥ 8 x ULN	2 (0.5)	0	0
	≥ 10 x ULN	2 (0.5)	0	0
AST*		N=417	N=210	N=355
	≥ 3 x ULN	7 (1.7)	0	2 (0.6)
	≥ 4 x ULN	4 (1.0)	0	2 (0.6)
	≥ 5 x ULN	4 (1.0)	0	0
	≥ 8 x ULN	1 (0.2)	0	0
	≥ 10 x ULN	0	0	0
Total bilirubin*		N=425	N=215	N=366
	≥ 2 x ULN	0	0	0
	≥ 3 x ULN	0	0	0
	≥ 4 x ULN	0	0	0

Source: reviewer's analysis, based on data from ADLB dataset
*N = number of patients with normal baseline values for the parameter
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

Table 48. Shift Table for Peak Post-Baseline ALT, AST, and Total Bilirubin (Baseline Elevations Excluded), Maintenance Period

		Re-randomized Patients		
Parameter	Criterion	Ozanimod 1 mg – Placebo (N = 227) n (%)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230) n (%)	Placebo (N = 69) n (%)
ALT*		N=205	N=212	N=65
	≥ 3 x ULN	0	4 (1.9)	0
	≥ 4 x ULN	0	2 (0.9)	0
	≥ 5 x ULN	0	2 (0.9)	0
	≥ 8 x ULN	0	0	0
	≥ 10 x ULN	0	0	0
AST*		N=212	N=216	N=66
	≥ 3 x ULN	0	3 (1.4)	0
	≥ 4 x ULN	0	2 (0.9)	0
	≥ 5 x ULN	0	1 (0.5)	0
	≥ 8 x ULN	0	1 (0.5)	0
	≥ 10 x ULN	0	0	0
Total bilirubin*		N=218	N=219	N=66
	≥ 2 x ULN	0	0	0

≥ 3 x ULN	0	0	0
≥ 4 x ULN	0	0	0

Source: reviewer's analysis, based on data from ADLB dataset
*N = number of patients with normal baseline values for the parameter
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

8.3.7. Vital Signs

During induction and maintenance, the systolic blood pressure, diastolic blood pressure, and heart rates were similar among the treatment arms. See Table 49 and Table 50 for hypertension TEAEs during Study 3101 induction and maintenance.

Table 49. Hypertension TEAEs, Induction Period, Study 3101

	Cohort 1		Cohort 2
Preferred Term, n (%)	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Hypertension	6 (1.4)	0	7 (1.9)

Source: Reviewer's table created from ADAE dataset
Abbreviations: TEAE = treatment-emergent adverse event

Table 50. Hypertension TEAEs, Maintenance Period, Study 3101

		Re-randomized Patients	
Preferred Term, n (%)	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Hypertension	1 (1.4)	4 (1.8)	5 (2.2)

Source: Reviewer's table created from ADAE dataset
Abbreviations: TEAE = treatment-emergent adverse event

8.3.8. Electrocardiograms (ECGs) and QT evaluation

The reported bradycardic events, AV blocks (1st degree and 2nd degree Mobitz 1), and variations of heart rate, were consistent with previous findings from the MS application. Other than bradycardia, the cardiovascular events reported in this sNDA were low in number and not significantly different from placebo. See Section 8.3.9.1 below for further discussion of cardiac specific safety issues.

Per QTIRT consultation dated March 26, 2019, no relevant QTc prolongation effects of ozanimod's major metabolites were detected in their assessment. In Study 3101, QTcF prolongations were evenly distributed amongst the treatment arms; thus, no safety signal was observed.

8.3.9. Analysis of Submission-Specific Safety Issues – Adverse Events of Special Interest (AESIs)

Adverse events of special interest were those that could be a consequence of S1P1 modulation; these AEs were closely monitored during the trial and included bradycardia, heart conduction

abnormalities (2nd degree and higher AV block), macular edema, malignancy, serious or opportunistic infection, pulmonary effects, and hepatic effects.

8.3.9.1. Cardiac

Ozanimod hydrochloride activates the sphingosine 1-phosphate (S1P)-1 receptor (S1P1) and the S1P-5 receptor (S1P5). S1P1 agonism causes activation of G-protein coupled inwardly rectifying potassium (GIRK) channels that regulate cardiac pacemaker activity. Influx of potassium through GIRK channels has a negative chronotropic effect (i.e., reduced frequency of contraction) on the sino-atrial node and a negative dromotropic effect (i.e., reduced conduction speed) on the atrio-ventricular node. The selective S1P1 agonist is therefore thought to reduce heart rate during the time period between S1P1 activation and S1P1 internalization. Once internalized, GIRK channels are no longer activated. Potassium inflow through the GIRK channels therefore decreases, thus attenuating the negative chronotropic and negative dromotropic effects.

The S1P1 receptor is highly expressed in atrial, septal, and ventricular cardiomyocytes. It is also expressed in the endothelial cells of cardiac vessels and in other endothelial and vascular smooth muscle cells, where it contributes to the regulation of endothelial barrier function and peripheral vascular tone. The modulation of the receptor could thus lead to vasoconstriction causing an increase in blood pressure.

Cardiovascular adverse events included bradycardia in the induction period (five patients in the ozanimod arms and no patients in the placebo arm). Nadir heart rates relative to baseline were recorded at Hour 6 post treatment (sixteen patients in the ozanimod arms and two in the placebo arm). None of the heart rates fell below 45 bpm. In the maintenance period, patients on ozanimod had a tendency for a lower heart rate compared to patients on placebo, but the differences in heart rate were not clinically significant. The hypertension events noted in the maintenance period were evenly distributed between the ozanimod and the placebo arms (previously discussed as discussed as shown in Table 50 above). Other cardiovascular events were sporadic and did not point to a safety signal.

The reported bradycardic events, AV blocks (1st degree and 2nd degree Mobitz 1), and variations of heart rate, were consistent with previous findings from the MS application. Other than bradycardia, the cardiovascular events reported in this sNDA were low in number and not significantly different from placebo. See cardiology consult dated January 21, 2021 by Dr. Fred Senatore for further details. The language in approved prescribing information accurately describes the potential cardiovascular adverse events that can be associated with ozanimod treatment, and outlines risk mitigation strategies where appropriate (e.g., dose titration, when to seek cardiovascular consultation prior to initiation, contraindications based on underlying cardiac pathology).

8.3.9.2. Ophthalmology

Approved S1P modulators are associated with a low but increased risk of macular edema. Please see ophthalmology consult dated December 29, 2020 by Dr. Wiley Chambers for further details.

Table 51. Cases of Macular Edema, Induction Period, Study 3101

AESI Category Preferred Term, n (%)	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Macular edema	1 (0.2)	0	0

Source: Ophthalmology consult dated 12/29/2020 by Dr. Wiley Chambers
Abbreviations: AESI = Adverse event of special interest

Table 52. Cases of Macular Edema, Maintenance Period, Study 3101

AESI Category Preferred Term, n (%)	Placebo (N = 69)	Re-randomized Subjects	
		Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg- Ozanimod 1 mg (N = 230)
Macular edema	0	0	1 (0.4)

Source: Ophthalmology consult dated 12/29/2020 by Dr. Wiley Chambers
Abbreviations: AESI = Adverse event of special interest

Table 51 and Table 52 summarize the number and proportion of patients who experienced macular edema during induction and maintenance. In the induction period, 1 patient (0.2%) in the cohort 1 ozanimod 1 mg group and no patients in the placebo group had a TEAE of macular edema. Additionally, one patient (0.3%) in the cohort 2 ozanimod 1 mg group had a TEAE of peri-macular edema (coded as macular edema; but was not macular edema on review). One patient (0.4%) re-randomized to the ozanimod group in the maintenance period had a TEAE of macular edema. Overall, patients with UC treated with ozanimod reported low rate (0.5%) of macular edema, which was similar to that reported for MS.

Within the UC program, an increased risk of macular edema was not observed specifically in patients with underlying diabetes or previous diagnosis of uveitis. Consideration should be given to removing the language in the approved prescribing information which specifically indicates that these patients are at increased risk. This was discussed with the Neurology Division, and labeling updates to both indications regarding risk factors for macular edema will be considered in the future as additional information is received on this risk within the class.

The current prescribing information includes relevant information to inform prescribers about the risk of macular edema and provides guidance on appropriate evaluation of ozanimod-

treated patients should they experience new-onset vision changes, and is adequate to communicate the risk and provide risk mitigation.

8.3.9.3. Pulmonary

S1P modulators are associated with an increased risk of pulmonary adverse events including bronchoconstriction and decreases in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), which have been attributed in preliminary data to non-selective binding of other sphingosine 1-phosphate receptors.

Within study RPC01-3101 induction period, patients who received ozanimod experienced a mean change (decline) from baseline in FEV1 of 0.057 L (57 mL) compared to a mean change (decline) from baseline in FEV1 of 0.035 L (35 mL) among placebo patients (see Table 53), resulting in a mean difference of 22 mL. The clinical relevance of this change and the corresponding to change in percent predicted FEV1 (0.81%) are unclear since the mean baseline FEV1 for these groups was normal. Similarly, patients who received ozanimod experienced a mean change (decline) from baseline in FVC of 0.043 L (43 mL) compared to a mean change from baseline (improvement) from baseline in FVC or 0.001 L (1 mL) among placebo patients, resulting in a mean difference of 44 mL. The clinical relevance of this change and the corresponding to changes in percent predicted FVC (0.53%) is also unclear.

Table 53. RPC01-3101, Cohort 1 Induction Period, Randomized Comparisons: Mean Change From Baseline in Pulmonary Function Measures

	Cohort 1					
	Ozanimod 1 mg (N = 429)			Placebo (N = 216)		
Parameter	n	Percent change (SD)	Absolute change (SD)	n	Percent change (SD)	Absolute change (SD)
FEV_1 (L)	388	-1.122 (10.777)	-0.057 (0.373)	183	-0.617 (8.313)	-0.035 (0.284)
FEV_1 PPN	389	-1.000 (10.525)	-1.574 (10.757)	184	-0.391 (9.220)	-0.764 (9.214)
FVC (L)	388	-0.653 (9.861)	-0.043 (0.408)	183	0.488 (8.861)	0.001 (0.366)
FVC PPN	389	-0.269 (9.935)	-0.760 (9.971)	184	0.315 (9.642)	-0.230 (9.723)
DLCOhgb[a] (mM/min/kPa)	146	-2.625 (186.655)	-0.475 (16.728)	61	-4.509 (19.565)	-0.847 (3.143)

Source: Pulmonary consult dated March 23, 2021 by Dr. Robert Busch
Abbreviations: FEV1= forced expiratory volume; PPN=percent of predicted normal ; FVC= forced vital capacity; DLCO=diffusing capacity of the lungs for carbon monoxide; SD=standard deviation; L =liters ; hgb = hemoglobin; kPa =kilo pascal

Non-randomized comparisons based on exposure group in induction and maintenance of Study RPC01-3101 did not present additional clinically significant safety concerns. The pulmonology

consultant concluded that reliable conclusions regarding differences between treatment arms at Week 52, and on reversibility of the small declines in FEV1 / FVC that were observed could not be made, owing to the study design (including re-randomization at Week 10 based upon a post-randomization variable of clinical response). Please see pulmonary consult dated March 23, 2021 by Dr. Robert Busch for further details.

The language in the prescribing information was updated to describe the findings from the induction period by treatment group (noting this to be the most robust comparison for pulmonary safety) and the limitations of the data regarding reversibility or progression are noted.

8.3.9.4. Malignancy

Induction
During the induction period of Study 3101, there were 2 cases of malignancy (both patients were from cohort 2 and received open-label ozanimod 1 mg): basal cell carcinoma and cervical carcinoma stage 0.

Maintenance
During the maintenance period of the same study, there were four cases of malignancy. This included 2 cases of malignancy in the ozanimod 1 mg-ozanimod 1 mg treatment arm (basal cell carcinoma and rectal adenocarcinoma) and 2 cases in the ozanimod 1 mg-placebo treatment arm (breast cancer and carcinoma of the colon). The case of rectal adenocarcinoma was in a 51 year old male who had longstanding (almost 20 year history) UC prior to malignancy diagnosis. The case of carcinoma of the colon was in a 35 year old male who also had longstanding (18 year history) UC as well as a 15 year history of smoking prior to malignancy diagnosis.

Extension period
During the OLE study, there were 2 additional cases of malignancy reported, both basal cell carcinoma. One patient (in the ozanimod 1 mg – placebo treatment group followed by ozanimod 1 mg in the OLE) was in the study for 629 days prior to diagnosis. The other patient (treated with ozanimod 1 mg during induction followed by ozanimod 1 mg in the OLE) was in the study for 397 days prior to diagnosis.

Exposure-adjusted analyses of malignancy
Within Pool G, the EAIR per 1000 PY for any malignancy was 8.1 for placebo versus 6.4 for ozanimod-treated patients, which was reassuring (Table 54). The incidence of malignancy reported within the UC development program was low and does not appear to represent a new safety signal, although the total exposure time in the submitted data may not be adequate to fully characterize this risk.

For cutaneous malignancy, the EAIR per 1000 PY was estimated to be 3.2 and 0.0 in ozanimod and placebo treated patients, respectively, with a risk difference of 3.2, 95% CI: (-3.8, 10.3). Details regarding EAIRs and 95% CIs for the differences in EAIRs are in Appendix Section 15.6.

For analysis of any malignancy, or cutaneous malignancy, since the 95% CI for the risk difference contains 0, there is insufficient evidence to suggest that the EAIRs differ between treatment groups. Thus, at this time we cannot conclude that malignancy and cutaneous malignancy represent a strong safety signal. However, in order to more comprehensively assess the risk for these events of long latency in the patient population, further monitoring is necessary. This will be initiated by conducting enhanced pharmacovigilance, including the use of a standardized form for data collection for any reported malignancy, and expedited reporting of any cases to FDA.

Table 54. Exposure-Adjusted Incidence Rates for Malignancy in Pool G (Safety Population)

	Placebo (N = 508)	Ozanimod 1 mg (N = 1158)
Patients experiencing at least 1 malignancy, n (%)	2 (0.4)	14 (1.2)
EAIR/1000 PY[a]	8.1	6.4
Difference in EAIR (ozanimod-placebo), 95% CI[b]	-1.6 (-12.3, 9.0)	
Patients experiencing at least 1 cutaneous malignancy, n (%)	0	7 (0.6)
EAIR/1000 PY[a]	0.0	3.2
Difference in EAIR (ozanimod-placebo), 95% CI[b]	3.2 (-3.8, 10.3)	

Source: SCS Table 31 (p. 89), 3-month safety update Table 18 (p. 53), statistical reviewer's analysis
Abbreviations: CI = confidence interval; EAIR = exposure-adjusted incidence rate; PY = patient-years
[a] EAIR per 1000 PY is calculated as number of patients/patient-years x 1000.
[b] 95% CI was based on the normal approximation.

8.3.9.5. Hepatotoxicity

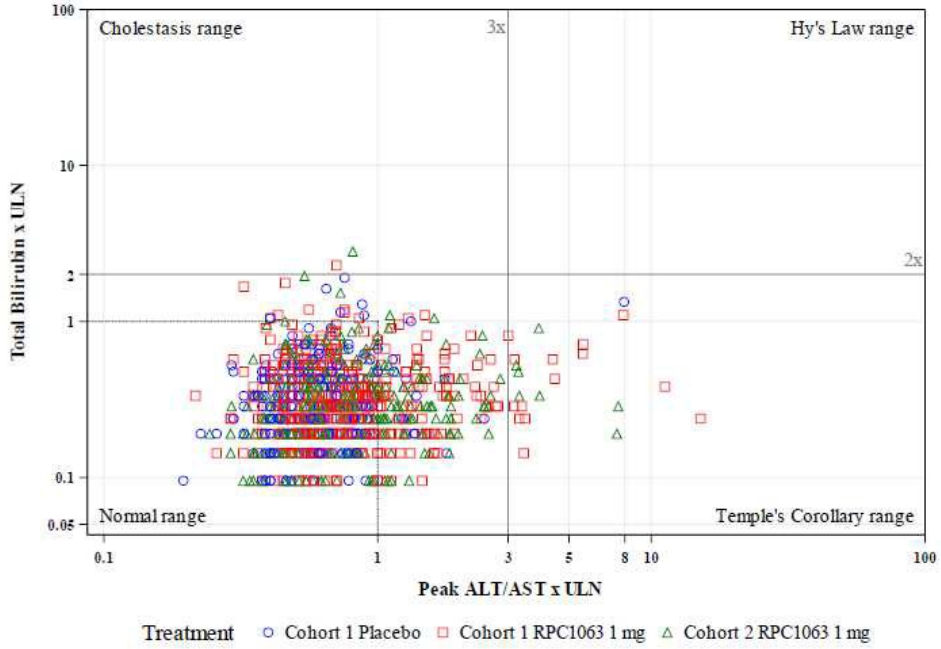
Ozanimod and other S1P receptor modulators are known to cause hepatoxicity. Although there were no confirmed Hy's law cases in the UC program, imbalances in the rates of transaminase elevations suggest the potential for hepatotoxicity.

In the UC program, elevations in hepatic transaminases (AST and/or ALT) occurred more frequently in ozanimod-treated patients than placebo, as described above in Section 8.3.6. Because the studies excluded patients with AST or ALT >2X ULN, data on hepatoxicity in patients with underlying liver disease are not available.

There were no cases of fulminant hepatic failure in the UC program. The Division of Pharmacovigilance reviewed spontaneous AE reports for ozanimod since its approval for MS in March 2020 and did not identify any reports of serious hepatoxicity or hepatic failure. The most recent Annual Report submitted to the MS IND also did not identify any cases of severe hepatic failure related to ozanimod use to date.

Below, in Figure 8, peak AST/ALT is plotted versus elevation of total bilirubin, for the induction period of RPC01-3101. The figure shows the lack of Hy's law cases, and a number of patients with marked elevations of AST or ALT, consistent with Temple's Corollary (occurring in 3.3% of ozanimod-treated patients in cohort 1, compared to 0.5% of placebo.

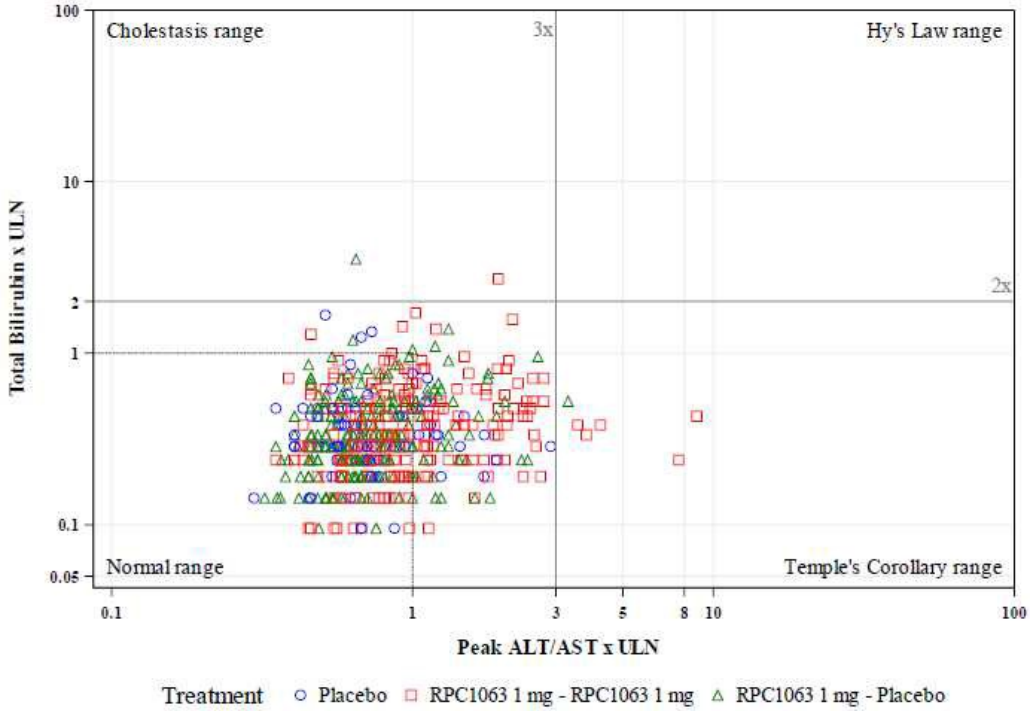
Figure 8. Hepatocellular Drug-Induced Liver Injury Case Screening Plot – Study RPC01-3101 Induction Period



Source: Response to FDA Information Request Dated March 1, 2021

During maintenance, similarly there were no Hy's Law cases reported (Figure 9 below). There were 5 (2.2%) patients in the ozanimod 1 mg - ozanimod 1 mg treatment group and 1 patient (0.4%) in the ozanimod 1 mg-placebo treatment group whose transaminase elevations also fell under Temple's Corollary.

Figure 9. Hepatocellular Drug-Induced Liver Injury Case Screening Plot – Study RPC01-3101 Maintenance Period



Source: Response to FDA Information Request Dated March 1, 2021

Jaundice without elevation of AST or ALT to ≥3 X ULN occurred in a total of 2 patients, as noted above, in equal proportions in patients re-randomized to ozanimod or placebo, which does not suggest a signal for cholestatic hepatotoxicity.

Within the Appendix, Table 72 shows detailed outcomes for the patients who experienced marked elevation of AST and/or ALT within RPC01-3101. In summary, there were no hepatic-related serious TEAEs and 69% of events had resolution of the transaminase elevation (defined as AST or ALT ≤3 x ULN); 8 events resolved off ozanimod treatment, with 4 patients discontinuing prior to resolution. The median time to recovery was 26 days for ozanimod-treated patients and all but 2 patients recovered within 69 days (2.3 months).

Table 55 below provides EAIR estimates for Pool G, for marked elevations in liver biochemical parameters.

Table 55. Proportion of Patients With, and Incidence Rate Per 100 Patient-Years of, Hepatic Laboratory Parameter Elevations at Any Postbaseline Visit – Pool G (Safety Population)

	Placebo (N = 508) Total PY[a] = 249.2		Ozanimod 1 mg (N = 1158) Total PY[a] = 1922.5		Ozanimod 1 mg Versus Placebo	
Laboratory Abnormality	n (%)	EAIR/ 100 PY[b]	n (%)	EAIR/ 100 PY[b]	Risk Difference (95% CI)[c]	EAIR Ratio (95% CI)[d]
Alanine						

Laboratory Abnormality	Placebo (N = 508) Total PY[a] = 249.2 n (%)	EAIR/ 100 PY[b]	Ozanimod 1 mg (N = 1158) Total PY[a] = 1922.5 n (%)	EAIR/ 100 PY[b]	Ozanimod 1 mg Versus Placebo Risk Difference (95% CI)[c]	EAIR Ratio (95% CI)[d]
aminotransferase > ULN	58 (11.4)	25.5	508 (43.9)	44.9	0.325 (0.285, 0.364)	1.765 (1.345, 2.316)
> 3 x ULN	1 (0.2)	0.4	69 (6.0)	3.7	0.058 (0.043, 0.072)	9.323 (1.295, 67.127)
> 5 x ULN	1 (0.2)	0.4	19 (1.6)	1.0	0.014 (0.006, 0.023)	2.476 (0.331, 18.498)
> 10 x ULN	0	0	5 (0.4)	0.3	0.004 (0.001, 0.008)	NE
> 20 x ULN	0	0	1 (< 0.1)	0.1	0.001 (-0.001, 0.003)	NE
Aspartate aminotransferase > ULN	35 (6.9)	14.7	356 (30.7)	25.6	0.239 (0.204, 0.273)	1.746 (1.234, 2.471)
> 3 x ULN	1 (0.2)	0.4	39 (3.4)	2.1	0.032 (0.021, 0.043)	5.152 (0.708, 37.498)
> 5 x ULN	0	0	12 (1.0)	0.6	0.010 (0.005, 0.016)	NE
> 10 x ULN	0	0	3 (0.3)	0.2	0.003 (-0.000, 0.006)	NE
> 20 x ULN	0	0	0	0	NE	NE
Alkaline phosphatase > 2 x ULN	7 (1.4)	2.8	30 (2.6)	1.6	0.012 (-0.002, 0.026)	0.562 (0.247, 1.280)
> 3 x ULN	2 (0.4)	0.8	9 (0.8)	0.5	0.004 (-0.004, 0.011)	0.583 (0.126, 2.701)
Total bilirubin > 2 x ULN	2 (0.4)	0.8	12 (1.0)	0.6	0.006 (-0.002, 0.014)	0.783 (0.175, 3.498)
> 5 x ULN	0	0	2 (0.2)	0.1	0.002 (-0.001, 0.004)	NE
> 8 x ULN	0	0	0	0	NE	NE
Direct bilirubin > 2 x ULN	2 (0.4)	0.8	13 (1.1)	0.7	0.007 (-0.001, 0.015)	0.849 (0.192, 3.761)
> 5 x ULN	0	0	1 (< 0.1)	0.1	0.001 (-0.001, 0.003)	NE
Gamma-glutamyltransferase > 2 x ULN						

	Placebo (N = 508) Total PY[a] = 249.2		Ozanimod 1 mg (N = 1158) Total PY[a] = 1922.5		Ozanimod 1 mg Versus Placebo	
Laboratory Abnormality	**n (%)**	**EAIR/ 100 PY[b]**	**n (%)**	**EAIR/ 100 PY[b]**	**Risk Difference (95% CI)[c]**	**EAIR Ratio (95% CI)[d]**
	20 (3.9)	8.3	252 (21.8)	16.5	0.178 (0.149, 0.207)	1.990 (1.262, 3.137)
Prothrombin times						
> 1.5 x ULN	0	0	1 (< 0.1)	0.1	0.001 (-0.001, 0.003)	NE
> 3 x ULN	0	0	0	0	NE	NE
> 5 x ULN	0	0	0	0	NE	NE

Source: Response to FDA Information Request Dated 3/1/2021
Abbreviations: CI = confidence interval; EAIR = exposure-adjusted incidence rate; NE = not evaluable; PY = patient-years; ULN = upper limit of normal
[a] Total patient years equals the sum of the number of years on study contributed by each subject from time of first dose to last date on study.
[b] EAIR per 100 subject-years is calculated as number of subjects / subject-years x 100 for specific category.
[c] 95% CI was based on the normal approximation.
[d] 95% CI of EAIR ratio = (EAIR1/EAIR0)*exp(±1.96*sqrt(1/d1+1/d0)), where EAIR1: EAIR of ozanimod 1 mg; EAIR0: EAIR of placebo; d1: number of subjects with events in ozanimod 1 mg; d0: number of subjects with events in placebo.

In Pool G, treatment with ozanimod 1 mg was associated with a higher incidence and EAIR of elevations in ALT (> ULN, > 3 x ULN) and in AST (> ULN and > 3 x ULN) as compared with placebo. The incidence of patients treated with ozanimod with more significant elevations was infrequent (AST or ALT > 5 x ULN (< 2%) and > 10 x and > 20 x ULN (< 0.5%). There was also no significant difference in the incidence and EAIR for hepatic measurements indicative of cholestasis (elevations in alkaline phosphatase (ALP), TB, or DB) between the ozanimod 1 mg and placebo treatment groups. Patients treated with ozanimod 1 mg had a higher incidence of GGT ≥ 2 x ULN compared with placebo. However, due to different treatment regimens, randomization schemes and various follow-up times across the controlled and uncontrolled studies in Pool G, risk difference and risk ratio comparison between the two groups should be interpreted with caution.

In summary, there were no potential cases of Hy's Law (defined as jaundice [TB ≥ 2 x ULN] with ALT or AST ≥ 3 x ULN) or cholestatic liver injury (defined as jaundice [TB ≥ 2 x ULN] with ≥ 3 x ULN elevation in ALP) during the UC studies. In the controlled trial, a higher proportion of patients treated with ozanimod compared with placebo had liver biochemistry studies that fell under Temple's Corollary (ALT or AST ≥ 3 x ULN without a concurrent TB elevation ≥ 2 x ULN). The majority of these events occurred during the induction period of RPC01-3101 (80%), had resolution of the transaminase elevation (defined as AST or ALT ≤3 x ULN) while on ozanimod (69%), and were not associated with any hepatic-related SAEs. No patient's R value represented a cholestatic injury pattern. Similarly in Pool G, treatment with ozanimod 1 mg was associated with a higher incidence and EAIR of elevations in ALT (> ULN, > 3 x ULN) and in AST (> ULN and > 3 x ULN) as compared with placebo. Generally similar trends were observed in subsets of patients with normal and elevated liver biochemistry studies at baseline.

There were no TEAEs indicative of hepatic failure reported in the UC clinical program. Patients treated with ozanimod had a higher incidence of TEAEs of ALT increased and AST increased, but not of TEAEs related to cholestatic injury. Two patients treated with ozanimod had TEAE of drug-induced liver injury and had an elevation of ALT < 2 x ULN who recovered after discontinuing treatment.

Hepatotoxicity appears to represent an important potential risk associated with ozanimod. Additional surveillance for serious liver injury and potential hepatic failure will occur via enhanced pharmacovigilance post-approval.

8.3.9.6. Infection

Specified infections were considered adverse events of special interest, including TB, serious bacterial infections, systemic fungal infections, viral infections such as herpes infections (including herpes zoster and disseminated herpes simplex) and protozoan infections.

Study 3101 induction period

Table 56 below shows the reported infections that were considered AESIs.

Table 56. Infections of Special Interest, Induction Period, Study 3101

	Cohort 1		Cohort 2
Preferred Term, n (%)	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Herpes zoster	2 (0.5)	0	1 (0.3)
Herpes simplex	1 (0.2)	0	3 (0.8)
Amebiasis	0	0	1 (0.3)

Source: Reviewer's table, created from ADAE dataset

The rates of herpes zoster and herpes simplex were overall low. All cases of herpes simplex were mild, non-disseminated, non-serious, and resolved with no changes in ozanimod dose. There was one case of amebiasis in cohort 2, which was moderate in severity, non-disseminated, non-serious, and "resolving" with no changes in ozanimod dose. There were no cases of tuberculosis, systemic fungal infections, or cryptococcal infections.

Study 3101 maintenance period

Table 57 below shows a similar analysis for the maintenance period.

Table 57. Infections of Special Interest, Maintenance Period, Study 3101

		Re-randomized Patients	
Preferred Term, n (%)	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Herpes zoster	**0**	**1 (0.4)**	**5 (2.2)**
Herpes simplex	**0**	**0**	**4 (1.7)**

Source: Reviewer's table, created from ADAE dataset

The rates of herpes zoster and Herpes simplex were higher in patients re-randomized to ozanimod versus placebo. All cases of herpes simplex were mild, non-disseminated, non-serious, and resolved (in 3 cases with no changes in ozanimod dose and 1 case with dose interruption).re-randomized There were no cases of tuberculosis, systemic fungal infections, protozoan infections, or cryptococcal infections.

8.3.10. Safety Analyses by Demographic Subgroup

Subgroup analyses for safety were conducted for age, sex, race, prior TNF failure, and CS use at baseline.

The number of geriatric patients (aged ≥65 years of age) was too small to make meaningful interpretation of subgroup analyses.

The safety profile appeared comparable for males versus females; no clear trend was observed.

Evaluation by reported racial group is shown below in Table 58 below, for the induction period in Study 3101. There was no clear signal of a differential safety profile in different racial subgroups (Asian, black, other) as compared to white – though the interpretations are limited by the small number of patients in several subgroups.

Table 58. Safety Analyses by Race, Induction Period, Cohort 1, Study 3101

Race	Ozanimod	Placebo	Treatment Difference
Asian	**N = 36 (%)**	**N = 17 (%)**	
TEAEs	13 (36.1%)	7 (41.2%)	-5.1%
SAEs	4 (11.1%)	2 (11.8%)	-0.7%
Severe AEs	4 (11.1%)	1 (5.9%)	5.2%
Black	**N = 14 (%)**	**N = 4 (%)**	
TEAEs	6 (42.9%)	1 (25%)	17.9%
SAEs	0 (0%)	0 (0%)	0%
Severe AEs	0 (0%)	0 (0%)	0%
White	**N = 370 (%)**	**N = 192 (%)**	
TEAEs	149 (40.3%)	73 (38.0%)	2.3%
SAEs	12 (3.2%)	4 (2.1%)	1.1%
Severe AEs	10 (2.7%)	3 (1.6%)	1.1%
Other	**N = 9 (%)**	**N = 3 (%)**	
TEAEs	4 (44.4%)	1 (33.3%)	11.1%
SAEs	1 (11.1%)	1 (33.3%)	-22.2%
Severe AEs	0 (0%)	0 (0%)	0%

Source: Reviewer's table, created from ADAE dataset
Abbreviations: SAEs = severe adverse events; TEAEs = treatment-emergent adverse events

Safety analyses based upon corticosteroid (CS) use at screening (yes or no) were conducted for the induction and maintenance periods in Study 3101. Details shown in Appendix, Subgroup Analyses, Table 89 and Table 90. Overall, for the subgroup of patients who reported CS use at

screening, in both the induction and maintenance periods, there were more TEAEs in the ozanimod treatment arm when compared to the placebo arm (induction: 47% versus 37%, maintenance: 65% versus 37%). However, in the subgroup of patients that did not report use of CS at screening, the percentages of TEAE were similar between ozanimod and placebo (induction: 37% versus 39%, maintenance: 43% versus 36%). Reassuringly, the rates of SAEs, severe AEs, and serious infections were similar regardless of CS status at screening. The higher rates of TEAEs overall in the subgroup of patients who reported use of CS at screening may be related to more severe or refractory disease at baseline.

Safety analyses by prior TNFi status (yes or no) for the induction and maintenance periods in Study 3101 were also conducted. Similar to prior CS use, during the induction and maintenance periods, in the subgroup of patients who reported prior TNF use, there was a higher rate of ozanimod-treated patients reporting one or more TEAEs when compared to placebo (induction: 56% versus 48%, maintenance: 58% versus 40%). Again, patients with prior TNF exposure are known to have more refractory disease, and may be expected to have an increased rate of any TEAEs, which may be driven in part by UC related AEs. The rates of severe and serious AEs were not consistently different between subgroups and do not suggest an overall worse safety profile in patients with prior TNF exposure. See Table 91 and Table 92 in the Appendix, Subgroup Analyses.

8.3.11. Additional Safety Explorations

Supportive Safety Data – Study RPC01-3103

Study PRC01-3103 is a phase 2/3 multicenter, randomized, double-blind, placebo-controlled study of ozanimod being conducted in Japan. Currently 88 patients have been randomized, and 9 have completed Week 52. Within the 90 day safety update, the Applicant provided a summary of reported SAEs in this trial (which remains blinded). This included 5 SAEs, 3 of which occurred prior to any study treatment administered. The remaining 2 events were worsening of bipolar disorder, and worsening of UC.

Human Reproduction and Pregnancy

Ozanimod is labeled with a Warning for fetal risk, on the basis of animal data (details in Section 8.1 of current prescribing information). No new data on the riks in pregnancy were submitted in this sNDA. The Applicant was issued post-marketing requirements to collect data on pregnancy outcomes in women who may be exposed to ozanimod during pregnancy at the time of approval for the MS indication. Similar PMRs will be issued for UC (see Section 13 below).

Pediatrics and Assessment of Effects on Growth

Currently no data are available on the use of ozanimod in pediatric patients. The Applicant received orphan designation for the indication of pediatric UC, however, does plan to complete a pediatric development program. See Sections 10 and 13 for additional detail.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There are no specific concerns about drug abuse potential or withdrawal with ozanimod use in UC.

Safety in the Postmarket Setting

Ozanimod was recently approved (March 2020) for the MS indication; therefore, safety data from the post-marketing setting are still somewhat limited. The most recent periodic safety report was reviewed by DNP (report in DARRTS by Dr. David Jones, dated April 30, 2021) and did not identify any new safety signals.

Expectations on Safety in the Postmarket Setting

Enhanced pharmacovigilance will be conducted to further assess the risk of hepatotoxicity and the potential increased risk of malignancy. The Applicant agreed to expedite reports of liver injury or malignancy (from any indication) (b) (4)

8.4. Conclusions on Safety

The safety profile of ozanimod for the treatment of moderately to severely active UC was appropriately characterized within the UC development program and supports approval of this supplemental NDA.

Safety in the induction period was assessed both utilizing RPC01-3101 (blinded comparison between treatment arms in cohort 1) and in an integrated analysis utilizing Study RPC01-3101, as well as additional data from the phase 2 trial RPC01-202, which had similar trial design and patient population. Within the induction period, the most common adverse reactions included upper respiratory tract infection, liver test elevation, headache, pyrexia, nausea and arthralgia.

In the maintenance period, safety was assessed using the maintenance period data from RPC01-3101 (patients who achieved clinical response to ozanimod at the end of induction, and were re-randomized to receive ozanimod or placebo through Week 52). The most common adverse reactions in the maintenance period included liver test elevation elevation and headache.

Exposure-adjusted analyses of the Pool G data (all controlled trials for UC indication),which incorporated the open-label extension data, did not identify other safety signals.

In general, the safety profile of ozanimod for the treatment of UC was similar to the labeled safety profile in MS patients. Signals of potential hepatotoxicity were identified. At this time no cases of hepatic failure have been identified with ozanimod use, and the label contains information for providers to monitor patients' liver enzymes, and to discontinue use if clinically significant elevations occur, or if clinically apparent hepatic injury occurs. Further evaluation of this safety signal will occur via enhanced pharmacovigilance and expedited reporting of hepatoxicity events.

The safety database and overall exposure to the drug in UC patients was reasonable and comparable to what has been utilized to support the approval of other drugs for UC. Feasibility limits the size and scope of the safety database and therefore some residual uncertainty exists, particularly around potential AES with long latency periods, such as malignancy. Although a clear signal for increased risk of malignancy in UC patients treated with ozanimod was not identified within the available pre-market database, additional enhanced pharmacovigilance will be conducted for malignancy as well.

In conclusion, the risks of ozanimod will be communicated via labeling, and the overall benefit-risk profile supports approval.

9. Advisory Committee Meeting and Other External Consultations

Not applicable

10. Pediatrics

On December 29, 2015, orphan-drug designation was granted for ozanimod, for the treatment of UC in pediatric patients (0 through 16 years of age). The UC program is therefore exempt from the Pediatric Research Equity Act (PREA) requirements. The Applicant is requesting a waiver of the requirement to perform a pediatric trial for patients with UC.

Although the Applicant tried to enroll adolescents into Study RPC01-3101 (via Protocol RPC01-3101 Amendment #6 and RPC01-3102 Amendment #6, submitted in 2019) they ultimately were not able to recruit any adolescent patients.

The Applicant now intends to conduct a single phase 2/3 trial in pediatric patients aged 2 to <18 years of age, intended to support expansion of the label to include pediatric UC population. The Division and the Applicant have met several times to negotiate the details of the proposed study, including via parallel scientific advice process including EMA to achieve alignment on a global program, and the protocol is expected to be finalized in the next 2 months. The Applicant

has agreed to conduct the pediatric program as a post-marketing commitment (see Section 13 below).

11. Labeling Recommendations

11.1. Prescribing information

Refer to the approved labeling for the final language. The key changes made to the label are summarized below:

Section 1: Indications and Usage:
- Added indication of moderately to severely active UC in adults.

Section 2: Dosage and Administration:
- Modified to note that the approved dosage and titration schedule apply to both MS and UC indications.

Section 5: Warnings and Precautions:
- No new Warnings and Precautions were added.
- The information was updated to include UC specific data to the existing Warnings where applicable

Section 6: Clinical Trials Experience:
- A separate subsection was added for UC, detailing adverse reaction data for induction and maintenance periods separately. The safety profile was generally comparable in UC to that observed in MS.
- Peripheral edema was added as an additional item under "other adverse reactions".

Section 7: Drug Interactions:
- Information was reorganized into tabular format.
- Details were added regarding the potential additive effect on HR with co-administration of a beta blocker and calcium channel clocker.
- Information with co-administration of cyclosporine was updated based on a new drug interaction study with cyclosporine.

Section 12: Clinical Pharmacology:
- (b) (4)
- Information from a new drug interaction study with cyclosporine was added providing PK data for ozanimod's major active metabolites, CC112273 and CC1084037.

- Information for PK of ozanimod and CC112273 in patients who were on concomitant prednisone or prednisolone was added based on population PK analysis.

Section 14: Clinical Studies:

- A new subsection was added providing efficacy data for primary and key secondary endpoints for UC.
    - Information by subgroup based on prior TNF failure was included descriptively.
- The endpoint that the Applicant described as (b) (4) was included but described as "endoscopic-histologic improvement" as there is no agreed upon definition of the term (b) (4) which may be considered promotional. Given uncertainties surrounding optimal evaluation of histologic improvement, a statement was included noting that the association between endoscopic-histologic improvement and long term clinical outcomes / disease progression was not evaluated.
- (b) (4)

11.2. Medication Guide

Ozanimod has an approved medication guide. Minor updates were made to be consistent with the updated labeling and to include information on UC.

12. Risk Evaluation and Mitigation Strategies (REMS)

The risks of ozanimod are adequately communicated in the prescribing information. A REMS is not considered necessary at this time.

13. Postmarketing Requirements and Commitment

13.1. Post-Marketing Requirements (PMRs)

The review team identified the need for additional safety information that cannot be obtained by spontaneously submitted post-marketing reports. The following studies will be required as post-marketing requirements under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.

4066-1 An international, prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of females exposed to ZEPOSIA (ozanimod) during pregnancy with women exposed to any other ulcerative colitis therapy during pregnancy and an unexposed comparator population. External disease matched comparators and use of existing disease registries can be considered. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. This study can be conducted as part of the ongoing study under NDA 209899 PMR 3809-3.

Draft Protocol Submission: 11/2021
Final Protocol Submission: 06/2022
Interim Report #1 Submission: 06/2025
Interim Report #2 Submission: 06/2028
Study Completion: 06/2032
Final Study Report 06/2033

4066-2 A pregnancy outcomes study using a different study design than provided for in PMR 4066-1 (for example, a retrospective cohort study using claims or electronic medical record data) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in females exposed to ZEPOSIA (ozanimod) during pregnancy compared to an unexposed control population. This study can be conducted as part of the ongoing study under NDA 209899 PMR 3809-4.

Draft Protocol Submission: 11/2021
Final Protocol Submission: 06/2022
Interim Report #1 Submission: 06/2025
Interim Report #2 Submission: 06/2028
Study Completion: 06/2032
Final Study Report 06/2033

4066-3 A lactation study (milk only) in lactating women who have received therapeutic doses of ZEPOSIA (ozanimod) using a validated assay to assess concentrations of ZEPOSIA (ozanimod) and its major metabolites in breast milk, and effects on the breastfed infant.

Draft Protocol Submission: 02/2022
Final Protocol Submission: 09/2022
Study Completion: 09/2024
Final Study Report: 09/2025

The Division carefully considered the potential utility of a large, long-term, prospective, observational study to further quantify identified and potential risks that may not have been fully characterized within the pre-market databased (e.g., the potential for increased risk of malignancy, which may take years of treatment exposure to identify). The Division ultimately chose not to require such a study at this time, for the following reasons:

Informed by the enrollment challenges experienced with other such studies that were issued in the past for biologic therapies used for this population, and increasing accessibility to alternate treatment options across multiple mechanisms of action, it is not considered feasible to enroll a new cohort of UC patients into a registry study and generate interpretable data in a reasonable timeframe.

Further, unique challenges exist in attempting to interpret data derived from a prospective, controlled, observational study in UC patients, including the fact that most patients have prior exposure to other treatments with the same types of risks (malignancy, serious infection, etc.), making it difficult to truly isolate any potential additive or new risk that may be incurred from exposure to the study drug. This is further compounded by the fact that many patients switch therapies multiple times over the course of their lifetime. Even if a cohort of patients with limited or well defined prior therapy exposure could be identified and enrolled, the likelihood of subsequent therapy switches occurring while in the study would ultimately limit the ability to generate long-term data on each individual exposure.

The Division requested the Applicant conduct enhanced pharmacovigilance both for malignancy, and also for hepatotoxicity. The Applicant will develop detailed questionnaires to ensure consistent and complete data collection for these events of interest, and expedite reporting of these events (for both indications). The need for further studies can be reconsidered if new safety concerns are identified in the post-marketing surveillance.

13.2. Post-Marketing Commitments

The Applicant received Orphan Drug Designation for the indication of pediatric UC (see Section 10 above) and is exempt from required pediatric studies under PREA. However, the Division anticipates a need for the use of ozanimod in pediatric UC patients, as the treatment was demonstrated to have a favorable benefit-risk profile in adults with UC, and provides a treatment with novel mechanism of action and oral route of administration. Therefore, the Division requested the Applicant's commitment to complete the pediatric UC development program. The Applicant agreed to conduct the development program in pediatric UC as outlined below.

4066-4 A one year, randomized, blinded trial to evaluate the safety, efficacy, and pharmacokinetics of ZEPOSIA (ozanimod) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

Draft Protocol Submission: 12/2020 (received and reviewed)
Final Protocol Submission: 6/2021
Trial Completion: 12/2025
Final Study Report: 06/2026

4066-5 A long term extension study to evaluate the long-term safety of ZEPOSIA (ozanimod) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in postmarketing commitment Study 3. This study can be conducted as part of postmarketing commitment study 4066-4.

Draft Protocol Submission: 12/2020 (received and reviewed as part of the protocol for Study 3 above)
Final Protocol Submission: 06/2021
Trial Completion: 12/2026
Final Study Report: 06/2027

14. Division Director (Clinical, Designated Signatory Authority) Comments

I concur with the recommendation of the review team to approve supplemental NDA 209899/S-001 for Zeposia (ozanimod) for the treatment of moderately to severely active ulcerative colitis (UC) in adults. Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Ozanimod was approved in 2020 for the treatment of relapsing forms of multiple sclerosis, and it will be the first product in this class to be approved for use in patients with UC. The recommended dosage is 0.92 mg taken orally once daily after a 7-day titration. Data submitted in the sNDA support the conclusion that the benefits of treatment with ozanimod in the intended population outweigh the identified risks.

I agree with the review team that data submitted in this sNDA are adequate to support a conclusion that the effectiveness of ozanimod has been established in the intended adult population. The submission included a single, large, adequate and well-controlled trial that included a 10-week induction period and a 42-week maintenance period, for a total controlled study duration of 52 weeks. The primary endpoint of clinical remission achieved statistical significance during both induction and maintenance periods. Secondary endpoints also supported the primary efficacy analyses.

The safety profile was generally consistent with the known adverse event profile for S1P receptor modulators. Some of the adverse events of special interest, such as infections including herpes zoster, and liver injury, are shared across multiple drugs used to treat UC; however, other risks, such as bradyarrhythmia and atrioventricular conduction delays, respiratory effects, and macular edema, are unique to this drug class. The most common adverse reactions reported in clinical trials of patients with UC include liver test increased, upper respiratory infection, and headache. Product Labeling and Medication Guide are adequate to communicate these known and potential risks to healthcare providers and patients, respectively. A REMS will not be required. Post-marketing required studies will assess the pregnancy outcomes following ozanimod exposure during pregnancy and the effect of ozanimod on lactation. In addition, the Applicant will conduct enhanced pharmacovigilance for hepatotoxicity and malignancy.

Ozanimod has an orphan drug designation for pediatric UC and, therefore, the Applicant is exempt from Pediatric Research Equity Act requirements. However, the Applicant agreed to conduct postmarketing commitment studies to assess 1) the safety, efficacy, and pharmacokinetics of ozanimod in pediatric patients 2 to 17 years of age with moderately to severely active UC, and 2) the long-term safety of ozanimod in these pediatric patients.

15. Appendices

15.1. References

Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): RPC01-3101, RPC01-3102, RPC01-202

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1592		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: $70,592 Proprietary interest in the product tested held by investigator: no Significant equity interest held by investigator in Sponsor of covered study: no		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant) Adequate information was provided upon request (response to IR received May 19, 2021)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.3.1. Bioanalytical Method Report

Concentrations in human plasma

The bioanalytical methods for ozanimod and its metabolites CC112273, CC1084037, and RP101988, RP101075, and RP101442 concentrations in plasma in this UC submission were the same as those submitted and reviewed in the original NDA.

Briefly, the Applicant used the validated high-performance liquid chromatography with tandem mass spectrometry detection (LC-MS/MS) methods for the measurement of plasma concentrations for ozanimod and its metabolites.

Bioanalytical analysis reports for phase 1 studies RPC01-1915 and RPC-1063-CP-001 in healthy subjects, phase 2 trial RPC01-202 and phase 3 trial RPC01-3101 in patients with UC are provided in this submission. Assay performance statistics of these bioanalytical in-study analysis are briefly summarized in the table below.

Table 59. Summary of Bioanalytical Methods by Study With Assay Performance Statistics

Clinical Study Brief Name (CTD Module and Section)	Analyte	Matrix	CRO	Method Number	Assay Performance (QC Accuracy, % RE)	Assay Performance (QC Precision, % CV)
Submitted for UC						
RPC01-1915 CSR PK/PD	RPC1063 (ozanimod); CC112273; CC1084037	Plasma	(b) (4)		-0.625 to 5.83 (RPC1063) 4.00 to 7.40 (CC112273) -2.50 to 5.33 (CC1084037)	≤ 9.45 (RPC1063) ≤ 3.45 (CC112273) ≤ 3.48 (CC1084037)
RPC01-202 CSR UC P2	RPC1063 (ozanimod); RP101075; RP101442; RP101988	Plasma			-3.33 to -1.20 -2.50 to 2.13 -4.81 to 0.00 2.59 to 4.50	≤ 5.79 ≤ 8.38 ≤ 6.25 ≤ 9.44
	CC112273	Plasma			-0.400 to 0.00	≤ 4.90
RPC1063-CP-001 CSR	RPC1063 (ozanimod); CC112273; CC1084037	Plasma			-1.50 to 2.00 -0.400 to 3.73 -2.50 to 1.67	≤ 5.85 ≤ 5.94 ≤ 3.93
	RP101988	Plasma			-0.833 to 2.50	≤ 7.90
RPC01-3101 CSR UC P3	RPC1063 (ozanimod)	Plasma			-1.38 to 0.833	≤ 14.7
	CC112273	Plasma			-0.163 to 2.00	≤ 10.9
	CC1084037	Plasma			1.67 to 5.47	≤ 6.77

Source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 15
Abbreviations: CRO = contract research organization; CTD = Common Technical Document; CV = coefficient of variation; QC = quality control; UC = ulcerative colitis

15.3.2. Pharmacometric Assessment

The Applicant's population PK (PopPK) analysis included pooled PK data from phase 2 trial RPC01-202 and phase 3 trial RPC01-3101 in patients with moderate to severe UC, three relapsing forms of multiple sclerosis (RMS) studies for disease comparison (RPC01-1001, RPC01-

201B and RPC01-301); and six phase 1 clinical pharmacology studies in healthy volunteers (RPC01-1910, -1911, -1912, -1913, -1914 and -1915). For population PK/PD analysis, all studies included in the PopPK analysis were also included for the ALC PK/PD analysis. For E-R efficacy analysis for clinical remission, only the UC phase 3 study (RPC01-3101) was included. For the E-R safety analysis (ALT/AST, infections), 2 RMS studies (RPC01-201B and RPC01-301) were also included along with the UC phase 3 study (RPC01-3101).

Table 60. Summary of Phase 2 and 3 Clinical Trials in Patients With Moderate to Severe Ulcerative Colitis Included in the Population PK and PK/PD Analysis

Protocol Number and Title	Treatment	Sample Size	PK Sampling Schedule
RPC01-202: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Parallel-group Study to Evaluate the Clinical Efficacy and Safety of Induction Therapy With RPC1063 in Patients With Moderately to Severely Active Ulcerative Colitis	Ozanimod 0.25 mg on Days 1-4, 0.5 mg on Days 5-7 and the assigned treatment dose of 0.5 or 1 mg QD, starting on Day 8 up to 8 weeks.	Up to 180 patients	Day 1: Predose and just prior to discharge from the clinic (6-8 hours postdose). Weeks 4 and 20: 2-6 hours after dosing. Weeks 8 and 32: trough level, taken just prior to dose administration.
RPC01-3101: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis	Cohort 1: RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod0.92 mg) or placebo QD Cohort 2: Open-label RPC1063 1 mg QD Cohort 3: RPC1063 1 mg or placebo QD	Up to 900 adult patients	Induction Period: Day 1: Predose and 6-8 hours postdose. Day 35: 2-6 hours after dosing Day 70: Predose Maintenance Period: Day 1: Predose Day 294: Predose

Source: Clinical PK Report CLG-Certara-UC-358-1, Table 1
Abbreviations: PK = pharmacokinetics; PD = pharmacodynamics; QD = once daily

Table 61. Summary of Key Categorical Demographics for Subjects Included in Population Pharmacokinetic Analysis

	RPC01-1910 (N=56)	RPC01-1911 (N=69)	RPC01-1912 (N=80)	RPC01-1913 (N=26)	RPC01-1914 (N=28)	RPC01-1001 (N=24)	RPC01-201B (N=830)	RPC01-301 (N=892)	RPC01-202 (N=96)	RPC01-3101 (N=789)	Overall (N=2890)
Sex											
Female	26 (46.4%)	13 (18.8%)	34 (42.5%)	11 (42.3%)	12 (42.9%)	17 (70.8%)	551 (66.4%)	588 (65.9%)	47 (49.0%)	334 (42.3%)	1633 (56.5%)
Male	30 (53.6%)	56 (81.2%)	46 (57.5%)	15 (57.7%)	16 (57.1%)	7 (29.2%)	279 (33.6%)	304 (34.1%)	49 (51.0%)	455 (57.7%)	1257 (43.5%)
Race											
White	33 (58.9%)	36 (52.2%)	42 (52.5%)	13 (50.0%)	13 (46.4%)	18 (75.0%)	820 (98.8%)	887 (99.4%)	87 (90.6%)	701 (88.8%)	2650 (91.7%)
Black or African American	22 (39.3%)	0 (0%)	31 (38.8%)	12 (46.2%)	12 (42.9%)	5 (20.8%)	8 (1.0%)	2 (0.2%)	2 (2.1%)	24 (3.0%)	118 (4.1%)
Asian	0 (0%)	33 (47.8%)	4 (5.0%)	1 (3.8%)	0 (0%)	1 (4.2%)	0 (0%)	2 (0.2%)	4 (4.2%)	48 (6.1%)	93 (3.2%)
American Indian/Alaskan Native	0 (0%)	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.0%)
Other	1 (1.8%)	0 (0%)	2 (2.5%)	0 (0%)	3 (10.7%)	0 (0%)	2 (0.2%)	1 (0.1%)	2 (2.1%)	16 (2.0%)	27 (0.9%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)	1 (0.0%)
Health Status											
Healthy	56 (100%)	69 (100%)	80 (100%)	26 (100%)	28 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	259 (9.0%)
Relapsing multiple sclerosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	24 (100%)	830 (100%)	892 (100%)	0 (0%)	0 (0%)	1746 (60.4%)
Ulcerative Colitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	96 (100%)	789 (100%)	885 (30.6%)
Hepatic Function Categories											
Normal	56 (100%)	65 (94.2%)	78 (97.5%)	24 (92.3%)	28 (100%)	21 (87.5%)	734 (88.4%)	793 (88.9%)	91 (94.8%)	732 (92.8%)	2622 (90.7%)
Mild	0 (0%)	4 (5.8%)	2 (2.5%)	2 (7.7%)	0 (0%)	3 (12.5%)	90 (10.8%)	93 (10.4%)	5 (5.2%)	56 (7.1%)	255 (8.8%)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (0.7%)	6 (0.7%)	0 (0%)	1 (0.1%)	13 (0.4%)
Renal Function Categories											
Normal	45 (80.4%)	60 (87.0%)	52 (65.0%)	17 (65.4%)	25 (89.3%)	12 (50.0%)	703 (84.7%)	616 (69.1%)	55 (57.3%)	436 (55.3%)	2021 (69.9%)
Mild	11 (19.6%)	9 (13.0%)	28 (35.0%)	9 (34.6%)	3 (10.7%)	11 (45.8%)	126 (15.2%)	272 (30.5%)	37 (38.5%)	334 (42.3%)	840 (29.1%)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.2%)	1 (0.1%)	4 (0.4%)	4 (4.2%)	19 (2.4%)	29 (1.0%)
Smoking Status											
Smoker	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (41.7%)	191 (23.0%)	212 (23.8%)	4 (4.2%)	42 (5.3%)	459 (15.9%)
Non-smoker	56 (100%)	69 (100%)	80 (100%)	26 (100%)	28 (100%)	14 (58.3%)	639 (77.0%)	680 (76.2%)	92 (95.8%)	747 (94.7%)	2431 (84.1%)

Source: Clinical PK Report CLG-Certara-UC-358-1, Table 3.1
Note: Hepatic function classification was based on Organ Dysfunction Working Group of the National Cancer Institute (NCI-ODWG) using total bilirubin and AST or ALT.

Table 62. Summary of Key Continuous Demographics for Subjects Included in Population Pharmacokinetic Analysis

	RPC01-1910 (N=56)	RPC01-1911 (N=69)	RPC01-1912 (N=80)	RPC01-1913 (N=26)	RPC01-1914 (N=28)	RPC01-1001 (N=24)	RPC01-201B (N=830)	RPC01-301 (N=892)	RPC01-202 (N=96)	RPC01-3101 (N=789)	Overall (N=2890)
Age (years)											
Mean (SD)	36.3 (9.90)	35.8 (9.19)	34.8 (10.0)	35.8 (8.28)	38.3 (12.0)	38.8 (8.36)	35.7 (8.88)	35.4 (9.37)	41.4 (12.2)	41.7 (13.6)	37.5 (11.1)
Median [Min, Max]	36.5 [19.0, 53.0]	35.0 [20.0, 53.0]	33.0 [18.0, 55.0]	34.0 [25.0, 53.0]	37.5 [19.0, 55.0]	38.5 [23.0, 51.0]	35.0 [18.0, 55.0]	35.0 [18.0, 55.0]	40.0 [18.0, 73.0]	40.0 [18.0, 74.0]	36.0 [18.0, 74.0]
Height (cm)											
Mean (SD)	169 (10.2)	171 (8.92)	170 (9.26)	170 (8.43)	168 (9.51)	169 (5.91)	170 (9.13)	170 (8.68)	171 (8.91)	171 (9.18)	170 (9.01)
Median [Min, Max]	171 [147, 193]	172 [150, 193]	170 [149, 190]	171 [152, 183]	167 [151, 193]	169 [157, 182]	169 [150, 198]	168 [140, 197]	170 [152, 195]	171 [146, 203]	170 [140, 203]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)	0 (0%)	0 (0%)	2 (0.3%)	4 (0.1%)
Weight (kg)											
Mean (SD)	74.9 (12.4)	69.4 (10.9)	75.3 (11.4)	74.0 (11.7)	75.4 (12.9)	86.8 (23.8)	70.0 (15.9)	69.6 (15.5)	73.2 (16.7)	75.3 (18.4)	71.9 (16.6)
Median [Min, Max]	75.5 [51.7, 110]	69.2 [45.9, 88.6]	75.0 [51.8, 102]	74.1 [52.3, 97.1]	77.0 [52.3, 110]	80.9 [54.1, 132]	68.0 [40.5, 165]	67.0 [40.0, 162]	70.0 [45.4, 128]	73.0 [37.8, 173]	70.0 [37.8, 173]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	1 (0.0%)
Body Mass Index (kg/m^2)											
Mean (SD)	26.0 (2.77)	23.5 (2.46)	26.0 (2.45)	25.4 (2.71)	26.4 (2.60)	30.2 (7.88)	24.2 (4.67)	24.1 (4.68)	25.0 (5.27)	25.6 (5.64)	24.7 (4.95)
Median [Min, Max]	26.6 [19.4, 29.8]	23.1 [18.2, 29.6]	26.4 [20.3, 30.0]	25.2 [20.5, 29.6]	27.2 [20.9, 29.8]	28.1 [18.5, 45.4]	23.7 [15.8, 55.8]	23.4 [14.9, 48.4]	24.1 [17.4, 44.3]	24.7 [15.3, 51.8]	24.1 [14.9, 55.8]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)	0 (0%)	0 (0%)	2 (0.3%)	4 (0.1%)

Source: Clinical PK Report CLG-Certara-UC-358-1, Table 3.2
Abbreviations: SD = standard deviation; min = minimum; max = maximum

Population PK Analysis

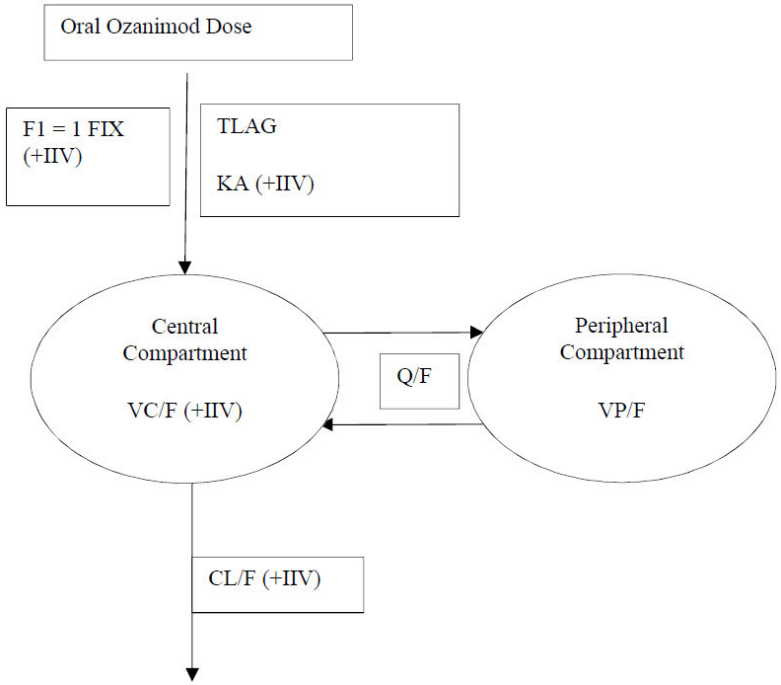
The PopPK model used to characterize the PK of ozanimod and its major active metabolite CC112273 in patients with UC is the same model that characterized the PK in healthy subjects and patients with MS in the original NDA submission. Refer to the Office of Clinical Pharmacology Review in DARRTS (dated December 9, 2019) for more details of the model.

The final PopPK dataset included 3120 ozanimod plasma concentrations from 982 patients with UC and 2561 CC112273 plasma concentrations from 885 patients with UC from phase 2 trial RPC01-202 and phase 3 trial RPC01-3101.

PopPK analysis of CC112273

The basic PopPK structure model for CC112273 consisted of a two-compartment model with first-order formation rate of CC112273 (including a fixed-length lag time) and first-order elimination.

Figure 10. Schematic Representation of the Structural Population Pharmacokinetic Model of CC112273



Source: Clinical PK Report CLG-Certara-UC-358-1, Figure 5
Abbreviations: CL/F = apparent clearance; F1 = relative bioavailability; IIV = interindividual variability; KA = first order absorption rate constant; Q/F = apparent intercompartmental clearance; TLAG = lag time; VC/F = apparent volume of distr bution of the central compartment; VP/F = apparent volume of distribution of the peripheral compartment

For covariate analyses, baseline age, sex, race, body weight, bilirubin, hepatic function (subjects with hepatic impairment versus subjects with normal hepatic function, based on NCI-ODWG classification using total bilirubin and AST or ALT), eGFR, renal function, disease type, and smoking status were tested for their potential influence on the apparent clearance, apparent central volume of distribution, and absorption rate constant (i.e., formation rate from ozanimod to CC112273) of CC112273 as presented in Table 63.

Table 63. Summary of Covariates Assessed in the Population Pharmacokinetic Analysis of CC112273

Covariate	CL/F	VC/F	KA
Age	√	√	√
Sex	X	X	X
Race	√	-	-
Body weight	X	X	X
Bilirubin	X	-	-
Hepatic Function	X	X	X
eGFR	√	-	-
Renal Function	√	-	-
Disease Type	X	√	√
Smoking Status	X	-	-

Source: Clinical PK Report CLG-Certara-UC-358-1, Table 7.2
Abbreviations: CL/F = apparent clearance; eGFR = estimated glomerular filtration rate (derived using the Modification of Diet in Renal Disease formula); KA = first-order formation rate constant; VC/F = apparent volume of distribution of the central compartment.
Note: √ = to be tested; X = included as part of the previous model

Briefly, the full-model approach was implemented as the primary covariate analysis methodology. A univariate analysis was used to assist in selecting covariates for the full model. In this process, the covariates of interest were introduced into the previous PK model one at a time. Only the covariates that are deemed significant (i.e., a decrease >6.63 in objective function value [OFV]) were included in the full model. In the full-model, covariates were statistically insignificant if the 95% confidence intervals (CIs) of the covariate effect parameter include the null value (1 for categorical and 0 for continuous). Covariates are considered clinically unimportant if the 95% CIs of the covariate effect is within 25% of the null value. During backward elimination, a covariate that was deemed insignificant (i.e., an increase >10.83 in OFV) was removed from the model for the following step. The final PopPK model that best described CC112273 PK was a 2-compartment model with first-order absorption rate to reflect a formation rate from ozanimod to CC112273 and first-order elimination rate. The PK parameter estimates from the final PopPK model are summarized in Table 64.

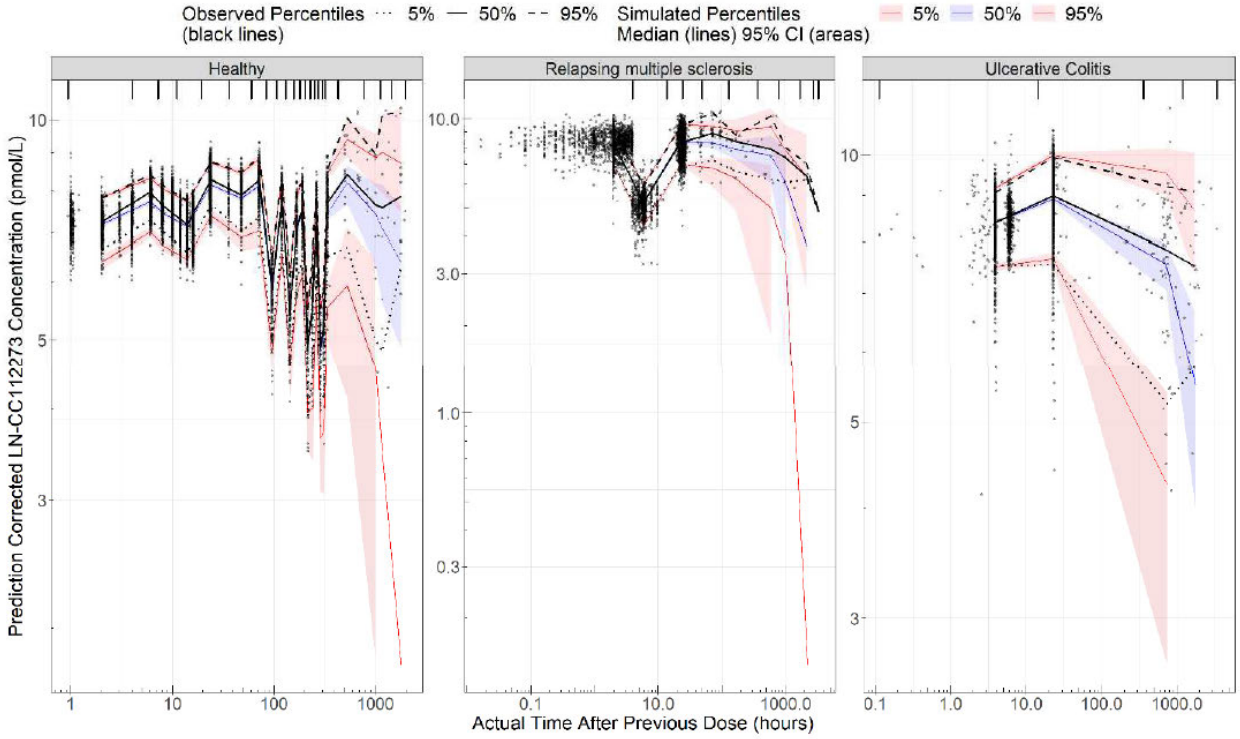
Table 64. Parameter Estimates for the Final PopPK Model for CC112273

Parameter [Units]	Parameter Estimate	SIR Median	RSE (%)	95% CI[a]
Fixed Effects				
KA [h^{-1}]	0.0593	0.0592	0.0547	0.0591, 0.0593
CL/F [L/h]	13.9	13.9	3.23	13.0, 14.8
Q/F [L/h]	66.0	66.0	2.10	63.3, 68.7
VC/F [L]	870	866	6.39	782, 971
VP/F [L]	3909	3910	1.53	3790, 4030
TLAG [h]	0.917	0.917	0.773	0.904, 0.931
F1	1.00 Fixed	1.00 Fixed	NA	NA
Covariates Effects				
Body weight on CL/F	-0.429	-0.429	18.2	-0.579, -0.274
Age on CL/F	-0.238	-0.239	22.2	-0.340, -0.139
Bilirubin on CL/F	-0.0560	-0.0562	53.7	-0.114, 0.00416
Sex on CL/F (female)	-0.396	-0.397	8.94	-0.464, -0.325
Race on CL/F (non-white)	-0.336	-0.338	17.2	-0.462, -0.232
Disease type on CL/F (healthy)	0.119	0.118	47.2	0.0101, 0.228
Disease type on CL/F (RMS)	0.155	0.152	22.8	0.0877, 0.226
Smoking status on CL/F (smoker)	0.735	0.733	5.50	0.649, 0.806
Hepatic impairment on CL/F	-0.0945	-0.0962	55.0	-0.198, 0.0101
Body weight on VC/F	2.73	2.73	4.78	2.47, 2.97
Sex on VC/F (female)	0.507	0.507	8.34	0.425, 0.582
Hepatic impairment on VC/F	0.136	0.138	78.6	-0.0889, 0.334
Body weight on KA	2.38	2.37	5.28	2.13, 2.62
Sex on KA (female)	0.807	0.807	1.82	0.780, 0.836
Hepatic impairment on KA	0.125	0.127	95.0	-0.103, 0.356
Disease type on KA (healthy)	-0.228	-0.228	5.03	-0.249, -0.206
Disease type on KA (RMS)	-0.0147	-0.0143	31.4	-0.0232, -0.00567
IIV Model Parameters				
Variance for *KA*	0.0875	0.0874	8.50	0.0733, 0.102
Variance for *CL/F*	0.469	0.468	3.10	0.441, 0.498
Variance for *VC/F*	0.0443	0.0442	17.1	0.0306, 0.0596
Variance for *F1*	0.0508	0.0510	6.68	0.0434, 0.0570

Residual Error				
Additive error for subjects with RMS or UC	0.264	0.264	1.04	0.258, 0.269
Additive error for healthy	0.136	0.136	0.777	0.134, 0.138

Source: Clinical PK Report CLG-Certara-UC-358-1, Table 18
Abbreviations: CI = confidence interval; CL/F = apparent clearance; F1 = bioavailability; IIV = interindividual variability; KA = first-order absorption rate constant; NA = not applicable; Q/F = apparent intercompartmental clearance; RMS = relapsing multiple sclerosis; RSE = relative standard error; SIR = sampling importance resampling; VC/F =apparent volume of distribution of the central compartment; VP/F = apparent volume of distribution in the peripheral compartment; UC = ulcerative colitis
a) CI values are based on the SIR calculations (0.025 and 0.975 quantiles

Figure 11. Visual Predictive Check of the Final PopPK Model for CC112273



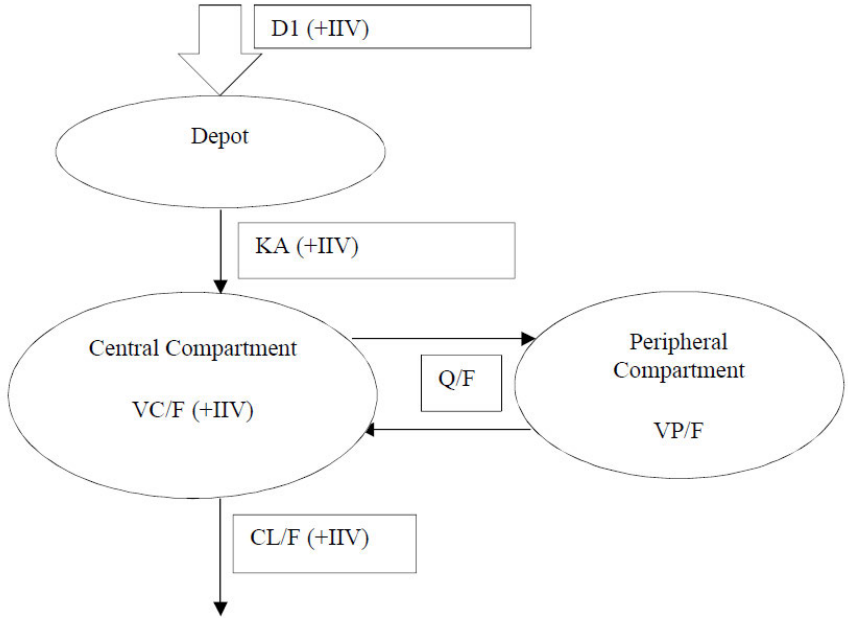
Source: Clinical PK Report CLG-Certara-UC-358-1, Figure 11
Note: Black dots represent observed data, and black dash lines represent observed 5th, 50th, and 95th percentiles. Solid lines represent the 5th (blue), 50th (red), and 95th (blue) percentiles of the simulated data. Shaded areas represent 95% CIs about the 5th, 50th, and 95th percentiles for the corresponding simulated data.

Overall, the PopPK model estimated the typical values of CL/F (UC population) and VC/F of CC112273 were 13.9 L/h and 870 L, respectively. The terminal elimination half-life of CC112273 was 272.8 hours (approximately 11.4 days). Mean CC112273 PK parameters in patients with UC estimated using PopPK analysis are summarized in Table 6.

PopPK analysis of ozanimod

The overall approach for the development of the ozanimod PopPK model was similar to that described for CC112273. The basic PopPK structure model for ozanimod consisted of a two-compartment model with combined zero- and first-order absorption processes.

Figure 12. Schematic Representation of the Structural Population Pharmacokinetic Model of Ozanimod



Source: Clinical PK Report CLG-Certara-UC-358-1, Figure 6
Abbreviations: CL/F = apparent clearance; D1 = zero order input duration; IIV = interindividual variability; KA = first order absorption rate constant; Q/F = apparent intercompartmental clearance; VC/F = apparent volume of distribution of the central compartment; VP/F = apparent volume of distribution of the peripheral compartment

For covariate analyses, baseline age, sex, race, body weight, ALT, AST, bilirubin, hepatic function (subjects with hepatic impairment versus subjects with normal hepatic function), eGFR, renal function (subjects with renal impairment versus subjects with normal renal function), disease type, formulation, and smoking status were tested for their potential influence on the apparent clearance, apparent central volume of distribution, and absorption rate constant of ozanimod as presented in Table 65.

Table 65. Summary of Covariates Assessed in the Population Pharmacokinetic Analysis of Ozanimod

Covariate	CL/F	VC/F	KA
Age	X	√	-
Sex	√	√	√
Race	√	-	-
Body weight	X	√	√
ALT[a]	√	√	-
AST[a]	√	√	-
Total bilirubin[a]	√	√	-
Hepatic function[a]	√	√	-
eGFR	√	-	-
Renal function	√	-	-
Disease type	√	√	√
Formulation	-	-	√
Smoking status	√	-	-

Source: Clinical PK Report CLG-Certara-UC-358-1, Table 14
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CL/F = apparent clearance; eGFR = estimated glomerular filtration rate; KA = first-order absorption rate constant; VC/F = apparent volume of distribution of the central compartment.
a) For covariates identified to show collinearity (correlation efficient >0.5), only one of them was considered for the covariate modeling.
Note: √ = to be tested; X = included as part of the previous model

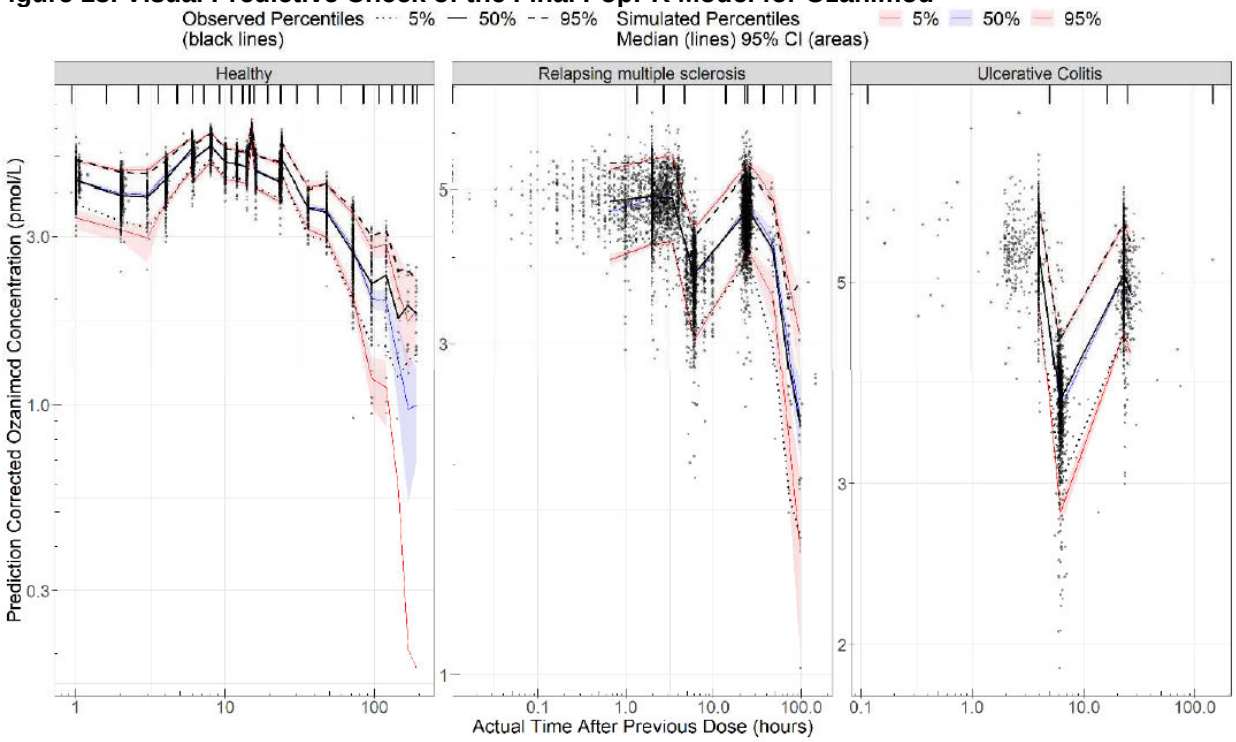
A similar PopPK strategy was followed for the final model of ozanimod as described for CC112273. The final PopPK model that best described ozanimod PK was a 2-compartment open model with combined zero- and first-order absorption processes. The PK parameter estimates from the final PopPK model are summarized in Table 66.

Table 66. Parameter Estimates for the Final PopPK Model for Ozanimod

Parameter [Units]	Parameter Estimate	SIR Median	RSE (%)	95% CI[a]
Fixed Effects				
KA [h^{-1}]	0.0448	0.0449	2.31	0.043, 0.0471
CL/F [L/h]	174	174	1.08	171, 178
Q/F [L/h]	16.4	16.3	15.7	12, 21.9
VC/F [L]	119	120	10.3	95.4, 143
VP/F [L]	840	838	7.99	720, 980
D1[h]	6.74	6.74	0.0237	6.74, 6.74
Covariates Effects				
Body weight on CL/F	0.523	0.525	4.74	0.477, 0.576
Age on CL/F	-0.144	-0.143	14.5	-0.183, -0.102
eGFR on CL/F	0.126	0.127	22	0.0686, 0.178
Bilirubin on CL/F	0.0538	0.0538	21.3	0.03, 0.0741
Disease type on CL/F (healthy)	0.0590	0.0587	32.9	0.0197, 0.0966
Disease type on CL/F (RMS)	-0.0834	-0.082	16.5	-0.108, -0.0563
Disease type on VC/F (healthy)	-0.0140	0.0119	689	-0.16, 0.231
Disease type on VC/F (RMS)	-0.923	-0.981	9.84	-1.17, -0.795
Body weight on KA	-0.353	-0.357	10.2	-0.427, -0.285
Sex on KA (female)	0.0861	0.086	18.3	0.0537, 0.115
Disease type on KA (healthy)	-0.0981	-0.101	20.1	-0.134, -0.0578
Disease type on KA (RMS)	-0.175	-0.18	10.6	-0.21, -0.139
IIV Model Parameters				
Variance for *KA*	0.0286	0.0288	8.7	0.024, 0.0337
Variance for *CL/F*	0.0612	0.0613	4.12	0.0563, 0.0663
Variance for *VC/F*	1.58	1.58	7.58	1.36, 1.83
Variance for *D1*	0.0483	0.0487	11.9	0.0382, 0.061
Residual Error				
Additive error for subjects with RMS or UCs	0.322	0.322	1.04	0.316, 0.329
Additive error for healthy	0.151	0.151	0.0144	0.151, 0.152

Source: Clinical PK Report CLG-Certara-UC-358-1, Table 27
Abbreviations: CI = confidence interval; CL/F = apparent clearance; D1 = zero-order input duration; IIV = interindividual variability; KA = first-order absorption rate constant; Q/F = apparent intercompartmental clearance; RSE = relative standard error; VC/F = apparent volume of distribution of the central compartment; VP/F = apparent volume of distribution of the peripheral compartment; UC = ulcerative colitis

Figure 13. Visual Predictive Check of the Final PopPK Model for Ozanimod



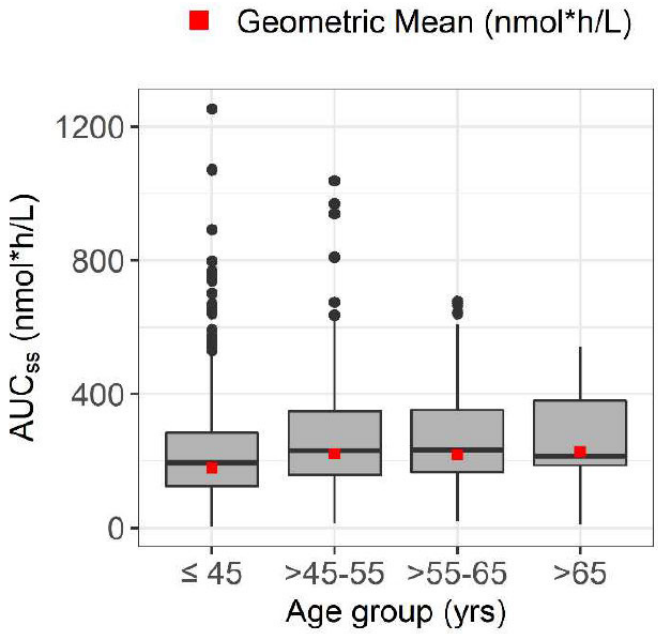
Source: Clinical PK Report CLG-Certara-UC-358-1, Figure 23
Note: Black dots represent observed data, and black dash lines represent observed 5th, 50th, and 95th percentiles. Solid lines represent the 5th (blue), 50th (red), and 95th (blue) percentiles of the simulated data. Shaded areas represent 95% CIs about the 5th, 50th, and 95th percentiles for the corresponding simulated data.

Overall, the PopPK model estimated typical values of CL/F and VC/F of ozanimod were 174.0 L/h and 119 L, respectively. The terminal elimination half-life of ozanimod was 38.9 hours. Mean ozanimod pharmacokinetic parameters in patients with UC estimated using PopPK analysis are summarized in Table 6.

Effect of Age on PK

Although age was identified as a statistically significant covariate on CL/F of CC112273 and included in the final PopPK model, the CL/F of CC112273 appears to only slightly decrease with increasing age. Population PK analyses estimated that steady state AUCss of CC112273 in UC patients over 65 years of age was approximately 3% to 4% greater than patients 45 to 65 years of age and approximately 27% greater than adult patients under 45 years of age (Figure 14.). As such, the effect of age on the steady state exposure of CC112273, the major active metabolite, is not considered clinically relevant in UC patients based on PopPK analysis.

Figure 14. Estimated AUCs of CC112273 Following 0.92 mg Once Daily by Age Group in UC Patients



Source: Clinical PK/PD Report CLG-Certara-UC-358-1, Appendix A, Figure 8.11.

Concomitant use of prednisone and prednisolone

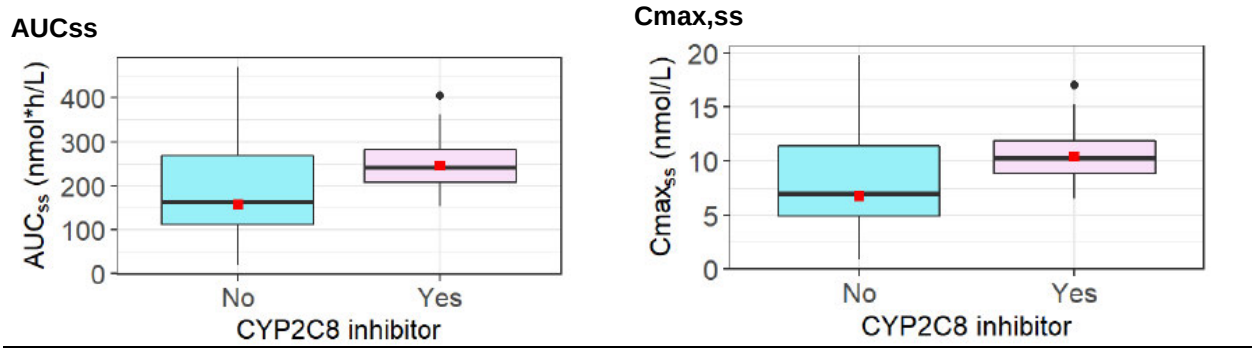
Concomitant administration of prednisone or prednisolone was evaluated in the PopPK analysis as a time-dependent covariate on PK of ozanimod and CC112273. Based on results, the impact on PK was insignificant for both CC112273 and the parent drug ozanimod. Concomitant use of prednisone or prednisolone (N=263 subjects) was associated with a 7.1% reduction in apparent clearance of CC112273 and a 12% reduction in apparent clearance of ozanimod.

Of note, PopPK analysis for CC1084037 has not been conducted and the impact of prednisone or prednisolone on the exposure of CC1084037 is not yet known.

Effect of CYP2C8 inhibitors on PK

The effect of co-administration of CYP2C8 inhibitors on PopPK-estimated post hoc exposure estimates (Cmax,ss and AUCss for ozanimod 0.92 mg) based on data from a previously conducted dedicated DDI study RPC01-1912 in healthy subjects (reviewed in the original NDA) was also explored using boxplots for subjects from group A (treated with ozanimod) and from group B (treated with ozanimod with concomitant intake of gemfibrozil), as presented in Figure 15.

Figure 15. Comparison of CC112273 Individual Estimates of AUCss and Cmax,ss at a Dose of 0.92 mg Ozanimod Between Arm 19 and Arm 20 of Study RPC01-1912



Source: Clinical PK/PD Report CLG-Certara-UC-358-1, Figure 17.
Red solid squares represent geometric means.

Based on PopPK analysis, the geometric mean of individual estimates of exposure parameters for CC112273 was higher in subjects who had concomitant intake of CYP2C8 inhibitors compared to subjects who received ozanimod alone. Of note, in the original NDA, data from this dedicated DDI study RPC01-1912 indicated that 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. Overall, PopPK estimated exposure parameters for CC112273 are generally consistent with the previous findings from the dedicated DDI study RPC01-1912.

In this submission, the Applicant proposed to revise the labeling to state that (b) (4) instead of "co-administration of ZEPOSIA with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended" as stated in the current labeling. From a clinical pharmacology perspective, given that the current labeling regarding strong CYP2C8 inhibitors is based on the PK results from the previously conducted and reviewed dedicated DDI study RPC01-1912 and no new data are provided, we do not agree with the Applicant's proposal. Thus, no change regarding coadministration of ozanimod with strong CYP2C8 inhibitors is recommended.

Population PK/PD Analysis

In the original NDA submission, an exposure-response (E-R) relationship for ozanimod's major active metabolite CC112273 and ALC was observed; however, there was no PK-PD relationship between the parent drug ozanimod and ALC. In the submission, the E-R relationships were characterized between CC112273 (the most predominant circulating active metabolite of ozanimod) and the PD biomarker ALC, primary efficacy endpoints, i.e., clinical remission at Week 10 (induction phase) and at Week 52 (maintenance phase), as well as safety endpoints (ALT/AST, infections). Of note, all studies included in the PopPK analysis were also included for the ALC PK/PD analysis. Only the UC phase 3 study (RPC01-3101) was included in the E-R

efficacy analysis for clinical remission. For the Applicant's E-R safety analysis, 2 RMS studies (RPC01-201B and RPC01-301) were also included along with the UC phase 3 study (RPC01-3101).

ALC

Exploratory graphical evaluations of ALC as a function of time after dose and function of CC112273 exposure were initially performed prior to analysis. A longitudinal direct PK-PD Emax model was used to describe the CC112273 and ALC relationship. Covariate analysis was performed using a full model approach. The covariates tested in the full model are presented in the following table.

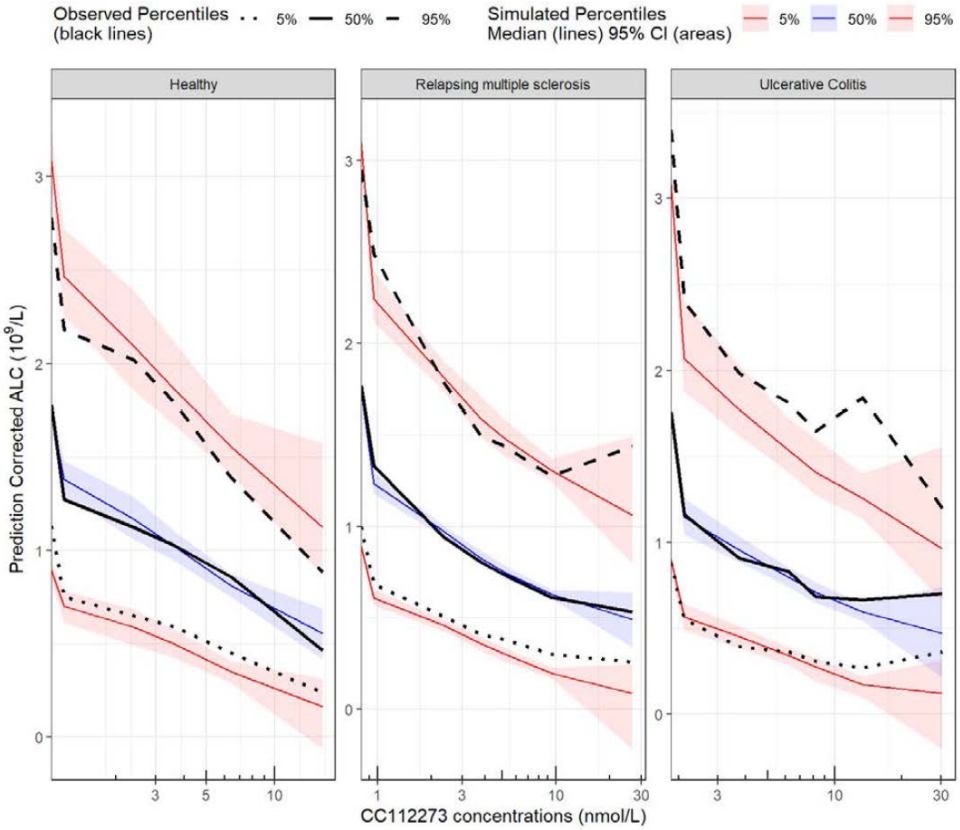
Table 67. Summary of Covariate Effects Evaluated in the Population PK/PD Analysis for ALC

Covariate	Maximum fractional change from baseline (Emax)	CC112273 concentration achieving 50% the maximum ALC reduction (EC50)
Age	Yes	Yes
Sex	No	No
Race	Yes	Yes
Body weight	No	No
Total Bilirubin	No	No
Disease Type	No	Yes
Smoking Status	No	No
Observed Baseline ALC	No	No

Source: Clinical PK/PD Report CLG-Certara-UC-358-2, Table 15
Abbreviations: ALC = absolute lymphocyte count; EC50 = CC112273 with 50% reduction of maximum effect on ALC; Emax = maximum effect a drug produces; No = included in the base ALC model; PD = pharmacodynamic; PK = pharmacokinetic; Yes = not included in the Base Model to be evaluated in the full ALC model

Overall, visual inspection indicates that the E-R model for ALC is generally predictive for the central tendency of ALC since the median of the observed ALC are generally within the 90% CI of the simulated data in patients with UC, as presented in Figure 16.

Figure 16. Visual Predictive Check of the Final Population Exposure Response Model for ALC



Source: Clinical PK/PD Report CLG-Certara-UC-358-2, Figure 8
Abbreviations: ALC = absolute lymphocyte count; CI = confidence interval.

Of note, population PK/PD analyses indicate that the decrease in ALC appears to be generally similar for UC patients who are smokers and non-smokers for ozanimod 0.92 mg QD dose (median reduction in ALC of 58% in nonsmokers and 54.3% in smokers) based on this longitudinal direct PK-PD Emax model. See Section 6 for detailed discussion.

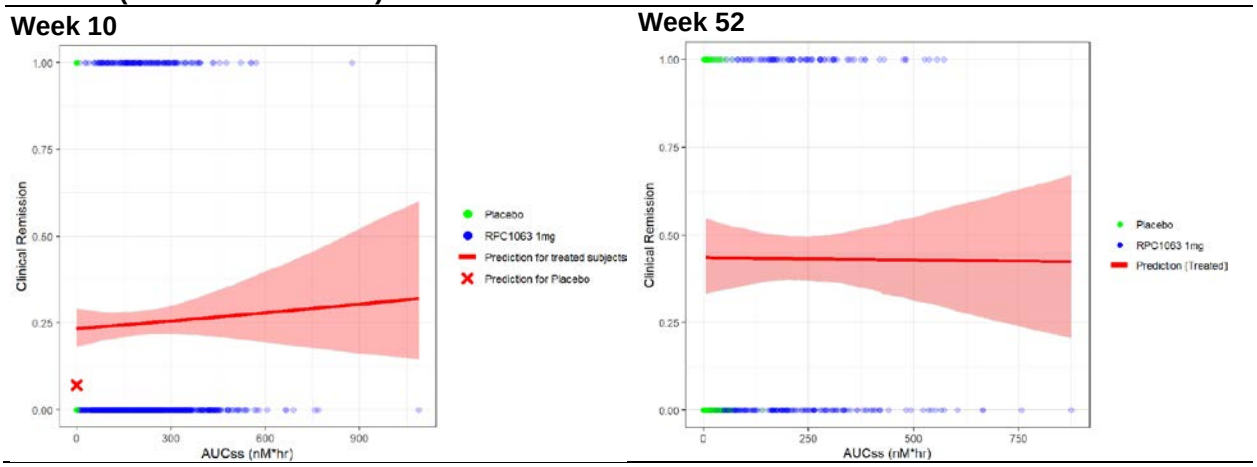
Clinical Remission

An E-R analysis on the phase 3 efficacy endpoint (clinical remission at Week 52) was performed using data from study RPC01-3101 in UC patients. A second E-R analysis was performed with clinical remission at Week 10. Logistic regression analyses were performed to develop a model describing the relationship between the steady state exposure of CC112273 (AUCss), and the probability of clinical remission at Week 10 or Week 52.

The following covariates were tested in the full model: age, sex, smoking, weight, baseline disease markers (fecal calprotectin, C-reactive protein [CRP], albumin concentration, and total Mayo score), background therapy, and patient stratification at the beginning of the induction period (corticosteroid use [yes or no] and prior anti-tumor necrosis factor [TNF] use [yes or no]).

Visual inspection of the E-R models for clinical remission at Week 10 and Week 52 appear to be generally predictive as presented in Figure 4. The exposure-response relationships for clinical remission at Week 10 and Week 52 are presented in Figure 17.

Figure 17. Observed and Model-Predicted Clinical Remission at Week 10 (Induction Phase) and Week 52 (Maintenance Phase) in Patients with UC



Source: Clinical PK/PD Report CLG-Certara-UC-358-2, Figure 10.7.
Abbreviations: AUC,ss = average concentration during a dosing interval at steady state
Note: Solid lines and bands are model estimated response rate with corresponding 90% prediction intervals. Circles are observed proportion of patients achieving an at least a 4 point improvement in the Itch NRS scores, with 90% confidence interval, for data combined from Studies JAHL and JAHM. Data were censored and treated as missing after TCS rescue therapy or permanent study drug discontinuation.

The final model for Week 10 clinical remission exposure response indicated a clear difference in response between subjects treated with placebo or ozanimod, with higher response rates in the ozanimod treatment group. Across the range of exposures from the 0.92 mg ozanimod dose, the Week 10 clinical remission response rate appeared to be similar, with a slight trend toward greater response with higher exposure. The final model for Week 52 clinical remission exposure response showed that across the range of exposures from the 0.92 mg ozanimod dose, the Week 52 clinical remission response rate was similar.

ALT/AST/Infections

Exposure-safety analyses were performed on the following endpoints:

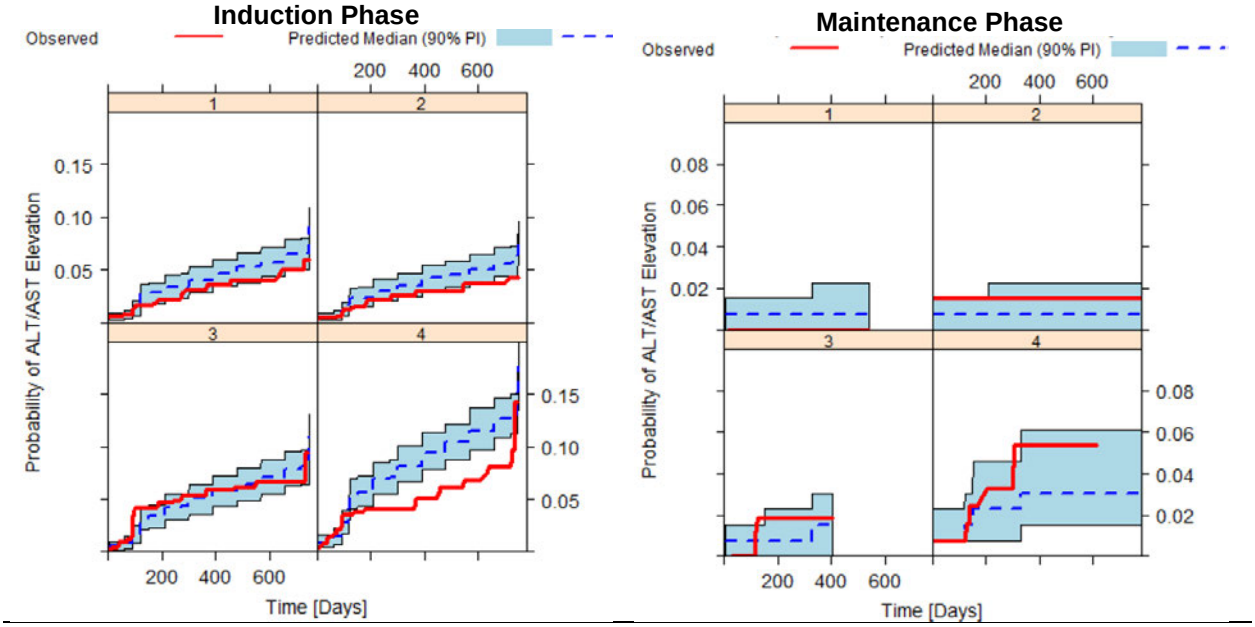
- Elevated ALT levels ≥3x ULN and/or elevated AST levels ≥3x ULN
- Adverse event of infections and infestations

Time-to-event analyses were performed for the probability of first event for each endpoint. For the time of first categorical event after the beginning of the treatment, Kaplan-Meier plots were derived for E-R evaluation according to exposure quartiles. Cox Regression results for the time to event analyses for each safety endpoint were derived based on exposure levels of CC112273.

The following covariates were tested in the full model: age, sex, smoking, weight, baseline disease markers (fecal calprotectin, CRP, albumin concentration, and total Mayo score), background therapy, and patient stratification at the beginning of the induction period (corticosteroid use [yes or no] and prior anti-TNF use [yes or no]).

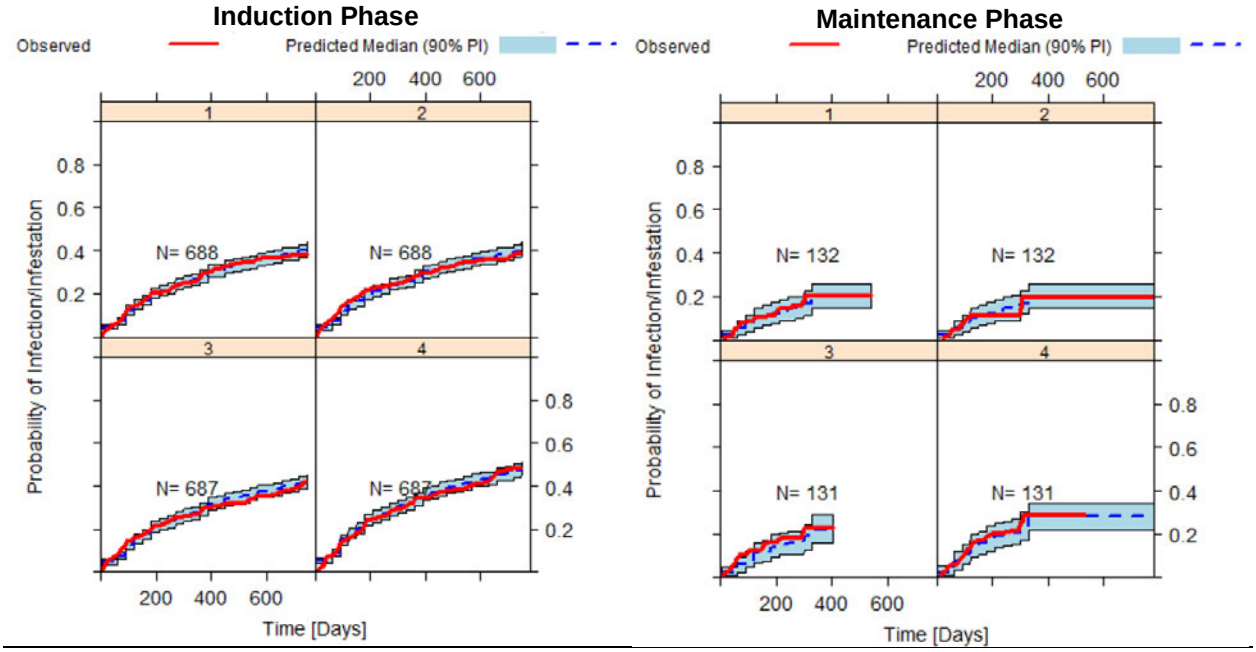
Visual inspection of the E-R models for ALT/AST elevation events are presented in Figure 18. Of note, there was a slight overprediction of the incidence rate of ALT/AST elevations during the induction phase; however, the overall probability of an ALT/AST elevation appeared to be low (<15%). Visual inspection indicates that the E-R models for infections are generally predictive, as presented in Figure 19.

Figure 18. Visual Predictive Check for ALT/AST Elevation Events for Induction Phase and Maintenance Phase Stratified by CC112273 Exposure Quartiles



Source: Clinical PK/PD Report CLG-Certara-UC-358-2, Figure 31, Figure 37
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number; PI = prediction interval.
Note: The numbers in the shaded regions above each plot represent the CC112273 exposure quartiles 1 through 4. Applicant's analysis of the induction phase included patients from RMS Studies RPC01-201B and RPC01-301, and the induction phase of UC Study RPC01-3101. Analysis of the maintenance phase included patients from the maintenance phase of UC Study RPC01-3101.

Figure 19. Visual Predictive Check for Infection Rate for Induction Phase and Maintenance Phase Stratified by CC112273 Exposure Quartiles



Source: Clinical PK/PD Report CLG-Certara-UC-358-2, Figure 43, Figure 54
Abbreviations: N = number; PI = prediction interval.
Note: The numbers in the shaded regions above each plot represent the CC112273 exposure quartiles 1 through 4. Applicant's analysis of the induction phase included patients from RMS Studies RPC01-201B and RPC01-301, and the induction phase of UC Study RPC01-3101. Analysis of the maintenance phase included patients from the maintenance phase of UC Study RPC01-3101.

Overall, population PK/PD analyses estimate an increasing trend of probability for the ALT/AST elevations at Week 10 and at Week 52 over the range of steady-state CC112273 exposures in UC patients. Slightly increasing trends of probability for infection/infestation at Week 10 and at Week 52 over the range of steady-state CC112273 exposures were predicted by population PK/PD analyses in UC patients.

Of note, all patients with RMS included in the Applicant's E-R analysis for safety events (i.e., ALT/AST elevations, infection/infestations) received concomitant interferon β-1a in two RMS studies (RPC01-201B and RPC01-301). Given the differences in study design and patient characteristics between RMS patients and UC patients, the Applicant's E-R analysis using pooled safety dataset from UC and RMS patients may have limitations and are not further discussed in detail in this review. Refer to Section 8 of this multi-discipline review for the safety data.

15.4. Additional Clinical Information

15.4.1. Summary of Amendments to the Phase 3 Study Protocol

Amendment 1 - June 7, 2016

- The definition of the maintenance of remission was added and definitions of mucosal healing and histologic remission were updated.

- The study schematic was updated to clarify that patients who were randomized to placebo in cohort 1 continued to receive placebo in the maintenance period.
- Inclusion criterion 5 was revised to clarify that the patient should have been on a stable dose of required medications prior to Screening endoscopy.
- Exclusion criterion 8 was revised to exclude patients who had a history of uveitis (within the last year).
- Exclusion criterion 14 was revised to exclude biologic agents within 10 weeks or 5 elimination half-lives (whichever was less).
- Exclusion criterion 16 was revised to clarify that topical rectal steroids were to be excluded within 2 weeks of the Screening endoscopy.
- Tofacitinib was added as an excluded medication within 2 weeks of Screening.
- Methotrexate was added as an example of an immunosuppressive agent in exclusion criterion 23 and under excluded medications.
- Exclusion criterion 28 was revised to include biologic agents approved for the treatment of UC rather than only anti-TNF agents. Patients were still excluded if they were primary non-responders to 2 or more agents.
- Exclusion criterion 32 was revised to hemoglobin < 8.0 g/dL.
- New information was added based on the results of the food effect study (Study RPC01-1901): ozanimod was to be taken with or without food, and the requirement to take investigational drug in a fasted condition was removed.
- QT prolonging drugs were removed from the exclusion criterion, list of excluded medications, and table of prohibited cardiac medications.
- An additional alternate definition of remission was added to the list of sensitivity analyses.
- The description of primary efficacy analysis was revised since the results of primary efficacy analysis were expressed as odds ratio and not relative risk.
- Guidelines on treatment failure rules applied to the primary analyses of all efficacy endpoints were added. These included any protocol-prohibited change in UC medications, a colectomy (partial or total) or an ostomy, and discontinuation of investigational drug for lack of therapeutic effect before the Week 10 or Week 52 efficacy evaluation.

<u>Amendment 2 - June 7, 2017</u>

- The proportion of patients who have previously received anti-TNF therapy was changed from ≤ 30% to approximately 35% to reflect the increasing number of patients who have previously received biologic treatment.
- The prohibition on concomitant use of cytochrome P450 3A4 (CYP3A4) inhibitors and inducers was removed based on the results of the clinical pharmacology study RPC01-1902.
- The prohibition on concomitant use of beta blockers and calcium channel blockers was removed based on the results of the clinical pharmacology study RPC01-1908.

<u>Amendment 3 - December 7, 2017</u>

- The proportion of patients in cohort 1 and cohort 2 was adjusted to reinstate the original limit of ≤ 30% of patients who have received anti-TNF from RPC01-3101 protocol versions

2.0 (main protocol), 2.1 (region protocol), 2.2 (Germany), and 2.3 (Italy). The planned total sample size was to remain unchanged. A limit of ≤ 50% of such patients was established for cohort 2. These limits were established based on ongoing development programs in UC that have confirmed that patients with anti-TNF experience achieved limited clinical response.

Amendment 4 - May 29, 2018

- A 75-day (± 10 days) Safety Follow-up Visit was added to ensure adequate collection of adverse events (AEs) that could be associated with the investigational drug. The timing of the visit was based on the estimated time needed to clear the major active metabolite of ozanimod (i.e., 5 half-lives of CC112273).
- Added additional assessment of ALC for patients who had a confirmed ALC below the 200 cells/µL limit and permanently discontinued these patients from participation in the study in order to evaluate the rebound effect after long-term exposure to ozanimod.
- Added guidance for further liver function evaluation if a patient discontinues investigational drug due to elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × ULN, or ALT or AST > 3 × ULN and bilirubin > 2 × ULN.
- Added BCRP inhibitors to the list of medications that were prohibited during the study until the 30-Day Safety Follow-up Visit.
- Added MAO inhibitors to the list of medications that were prohibited during the study and safety follow-up period.
- Added CYP2C8 inhibitors or inducers to the list of medications were not to be used during the study or after investigational drug discontinuation.

Amendment 5 - November 16, 2018

- Included adolescent patients based on feedback from the FDA. Eligible adolescent patients entered the study via a separate cohort (cohort 3) utilizing 2:1 randomization. Adolescent patients who met clinical response criteria at the end of the induction period were to be re-randomized into a controlled maintenance period, consistent with the current plan for adults.
- For statistical analysis purposes, calculation of clinical remission and clinical response was changed to use the 3-component Mayo definition (unless specified as the 4-component Mayo definition), in order to remove subjectivity of the Physician's Global Assessment (PGA) from the calculation of the 4-component Mayo score.
- The Pediatric Ulcerative Colitis Activity Index was added and included in the schedule of events, efficacy assessments, disposition, demographics and baseline characteristics.
- Cholestyramine was removed as a prohibited medication because bile acid malabsorption was not known to have an effect on UC disease status.
- Hematology blood draw and optional safety assessments were added at the 75-day Safety Follow-up Visit to monitor safety.
- The pulmonary function test was clarified to state that verification by pulmonologist was only required if the results were not within normal range. If the patient had a decline in pulmonary function test values, the patients should have had adequate evaluations as clinically indicated by a pulmonologist.

Amendment 6 – May 20, 2019

- The 75-day (±10 days) Safety Follow-up Visit was changed to a 90-day (±10 days) Safety Follow-up Visit, in order to ensure adequate collection of AEs that were associated with the investigational drug. The timing of the visit was based on the estimated time needed to clear the major active metabolites of ozanimod in the vast majority of patients (i.e., 5 half-lives of CC112273 and CC1084037 and accounting for variation of half-life duration in a human population).
- Revised the inclusion for patients who enter the study as adolescents should continue to be assessed for Pediatric Ulcerative Colitis Activity Index throughout the study, regardless of an age change. Added language that patients who enter the study as adolescents should continue to be assessed as adolescents throughout the study, regardless of an age change.
- Updated the criteria for cardiac monitoring to read "6 hours postdose is at the lowest value postdose and lower than any other timepoint."
- Revised Treatment Failure Rules: Added tofacitinib to the list of prohibited medications changes and updated prolonged use of systemic corticosteroids to > 14 days.
- International normalized ratio was removed from the discontinuation criteria with respect to hepatic effects.

15.4.2. Mayo Scoring Algorithm and Endpoint Derivation

Table 68. Three-Component Mayo Score

Subscore	0	1	2	3
Endoscopic Appearance	Normal or inactive disease	Mild disease (erythema, decreased vascular pattern) **Does not include any friability.**	Moderate disease (marked erythema, absent vascular pattern, **any friability**, erosions)	Severe disease (spontaneous bleeding, ulcerations)
Stool Frequency+	Normal number of stools per day for patient	1 to 2 more stools per day than normal	3 to 4 more stools per day than normal	≥5 more stools per day than normal
Rectal Bleeding*	No blood seen	Streaks of blood with stool less than half the time	Obvious blood with stool most of the time	Passing blood alone

Source: Reviewer's table based upon information contained in clinical study protocol v7.1 (page 68-69)
+ Each patient serves as his/her own control to establish the degree of abnormality of the stool frequency.
* Daily bleeding score represents the most severe bleeding of the day.

Patients were to complete the stool frequency and rectal bleeding components of the Mayo score into an electronic diary system daily from the first screening visit to the last study visit. The PGA was to be entered into the electronic diary system during study visits.

The SAP contained 3 scoring algorithms for Mayo score derivation: 14-day algorithm A, 14-day algorithm B, and a 7-day scoring algorithm. The 7-day scoring algorithm was the primary analysis algorithm for the primary and key secondary endpoints. Details regarding the scoring algorithms as specified in the SAP are included below.

14-day algorithm A
In the 14-day algorithm A, stool frequency and rectal bleeding subscores were derived from e-diary entries completed by the patient 2 weeks prior to each PGA entry, using "3 allowable days". A day was considered as an allowable day if it satisfied the following: had non-missing stool frequency and rectal bleeding data and was not excluded due to endoscopy procedure requirements.

The determination of "3 allowable days" was in the following order:
1. If there were 3 consecutive days with non-missing stool frequency and rectal bleeding data, then the 3 consecutive days closest to the visit date were used.
2. If there were only 2 consecutive days with non-missing stool frequency and rectal bleeding data, then the 2 consecutive days closest to the visit date plus one day with non-missing stool frequency and rectal bleeding closest to the visit date were used.
3. If there were 3 days with non-missing stool frequency and rectal bleeding data, but they were not consecutive, then the 3 days closest to the visit date were used.
4. If there were no 3 days with both non-missing stool frequency and rectal bleeding data, then the subscores were set to missing.

The day of the endoscopy procedure, the day(s) the patients prepared for the procedure, and the day(s) after the procedure (1 day for flexible sigmoidoscopy and 2 days for colonoscopy) were excluded from the subscore calculations due to the impact of the procedure on stool frequency and rectal bleeding.

14-day algorithm B
The 14-day algorithm B used criteria 1 and 2 in the 14-day algorithm A and also utilized the following:
- For calculation of stool frequency and rectal bleeding subscores, 3 days were required.
- If data from 3 consecutive days were not available, then data from 2 consecutive days and a non-consecutive day closest to the visit date (without including the day(s) before, day of, or day(s) after endoscopy) were used.
- Both stool frequency and rectal bleeding data must have been available on the same day.

7-day scoring algorithm
The 7-day scoring algorithm used 7 days prior to a visit to derive the stool frequency and rectal bleeding subscores. The 7-day algorithm was identical to the 14-day algorithm A, except that determination of "3 allowable days" was based on 7 days prior to each PGA entry, instead of 2 weeks.

The Applicant's clinical remission and clinical response results based on the 14-day Mayo scoring algorithms were consistent with the primary analysis results for both endpoints in the induction period (CSR Tables 14.2.1.8.1A, 14.2.1.8.2A, 14.2.2.9.1A, 14.2.2.9.2A) and in the maintenance period (CSR Tables 14.2.1.6.1B, 14.2.1.6.2B, 14.2.2.6.1B, 14.2.2.6.2B).

15.4.3. Schedule of Assesssments

Table 69. Schedule of Assessments, Study RPC01-3101

	Trial Procedures		Induction			Maintenance						Early Term[q]	Safety Follow-up[r]	
			Dose Escalation	Assigned Dose		Treatment								
	(Visit Label)	Screening	Visit I 1[a,b] (Week 0)	Visit I 2[a] (Week 5)	(EoT) Visit Visit I 3[b] (Week 10)	Visit M 1[b,c] (Week 0)	Visit M 2 (Week 8)	Visit M 3 (Week 18)	Visit M 4 (Week 30)	Relapse Visit (When Indicated)	(EoT) Visit M 5[b] (Week 42)			
	(Visit Day and Window)	Day -35 to 0	Day 1	Day 35±5	Day 70±10	Day 1	Day 56±10	Day 126±10	Day 210±10		Day 294±10	Day of Early Term	Last dose + 30 to 60 days	Last dose + 90 days ± 10 days[r]
	(Overall Duration)		0 weeks	5 weeks	10 weeks	10 weeks	18 weeks	28 weeks	40 weeks		52 weeks			
	Informed consent/assent	X												
	Inclusion/exclusion criteria	X	X			X								
	Demographics	X												
	Medical history[d,e]	X	X											
	Viral serology[f]	X												
	Stool cultures[g]	X												
	Randomization		X			X								
	Dispense investigational drug		X	X	X[h]	X	X	X	X	X	X[y]			
	Administer investigational drug at clinic		X		X	X					X			
	Review drug compliance			X	X	X	X	X	X	X	X	X		
	Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
	Medical procedures (non-trial)		X	X	X	X	X	X	X		X	X	X	

	Trial Procedures		Induction			Maintenance						Early Term[q]	Safety Follow-up[r]	
			Dose Escalation	Assigned Dose		Treatment								
	(Visit Label)	Screening	Visit I 1[a,b] (Week 0)	Visit I 2[w] (Week 5)	(EoT) Visit Visit I 3[b] (Week 10)	Visit M 1[b,c] (Week 0)	Visit M 2 (Week 8)	Visit M 3 (Week 18)	Visit M 4 (Week 30)	Relapse Visit (When Indicated)	(EoT) Visit M 5[b] (Week 42)			
	(Visit Day and Window)	Day -35 to 0	Day 1	Day 35±5	Day 70±10	Day 1	Day 56±10	Day 126±10	Day 210±10		Day 294±10	Day of Early Term	Last dose + 30 to 60 days	Last dose + 90 days ± 10 days[t]
	(Overall Duration)		0 weeks	5 weeks	10 weeks	10 weeks	18 weeks	28 weeks	40 weeks		52 weeks			
Safety Assessments	Adverse events[z]		X	X	X	X	X	X	X	X	X	X	X	X
	12-Lead ECG	X	X		X						X	X		X[y]
	Vital signs	X	X	X	X	X	X	X	X		X	X	X	X[y]
	Hematology[v]	X	X	X	X	X	X	X	X		X	X	X	X
	Blood chemistry[x]	X	X	X	X	X	X	X	X		X	X	X	X[y]
	Pregnancy test[i]	X	X	X	X	X	X	X	X		X	X	X	X
	Contraception education	X	X	X	X	X	X	X	X	X	X	X	X	
	Urinalysis	X			X						X	X	X	X[y]
	Pulmonary function tests[p]	X			X			X			X	X		X[y]
	Complete Physical examination[j]	X									X	X		X[y]
	Interim Physical examination[j]		X	X	X	X	X	X	X				X	X[y]
	Height and Weight (adults)	X												X[y]
	Height (adolescents)	X									X	X		X[y]
	Weight (adolescents)	X	X	X	X			X			X	X		X[y]
	Optical coherence tomography	X			X						X	X		X[y]

	Trial Procedures		Induction			Maintenance						Early Term[q]	Safety Follow-up[r]	
			Dose Escalation	Assigned Dose		Treatment								
	(Visit Label)	Screening	Visit I 1[a,b] (Week 0)	Visit I 2[w] (Week 5)	(EoT) Visit Visit I 3[b] (Week 10)	Visit M 1[b,c] (Week 0)	Visit M 2 (Week 8)	Visit M 3 (Week 18)	Visit M 4 (Week 30)	Relapse Visit (When Indicated)	(EoT) Visit M 5[b] (Week 42)			
	(Visit Day and Window)	Day -35 to 0	Day 1	Day 35±5	Day 70±10	Day 1	Day 56±10	Day 126±10	Day 210±10		Day 294±10	Day of Early Term	Last dose + 30 to 60 days	Last dose + 90 days ± 10 days[t]
	(Overall Duration)		0 weeks	5 weeks	10 weeks	10 weeks	18 weeks	28 weeks	40 weeks		52 weeks			
PK and PD Assessments	Stool collection for fecal biomarkers[n]	X			X						X	X	X	
	Inflammatory biomarkers plasma sampling[n]	X			X						X	X	X	X[y]
	PK blood sampling[k, u, x]		X	X	X	X					X	X	X	X
Efficacy Assessments	Patient survey (SF-36/ EQ-5D) (adults only)		X		X						X	X		
	Endoscopy[l,w] and colonic biopsy	X		X[w]	X[m]	X[m]				X	X[m]	X		
	Mayo patient diary	X[s]	X	X	X	X	X	X	X	X	X	X	X	
	Mayo full clinical score	X			X	X				X	X	X		
	Mayo partial clinical score		X[o]	X	X	X	X	X	X	X	X	X	X	
	PUCAI (adolescents only)		X	X	X	X	X	X	X	X	X	X		
	Health Resource Utilization (adults only)				X			X	X		X	X	X	
	Work Productivity (adults only)				X			X	X		X	X	X	

[a] The duration of Visit I 1 will be approximately 7 hours. Prior to dosing a 12-lead ECG will be performed and following dosing patients will have hourly vital signs recorded at 1, 2, 3, 4, 5, and 6 hours postdose. A second 12-lead ECG will be performed at the end of the observation period.
[b] Visit I 1, Visit I 3, Visit M 1, and Visit M 5 should be scheduled in the morning, where possible. On Visits I 1, I 3, M 1, and M 5, since trough PK samples are to be drawn, patients should be instructed to withhold the dose until the trial visit and the dose should be administered during the visit.
[c] In general, for patients completing the IP and entering the MP, Visit 3 of the IP (Visit I 3) will serve as Visit 1 of the MP (Visit M 1). Patients should enter the MP within 21 days of the Visit I 3 endoscopy. Procedures completed during Visit I 3 do not need to be repeated if Visit M 1 occurs within 14 days of I 3 visit. Patients may complete the M 1 visit prior to completing the OCT and PFT scheduled for the I 3 visit. OCT and PFT must be completed within 14 days of the I 3 visit.
[d] Medical history will include smoking history. The Visit I 1 medical history can be abbreviated, noting events that occurred between Screening and Visit I 1.
[e] TB must be ruled out according to local medical practices, such as a TB skin test, QuantiFERON Gold test, or other interferon gamma release assay (eg, T-SPOT). Subjects with a positive test result using a TB skin test or QuantiFERON Gold test must have documentation of completed TB treatment by local standard of care.
[f] Serology testing will be performed at Screening to determine the patient's immune status with respect to the following viruses (see Section 12.1.11): Human immunodeficiency virus antibodies, anti-hepatitis A virus IgM, hepatitis B surface antigen, anti-hepatitis B core antigen, hepatitis B DNA, anti-hepatitis C virus IgG or IgM. In addition, patients must have documentation of positive Varicella Zoster Virus IgG antibody status or complete Varicella Zoster Virus vaccination at least 30 days prior to first dose of investigational drug.
[g] At Screening, the stool sample should be used to rule out serious infection and should include evaluation for C. difficile toxin as well as ova and parasitic examination.
[h] Investigational drug will only be dispensed for patients that could not complete the M1 Visit on the same day as the I 3 Visit.
[i] For females of childbearing potential only, a serum β-hCG pregnancy test at Screening is required and a urine β-hCG pregnancy test is required at each visit. Between scheduled visits up until the 90-day Safety Follow-up Visit, monthly home urine pregnancy tests should be performed by the patient. If a urine pregnancy test result is positive, the investigator will instruct the patient to suspend further study dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including after the 90-day Safety Follow-up Visit, if needed.
[j] For all patients, a complete physical examination (which includes height and weight) will be performed at Screening. For adult patients, the complete physical examination at M 5/EoT/Early Term visit does not include height and weight. Patients who enter the trial as adolescents should continue to be assessed as adolescents throughout the trial, regardless of an age change. The complete physical examination consists of a full examination of the skin for lesions as well as a check for visual symptoms (ie, blurred vision or decreased visual acuity). A check for visual symptoms and a full examination of the skin should be repeated every 6 months. At all other visits following Screening (except M 5/EoT/Early Term), an interim physical examination will be performed. The interim physical examination will include body systems with previously noted abnormalities and/or those body systems associated with any new complaints from the patient.
[k] At Visit I 1, blood samples for PK evaluation are to be taken prior to the administration of investigational drug (predose) and just prior to discharge from the clinic (6 to 8 hours postdose). At Visit I 2, blood samples should be taken 2 to 6 hours after dosing; therefore, patients should be instructed to take investigational drug at home prior to arriving for this visit. At Visits I 1, I 3, M 1, and M 5, blood samples will be used to determine trough level, therefore patients should be instructed to withhold the dose until the trial visit, where the dose will be administered after the PK blood draw is done. The actual time of investigational drug administration for all visits with PK evaluation will be recorded on the dosing log. The blood sample at the 30-day and 90-day Safety Follow-up Visits can be collected at any point during the visit. An additional PK sample will be obtained for patients with any adverse event resulting in unblinding, discontinuation, or serious adverse event.
[l] At Screening, a flexible sigmoidoscopy may be used if a colonoscopy is not required. A colonoscopy will be required if the patient has had left-sided colitis of > 12 years duration or total/extensive colitis of > 8 years duration and has not had a colonoscopy within 2 years (unless otherwise recommended by local and national guidelines) of the screening date to rule out dysplasia, or if the patient's age is > 45 years and the patient has not had a colonoscopy within 5 years to screen for polyps. The screening endoscopy must be completed no more than 21 days prior to randomization. A flexible rectosigmoidoscopy will be performed at Week 5 or later for adolescent patients who meet clinical symptom criteria for early discontinuation, with the understanding that the procedure may occur within approximately 7 days from the last visit prior to entering the OLE, to allow for preparation. The final decision to discontinue the patient early for entry into the OLE will be left to the discretion of the Investigator based on the Partial Mayo score and the endoscopy score.
[m] Sigmoidoscopy should be performed no more than 10 days prior to the I 3 visit date in Induction and no more than 10 days prior to the M 5 visit date in Maintenance.
[n] At Screening, patients will be issued with a Mayo diary and will be trained in the completion of the diary.
[o] The Mayo partial clinical score on Visit I 1 should be combined with the central endoscopic read in order to assess the patient for "Mayo Score" entrance criteria.
[p] DLCO, if locally available, will be done at Screening, Visit I 3, Visit M 3, and M 5/Early Term visit.
[q] Early Term procedures performed at the Relapse Visit do not need to be repeated for patients who are early terminating due to relapse.

[r] In cases when a patient's End of Treatment (Week 42 of Maintenance) visit and the first visit of the open-label extension study do not occur on the same day, an extra bottle of investigational drug may be dispensed to cover the period of time prior to entering the open-label extension.
[s] The Safety follow-up visit should occur between 30 days to 60 days and at 90 days (±10 days) after the last dose of investigational drug in the RPC01-3101 trial. However, if the patient continues treatment in the open-label extension, the safety follow-up visits are not required for the RPC01-3101 trial.
[t] Every effort should be made to conduct the 90-day Safety Follow-up Visit as a clinic visit in order to allow PK and hematology blood samples to be drawn. In addition, additional safety assessments may be required for patients who have an ongoing AE or safety issue at the 90-day Safety Follow-up Visit, at the Investigator's discretion. Patients may be followed as necessary for an additional of period of time after the 90-day Safety Follow-up Visit to review the results of any assessments which were conducted at the 90-day Safety Follow-up Visit (eg, ALC < 200 cells/μL).
[u] Residual samples will be stored and may be used for additional analyses if the patient has granted consent/assent for either optional future biomarker testing or optional genetic testing where allowed by the regulatory authorities and the local ethics committee.
[v] If the ALC is confirmed below the 200 cells/μL limit, the Investigator will temporarily discontinue investigational drug. Laboratory testing will be repeated weekly during the treatment period until ALC > 500 cells/μL. For patients who have a confirmed ALC below the 200 cells/μL limit at the Early Termination visit, or at the 30-day or 90-day Safety follow-up visit, central laboratory testing will continue every 14 days (± 3 days) after the Early Termination Visit until the ALC is above the lower limit of normal.
[w] Starting at Week 5 or later, adolescent patients (Cohort 3) may request early discontinuation from the Induction Period if they meet either of the following criteria: 1) Partial Mayo score is ≥ 7 and is the same or worse than baseline or, 2) Partial Mayo score is 6 and worse than baseline. A flexible rectosigmoidoscopy must be performed before entering the OLE. The final decision to discontinue the patient early for entry into the OLE will be left to the discretion of the Investigator based on the Partial Mayo score and the endoscopy score.
[x] The following amounts of blood will be taken per visit: At the Screening Visit, up to 26 mL (about 5 teaspoons); at Visit I1, 20 mL (about 4 teaspoons); at Visits I3, M5 or the Early Termination Visit, 18.5 mL (less than 4 teaspoons); Safety Follow-Up Visits, up to 18.5 mL (less than 4 teaspoons); at Visits I2 and M1, 12.5 mL (less than 3 teaspoons); at Visit M2, M3 and M4 6.5 mL (less than 2 teaspoons). In total, about 164.5 mL maximum (about 33 teaspoons) of blood will be collected during the whole study for patients who complete the study.
[y] Additional safety assessments may be requested at the PI's discretion in case of an ongoing safety event at the 90-day Safety Follow-up Visit.
[z] The reporting of AEs will begin at Induction Day 1 post first dose for all randomized patients. The reporting of SAEs for any patient will begin from the time written informed consent/assent is signed through the last visit. Any SAE that is ongoing when the patient completes the trial or discontinues from the trial will be followed by the Investigator until the event has resolved, stabilized, or returned to Baseline status.

Abbreviations: β-hCG = beta human chorionic gonadotrophin; DLCO = diffusion capacity of the lung for carbon monoxide; Early Term = Early Termination; ECG = electrocardiogram; EoT = End of Treatment; I = Induction Period; Igs = immunoglobulins; M = Maintenance Period; PD = pharmacodynamic; PK = pharmacokinetic; PUCAI = Pediatric Ulcerative Colitis Activity Index; TB = tuberculosis

Source: Applicant's submission, Study 3101 protocol v7.1, pages 42-46

15.4.4. Adverse Event Recoding

Table 70. Study 3101 Adverse Event Dataset Recoded Terms

Recoded (Pooled) Term	Included Preferred Terms
Abdominal pain	Abdominal pain, Abdominal pain upper, Abdominal pain lower
Anaemia	Anaemia, Iron deficiency anaemia, Anaemia of chronic disease, Pernicious anaemia
Anxiety	Anxiety, Anxiety disorder, Generalized anxiety disorder, Panic disorder, Procedural anxiety
Appendicitis	Appendicitis, Complicated appendicitis
Bradycardia	Bradycardia, Sinus bradycardia
Clostridium difficile infection	Clostridium difficile infection, Clostridium difficile colitis, Clostridium test positive
Coronary artery disease	Coronary artery disease, Coronary artery disease
Diarrhoea	Diarrhoea, Diarrhoea haemorrhagic
Fungal infection	Fungal infection, Fungal skin infection
Gastroenteritis	Gastroenteritis, Gastroenteritis viral, Gastrointestinal viral infection, Campylobacter gastroenteritis, Gastroenteritis norovirus, Gastroenteritis rotavirus, Gastrointestinal infection, Large intestine infection
Haemorrhoids	Haemorrhoids, Haemorrhoidal haemorrhage, Haemorrhoids thrombosed
Headache	Headache, Tension headache, Migraine, Migraine with aura, Head discomfort
Hypertension	Hypertension, Hypertensive crisis
Influenza	Influenza, Influenza like illness, Pneumonia influenzal
Insomnia	Insomnia, Initial insomnia
Large intestine polyp	Large intestine polyp, Colon adenoma
Liver test increased	Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Liver function test increased, Blood alkaline phosphatase increased, Transaminases increased
Lymphopenia	Lymphopenia, White blood cell count decreased
Migraine	Migraine, Migraine with aura
Myalgia	Myalgia, Musculoskeletal pain
Nausea	Nausea, Procedural nausea
Non-cardiac chest pain	Non-cardiac chest pain, Musculoskeletal chest pain
Pain	Pain in extremity, Pain, Procedural pain
Peripheral swelling	Oedema peripheral, Peripheral swelling
Presyncope	Dizziness, Presyncope
Proteinuria	Proteinuria, Protein urine present
Pyelonephritis	Pyelonephritis, Pyelonephritis chronic
Pyrexia	Pyrexia, Hyperpyrexia, Hyperthermia, Post procedural fever
Rash	Rash, Dermatitis, Rash pruritic, Rash macular, Rash maculo-papular, Rash pustular, Dermatitis allergic, Dermatitis contact
Respiratory tract infection	Respiratory tract infection viral, Respiratory tract infection, Tracheitis, Respiratory syncytial virus test positive
Retinal disorder	Retinal disorder , Retinal vasculitis
Rhinitis	Rhinitis, Rhinitis allergic
Scar	Scar, Scab
Thrombocytosis	Thrombocytosis, Secondary thrombocytosis
Tooth infection	Tooth infection, Tooth abscess

Recoded (Pooled) Term	Included Preferred Terms
Ulcerative colitis	Colitis ulcerative, Proctitis ulcerative
Upper respiratory tract infection	Nasopharyngitis, Upper respiratory tract infection, Sinusitis, Pharyngitis, Viral upper respiratory tract infection, Tonsillitis, Viral sinusitis, Pharyngitis streptococcal, Pharyngotonsillitis
Urinary tract infection	Urinary tract infection, Urine leukocyte esterase positive
Visual impairment	Visual impairment, Vision blurred, Visual field defect

Table 71. ISS Adverse Event Dataset Recoded Terms

Recoded (Pooled) Term	Included Preferred Terms
Abdominal pain	Abdominal pain upper, Abdominal pain, Abdominal pain lower, Abdominal tenderness, Gastrointestinal pain
Activated partial thromboplastin time abnormal	Activated partial thromboplastin time prolonged, Activated partial thromboplastin time abnormal
Acute coronary syndrome	Acute myocardial infarction, Acute coronary syndrome
Acute kidney injury	Acute kidney injury, Acute prerenal failure
Adjustment disorder	Adjustment disorder, Adjustment disorder with depressed mood
Affective disorder	Affective disorder, Affect lability
Alopecia	Alopecia, Alopecia areata, Androgenetic alopecia, Diffuse alopecia
Anaemia	Anaemia, Iron deficiency anaemia, Haemoglobin decreased, Microcytic anaemia, Hypochromic anaemia, Haemolytic anaemia, Haematocrit decreased, Anaemia of chronic disease, Autoimmune haemolytic anaemia, Blood loss anaemia, Deficiency anaemia, Pernicious anaemia, Normochromic normocytic anaemia
Anxiety	Anxiety, Anxiety disorder, Panic attack, Panic disorder, Generalized anxiety disorder
Appendicitis	Appendicitis, Complicated appendicitis
Arrhythmia	Arrhythmia, Arrhythmia supraventricular, Paroxysmal arrhythmia, Sinus arrhythmia, Ventricular arrhythmia
Arthritis	Arthritis, Arthritis reactive, Polyarthritis
Benign neoplasm of cervix uteri	Benign neoplasm of cervix uteri , Cervical cyst, Cervical polyp
Biliary polyp	Biliary polyp, Gallbladder polyp
Bladder disorder	Bladder pain, Bladder disorder, Bladder discomfort, Bladder spasm
Blepharitis	Blepharitis, Blepharitis allergic
Blood uric acid abnormal	Blood uric acid increased; Blood uric acid abnormal
Bradycardia	Bradycardia, Sinus bradycardia, Heart rate decreased
Breast cancer	Breast cancer, Invasive breast carcinoma, Invasive ductal breast carcinoma
Breast disorder	Breast disorder, Breast dysplasia, Breast pain, Breast hyperplasia, Breast oedema
Breast neoplasm	Breast cyst, Benign breast neoplasm, Breast mass, Breast neoplasm
Bronchitis	Bronchitis, Bronchitis chronic, Bronchitis bacterial, Bronchitis viral
Cardiac failure	Cardiac failure chronic, Cardiac failure
Cataract	Cataract, Cataract subcapsular, Cataract nuclear
Cerebrovascular accident	Cerebral infarction, Cerebrovascular accident

Recoded (Pooled) Term	Included Preferred Terms
Cervicitis	Cervicitis, Cervicitis human papilloma virus, Cervix inflammation
Chest pain	Chest pain, Chest discomfort
Cholecystitis	Cholecystitis chronic, Cholecystitis, Cholecystitis acute
Clostridium difficile infection	Clostridium difficile infection, Clostridium difficile colitis, Clostridium test positive, Pseudomembranous colitis
Confusional state	Confusional state, Disturbance in attention, Disorientation
Conjunctival hyperaemia	Conjunctival haemorrhage, Conjunctival hyperaemia
Conjunctivitis	Conjunctivitis, Conjunctivitis allergic, Conjunctivitis viral, Conjunctivitis bacterial
Corneal abrasion	Corneal abrasion, Corneal erosion
Coronary artery disease	Coronary artery stenosis, Coronary artery disease
Cystitis	Cystitis, Cystitis noninfective, Cystitis haemorrhagic, Cystitis Escherichia
Deafness	Deafness, Deafness neurosensory
Depression	Depression, Depressed mood, Persistent depressive disorder, Depressive symptom, Major depression
Detachment of retinal pigment epithelium	Detachment of retinal pigment epithelium, Detachment of macular retinal pigment epithelium
Diabetes mellitus	Diabetes mellitus, Type 1 diabetes mellitus, Type 2 diabetes mellitus
Diarrhoea	Diarrhoea, Diarrhoea infectious, Frequent bowel movements, Diarrhoea haemorrhagic, Viral diarrhea
Diastolic hypertension	Diastolic hypertension, Blood pressure diastolic increased
Duodenitis	Duodenitis, Erosive duodenitis
Dyslipidaemia	Hypercholesterolaemia, Hyperlipidaemia, Dyslipidaemia, Blood cholesterol increased, Blood triglycerides increased, Hypertriglyceridaemia, Lipids increased, Type V hyperlipidaemia, Low density lipoprotein increased, Type IIb hyperlipidaemia
Dyspepsia	Dyspepsia, Abdominal discomfort, Epigastric discomfort
Ear infection	Ear infection, Ear infection fungal
Electrocardiogram abnormal	Electrocardiogram QT prolonged, Electrocardiogram abnormal, Electrocardiogram T wave amplitude decreased, Electrocardiogram T wave inversion, Electrocardiogram PQ interval shortened, Electrocardiogram PR shortened, Electrocardiogram repolarisation abnormality
Encephalopathy	Vascular encephalopathy, Hypoxic-ischaemic encephalopathy
Enterocolitis	Enterocolitis, Enterocolitis viral
Eosinophilia	Eosinophilia, Eosinophil count increased
Escherichia infection	Escherichia infection, Escherichia urinary tract infection
Eustachian tube disorder	Eustachian tube disorder, Eustachian tube dysfunction
Eye disorder	Eye disorder, Eye degenerative disorder
Eye inflammation	Eye inflammation, Eye swelling
Eyelid oedema	Eyelid oedema, Swelling of eyelid
Face oedema	Swelling face, Face oedema
Fistula	Anal fistula, Fistula, Intestinal fistula, Perineal fistula, Enterocolonic fistula, Enterocutaneous fistula, Female genital tract fistula, Fistula discharge, Fistula of small intestine

Recoded (Pooled) Term	Included Preferred Terms
Fungal infection	Vulvovaginal candidiasis, Tinea versicolour, Fungal skin infection, Fungal infection, Tinea pedis, Oesophageal candidiasis, Oral candidiasis, Genital infection fungal, Candida infection, Oral fungal infection, Body tinea, Dermatophytosis, Dermatophytosis of nail, Genital candidiasis, Tinea infection, Anal tinea, Fungal paronychia, Gastrointestinal candidiasis, Skin candida, Oropharyngeal candidiasis, Anal fungal infection, Tongue fungal infection
Gastric disorder	Gastric disorder, Gastric atony
Gastritis	Gastritis, Chronic gastritis, Gastritis erosive, Reflux gastritis, Helicobacter gastritis, Haemorrhagic erosive gastritis
Gastroenteritis	Gastroenteritis, Gastroenteritis viral, Gastrointestinal viral infection, Gastrointestinal infection, Gastrointestinal inflammation, Gastroduodenitis, Campylobacter gastroenteritis, Gastroenteritis norovirus, Gastroenteritis rotavirus, Gastroenteritis staphylococcal, Large intestine infection
Gastrooesophageal reflux disease	Gastrooesophageal reflux disease, Reflux laryngitis, Gastrooesophageal sphincter insufficiency
Genital discomfort	Genital hyperaesthesia, Genital discomfort, Genital burning sensation
Gingivitis	Gingivitis, Gingivitis ulcerative
Glaucoma	Glaucoma, Glaucoma traumatic
Glycosuria	Glycosuria, Glucose urine present
Haemangioma	Haemangioma, Haemangioma of skin, Haemangioma of liver, Haemangioma of breast, Choroidal haemangioma, Gastric haemangioma, Eyelid haemangioma, Haemangioma of bone
Haemorrhoids	Haemorrhoids, Haemorrhoidal haemorrhage, Haemorrhoids thrombosed
Headache	Headache, Migraine, Tension headache, Migraine without aura, Migraine with aura, Premenstrual headache, Cluster headache, Head discomfort, Cervicogenic headache, Sinus headache, Ophthalmoplegic migraine, Retinal migraine
Hepatic lesion	Hepatic cyst, Hepatic lesion, Benign hepatic neoplasm
Hepatitis	Hepatitis, Hepatitis toxic, Hepatocellular injury, Chronic hepatitis, Chronic hepatitis B, Hepatitis A, Hepatitis acute, Hepatitis alcoholic, Hepatitis C, Hepatotoxicity
Hepatobiliary disease	Biliary dyskinesia, Gallbladder disorder, Hepatobiliary disease, Biliary colic, Biliary tract disorder, Gallbladder cholesterolosis
Herpes simplex	Oral herpes, Herpes simplex, Genital herpes, Herpes virus infection, Herpes dermatitis, Nasal herpes, Ophthalmic herpes simplex
Herpes zoster	Herpes zoster, Varicella zoster virus infection, Ophthalmic herpes zoster
Hyperglycaemia	Blood glucose increased, Hyperglycaemia
Hypertension	Hypertension, Blood pressure increased, Hypertensive crisis, Essential hypertension, Orthostatic hypertension, Labile hypertension, Systolic hypertension
Hypoaesthesia	Hypoaesthesia, Hypoaesthesia oral
Hypotension	Hypotension, Blood pressure decreased, Blood pressure systolic decreased
Hypothermia	Hypothermia, Body temperature decreased

Recoded (Pooled) Term	Included Preferred Terms
Hypothyroidism	Hypothyroidism , Congenital hypothyroidism
Increased upper airway secretion	Increased upper airway secretion, Increased viscosity of upper respiratory secretion
Influenza	Influenza like illness, Influenza, Influenza virus test positive, Pneumonia influenzal
Injection related reaction	Injection site erythema, Injection site pain, Injection related reaction, Injection site bruising, Injection site haemorrhage, Injection site abscess, Injection site discomfort, Injection site haematoma, Injection site inflammation, Injection site reaction, Injection site swelling, Infusion site nodule
Insomnia	Insomnia, Initial insomnia
Intervertebral disc disorder	Intervertebral disc protrusion, Intervertebral disc disorder, Intervertebral disc degeneration, Intervertebral discitis
Iron deficiency	Iron deficiency, Blood iron decreased
Large intestine polyp	Large intestine polyp, Rectal polyp, Colon adenoma, Rectal adenoma, Rectal polypectomy
Leukocytosis	Leukocytosis, White blood cell count increased, Lymphocytosis
Leukopenia	Lymphopenia, Lymphocyte count decreased, Leukopenia, White blood cell count decreased
Libido disorder	Libido decreased, Libido disorder
Liver test increased	Gamma-glutamyltransferase increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Hyperbilirubinaemia, Blood bilirubin increased, Liver function test increased, Blood alkaline phosphatase increased, Liver function test abnormal, Transaminases increased, Bilirubin conjugated increased, Hypertransaminasaemia, Drug-induced liver injury, Alanine aminotransferase abnormal
Lower respiratory tract infection	Pneumonia, Lower respiratory tract infection, Pneumonia bacterial, Atypical pneumonia, Pneumonia pneumococcal, Viral tracheitis
Lumbar radiculopathy	Lumbar radiculopathy, Lumbosacral radiculopathy
Malignant melanoma	Malignant melanoma, Malignant melanoma in situ
Menopause	Menopause, Menopausal symptoms
Menstrual disorder	Menstruation irregular, Menorrhagia, Menstrual disorder, Metrorrhagia, Menometrorrhagia, Oligomenorrhoea, Menstruation delayed, Premenstrual syndrome, Polymenorrhoea, Premenstrual pain
Mental disorder	Mental disorder, Mental disorder due to a general medical condition
Micturition disorder	Micturition urgency, Micturition disorder
Monocytosis	Monocyte count increased, Monocytosis
Mood altered	Mood altered, Mood swings, Substance-induced mood disorder
Mucosal disorder	Mucosal membrane hyperplasia, Mucous membrane disorder, Mucosal disorder, Mucosal inflammation
Multiple sclerosis	Multiple sclerosis relapse, Multiple sclerosis
Myalgia	Myalgia , Musculoskeletal pain, Musculoskeletal discomfort
Nail disorder	Nail ridging, Nail disorder, Nail dystrophy, Nail fold inflammation
Nephrolithiasis	Nephrolithiasis, Calculus urinary
Neutropenia	Neutropenia, Neutrophil count decreased

Recoded (Pooled) Term	Included Preferred Terms
Non-cardiac chest pain	Non-cardiac chest pain, Musculoskeletal chest pain
Obesity	Weight increased, Obesity, Body mass index increased, Overweight
Oedema	Oedema, Swelling
Oedema peripheral	Oedema peripheral, Peripheral swelling
Oesophagitis	Oesophagitis, Erosive oesophagitis
Orchitis	Orchitis, Orchitis noninfective
Osteoarthritis	Osteoarthritis, Spinal osteoarthritis
Otitis externa	Otitis externa, Otitis externa fungal
Otitis media	Otitis media, Otitis media acute, Otitis media chronic
Ovarian disorder	Ovarian disorder, Ovarian failure
Pancreatic carcinoma	Pancreatic carcinoma, Pancreatic carcinoma metastatic
Pancreatitis	Pancreatitis chronic, Pancreatitis acute, Pancreatitis
Papilloma	Papilloma viral infection, Papilloma
Peptic ulcer	Duodenal ulcer, Gastric ulcer, Peptic ulcer, Gastric ulcer helicobacter, Duodenal ulcer haemorrhage
Periodontal disease	Periodontitis, Periodontal disease, Periodontal inflammation
Periorbital swelling	Periorbital oedema, Periorbital swelling
Peripheral vascular disorder	Peripheral venous disease, Peripheral vascular disorder, Poor peripheral circulation, Peripheral arterial occlusive disease
Pityriasis	Pityriasis, Pityriasis rosea
Presyncope	Dizziness, Presyncope, Dizziness postural
Proteinuria	Proteinuria, Protein urine present
Pruritus	Pruritus, Pruritus allergic, Pruritus generalized, Pruritus genital
Pulmonary function test abnormal	Lung diffusion test decreased, Pulmonary function test decreased, Pulmonary function test abnormal
Pyelonephritis	Pyelonephritis acute, Pyelonephritis, Pyelonephritis chronic
Pyoderma	Pyoderma, Pyoderma streptococcal
Pyrexia	Pyrexia, Hyperthermia, Hyperpyrexia, Post procedural fever
Rash	Rash, Eczema, Erythema, Urticaria, Dermatitis contact, Dermatitis, Dermatitis allergic, Erythema nodosum, Furuncle, Rash popular, Rash pustular, Rash pruritic, Dyshidrotic eczema, Erysipelas, Rash macular, Dermatitis atopic, Skin infection, Dermatitis acneiform, Rash maculo-papular, Dermatitis infected, Dermatitis psoriasiform, Erythema migrans, Carbuncle, Petechiae, Rash erythematous, Eczema eyelids, Eczema infected, Eczema nummular, Erythema of eyelid, Erythrasma, Exfoliative rash, Rash papulosquamous, Viral rash
Renal cyst	Renal cyst, Renal cyst haemorrhage
Respiratory tract infection	Respiratory tract infection, Respiratory tract infection viral
Retinal disorder	Retinal disorder, Retinal degeneration, Retinal dystrophy, Retinal fibrosis, Retinal oedema, Retinal depigmentation, Retinal vasculitis, Retinal vein thrombosis, Retinal artery spasm, Retinal detachment, Retinal haemorrhage, Retinal tear, Retinal exudates
Retinopathy	Retinopathy, Retinopathy hypertensive
Rhinitis	Rhinitis, Rhinitis allergic, Viral rhinitis, Vasomotor rhinitis, Rhinitis hypertrophic, Acute rhinitis
Scar	Scar, Scab

Recoded (Pooled) Term	Included Preferred Terms
Seizure	Epilepsy, Seizure, Status epilepticus, Partial seizures, Generalised tonic-clonic seizure
Sexual dysfunction	Sexual dysfunction, Disturbance in sexual arousal
Sleep disorder	Sleep disorder, Sleep disorder due to general medical condition, insomnia type
Somatoform disorder	Somatoform disorder, Somatoform disorder cardiovascular
Spinal column injury	Spinal compression fracture, Spinal fracture, Spinal column injury
Spirometry	Spirometry abnormal, Spirometry
Steatohepatitis	Non-alcoholic steatohepatitis, Steatohepatitis
Tachycardia	Tachycardia, Sinus tachycardia, Heart rate increased, Supraventricular tachycardia, Tachycardia paroxysmal, Atrial tachycardia, Ventricular tachycardia
Thrombocytopenia	Thrombocytopenia, Platelet count decreased
Thrombocytosis	Platelet count increased, Thrombocytosis, Secondary thrombocytosis
Thyroid neoplasm	Thyroid mass, Thyroid neoplasm
Thyroiditis	Thyroiditis chronic, Thyroiditis, Thyroiditis fibrous chronic, Thyroiditis subacute
Tooth disorder	Toothache, Tooth impacted, Tooth disorder
Tooth infection	Tooth abscess, Tooth infection
Ulcerative colitis	Colitis ulcerative, Colitis, Proctitis ulcerative, Inflammatory bowel disease, Proctitis
Upper respiratory tract infection	Pharyngitis streptococcal, Pharyngotonsillitis, Pharyngitis bacterial, Nasopharyngitis, Upper respiratory tract infection, Pharyngitis, Sinusitis, Tonsillitis, Viral upper respiratory tract infection, Laryngitis, Acute sinusitis, Catarrh, Chronic sinusitis, Upper respiratory tract inflammation, Chronic tonsillitis, Viral pharyngitis, Viral sinusitis, Sinusitis bacterial, Upper respiratory tract infection bacterial, Viral labyrinthitis, Laryngeal inflammation, Pharyngeal inflammation
Urinary tract infection	Urinary tract infection, Urine leukocyte esterase positive, Urinary tract inflammation, Urinary tract infection bacterial
Uterine cervical metaplasia	Uterine cervical squamous metaplasia, Uterine cervical metaplasia
Vertigo	Vertigo, Vertigo positional
Vessel puncture site haematoma	Vessel puncture site haematoma, Vessel puncture site bruise
Visual acuity tests abnormal	Vision blurred, Visual impairment, Visual acuity reduced, Visual field defect, Visual acuity tests abnormal
Vitamin D deficiency	Vitamin D deficiency, Vitamin D decreased
Weight decreased	Weight decreased, Underweight
Wound infection	Wound infection, Wound infection bacterial, Wound infection staphylococcal

Source: reviewer's table summarizing clinical reviewer's logical groupings
Abbreviations: ISS = integrated summary of safety

15.4.5. Potential DILI- patient outcome information

Table 72. Patients With Potential Drug-induced Liver Injury - Study RPC01-3101 (Safety Population)

Subject ID	Age/Sex/ Race	Actual Treatment	Time to Onset[a]	Maximum Hepatic Function Test AST (U/L)	ALT (U/L)	ALP (U/L)	TB (µmol/L)	R Ratio[b]	Hepatic SAE	Outcome[e]
Temple's Corollary										
(b) (6)	56/M/ White	oza	(b) (6)	199	324	197	23	2.9	No	Resolved Off study drug Time to resolution: 58 days
	38/M/ White	oza-		115	231	52	20	14.3	No	Resolved Off study drug Time to resolution: 4 days
	52/F/ Black	oza		106	97	141	3	2.4	No	Resolved On study drug Time to resolution: 19 days
	51/M/ White	oza-oza		64	155	157	8	3.1	No	Resolved On study drug Time to resolution:10 days
	47/M/ White	oza		50	129	113	17	4.5	No	Resolved On study drug Time to resolution: 9 days
	41/M/ White	oza		48	123	68	20	5.9	No	Resolved on study drug Time to resolution: 54 days
	44/M/ White	oza-		117	121	79	12	N/A	No	Resolved on study drug; Time to resolution: 33 Days
	60/F/ White	oza-Pb		102	93	578	11	N/A	No	Resolved on study drug; Time to resolution: 31 Days
	56/F/ White	oza		50	106	65	11	5.1	No	Resolved on study drug; Time to resolution: 15 Days
	40/F/ White	oza-oza		148	253	126	5	6.3	No	Resolved on study drug; Time to resolution: 10 Days

Subject ID	Age/Sex/ Race	Actual Treatment	Time to Onset[a]	Maximum Hepatic Function Test AST (U/L)	ALT (U/L)	ALP (U/L)	TB (µmol/L)	R Ratio[b]	Hepatic SAE	Outcome[e]
(b) (6)	32/M/ White	oza	(b) (6)	73	138	145	6	3.0	No	Resolved on study drug (within 3102) Time to resolution: 69 days
	29/M/ White	oza-		30	135	77	8	5.5	No	Resolved On study drug Time to resolution: 5 days
		oza-oza		50	145	112	11	4.1	No	Resolved on study drug Time to resolution: 14 days
	65/F/ White	oza-		81	129	248	9	2.6	No	Resolved on study drug Time to resolution: 172 days
	29/F/ Asian	oza		112	144	67	12	6.7	No	Resolved on study drug Time to resolution: 68 Days
	56/M/ White	Pb		87	326	125	28	18.0	No	Ongoing Off study drug as of June 2017 (LTFU)
	41/M/ White	oza		160	307	178	7	5.4	No	Resolved On study drug Time to resolution 13 Days
	28/M/ White	oza		64	134	117	21	4.7	No	Resolved On study drug Time to resolution:12 days
	25/M/ White	oza		50	142	180	5	2.5	No	Resolved On study drug Time to resolution 7 days
		oza-oza		305	326	236	23	3.9	No	Resolved Off study drug Time to resolution 48 days
	43/M/ White	oza		200	208	167	13	3.9	No	Resolved Off study drug Time to resolution 36 days

Subject ID	Age/Sex/ Race	Actual Treatment	Time to [a]	Maximum Hepatic Function Test AST (U/L)	ALT (U/L)	ALP (U/L)	TB (µmol/L)	R Ratio[b]	Hepatic SAE	Outcome[e]
(b) (6)	42/M/ White	oza	(b) (6)	108	182	242	9	2.1	No	Resolved Off study drug Time to resolution 99 days
	49/M/ White	oza		87	159	89	19	5.6	No	Resolved On study drug Time to resolution 49 days
	39/F/ White	oza-oza		107	139	67	8	6.5	No	Resolved within 3102 On study drug Time to resolution 35 days
	19/F/ White	oza		258	499	68	5	8.8	No	Resolved On study drug Time to resolution 22 days
	62/M/ White	oza		47	135	68	7	6.2	No	Resolved off study drug Time to resolution 30 days
	36/F/ White	oza		139	250	184	6	2.6	No	Resolved Off study drug Time to resolution 13 days
	29/M/ White	oza		244	460	398	8	3.6	No	Resolved Off study drug Time to resolution: 56 Days

Source: Applicant's response to Information Request dated 3/1/2021, page 32
Abbreviations: ALP = a kaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug-induced liver injury; ID = identifier; Oza = ozanimod; SAE = serious adverse event; TB = total bilirubin; Pb = placebo

[a] Time to onset is calculated as ([Day of onset of the first symptom, sign, or laboratory test abnormality indicative of DILI] – [the first day that the medication was given]).

[b] The values used to calculate the R ratio are the first values obtained that qualified as being indicative of DILI (usually ALT ≥ 3 x ULN, ALP ≥ 2 x ULN, or TB ≥ 2 x ULN in association with enzyme elevations). The ALT and ALP must be within 2 days of each other, whenever they are not drawn on the same day.
If they are not drawn within 2 days of each other, then R-value at maximum liver enzyme elevation should be rendered incalculable. In such cases, the reviewer has the discretion to calculate and use R-values at other time points.

[c] Met stopping criteria: ALT or AST > 8x ULN or ALT/AST > 5x ULN with confirmation within 2 weeks, or ALT/AST > 3x ULN and (total bilirubin > 2 x ULN), or ALT/AST > 3x ULN with the appearance of fatigue, nausea, vomiting, RUQ pain or tenderness, fever, rash, and/or eosinophilia (> 5%) and no apparent alternative causes for the finding.

[d] Hepatic AE resulting in discontinuation.

[e] Resolved = within 3*ULN; time to resolution = date resolved – date of onset

15.4.6. Details on Histologic Assessment

The initial protocol (May 2015) specified collection of 3 pairs of biopsy samples (rectum, sigmoid, descending colon). Subsequently in June 2016, the protocol was amended to specify that a single pair of biopsies would be collected from the most inflamed location of the left colon. The rationale was to better standardize the collection of samples so that the analysis was conducted on tissue from a single intestinal area for all patients.

Biospies were shipped to a central laboratory (b) (4) where they were fixed, and then were shipped via courier to (b) (4) for processing, mounting and digitization. Digital images were uploaded to (b) (4) for central reading of histology.

Histologic assessment was conducted by (b) (4) All samples from an individual subject were read by the same (b) (4), who was blinded to subject identifiers and the timepoint of sample collection. Histologic parameters were assessed using the Geboes index (Geboes et al. 2000).

As described in the review, the Applicant's definition of histologic remission included the elements of the Geboes scores 2, 3, 4, and 5, and required subscores of 0 for each component, as outlined in Table 73 below.

Table 73: Geboes Index

Grade 0	Structural (architectural change)
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	Chronic inflammatory infiltrate
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	Lamina propria neutrophils and eosinophils
2A Eosinophils	
2A. 0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B. 0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	Neutrophils in epithelium
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4	Crypt destruction
4.0	None
4.1	Probable—local excess of neutrophils in part of crypt
4.2	Probable—marked attenuation
4.3	Unequivocal crypt destruction
Grade 5	Erosion or ulceration
5.0	No erosion, ulceration, or granulation tissue
5.1	Recovering epithelium+adjacent inflammation
5.2	Probable erosion—focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

Source: (Geboes et al. 2000).

15.5. Supplementary Efficacy Tables and Figures

15.5.1. Supplementary Analyses

An exploratory analysis of the proportion of patients in clinical remission who had a SFS of 0 or 1 is shown in Table 74 and Table 75 for the induction and maintenance periods, respectively. While an SFS value of 0 or 1 is allowable for individual patients, a score of 1 in a significant number of patients may not be considered adequate evidence of stool normalization. In the induction period, larger proportions of patients in clinical remission in both treatment groups had an SFS value of 1. In the maintenance period, larger proportions of patients in clinical

remission in both treatment groups had an SFS value of 0. Thus, since a significant number of patients in both study periods did not have a SBS value of 1, there appears to be adequate evidence of stool normalization among patients in clinical remission in the induction and maintenance periods.

Table 74. Exploratory Analysis for Induction Period: Proportion of Patients in Clinical Remission at Week 10[a] by Stool Frequency Subscore (ITT Population)

	Cohort 1	
	Placebo (N = 216)	**Ozanimod 1 mg (N = 429)**
Number of patients in clinical remission at Week 10	13	79
Number of patients in clinical remission with SFS=1, n (%)[b]	8 (61.5)	44 (55.7)
Number of patients in clinical remission with SFS=0, n (%)[b]	5 (38.5)	35 (44.3)

Source: statistical reviewer's analysis
Abbreviations: ITT = intent-to-treat; SFS = stool frequency subscore
[a] Analyzed with NRI for missing data
[b] Percentages are based on the number of patients in clinical remission at Week 10.

Table 75. Exploratory Analysis for Maintenance Period: Proportion of Patients in Clinical Remission at Week 52[a] by Stool Frequency Subscore (ITT Population)

	Re-randomized Patients	
	Ozanimod 1 mg – Placebo (N = 227)	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Number of patients in clinical remission at Week 52	42	85
Number of patients in clinical remission with SFS=1, n (%)	14 (33.3)	24 (28.2)
Number of patients in clinical remission with SFS=0, n (%)	28 (66.7)	61 (71.8)

Source: statistical reviewer's analysis
Abbreviations: ITT = intent-to-treat; SFS = stool frequency subscore
[a] Analyzed with NRI for missing data
[b] Percentages are based on the number of patients in clinical remission at Week 52.

Table 76. Exploratory Analysis for Maintenance Period: Proportion of Patients in Corticosteroid-Free Remission at Week 52 Among Patients with Concomitant Corticosteroid Use at Study Baseline[a] (ITT Population)

		Re-randomized Patients	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Number of patients	21	69	80
Number of patients in corticosteroid-free remission at Week 52, n (%)	0	2 (2.9)	10 (12.5)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.095 (0.012, 0.177)	

Source: statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

15.5.2. Sensitivity Analyses

Sensitivity Analyses for Induction Period

The statistical reviewer's sensitivity analysis results for clinical remission and clinical response in the induction period are displayed in Table 77 and Table 78.

Table 77. Sensitivity Analysis for Induction Period: Proportion of Patients in Clinical Remission at Week 10 (ITT Population)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Number of patients with imputed subscore values	57	45	55
Percentage of patients in clinical remission at Week 10	18.9	7.3	21.1
Difference in proportions (ozanimod-placebo), 95% CI[a]	0.116 (0.065, 0.168)		

Source: statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 78. Sensitivity Analysis for Induction Period: Proportion of Patients in Clinical Response at Week 10 (ITT Population)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Number of patients with imputed subscore values	57	45	55
Percentage of patients in clinical response at Week 10	52.4	31.9	57.5
Difference in proportions (ozanimod-placebo), 95% CI[a]	0.205 (0.123, 0.287)		

Source: statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

In the Applicant's Figure 14.2.1.4A which contained TPA results for clinical remission, the missing data scenarios that did not result in a conclusion in favor of ozanimod appeared implausible, since in such scenarios, a larger proportion of patients in the placebo group with missing data were assigned as having clinical remission compared to patients with missing data in the ozanimod group. For example, according to the figure, in the scenario where 14/45 (31%) placebo patients with missing data were assigned as responders and 0/57 patients in the ozanimod group were assigned as responders, results favored the placebo group. However, given the observed rates of clinical remission in both groups at Week 10, such response proportions are not plausible. All of the scenarios contained in the Applicant's Figure 14.2.2.4A for clinical response resulted a conclusion in favor of ozanimod.

Sensitivity Analyses for Maintenance Period

The statistical reviewer's sensitivity analysis results for clinical remission and clinical response in the maintenance period are displayed in Table 79 and Table 80.

Table 79. Sensitivity Analysis for Maintenance Period: Proportion of Patients in Clinical Remission at Week 52 (ITT Population)

		Re-randomized Patients	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Number of patients with imputed subscore values	36	117	73
Percentage of patients in clinical remission at Week 52	34.7	16.0	41.6
Difference in proportions (ozanimod-placebo), 95% CI[a]		0.256 (0.174, 0.337)	

Source: statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 80. Sensitivity Analysis for Maintenance Period: Proportion of Patients in Clinical Response at Week 52 (ITT Population)

		Re-randomized Patients	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Number of patients with imputed subscore values	36	117	73
Percentage of patients in clinical response at Week 52	78.5	74.6	84.7
Difference in proportions (ozanimod-placebo), 95% CI[a]		0.101 (0.118, 0.191)	

Source: statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

In the Applicant's Figure 14.2.1.4B which contained TPA results for clinical remission, the missing data scenarios that did not result in a conclusion in favor of ozanimod appeared implausible, since in most scenarios, a larger proportion of patients in the placebo group with missing data were assigned as having clinical remission compared to patients with missing data in the ozanimod group. For example, according to the figure, in the scenario where 25/117 (21%) placebo patients with missing data were assigned as responders and 0/73 patients in the ozanimod group were assigned as responders, results favored the placebo group. However, given the observed rates of clinical remission in both groups at Week 52, it does not seem plausible to make such assumptions. This implausibility is further supported when we consider that most of the patients re-randomized to placebo who discontinued the study experienced a relapse in UC (77/103 patients [75%]). A similar interpretation applies to Figure 14.2.2.4B for clinical response.

Thus, limited conclusions can be made from a TPA conducted on binary endpoints in which overly optimistic results are assigned to a treatment group that experiences a large amount of study withdrawal over time due to an exacerbation of the condition being studied. Another limitation of the TPA is that the method does not take covariates into account when assigning response status.

15.5.3. Subgroup Analyses

Subgroup Analyses for Induction Period

Table 81. Subgroup Analysis for Induction Period: Proportion of Patients in Clinical Remission at Week 10[a] by Sex (ITT Population)

	Cohort 1		Cohort 2
Sex	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
Male			
Number of patients	245	143	214
Number of patients in clinical remission, n (%)	37 (15.1)	6 (4.2)	46 (21.5)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.109 (0.054, 0.165)		
Female			
Number of patients	184	73	153
Number of patients in clinical remission, n (%)	42 (22.8)	7 (9.6)	31 (20.3)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.132 (0.042, 0.223)		

Source: Study RPC01-3101 Table 14.2.1.9.4A (p. 278), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 82. Subgroup Analysis for Induction Period: Proportion of Patients in Clinical Remission at Week 10[a] by Age (ITT Population)

	Cohort 1		Cohort 2
Age	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
< 65 years			
Number of patients	410	202	346
Number of patients in clinical remission, n (%)	76 (18.5)	12 (6.0)	73 (21.1)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.126 (0.076, 0.176)		
≥ 65 years			
Number of patients	19	14	21
Number of patients in clinical remission, n (%)	3 (15.8)	1 (7.1)	4 (19.1)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.087 (-0.126, 0.299)		

Source: statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 83. Subgroup Analysis for Induction Period: Proportion of Patients in Clinical Remission at Week 10[a] by Race (ITT Population)

	Cohort 1		Cohort 2
Race	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
White			
Number of patients	370	192	336
Number of patients in clinical remission, n (%)	72 (19.5)	13 (6.8)	74 (22.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.127 (0.073, 0.181)		
Black or African American			
Number of patients	14	4	10
Number of patients in clinical remission, n (%)	3 (21.4)	0	2 (20.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.214 (0, 0.429)		
Asian			
Number of patients	36	17	12
Number of patients in clinical remission, n (%)	3 (8.3)	0	1 (8.3)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.083 (-0.007, 0.174)		
Other			
Number of patients	9	3	9
Number of patients in clinical remission, n (%)	1 (11.1)	0	0
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.111 (-0.094, 0.316)		

Source: statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 84. Subgroup Analysis for Induction Period: Proportion of Patients in Clinical Remission at Week 10[a] by Region (ITT Population)

	Cohort 1		Cohort 2
Region	**Ozanimod 1 mg (N = 429)**	**Placebo (N = 216)**	**Ozanimod 1 mg (N = 367)**
North America			
Number of patients	107	60	80
Number of patients in clinical remission, n (%)	17 (15.9)	2 (3.3)	16 (20.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.126 (0.043, 0.208)		
Western Europe			
Number of patients	62	21	60
Number of patients in clinical remission, n (%)	2 (3.2)	0	5 (8.3)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.032 (-0.012, 0.076)		
Eastern Europe			
Number of patients	215	112	200
Number of patients in clinical remission, n (%)	55 (25.6)	11 (9.8)	52 (26.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.158 (0.075, 0.238)		
Asia Pacific			
Number of patients	36	20	27
Number of patients in clinical remission, n (%)	3 (8.3)	0	4 (14.8)
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.083 (-0.007, 0.174)		
South America			
Number of patients	3	0	0
Number of patients in clinical remission, n (%)	1 (33.3)		
Difference in proportions (ozanimod-placebo), 95% CI[b]	N/A		
South Africa			
Number of patients	6	3	0
Number of patients in clinical remission, n (%)	1 (16.7)	0	
Difference in proportions (ozanimod-placebo), 95% CI[b]	0.167 (-0.132, 0.465)		

Source: Study RPC01-3101 Table 14.2.1.9.4A (p. 283), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat; N/A = not applicable
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Subgroup Analyses for Maintenance Period

Table 85. Subgroup Analysis for Maintenance Period: Proportion of Patients in Clinical Remission at Week 52[a] by Sex (ITT Population)

		Re-randomized Patients	
Sex	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
Male			
Number of patients	46	122	117
Number of patients in clinical remission, n (%)	11 (23.9)	23 (18.9)	39 (33.3)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.145 (0.035, 0.255)	
Female			
Number of patients	23	105	113
Number of patients in clinical remission, n (%)	6 (26.1)	19 (18.1)	46 (40.7)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.226 (0.109, 0.343)	

Source: Study RPC01-3101 Table 14.2.1.9.1B (p. 1051), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 86. Subgroup Analysis for Maintenance Period: Proportion of Patients in Clinical Remission at Week 52[a] by Age (ITT Population)

		Re-randomized Patients	
Age	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
< 65 years			
Number of patients	63	215 (18.1)	217 (37.8)
Number of patients in clinical remission, n (%)	16 (25.4)	39	82
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.197 (0.114, 0.279)	
≥ 65 years			
Number of patients	6	12	13
Number of patients in clinical remission, n (%)	1 (16.7)	3 (25.0)	3 (23.1)
Difference in proportions (ozanimod-placebo), 95% CI[b]		-0.019 (-0.355, 0.316)	

Source: statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 87. Subgroup Analysis for Maintenance Period: Proportion of Patients in Clinical Remission at Week 52[a] by Race (ITT Population)

		Re-randomized Patients	
Race	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
White			
Number of patients	62	202	205
Number of patients in clinical remission, n (%)	16 (25.8)	37 (18.3)	79 (38.5)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.202 (0.117, 0.288)	
Black or African American			
Number of patients	3	9	9
Number of patients in clinical remission, n (%)	1 (33.3)	3 (33.3)	3 (33.3)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0 (-0.436, 0.436)	
Asian			
Number of patients	4	12	13
Number of patients in clinical remission, n (%)	0	2 (16.7)	3 (23.1)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.064 (-0.247, 0.375)	
Other			
Number of patients	0	4	3
Number of patients in clinical remission, n (%)		0	0
Difference in proportions (ozanimod-placebo), 95% CI[b]		0 (N/A)	

Source: statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat; N/A = not applicable
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Table 88. Subgroup Analysis for Maintenance Period: Proportion of Patients in Clinical Remission at Week 52[a] by Region (ITT Population)

		Re-randomized Patients	
Region	**Placebo (N = 69)**	**Ozanimod 1 mg – Placebo (N = 227)**	**Ozanimod 1 mg – Ozanimod 1 mg (N = 230)**
North America			
Number of patients	13	49	56
Number of patients in clinical remission, n (%)	2 (15.4)	6 (12.2)	22 (39.3)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.270 (0.113, 0.428)	
Western Europe			
Number of patients	3	26	31
Number of patients in clinical remission, n (%)	0	3 (11.5)	8 (25.8)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.143 (-0.054, 0.340)	
Eastern Europe			
Number of patients	49	136	121
Number of patients in clinical remission, n (%)	15 (30.6)	30 (22.1)	48 (39.7)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.176 (0.065, 0.288)	
Asia Pacific			
Number of patients	4	13	20
Number of patients in clinical remission, n (%)	0	2 (15.4)	5 (25.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0.096 (-0.177, 0.369)	
South America			
Number of patients	0	1	1
Number of patients in clinical remission, n (%)		1 (100.0)	1 (100.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]		0 (N/A)	
South Africa			
Number of patients	0	2	1
Number of patients in clinical remission, n (%)		0	1 (100.0)
Difference in proportions (ozanimod-placebo), 95% CI[b]		100.0 (N/A)	

Source: Study RPC01-3101 Table 14.2.1.9.1B (p. 1056), statistical reviewer's analysis
Abbreviations: CI = confidence interval; ITT = intent-to-treat; N/A = not applicable
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation for the difference in binomial proportions.

Subgroup Analyses for Safety

Table 89. Safety Analyses by Corticosteroid Use at Screening (Yes or No), Induction Period, Cohort 1, Study 3101

	Corticosteroid Use			No Corticosteroid Use		
	Ozanimod N= 143 (%)	Placebo N= 73 (%)	Treatment Difference	Ozanimod N= 286 (%)	Placebo N= 143 (%)	Treatment Difference
TEAEs	67 (46.9%)	27 (37.0%)	9.9%	105 (36.7%)	55 (38.5%)	-1.8%
SAEs	8 (5.6%)	4 (5.5%)	0.1%	9 (3.1%)	3 (2.1%)	1.0%
Severe AEs	5 (3.5%)	2 (2.7%)	0.8%	9 (3.1%)	2 (1.4%)	1.7%
Serious infections	1 (0.7%)	1 (1.4%)	-0.7%	3 (1.0%)	0 (0%)	1.0%

Source: Reviewer's table, created from ADAE dataset
Abbreviations: CV = cardiovascular; SAEs = severe adverse events; TEAEs = treatment-emergent adverse events

Table 90. Safety Analyses by Corticosteroid Use at Screening (Yes or No), Maintenance Period, Study 3101

	Corticosteroid Use			No Corticosteroid Use		
	Ozanimod 1 mg – Ozanimod 1 mg N= 68 (%)	Ozanimod 1 mg – Placebo N= 65 (%)	Treatment Difference	Ozanimod 1 mg – Ozanimod 1 mg N= 162 (%)	Ozanimod 1 mg – Placebo N= 162 (%)	Treatment Difference
TEAEs	44 (64.7%)	24 (36.9%)	27.8%	69 (42.6%)	59 (36.4%)	6.2%
SAEs	1 (1.5%)	6 (9.2%)	-7.7%	11 (6.8%)	12 (7.4%)	-0.6%
Severe AEs	3 (4.4%)	1 (1.5%)	2.9%	6 (3.7%)	8 (4.9%)	-1.2%
Serious infections	0 (0%)	2 (3.1%)	-3.1%	2 (1.2%)	2 (1.2%)	0%

Source: Reviewer's table, created from ADAE dataset
Abbreviations: CV = cardiovascular; SAEs = severe adverse events; TEAEs = treatment-emergent adverse events

Table 91. Safety Analyses by Prior TNF Use (Yes or No), Induction Period, Cohort 1, Study 3101

	Prior TNF			No prior TNF		
	Ozanimod N= 130 (%)	Placebo N= 65 (%)	Treatment Difference	Ozanimod N= 299 (%)	Placebo N= 151 (%)	Treatment Difference
TEAEs	73 (56.2%)	31 (47.7%)	8.5%	99 (33.1%)	51 (33.8%)	-0.7%
SAEs	11 (8.5%)	5 (7.7%)	0.8%	6 (2.0%)	2 (1.3%)	0.7%
Severe AEs	9 (6.9%)	2 (3.1%)	3.8%	5 (1.7%)	2 (1.3%)	0.4%

Source: Reviewer's table, created from ADAE dataset
Abbreviations: CV = cardiovascular; SAEs = severe adverse events; TEAEs = treatment-emergent adverse events; TNF = tumor necrosis factor

Table 92. Safety Analyses by Prior TNF Use (Yes or No), Maintenance Period, Study 3101

	Prior TNF			No Prior TNF		
	Ozanimod 1 mg – Ozanimod 1 mg N= 76 (%)	Ozanimod 1 mg – Placebo N= 69 (%)	Treatment Difference	Ozanimod 1 mg – Ozanimod 1 mg N= 154 (%)	Ozanimod 1 mg – Placebo N= 158 (%)	Treatment Difference
TEAEs	44 (57.9%)	27 (39.1%)	18.8%	69 (44.8%)	56 (35.4%)	9.4%
SAEs	3 (3.9%)	6 (8.7%)	-4.8%	9 (5.8%)	12 (7.6%)	-1.8%
Severe AEs	4 (5.3%)	2 (2.9%)	2.4%	5 (3.2%)	7 (4.4%)	-1.2%

Source: Reviewer's table, created from ADAE dataset
Abbreviations: CV = cardiovascular; SAEs = severe adverse events; TEAEs = treatment-emergent adverse events; TNF = tumor necrosis factor

15.6. Statistical Methodology for Integrated Safety Analyses

The Applicant's ISS SAP contained pre-specified statistical methods for integrated safety analyses. Statistical methods described in the ISS SAP which were utilized in this review are described below.

Adjusted AE Incidence Rates

Adjusted AE incidence rates for Pool F were derived using CMH weighting described by (Chuang-Stein and Beltangady 2011). Weighting approaches, such as CMH weighting, allow for the derivation of adjusted incidence rates obtained from more than one study. Two-sided 95% CIs for the differences in adjusted incidence rates between treatment groups were derived using the normal approximation (Kim and Wong 2013).

EAIRs for AEs

An EAIR for a specific AE was calculated as (number of patients / PY) x 1000. Adjusted EAIRs for Pool F were derived using CMH weighting described by (Chan and Wang 2009). Two-sided 95% CIs for the differences in adjusted EAIRs between treatment groups were derived using the normal approximation (Chan and Wang 2009). Two-sided 95% CIs for the differences in EAIRs between treatment groups for an individual study were derived using a method described by (Sahai and Khurshid 1996).

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

/s/

JAY R FAJICULAY
05/26/2021 03:53:06 PM

JESSICA J LEE
05/26/2021 04:25:53 PM

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	sNDA 209899
Supplement #:	Supplement – 001
Related IND #:	
Product Name:	Ozanimod (Zeposia)
Indication(s):	Treatment of (b) (4) moderately to severely active ulcerative colitis (UC) in adults
Applicant:	Celgene International II Sàrl
Dates:	Submit Date: 11/30/2020 File Meeting Date: 1/11/2021 PDUFA Goal Date: 5/30/2021
Review Priority:	Priority
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Sara Jimenez, PhD
Concurring Reviewers:	David Petullo, MS (Statistical Team Leader)
Medical Division:	Division of Gastroenterology
Clinical Team:	Arushi deFonseka, MD Tara Altepeter, MD (Clinical Team Leader)
Project Manager:	Jay Fajiculay

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment Groups/ Sample Size	Endpoint/Analysis	Preliminary Findings
RPC01-3101	MC, R, DB, PG, PC	Induction period Cohort 1 N=645 subjects randomized 2:1 1. Ozanimod 1 mg (n=429) 2. Placebo (n=216) Cohort 2 N=367 subjects treated with ozanimod 1 mg	Induction period Primary endpoint: The proportion of subjects in clinical remission at Week 10 Primary endpoint analysis: Cochran-Mantel-Haenszel (CMH) test stratified by corticosteroid use at screening (yes or no) and prior anti-TNF use (yes or no) for the difference in proportions with non-responder imputation Key secondary endpoints (at Week 10): • The proportion of subjects with a clinical response • The proportion of subjects with endoscopic improvement • The proportion of subjects with mucosal healing Key secondary endpoint analysis: CMH test similar to primary endpoint analysis	Findings for induction period primary analysis (Cohort 1): placebo: 6.0%, ozanimod: 18.4%, difference in proportions= 12.4% [95% CI: 7.5, 17.2], p < 0.0001
		Maintenance period N=457 subjects randomized 1:1 1. Ozanimod 1 mg (n=230) 2. Placebo (n=227)	Maintenance period Primary endpoint: The proportion of subjects in clinical remission at Week 52 Primary endpoint analysis: CMH test stratified by clinical remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no) Key secondary endpoints (at Week 52): • The proportion of subjects with a clinical response • The proportion of subjects with endoscopic improvement • The proportion of subjects in clinical remission in the subset of subjects who were in remission at Week 10 • The proportion of subjects with corticosteroid-free remission • The proportion of subjects with mucosal healing • The proportion of subjects with	Findings for maintenance period primary analysis: placebo: 18.5%, ozanimod: 37.0%, difference in proportions= 18.6% [95% CI: 10.8, 26.4], p < 0.0001

			durable clinical remission Key secondary endpoint analysis: CMH test similar to primary endpoint analysis	

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel-group, PC: placebo-controlled

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	N/A
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	No novel statistical methodology was proposed.
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA209899\0058\m5\datasets\rpc01-3101\rpc01-3101-2020dbl\analysis
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	All submitted datasets were in CDISC format.
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the	adrs.xpt

Content Parameter	Response/Comments
primary endpoint(s)	
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups.	X			On January 21, 2021, as a response to the FDA's information request (IR), the Applicant submitted race and age subgroup analyses for efficacy.
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

No refuse-to-file issue was identified.

5.2. Information Requests/Review Issues

No additional IRs or review issues were identified.

Appears this way on original

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

/s/

SARA JIMENEZ
01/26/2021 03:33:55 PM

DAVID M PETULLO
01/28/2021 09:46:16 AM
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA209899Orig1s001

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. NDA Supplement Number: NDA-209899-SUPPL-1

2. Submission(s) Being Reviewed:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PAS, efficacy	11/30/2020	11/30/2020	12/07/2020	05/30/2021	05/24/2021
Clinical Information Amendment		12/11/2020	12/11/2020			05/24/2021
Clinical Information Amendment		01/12/2021	01/12/2021			05/24/2021
Clinical Information Amendment		01/25/2021	01/25/2021			05/24/2021
Clinical Information Amendment		02/05/2021	02/05/2021			05/24/2021
Clinical Information Amendment		02/10/2021	02/10/2021			05/24/2021
Clinical Pharmacology Information Amendment		02/19/2021	02/19/2021			05/24/2021
Clinical Information Amendment		02/22/2021	02/22/2021			05/24/2021
Multiple Categories Amendment		02/26/2021	02/26/2021			05/24/2021
Clinical Information Amendment		03/01/2021	03/01/2021			05/24/2021
Clinical Information Amendment		03/16/2021	03/16/2021			05/24/2021
Clinical Information Amendment		03/23/2021	03/23/2021			05/24/2021
Clinical Information Amendment		03/26/2021	03/26/2021			05/24/2021
Clinical Information Amendment		04/02/2021	04/02/2021			05/24/2021
Multiple Categories Amendment		04/08/2021	04/08/2021			05/24/2021
Clinical Information Amendment		04/09/2021	04/09/2021			05/24/2021
Multiple Categories Amendment		04/23/2021	04/23/2021			05/24/2021
Clinical Information Amendment		04/27/2021	04/27/2021			05/24/2021
Clinical Information Amendment		05/19/2021	05/19/2021			05/24/2021
Annual Report 1		05/19/2021	05/19/2021			05/24/2021
Multiple Categories Amendment		05/21/2021	05/21/2021			05/24/2021

3. Provides For:

- Addition of a new indication: “ZEPOSIA is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults”.

4. **Review #**: 1

5. **Clinical Review Division**: CDER/OND/ON/DN2

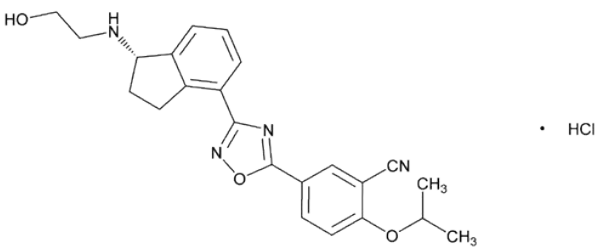
6. **Name and Address of Applicant**:
   Celgene International II Sàrl
   Rue du Pré-Jorat 14
   Couvet, Neuchatel 02108
   Switzerland

   Authorized U.S. Agent
   Celgene Corporation
   86 Morris Avenue
   Summit, New Jersey 07901
   USA

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
ZEPOSIA® (ozanimod) Capsules	Capsule	0.23 mg, 0.46 mg, and 0.92 mg	Oral	Rx	No

8. **Chemical Name and Structure of Drug Substance**:



USAN: Ozanimod Hydrochloride
Chemical name: (b) (4)
Molecular formula: $C_{23}H_{24}N_4O_3 \cdot HCl$
Molecular weight: 440.93 g/mol
CAS No.: *1306760-87-1 ozanimod;* (b) (4)

9. **Indication**: Treatment of patients with moderately to severely active ulcerative colitis (UC) in adults

10. **Supporting/Relating Documents**: See pages 4 to 8.

11. **Consults**: None

12. **Executive Summary**:
    This Prior Approval Efficacy supplement provides for the addition of a new indication: "ZEPOSIA is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults". This supplemental NDA describes the results of the Phase 3 RPC01-3101

study entitled "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis".

The currently-approved shelf life for 0.5 mg and 1.0 mg drug product is 36 months. The currently-approved shelf life for 0.25 mg and 1.0 mg drug product is 24 months. The applicant submitted Annual Report 1 on 05/19/2021 with 36 months long-term stability data for 0.25 mg, 0.5 mg, and 1.0 mg drug product. The provided stability data summary results provided in Annual Report 1 are acceptable. It is acceptable to extend the shelf life for the 0.25 mg drug product from 24 months to 36 months based on all long-term stability data meeting specifications through 36 months.

The proposed concentration in the environment is expected to be below 1 part per billion. No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). The requested categorical exclusion from the requirements of an environmental assessment, as provided in 21 CFR 25.31(b), is acceptable.

The proposed labeling (Prescribing Information) does not include changes in the CMC-related Sections 3, 11 or 16. The proposed labeling is acceptable from the CMC standpoint.

13. Conclusions & Recommendations:
This supplement, as amended, is recommended for Approval from the standpoint of CMC.

14. Comments/Deficiencies to be Conveyed to Applicant:
None

15. Primary Reviewer:
Le Zhang, Ph.D., CMC reviewer, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
David B. Lewis, Branch Chief, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC Assessment

I. Background Information

ZEPOSIA (ozanimod) has been approved by FDA for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease (approved on 25 March 2020).

This Prior Approval Efficacy supplement provides for a new indication: "ZEPOSIA is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults".

The applicant submitted Annual Report 1 on 05/19/2021 with 36 months long-term stability data for 0.25 mg, 0.5 mg, and 1.0 mg drug product.

II. Proposed Changes

This Prior Approval Efficacy supplement provides for the addition of a new indication: "ZEPOSIA is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults". This supplemental NDA describes the results of the Phase 3 RPC01-3101 study entitled "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis".

III. Data Submitted to Support the Proposed Changes

- Module 1.3.2 Field Copy Certification
- Module 1.3.3 Debarment Certification
- Module 1.12.14 Environmental Analysis
- Module 1.14 Labeling
- Module 3.2.P. Drug Product Information

Evaluation of these modules follows in the body of this review.

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety-Low

I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data

P. DRUG PRODUCT

P.8. Stability

P.8.1 Stability Summary and Conclusion

The following stability information were provided in Annual Report 1 submitted on 05/19/2021.

(b) (4)

3 Pages have been Withheld in Full as b4 (CCI/TS) Immediately Following this Page

Module 1.14: Labeling

1.14.1. Draft Labeling

The proposed labeling (Prescribing Information) does not include changes in the CMC-related Sections 3, 11 or 16. The proposed labeling is acceptable from the CMC standpoint.

Appears this way on original

Le Zhang

Digitally signed by Le Zhang
Date: 5/24/2021 04:18:02PM
GUID: 594abf46003a4cb7cc12cf6cfd6d8751

David Lewis

Digitally signed by David Lewis
Date: 5/24/2021 04:44:37PM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA-209899-SUPPL-1**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PAS, efficacy	11/30/2020	11/30/2020	12/07/2020	05/30/2021	04/07/2021
Clinical Information Amendment		12/11/2020	12/11/2020			04/07/2021
Clinical Information Amendment		01/12/2021	01/12/2021			04/07/2021
Clinical Information Amendment		01/25/2021	01/25/2021			04/07/2021
Clinical Information Amendment		02/05/2021	02/05/2021			04/07/2021
Clinical Information Amendment		02/10/2021	02/10/2021			04/07/2021
Clinical Pharmacology Information Amendment		02/19/2021	02/19/2021			04/07/2021
Clinical Information Amendment		02/22/2021	02/22/2021			04/07/2021
Multiple Categories Amendment		02/26/2021	02/26/2021			04/07/2021
Clinical Information Amendment		03/01/2021	03/01/2021			04/07/2021
Clinical Information Amendment		03/16/2021	03/16/2021			04/07/2021
Clinical Information Amendment		03/23/2021	03/23/2021			04/07/2021
Clinical Information Amendment		03/26/2021	03/26/2021			04/07/2021
Clinical Information Amendment		04/02/2021	04/02/2021			04/07/2021

3. **Provides For:**
   - Addition of a new indication: “ZEPOSIA is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults”.

4. **Review #**: 1

5. **Clinical Review Division**: CDER/OND/ON/DN2

6. **Name and Address of Applicant**:
   Celgene International II Sàrl

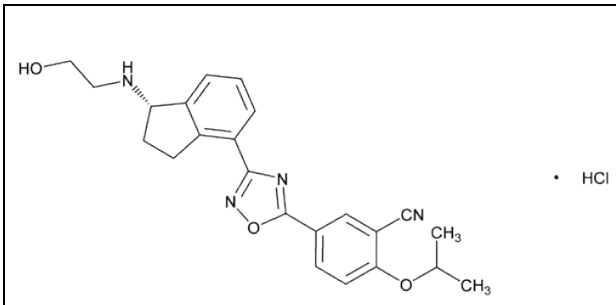
Rue du Pré-Jorat 14
Couvet, Neuchatel 02108
Switzerland

Authorized U.S. Agent
Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
USA

7. Drug Product:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
ZEPOSIA® (ozanimod) Capsules	Capsule	0.23 mg, 0.46 mg, and 0.92 mg	Oral	Rx	No

8. Chemical Name and Structure of Drug Substance:



USAN: Ozanimod Hydrochloride
Chemical name: (b) (4)
Molecular formula: $C_{23}H_{24}N_4O_3 \cdot HCl$
Molecular weight: 440.93 g/mol
CAS No.: *1306760-87-1 ozanimod;* (b) (4)

9. Indication: Treatment of patients with moderately to severely active ulcerative colitis (UC) in adults

10. Supporting/Relating Documents: See pages 4 to 5.

11. Consults: None

12. Executive Summary:
This Prior Approval Efficacy supplement provides for the addition of a new indication: "ZEPOSIA is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults". This supplemental NDA describes the results of the Phase 3 RPC01-3101 study entitled "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis".

The proposed concentration in the environment is expected to be below 1 part per billion. No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). The requested

categorical exclusion from the requirements of an environmental assessment, as provided in 21 CFR 25.31(b), is acceptable.

The proposed labeling (Prescribing Information) does not include changes in the CMC-related Sections 3, 11 or 16. The proposed labeling is acceptable from the CMC standpoint.

13. Conclusions & Recommendations:
This supplement, as amended, is recommended for Approval from the standpoint of CMC.

14. Comments/Deficiencies to be Conveyed to Applicant:
None

15. Primary Reviewer:
Le Zhang, Ph.D., CMC reviewer, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
David B. Lewis, Branch Chief, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC Assessment

I. Background Information

ZEPOSIA (ozanimod) has been approved by FDA for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease (approved on 25 March 2020).

This Prior Approval Efficacy supplement provides for a new indication: "ZEPOSIA is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults".

II. Proposed Changes

This Prior Approval Efficacy supplement provides for the addition of a new indication: "ZEPOSIA is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults". This supplemental NDA describes the results of the Phase 3 RPC01-3101 study entitled "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis".

III. Data Submitted to Support the Proposed Changes

- Module 1.3.2 Field Copy Certification
- Module 1.3.3 Debarment Certification
- Module 1.12.14 Environmental Analysis
- Module 1.14 Labeling

Evaluation of these modules follows in the body of this review.

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety-Low

I. Review of Common Technical Document-Quality (CTD-Q) Module 1

1.3.2 Field Copy Certification

Celgene International II Sàrl ("CIS II"), a subsidiary of Celgene Corporation, with Celgene Corporation, serves as an authorized representative (and authorized U.S. agent) for CIS II, hereby certifies the Sponsor has complied with 21 CFR 314.50(l)(3) Field Copy and has informed the New Jersey District Office of the submission of the supplemental NDA for ZEPOSIA (ozanimod), NDA 209899.

Evaluation: ***Adequate.***

1.3.3 Debarment Certification

Celgene Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Evaluation: ***Adequate.***

1.12.14 Environmental Analysis

Categorical Exclusion Statement

Celgene Corporation is requesting a categorical exclusion from the preparation of an environmental assessment (EA) for ozanimod (trade name Zeposia) according to section 505(b) of the Federal Food, Drug, and Cosmetic Act. This supplemental New Drug Application (sNDA) has been prepared to submit ozanimod capsules for the treatment of adult patients with moderately to severely active ulcerative colitis. Zeposia is already approved for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults (NDA 209899/SN0012, approved on 25 March 2020). This proposed action will increase the volume of active compound introduced into the environment. However, the proposed concentration in the environment is expected to be below 1 part per billion. No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). This drug is manufactured using a synthetic process and is not known to be derived from any wild-sourced plant and/or animal material 21 CFR 25.21(b). Therefore, the applicant requests a categorical exclusion from the requirements of an environmental assessment, as provided in 21 CFR 25.31(b). Additional information is provided below to justify exclusion from the requirements of an environmental assessment.

Evaluation: ***Adequate.*** The proposed concentration in the environment is expected to be below 1 part per billion. No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). The requested categorical exclusion from the requirements of an environmental assessment, as provided in 21 CFR 25.31(b), is acceptable.

Module 1.14: Labeling

1.14.1. Draft Labeling

The proposed labeling (Prescribing Information) does not include changes in the CMC-related Sections 3, 11 or 16. The proposed labeling is acceptable from the CMC standpoint.

Le Zhang

Digitally signed by Le Zhang
Date: 4/07/2021 01:19:37PM
GUID: 594abf46003a4cb7cc12cf6cfd6d8751

David Lewis

Digitally signed by David Lewis
Date: 4/08/2021 07:27:46AM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA209899Orig1s001

OTHER REVIEW(S)

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

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

Memorandum

Date: May 13, 2021

To: Jay Fajiculay, Pharm.D., Regulatory Health Project Manager
Division of Gastroenterology (DG)

Joette Meyer, MD, Associate Director for Labeling, (DG)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for ZEPOSIA (ozanimod)

NDA: 209899 / Supplement 001

In response to Division of Gastroenterology (DG) consult request dated December 02, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for ZEPOSIA (ozanimod) capsules, for oral use. This supplement (S001) pertains to the approval of indication of moderately to severely active ulcerative colitis in adults.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling that was available in SharePoint on May 4, 2021 at 10:52 am, and OPDP has no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on April 30, 2021.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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/s/

ADEWALE A ADELEYE
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 30, 2021
To:	Jay Fajiculay, PharmD Regulatory Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ZEPOSIA (ozanimod)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 209899
Supplement Number:	S-001
Applicant:	Bristol-Myers Squibb

1 INTRODUCTION

On November 30, 2020, Bristol-Myers Squibb submitted for the Agency's review a Prior Approval Supplement (PAS) - Efficacy for New Drug Application 209899/S-001 for ZEPOSIA (ozanimod). This PAS proposes an indication for the treatment of moderately to severely active ulcerative colitis (UC) in adults. ZEPOSIA (ozanimod) was originally approved on March 25, 2020 for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology (DG) on December 2, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZEPOSIA (ozanimod) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft ZEPOSIA (ozanimod) MG received on November 30, 2020, and received by DMPP on April 23, 2021.
- Draft ZEPOSIA (ozanimod) MG received on November 30, 2020, and received by OPDP on April 26, 2021.
- Draft ZEPOSIA (ozanimod) Prescribing Information (PI) received on November 30, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on April 23, 2021.
- Draft ZEPOSIA (ozanimod) Prescribing Information (PI) received on November 30, 2020, revised by the Review Division throughout the review cycle, and received by OPDP on April 26, 2021.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

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

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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MEDICATION GUIDE

ZEPOSIA® (zeh-poe'-see-ah)
(ozanimod)
capsules, for oral use

Read this Medication Guide before you start taking ZEPOSIA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ZEPOSIA?
ZEPOSIA may cause serious side effects, including:

1. **Infections.** ZEPOSIA can increase your risk of serious infections that can be life-threatening and cause death. ZEPOSIA lowers the number of white blood cells (lymphocytes) in your blood. This will usually go back to normal within 3 months of stopping treatment. Your healthcare provider may do a blood test of your white blood cells before you start taking ZEPOSIA.

   Call your healthcare provider right away if you have any of the following symptoms of an infection during treatment with ZEPOSIA and for 3 months after your last dose of ZEPOSIA:

   - fever
   - feeling very tired
   - flu-like symptoms
   - cough
   - painful and frequent urination (signs of a urinary tract infection)
   - rash
   - headache with fever, neck stiffness, sensitivity to light, nausea or confusion (these may be symptoms of meningitis, an infection of the lining around your brain and spine)

   Your healthcare provider may delay starting or may stop your ZEPOSIA treatment if you have an infection.

2. **Slow heart rate (also known as bradyarrhythmia) when you start taking ZEPOSIA.** ZEPOSIA may cause your heart rate to temporarily slow down, especially during the first 8 days that you take ZEPOSIA. You will have a test to check the electrical activity of your heart called an electrocardiogram (ECG) before you take your first dose of ZEPOSIA. Call your healthcare provider if you experience the following symptoms of slow heart rate:

   - dizziness
   - lightheadedness
   - feeling like your heart is beating slowly or skipping beats
   - shortness of breath
   - confusion
   - chest pain
   - tiredness

   Follow directions from your healthcare provider when starting ZEPOSIA and when you miss a dose. See **"How should I take ZEPOSIA?".**

See "**What are possible side effects of ZEPOSIA?**" for more information about side effects.

What is ZEPOSIA?
ZEPOSIA is a prescription medicine used to treat:

- adults with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.
- adults with moderately to severely active ulcerative colitis.

It is not known if ZEPOSIA is safe and effective in children.

Do not take ZEPOSIA if you:

- have had a heart attack, chest pain (unstable angina), stroke or mini-stroke (transient ischemic attack or TIA), or certain types of heart failure in the last 6 months.
- have or have had a history of certain types of an irregular or abnormal heartbeat (arrhythmia) that is not corrected by a pacemaker.
- have untreated, severe breathing problems during your sleep (sleep apnea).
- take certain medicines called monoamine oxidase (MAO) inhibitors (such as selegiline, phenelzine, linezolid).

Talk to your healthcare provider before taking ZEPOSIA if you have any of these conditions or do not know if you have any of these conditions.

Before taking ZEPOSIA, tell your healthcare provider about all of your medical conditions, including if you:

- have a fever or infection, or you are unable to fight infections due to a disease, or take or have taken medicines that lower your immune system.
- received a vaccine in the past 30 days or are scheduled to receive a vaccine. ZEPOSIA may cause vaccines to be less effective.

- Before you start treatment with ZEPOSIA, your healthcare provider may give you a chicken pox (Varicella Zoster Virus) vaccine if you have not had one before.
- have had chickenpox or have received the vaccine for chickenpox. Your healthcare provider may do a blood test for the chickenpox virus. You may need to get the full course of the vaccine for chickenpox and then wait 1 month before you start taking ZEPOSIA.
- have a slow heart rate.
- have an irregular or abnormal heartbeat (arrhythmia).
- have a history of a stroke.
- have heart problems, including a heart attack or chest pain.
- have high blood pressure.
- have liver problems.
- have breathing problems, including during your sleep.
- are pregnant or plan to become pregnant. ZEPOSIA may harm your unborn baby. Talk with your healthcare provider if you are pregnant or plan to become pregnant. If you are a female who can become pregnant, you should use effective birth control during your treatment with ZEPOSIA and for 3 months after you stop taking ZEPOSIA. Talk with your healthcare provider about what birth control method is right for you during this time. Tell your healthcare provider right away if you become pregnant while taking ZEPOSIA or if you become pregnant within 3 months after you stop taking ZEPOSIA.
- are breastfeeding or plan to breastfeed. It is not known if ZEPOSIA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ZEPOSIA.

Tell your healthcare provider about all the medicines you take or have recently taken, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using ZEPOSIA with other medicines can cause serious side effects. Especially tell your healthcare provider if you take or have taken:

- medicines that affect your immune system, such as alemtuzumab
- medicines to control your heart rhythm (antiarrhythmics), or heart beat
- CYP2C8 inducers such as rifampin
- CYP2C8 inhibitors such as gemfibrozil (medicine to treat high fat in your blood)
- opioids (pain medicine)
- medicines to treat depression
- medicines to treat Parkinson's disease
- medicines to control your heart rate and blood pressure (beta blocker medicines and calcium channel blocker medicines)

You should not receive **live** vaccines during treatment with ZEPOSIA, for at least 1 month before taking ZEPOSIA and for 3 months after you stop taking ZEPOSIA. Vaccines may not work as well when given during treatment with ZEPOSIA.

Talk with your healthcare provider if you are not sure if you take any of these medicines.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ZEPOSIA?

You will receive a 7-day starter pack. You must start ZEPOSIA by slowly increasing doses over the first week. Follow the dose schedule in the table below. This may reduce the risk of slowing of the heart rate.

Days 1-4	Take 0.23 mg (capsule in light grey color) 1 time a day
Days 5-7	Take 0.46 mg (capsule in half-light grey and half-orange color) 1 time a day
Days 8 and thereafter	Take 0.92 mg (capsule in orange color) 1 time a day

- Take ZEPOSIA exactly as your healthcare provider tells you to take it.
- Take ZEPOSIA 1 time each day.
- Swallow ZEPOSIA capsules whole.
- Take ZEPOSIA with or without food.
- Avoid certain foods that are high (over 150 mg) in tyramine such as aged, fermented, cured, smoked and pickled foods. Eating these foods while taking ZEPOSIA may increase your blood pressure.
- Do not stop taking ZEPOSIA without talking with your healthcare provider first.
- Do not skip a dose.

- Start taking ZEPOSIA with a 7-day starter pack.
- If you miss 1 or more days of your ZEPOSIA dose during the first 14 days of treatment, talk to your healthcare provider. You will need to begin with another ZEPOSIA 7-day starter pack.
- If you miss a dose of ZEPOSIA after the first 14 days of treatment, take the next scheduled dose the following day.

What are the possible side effects of ZEPOSIA?

ZEPOSIA may cause serious side effects, including:

- See **"What is the most important information I should know about ZEPOSIA?"**
- **liver problems.** ZEPOSIA may cause liver problems. Your healthcare provider will do blood tests to check your liver before you start taking ZEPOSIA. Call your healthcare provider right away if you have any of the following symptoms:
  - unexplained nausea
  - vomiting
  - stomach area (abdominal) pain
  - tiredness
  - loss of appetite
  - yellowing of the whites of your eyes or skin
  - dark colored urine
- **increased blood pressure.** Your healthcare provider should check your blood pressure during treatment with ZEPOSIA. A sudden, severe increase in blood pressure (hypertensive crisis) can happen when you eat certain foods that contain high levels of tyramine. See "**How should I take ZEPOSIA?**" section for more information.
- **breathing problems.** Some people who take ZEPOSIA have shortness of breath. Call your healthcare provider right away if you have new or worsening breathing problems.
- **a problem with your vision called macular edema.** Your healthcare provider should test your vision at any time you notice vision changes during treatment with ZEPOSIA. Call your healthcare provider right away if you have any of the following symptoms:
  - blurriness or shadows in the center of your vision
  - sensitivity to light
  - a blind spot in the center of your vision
  - unusually colored vision
- **swelling and narrowing of blood vessels in your brain**. A condition called PRES (Posterior Reversible Encephalopathy Syndrome) is a rare condition that has happened with ZEPOSIA and with drugs in the same class. Symptoms of PRES usually get better when you stop taking ZEPOSIA. If left untreated, it may lead to a stroke. Your healthcare provider will do a test if you have any symptoms of PRES. Call your healthcare provider right away if you have any of the following symptoms:
  - sudden severe headache
  - sudden confusion
  - sudden loss of vision or other changes in your vision
  - seizure
- **severe worsening of multiple sclerosis (MS) after stopping ZEPOSIA.** When ZEPOSIA is stopped, symptoms of MS may return and become worse compared to before or during treatment. Always talk to your healthcare provider before you stop taking ZEPOSIA for any reason. Tell your healthcare provider if you have worsening symptoms of MS after stopping ZEPOSIA.
- **allergic reactions.** Call your healthcare provider if you have symptoms of an allergic reaction, including a rash, itchy hives, or swelling of the lips, tongue or face.

The most common side effects of ZEPOSIA can include:

- upper respiratory tract infections
- low blood pressure when you stand up (orthostatic hypotension)
- back pain
- headache
- elevated liver enzymes
- painful and frequent urination (signs of urinary tract infection)
- high blood pressure

These are not all of the possible side effects of ZEPOSIA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZEPOSIA?

- Store ZEPOSIA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ZEPOSIA and all medicines out of the reach of children.

General information about the safe and effective use of ZEPOSIA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take ZEPOSIA for conditions for which it was not prescribed. Do not give ZEPOSIA to other people, even if they have the same

symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about ZEPOSIA that is written for health professionals.

What are the ingredients in ZEPOSIA?

Active ingredient: ozanimod

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The capsule shell contains: black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide.

Manufactured for: Celgene Corporation, Summit, NJ 07901

ZEPOSIA® is a registered trademark of Celgene Corporation.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approved: X/202X

ZEPMG.003

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Addendum Memo to the March 5, 2021 DPMH PMR memo

Date: 3/31/2021

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology (DG)

Drug: Zeposia (ozanimod) capsule, NDA 209899

Sponsor: Bristol-Myers Squibb

Subject: Addendum to the March 5, 2021 DPMH PMR memo

Approved Indication(s): For the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Proposed Indication: For the treatment of moderately to severely active ulcerative colitis (UC) in adults.

Brief Addendum

Ozanimod and/or metabolites were detected in the milk of lactating rat at levels higher than those in maternal plasma. There are no data on the presence of ozanimod in human milk. A lactation study should be considered. This was discussed with DG Clinical and Clinical Pharmacology teams, DPMH recommends the following language for a postmarking lactation study:

> Perform a lactation study (milk only) in lactating women who have received therapeutic doses of drug name using a validated assay to assess concentrations of drug name in breast milk and effects on the breastfed infant.

Further discussion with DG review division raised concerns over the feasibility of recruitment of pregnant women with moderate to severe ulcerative colitis who are unexposed to medications. DG asked that consideration be given to including an external disease-matched comparator or using an existing disease-based registry. Based on this discussion, DPMH revised the PMR language initially proposed for the pregnancy exposure registry in the DPMH MHT memo dated March 5, 2021.[1] See below for the updated language.

> An international, prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of females exposed to Zeposia (ozanimod) during pregnancy with a comparator population of women exposed to other ulcerative colitis therapies during pregnancy and an unexposed comparator population. External disease-matched comparators and use of existing disease registries can be considered. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. This study can be conducted as part of the ongoing study under NDA 209899 PMR 3809-3.

[1] See DPMH PMR memo, Reference ID 4757744

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

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 23, 2021
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 209899/S-001
Product Name and Strength:	Zeposia (ozanimod) capsule, 0.23 mg, 0.46 mg, 0.92 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celgene Corporation (Celgene)
FDA Received Date:	November 30, 2020
OSE RCM #:	2020-2597
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm. D.

1 REASON FOR REVIEW

Celgene Corporation (Celgene) submitted a supplement for Zeposia (ozanimod) capsule to propose an expansion of indication to moderately to severely active ulcerative colitis (UC) in adults. Subsequently, Division of Gastroenterology (DG) requested that we review the proposed Zeposia prescribing information (PI), carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D -N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Table 2 below include the identified medication error issues with the submitted prescribing information, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	(b) (4) [redacted]	Frequency of administration is typically presented after the dosage strength statement. (b) (4) [redacted]	We recommend to rewrite the statement as below: "After initial titration, the recommended dosage of

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN (b) (4)	RECOMMENDATION
			ZEPOSIA is 0.92 mg taken orally once daily starting on Day 8."

4 CONCLUSION

Our evaluation of the Zeposia prescribing information (PI) identified areas of vulnerability that may lead to medication errors. The container labels and carton labeling are acceptable from a medication error perspective. Above, we have provided recommendations in Table 2 for the Division.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Zeposia that Celgene Corporation (Celgene) submitted on November 30, 2020.

<table>
<tr><th colspan="2">Table 3. Relevant Product Information for Zeposia</th></tr>
<tr><td>Initial Approval Date</td><td>March 25, 2020</td></tr>
<tr><td>Active Ingredient</td><td>ozanimod</td></tr>
<tr><td>Indication</td><td>Treatment of:
Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
Moderately to severely active ulcerative colitis (UC) in adults.</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>capsules</td></tr>
<tr><td>Strength</td><td>0.23 mg, 0.46 mg, 0.92 mg</td></tr>
<tr><td>Dose and Frequency</td><td>Initiate Zeposia with a 7-day titration, (b) (4): After initial titration, the recommended (b) (4) dosage of ZEPOSIA is 0.92 mg taken orally starting on Day 8.
Days 1-4 0.23 mg once daily
Days 5-7 0.46 mg once daily
Day 8 and thereafter 0.92 mg once daily</td></tr>
<tr><td>How Supplied</td><td>
<table>
<tr><th>Package configuration</th><th>Tablet strength</th></tr>
<tr><td>Bottles of 30</td><td>0.92 mg</td></tr>
<tr><td>7-Day Starter Pack</td><td>7-capsule starter pack containing: (4) 0.23 mg capsules and (3) 0.46 mg capsules</td></tr>
<tr><td>Starter Kit
(7-Day Starter Pack
and 0.92 mg 30 count Bottle)</td><td>37-capsule starter kit
including:
one 7-capsule starter pack containing: (4) 0.23 mg capsules and (3) 0.46 mg capsules
and</td></tr>
</table>
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		one bottle containing (30) 0.92 mg capsules
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	

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APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 22, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Zeposia. Our search identified five previous reviews[a,bc,d, e], and we confirmed that our previous recommendations were implemented.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Zeposia labels and labeling submitted by Celgene Corporation (Celgene).

- Container label(s) received on November 30, 2020
- Carton labeling of 7 Day Starter pack received on November 30, 2020
- Blistercard labeling of 7 day Starter Pack received on November 30, 2020
- Carton Labeling of Started Kit received on November 30, 2020
  Container labeling of 0.92 mg (30 count) received on November 30, 2020
  Blistercard labeling of 7 day Starter Pack received on November 30, 2020
- Prescribing Information (Image not shown) received on November 30, 2020
  \\CDSESUB1\evsprod\nda209899\0058\m1\us\proposed-redlined.doc

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

[b]Morris, C. Label and Labeling Review for Zeposia (NDA 209899). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 23. RCM No.: 2018-48-1

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

[d]Morris, C. Label and Labeling Review for Zeposia (NDA 209899). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 2. RCM No.: 2018-48-3

[e] Morris, C. Label and Labeling Review for Zeposia (NDA 209899). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 10. RCM No.: 2018-48-4

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE
MEDICAL OFFICER CONSULTATION

Date:	23 Mar 2021
To:	Jay Fajiculay, PharmD, RPM, Division of Gastroenterology and Jessica Lee, MD, MMSc, Division Director, Division of Gastroenterology
From:	Robert Busch, MD MMSc, Medical Officer, Division of Pulmonology, Allergy, and Critical Care (DPACC)
Through:	Miya Paterniti, MD, Team Leader, DPACC
Through:	Banu Karimi-Shah, MD, Deputy Division Director, DPACC
Subject:	NDA 209899 Pulmonary Safety Labeling Consult Response

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General Information

NDA:	**209899**
Sponsor:	**Celgene Corporation**
Product:	**Zeposia (ozanimod), a sphingosine 1-phosphate receptor modulator (S1PRM), under development for the treatment of Ulcerative Colitis (UC)**
Purpose:	**Supplemental NDA (sNDA) Review Consultation; sNDA submitted to NDA 209899 as Supplement 001 on 11/30/2020**
Documents reviewed:	**Labeling submitted 02/19/2021, Sponsor's Response to Information Requests submitted 02/05/2021 and 02/23/2021, elements of prior FDA drug development programs, relevant literature**

I. Background

The Division of Gastroenterology (DG) has consulted the Division of Pulmonology, Allergy, and Critical Care (DPACC) regarding pulmonary safety labeling for ozanimod, which is a small molecule under development by Celgene Corporation (Sponsor) for the treatment of ulcerative colitis (UC). Ozanimod is already approved under NDA 209899 for "the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults". The supplemental NDA (NDA 209899, S-001) for the treatment of UC is currently under review in DG under a priority review with a goal date of May 27, 2021.

A. Ozanimod

Ozanimod is a sphingosine 1-phospate receptor modulator (S1PRM) under development for multiple inflammatory bowel disease (IBD) indications, including UC (IND 115243) (b) (4) The mechanism of action involves activation of sphingosine 1-phosphate 1 receptor and sphingosine 1-phosphate 5 receptor, resulting in retention of circulating lymphocytes in peripheral lymph nodes and gastrointestinal Peyer's patches. This leads to a reduction in circulating lymphocytes, which the Sponsor contends leads to a decrease in disease activity in UC (b) (4) Ozanimod and other S1PRM medications (e.g., fingolimod) have class labeling outlining pulmonary adverse events that include bronchoconstriction and decreases in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), which have been attributed in preliminary data to non-selective binding of other sphingosine 1-phosphate receptors. While the Sponsor claims that ozanimod's specificity for particular sphingosine 1-phosphate receptors leads to decreased pulmonary adverse effects, ozanimod's prescribing information also contains Warnings and Precautions related to "Respiratory Effects" and details a possible decline in lung function with recommendations for assessing pulmonary function through spirometry.

B. Ulcerative Colitis

UC is an IBD characterized by inflammatory lesions of the colon. The disease includes features of contiguous inflammation in the rectum, colon, and terminal ileum. Inflammation is generally confined to the mucosal layer (as opposed to transmural inflammation), and results in features such as infiltration of inflammatory cells and formation of crypt abscesses. UC is also characterized by symptoms of abdominal pain, diarrhea, colonic and rectal bleeding, resultant anemia, and sporadic disease exacerbations. Extra-gastrointestinal (extra-GI) manifestations of UC (b) (4) have often been studied (b) (4) under the heading of IBD, and IBD manifestations that affect the lung include airway inflammatory conditions such as bronchiectasis and chronic bronchitis, small airway disease and bronchiolitis, subglottic stenosis, and multiple patterns of interstitial lung diseases (e.g., organizing pneumonia, eosinophilic pneumonia, and nonspecific interstitial pneumonitis), as well as medication-related lung injury patterns. Serositis and thromboembolic disease are also reported.

C. Overview of Ozanimod Drug Development Programs

The drug development program for ozanimod in UC includes multiple studies conducted under IND 115243, which are the primary focus of this consult. The drug development program for ozanimod in UC includes a phase 2, randomized, double-blind, placebo-controlled trial (RPC01-202) with an open-label extension (RPC01-202olp) and a phase 3, randomized, double-blind, placebo-controlled trial (RPC01-3101) with an open-label extension trial (RPC01-3102). The focus of this consult is primarily on data and analyses from Study RPC01-3101; the different phases of this study are described as UC Studies 1 and 2 in the Sponsor-proposed labeling.

II. Consult Question

DG Consult Text:

Please review the results of the PFTs, mean changes over time, related respiratory system AEs, and reversibility of clinically important declines in PFTs if appropriate. Please provide your input on whether or not the concerns raised for the MS indication and this class broadly are applicable and similar in the UC population. Please review the findings in light of the current labeling for this drug (just approved in 2020 for MS) and advise on whether any additional or differential information should be included specific to the UC population as it pertains to this risk. Please plan to attend the midcycle meeting to discuss your findings, if possible.

III. Summary of Pulmonary Safety Findings

In general, review of the data provided in the supplemental NDA and the Response To Information Request support that the administration of ozanimod in the UC population presents similar respiratory effects and respiratory risks as compared to the multiple sclerosis program. Compared to subjects randomized to placebo, subjects randomized to ozanimod demonstrate mean declines in FEV1 and FVC of likely undetermined clinical significance, as well as a minority of subjects treated with ozanimod with changes in FEV1 or FVC ≥200 mL at 10 weeks. The study design of the pivotal studies for ozanimod in UC do not allow for evaluation of randomized comparisons of pulmonary function without introducing potential bias due to post-randomization inclusion/exclusion of subjects. These limitations of the study design limit our ability to make definitive statements regarding pulmonary safety signals at 52 weeks. Comparison of non-randomized, exposure-based groupings of ozanimod versus placebo that span the randomized studies and their open-label extensions, however, do not suggest additional potential safety signals beyond those labeled previously. (b) (4)

IV. Labeling Recommendations:

This Section documents the Sponsor's proposed labeling and DPACC's proposed modifications. For each labeling section pertinent to respiratory or pulmonary safety, the existing labeling is provided. The Sponsor-proposed amendments are underlined. Bold text indicates labeling language that DPACC suggests are unsupported by the submitted data or that are otherwise recommended for revision. Recommended revisions are described in the *Reviewer's Comments* and suggested labeling based on our review are provided below. In the revised labeling, "XX" denotes a confidence interval that should be requested and confirmed by the Sponsor.

A. Highlights

The Sponsor proposes no wording changes to the Highlights of Prescribing Information or Sections 1-4 that pertain to respiratory or pulmonary safety. Highlights of Prescribing Information contains the following text pertaining to respiratory safety:

> Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated (5.6)

> ***Reviewer's Comment****: In the opinion of this reviewer, the wording utilized in the Highlights of Prescribing Information is also appropriate to convey the pulmonary safety concerns and severity raised by the submitted data in UC and no modifications are proposed.*

B. Warnings and Precautions

The Sponsor proposes to amend Section 5.6 Respiratory Effects with the following underlined text indicated below:

> Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV_1) were observed in patients treated with ZEPOSIA as early as 3 months after treatment initiation. In the MS pooled analyses of Study 1 and Study 2, the decline in absolute FEV_1 from baseline in patients treated with ZEPOSIA compared to patients who received IFN beta-1a was 60 mL (95% CI: -100, -20) at 12 months. The mean difference in percent predicted FEV_1 at 12 months between patients treated with ZEPOSIA and patients who received IFN beta-1a was 1.9% (95% CI: -2.9, -0.8). Dose-dependent reductions in forced vital capacity (FVC) (absolute value and %-predicted) were also seen at Month 3 in pooled analyses comparing patients treated with ZEPOSIA to patients who received IFN beta-1a (60 mL, 95% CI (-110, -10); 1.4%, 95% CI: (-2.6, -0.2)), though significant reductions were not seen at other timepoints. There is insufficient information to determine the reversibility of the decrease in FEV_1 or FVC after drug discontinuation. One patient in the MS Study 1 discontinued ZEPOSIA because of dyspnea.

C. Adverse Reactions

The Sponsor proposes to amend Section 6.1 Respiratory Effects for ozanimod with the text indicated below:

Dose-dependent reductions in absolute FEV_1 and FVC were observed (b) (4)

(b) (4)

DPACC proposes reverting to the labeled text from the previous version, as indicated below:

Dose-dependent reductions in absolute FEV_1 and FVC were observed in patients treated with ZEPOSIA. [see Warnings and Precautions (5.6)].

V. Relevant Trial Design Elements

The study designs utilized for the UC drug development program relied on a 10-week, randomized Induction Phase (IndP) that selected for subjects with a clinical response to ozanimod or placebo (Responders). Responders continued in the original study's Maintenance Phase (MP), while the study design removed subjects who did not meet criteria for a clinical response (Non-Responders) from the initial study and allowed these Non-Responders to enter an open label extension (OLE) in which all subjects received ozanimod. This design

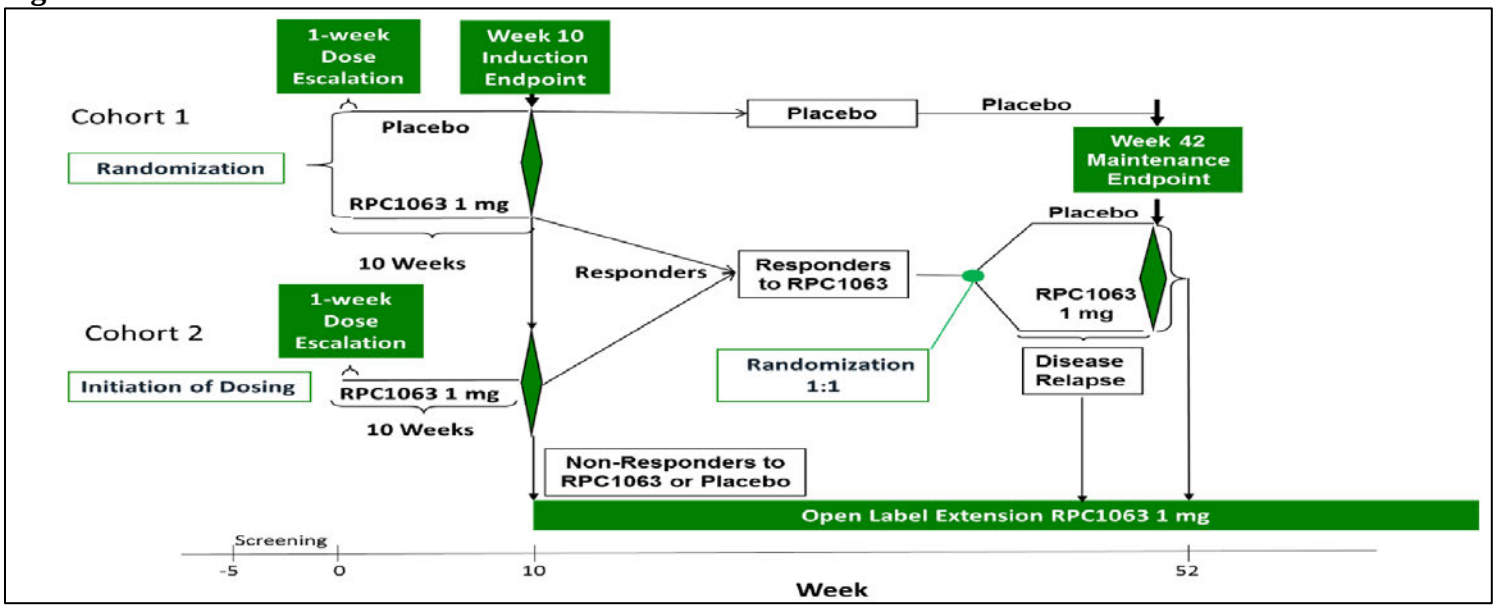
decision results in a MP study population at Week 52 that does not maintain comparator groups based on the initial randomized assignment, since a substantial number of subjects were dropped from the original randomized comparator groups based on post-randomization factors.

A. RPC01-3101 and RPC01-3102

Study Design

The schematic for trials RPC01-3101 (randomized, double-blind, placebo-controlled) and RPC01-3102 (open label extension) are presented in Figure 1.

Figure 1 Trial Schematic for RPC01-3101 and RPC01-3102



Source: Sponsor

For the purposes of this consult, the randomized comparison of subjects in "Cohort 1" is maintained through the IndP (i.e., Week 10). This randomized comparison of subjects in Cohort 1 through Week 10 (3101-IndP) forms the most reliable data to draw substantive conclusions regarding the pulmonary safety of ozanimod in UC from Trial RPC01-3101 for labeling purposes.

Cohort 2 was not randomized during the IndP. This design creates uncertainty in comparisons of Cohort 2 to any other group in the study at any timepoint.After the IndP and regardless of initial randomized treatment assignment, the subgroup of Non-Responders from Cohort 1 was allowed to enter the open label extension. In this open label extension, all subjects were assigned to receive ozanimod. Because of this design choice, after the IndP, the original randomized comparisons are not maintained in RPC01-3101, and subsequent pulmonary safety comparisons versus placebo in Trial RPC01-3101 only represent the subgroup of Responder subjects. In addition, the trial design of RPC01-3101 allowed Responder subjects from the non-randomized Cohort 2 to be combined with Responders from Cohort 1, and then re-randomized into new mixed comparator groups during the MP.

(b) (4)

Exposure-based Comparator Groups

Given that the initial randomized comparisons are not maintained through the MP in Trial RPC01-3101, and that data after the IndP from Non-Responders come exclusively from Trial RPC01-3102, DPACC requested analyses of pulmonary function testing based on ozanimod exposure spanning both RPC01-3101 and RPC01-3102 – regardless of Responder or Non-Responder status – to characterize any additional trends in pulmonary safety based on ozanimod exposure. This classification resulted in the following comparator groups based on IndP-MP (or equivalent OLE period) treatment exposure:

- **Placebo-placebo**
  - Subjects who were assigned to receive placebo during the IndP of RPC01-3101 and were assigned to receive placebo during the MP of RPC01-3101. Based on the study design, this grouping could only contain Responders.
- **Placebo-ozanimod**
  - Subjects who were assigned to receive placebo during the IndP of RPC01-3101 and then assigned to receive ozanimod through the open label extension in study RPC01-3102. Based on the study design, this grouping could only contain Non-Responders.
- **Ozanimod-placebo**
  - Subjects who were assigned to receive ozanimod during the IndP of RPC01-3101 (i.e., as part of "Cohort 1" or "Cohort2") and then were assigned to receive placebo during the MP of RPC01-3101. Based on the study design, this grouping could only contain Responders.
- **Ozanimod-ozanimod**
  - Subjects who were assigned to receive ozanimod during the IndP of RPC01-3101 (i.e., as part of "Cohort 1" or "Cohort 2") and then were assigned to receive ozanimod either through the re-randomization in trial RPC01-3101 or through the open-label extension in study RPC01-3102. Based on the study design, this grouping could contain both Responders and Non-Responders.

Reviewer's Comment*: The requested exposure-based comparator groups rely explicitly on non-randomized comparisons and include multiple subjects who received open-label administration of ozanimod at different points in Trial RPC01-3101 or RPC01-3102. This reviewer acknowledges that these exposure-based comparisons include the uncertainties and potential biases associated with non-randomized comparisons and unblinded comparisons. Acknowledging these potential limitations, the analyses were requested with an intent to evaluate for any suggestion of concerning safety trends (i.e.,*

larger safety effects) in the most complete comparator dataset available in the provided studies. These analyses are not intended as definitive evaluations of the effect of ozanimod on pulmonary safety.

Schedule and Extent of Pulmonary Function Testing

In Study RPC01-3101, pulmonary function testing was performed at Screening and at Week 10 in the IndP (see Table 1). Additional pulmonary function testing was performed at Week 18 and Week 42 in the MP, or on the date of early termination.

Table 1 RPC01-3101: Focused Schedule of Assessments

		Induction			Maintenance						Early Term[q]
Trial Procedures		Dose Escalation	Assigned Dose		Treatment						
(Visit Label)	Screening	Visit I 1[a,b] (Week 0)	Visit I 2[w] (Week 5)	(EoT) Visit Visit I 3[b] (Week 10)	Visit M 1[b,c] (Week 0)	Visit M 2 (Week 8)	Visit M 3 (Week 18)	Visit M 4 (Week 30)	Relapse Visit (When Indicated)	(EoT) Visit M 5[b] (Week 42)	
(Visit Day and Window)	Day -35 to 0	Day 1	Day 35±5	Day 70±10	Day 1	Day 56±10	Day 126±10	Day 210±10		Day 294±10	Day of Early Term
(Overall Duration)		0 weeks	5 weeks	10 weeks	10 weeks	18 weeks	28 weeks	40 weeks		52 weeks	
Adverse events[z]		X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X		X						X	X
Vital signs	X	X	X	X	X	X	X	X		X	X
Hematology[v]	X	X	X	X	X	X	X	X		X	X
Blood chemistry[x]	X	X	X	X	X	X	X	X		X	X
Pregnancy test[t]	X	X	X	X	X	X	X	X		X	X
Contraception education	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X			X						X	X
Pulmonary function tests[p]	X			X			X			X	X

Source: Sponsor

In Study RPC01-3102, pulmonary function testing was performed on Day 1, Week 22, and Week 46, or on the date of early termination (see Table 2).

Table 2 RPC01-3102: Focused Schedule of Assessments

Trial Procedures	Baseline	Treatment						Additional Visits[d]			
	Visit 1[a,b,c]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7				
	Day 1	Week 5	Week 10	Week 16	Week 22	Week 34	Week 46	12-week intervals	EoT/ ET		
	Day 1	Day 35 ± 5	Day 70 ± 5	Day 112 ± 7	Day 154 ± 7	Day 238 ± 14	Day 322 ± 14	Day (last visit calculated from Day 1 + 84 days ±14 days)	EoT/ ET	Last dose + 1 day[r]	Last dose + 4 (±1) days[r]
Contraception education	X	X	X	X	X	X	X	X	X		
Urinalysis	X								X		
Pulmonary function tests[i]	X				X		X	X	X		

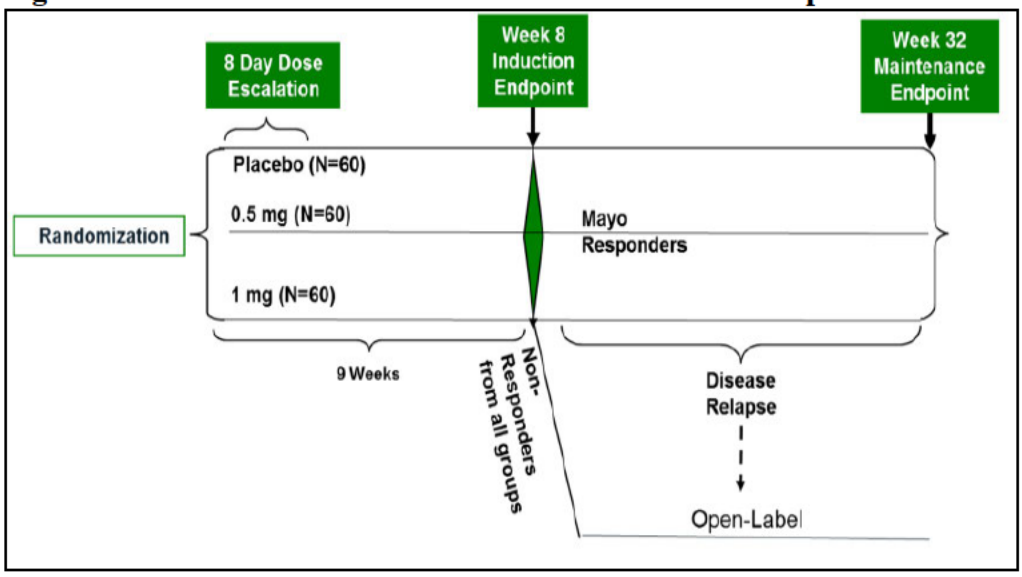
Source: Sponsor

In both studies, pulmonary function testing included measurements of FEV1 and FVC. DLCO was only measured at sites that had that capability, resulting in only a minority of subjects providing DLCO data for evaluation.

B. RPC01-202 and RPC01-202olp

Study Design
The schematic for trials RPC01-202 (phase 2, randomized, double-blind, placebo-controlled) and RPC01-202olp (open-label extension) are presented below in Figure 2.

Figure 2 Trial Schematic for RPC01-202 and RPC01-202olp



Source: Sponsor

For the purposes of this consult, the randomized comparison of subjects is maintained through the IndP (i.e., Week 8). This randomized comparison of subjects through Week 8 (202-IndP) forms the most reliable data to draw substantive conclusions regarding the pulmonary safety of ozanimod in UC from trial RPC01-202 for labeling purposes.

After the IndP and regardless of initial randomized treatment assignment, the subgroup of Non-Responders was allowed to enter the open label extension. In this open label extension, all subjects were assigned to receive ozanimod. Similar to study RPC01-3101, after the IndP, the original randomized comparisons are not maintained in RPC01-202, and subsequent pulmonary safety comparisons versus placebo in RPC01-202 only represent the subgroup of Responder subjects.

> ***Reviewer's Comment***: *The systematic selection (and discontinuation/withdrawal) of Non-Responder subjects from the original randomized treatment assignment based on post-randomization factors limits this Reviewer's ability to draw reliable conclusions from the MP data. Even a conclusion that the lung function changes represented by these MP comparisons would be applicable to patients in clinical practice who meet criteria for Responders is difficult to justify, given the small sample size of Trial RPC01-202 and the short timeframe (i.e., 32 weeks) of the evaluation.*

> ***Reviewer's Comment***: *No direct comparison of IndP data and MP data is possible in RPC01-202, since the treatment groups have changed dramatically in composition across these timeframes.* (b) (4) [redacted]

Exposure-based Comparator Groups
Given that the initial randomized comparisons are not maintained through the MP in Trial RPC01-202, and that data after the IndP from Non-Responders come exclusively from Trial RPC01-202olp, the DPACC again requested analyses of pulmonary function testing based on ozanimod exposure spanning both RPC01-202 and

RPC01-202olp – regardless of Responder or Non-Responder status – to characterize additional trends in pulmonary safety based on ozanimod exposure. This classification resulted in exposure-based comparator groupings that were conceptually similar to those described in RPC01-3101. However, the exposure-based groupings for these two studies are not further described in this consult because, upon review of the data, the small sample size in each grouping and imbalances in baseline characteristics between the non-randomized groups created significant uncertainty in the interpretation of analyses of pulmonary safety data (see Section F, below).

> ***Reviewer's Comment****: This reviewer acknowledges that these exposure-based comparisons for RPC01-202 and RPC01-202olp include the uncertainties and potential biases associated with non-randomized comparisons and unblinded comparisons, compounded by the smaller sample size of the study. As discussed in detail in Section F, it is the opinion of this reviewer that the labeling of ozanimod for the UC indication should focus solely on analyses and data from Study RPC01-3101.*

Schedule and Extent of Pulmonary Function Testing

In Study RPC01-202, pulmonary function testing was performed at Screening and at Week 8 in the IndP (see Table 3). Additional pulmonary function testing was performed at Week 20 and Week 32 in the MP, or on the date of early termination.

Table 3 RPC01-202: Focused Schedule of Assessments

Study Procedures	Screening	Induction Period (IP)			Maintenance Period (MP)			Safety Follow-up	
		Dose Escalation	Assigned Dose						
		Visit 1[a,b,c]	Visit 4[b,d]	Visit 5[b,d]	Relapse Visit	Visit 6[b]	End of Study Visit/ET		
		Dose Escalation Day 1	Week 4	Week 8		Week 20	Week 32		
	Day -35 to 0	Dose Escalation Day 1	Day 36±3	Day 64±3	Day 1OLP	Day 148±3	Day 232±3	Last dose + 30 days ± 7 days	Last dose + ~~7590~~ ± 10 days[r]
Pregnancy test (WOCBP only)[i]	X	X	X	X		X	X	X	X
Coagulation panel	X						X		
Urinalysis	X			X		X	X		
Physical examination[j]	X	X[k]		X[k]		X[k]	X	X[k]	
Pulmonary function tests[l]	X[l]			X[l]			X		

Source: Sponsor

In Study RPC01-202olp, pulmonary function testing was performed only at the End of Study visit (see Table 4).

Table 4 RPC01-202olp: Focused Schedule of Assessments

Study Procedures	Open-Label Period (OLP)					Safety Follow-up[m]	
	Dose Escalation	Assigned Dose (1 mg)					
	Visit 1OLP[a,b,c]	Visit 4OLP[b,d]	Visit 5OLP[b,d]	Additional OLP Visits[e]	End of Open-label Visit/ET[e]		
	Dose Escalation Day 1	Week 4OLP	Week 8OLP	12-week Intervals	End of Study		
	Dose Escalation Day 1OLP	Day 36 ± 3 OLP	Day 64 ± 3 OLP	Day (last visit calculated from Day 1 + 84) ± 14 OLP	Day of last dose	Last dose + 30 ± 7 days	Last dose + ~~75~~90 ± 10 days[n]
Dispense investigational drug	X	X	X	X	X[m]		
Administer investigational drug at clinic	X						
Review drug compliance		X	X	X	X		
Prior and concomitant medications	X	X	X	X	X	X	X
Total immunoglobulins (Igs) - IgA, IgG, IgM					X		
Adverse events	X	X	X	X	X	X	X
12-Lead ECG	X[a]				X		
Holter monitoring	X						
Vital signs	X[a]	X	X	X	X		
Clinical laboratory tests							
Hematology[o]		X	X	X	X	X	
Blood chemistry		X	X	X	X	X	
Pregnancy test (WOCBP only)[f]		X	X	X	X	X	X
Coagulation panel					X		
Urinalysis			X		X		
Physical examination[g]			X[h]		X[g]	X[h]	
Pulmonary function tests[i]					X		

Source: Sponsor

VI. Pulmonary Safety Data and Analyses

A. DPACC Summary Interpretation

DPACC Interpretation

Due to their trial designs, there are limitations and uncertainties in interpreting data from Trials RPC01-3101 and RPC01-3102. While randomized comparisons during the IndP of RPC01-3101 and RPC01-202 provide useful data to inform pulmonary safety labeling, data from the MP of these trials include uncertainties that limit the interpretation. Because of these uncertainties, this reviewer advocates for an interpretation that is partially quantitative (based primarily on data from a randomized comparison during the IndP of Trial RPC01-3101) and partially qualitative (based on interpretation of the MP "re-randomized" comparisons and the exposure-based comparisons of RPC01-3101). While data from RPC01-202 and RPC01-202olp suggest similar general trends, Uncertainties related to sample size and study design limit the ability of Study RPC01-202 and RPC01-202olp to provide additional reliable data for labeling purposes.

The available comparisons suggest that ozanimod is responsible for a mild bronchoconstrictive response observable in FEV1 and FVC as early as Week 10 in Study RPC01-3101. This mild bronchoconstrictive response is generally consistent with the purported mechanism and previous drug development in other indications, and the clinical significance of the pulmonary safety signal in the UC population is similar to that reported in existing ozanimod drug labeling for MS. While the average bronchoconstrictive response is mild, in a "threshold" analysis of subjects with larger bronchoconstrictive responses, a higher proportion of subjects in the ozanimod group experienced FEV1 and FVC changes ≥200 mL compared to placebo. The clinical significance of this bronchoconstrictive response is unclear and in clinical practice the significance would be dependent upon patients' baseline pulmonary function or underlying pulmonary disease considerations. This reviewer also does not suggest that the "threshold" analysis results warrant separate labeling, only that these data suggest that pulmonary safety labeling for the UC indication should still be included and should mimic the recommendations labeled in the MS indication.

In addition, the available data from Study RPC01-3101 do not allow for a determination of the reversibility or progression of this bronchoconstrictive effect.

B. Study RPC01-3101: Baseline Demographics and Pulmonary Function Data

Randomized Comparator Groups

Baseline assessments for randomized comparisons of lung function changes rely on the randomized comparator groups provided by Cohort 1. Demographic features at baseline did not show differences across randomized groups in Cohort 1 at Baseline/Screening that would limit the pulmonary safety assessments in clinically significant ways. Age, sex, BMI, race, ethnicity, and categorical assessment of smoking history were comparable across groups for the purposes of this pulmonary safety assessment (see Sponsor's CSR).

Baseline pulmonary function testing in this randomized comparison showed comparable measures of FEV1, FEV1 percent predicted, FVC, and FVC percent predicted across groups (see Table 5).

$DLCO_{Hgb}$ was only recorded in a subset of study subjects, and this measure showed an imbalance at baseline. Given that many subjects did not have $DLCO_{Hgb}$ measured at baseline, the significance of this imbalance is not clear.

Table 5 RPC01-3101: Baseline/Screening Pulmonary Function Test Results for Cohort 1

	Cohort 1					
	Ozanimod 1mg (N = 429)			Placebo (N = 216)		
Parameter	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
FEV1[1] (L)	427	3.501	0.874	215	3.553	0.818
FEV1 (percent predicted normal)	427	100.9	15.5	215	99.4	14.2
FVC[2] (L)	427	4.280	1.051	216	4.361	1.026
FVC (percent predicted normal)	427	101.4	15.8	216	100.5	15.4
$DLCO_{Hgb}$ (mmol/min/kPa)	192	11.679	26.749	85	9.546	6.042

$DLCO_{hgb}$: diffusion capacity of the lung for carbon monoxide corrected for hemoglobin; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity

Source: Reviewer, adapted from Sponsor's CSR data tables for Study RPC01-3101

[1]Represents the largest FEV1 recorded at the visit

[2]Represents the largest FVC recorded at the visit

Exploratory Exposure-based Comparator Groups

Baseline assessments for exposure-based comparisons of lung function changes rely on the comparator groups described in Section IV A, Exposure-based Comparator Groups. Baseline demographic features revealed the following imbalances between the Placebo-placebo and ozanimod-ozanimod groups: a higher proportion of females in the ozanimod-ozanimod group (41%, compared to 33% in the placebo-placebo group), a lower age in the ozanimod-ozanimod group (44 years, compared to 41 years in the placebo-placebo group), and a lower proportion of "Never Smokers" in the ozanimod-ozanimod group (70%, compared to 75% in the placebo-placebo group). Mean BMI was comparable across these two groups, and categorical measures of self-identified race did not present clinically significant differences that would limit the interpretation of pulmonary safety data (see Sponsor's Response to Information Request, dated 02/23/2021).

Baseline pulmonary function testing in this exposure-based comparison showed comparable measures of FEV1, FEV1 percent predicted, FVC, and FVC percent predicted across groups (see Table 6).

Table 6 RPC01-3101: Baseline/Screening Pulmonary Function Testing by Ozanimod Exposure Categories

Parameter	Placebo-Placebo[a] N = 69	Placebo-Ozanimod[b] N = 120	Ozanimod-Placebo[c] N = 227	Ozanimod-Ozanimod[d] N = 466
FEV_1 (L)				
n	69	119	226	465
Mean (SD)	3.480 (0.827)	3.605 (0.758)	3.425 (0.832)	3.505 (0.859)
Parameter	**Placebo-Placebo[a] N = 69**	**Placebo-Ozanimod[b] N = 120**	**Ozanimod-Placebo[c] N = 227**	**Ozanimod-Ozanimod[d] N = 466**
FEV_1 PPN (%)				
N	69	119	226	465
Mean (SD)	100.7 (14.50)	99.0 (13.68)	100.7 (14.51)	99.7 (15.35)
FVC (L)				
n	69	120	226	465
Mean (SD)	4.269 (1.074)	4.409 (0.907)	4.176 (1.015)	4.316 (1.043)
FVC PPN (%)				
N	69	120	226	465
Mean (SD)	101.3 (15.98)	100.0 (14.70)	100.8 (14.78)	100.9 (15.18)
Baseline lung disease[e]				
Yes	3 (4.3)	8 (6.7)	12 (5.3)	28 (6.0)
No	66 (95.7)	112 (93.3)	215 (94.7)	438(94.0)

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PPN = percent of predicted normal; SD = standard deviation.

[a] Subjects who were assigned to receive placebo until Week 10 and were assigned to receive placebo until Week 52 in Study RPC01-3101. Corresponds to "placebo" group in the RPC01-3101 Maintenance Period (NDA 209899/SN0063, M1.11.3, Table 4).

[b] Subjects who were assigned to receive placebo until Week 10 and then were assigned to receive ozanimod (ie, through the open label extension in study RPC01-3102) until Week 52.

[c] Subjects who were assigned to receive ozanimod (ie, as part of "Cohort 1" or "Cohort2") until Week 10 and then were assigned to receive placebo until Week 52. Corresponds to "Ozanimod 1 mg – Placebo" group in RPC01-3101 Maintenance Period (NDA 209899/SN0063, M1.11.3, Table 4).

[d] Subjects who were assigned to receive ozanimod until Week 10 (ie, as part of "Cohort 1" or "Cohort 2") and then were assigned to receive ozanimod (ie, either through the re-randomization in RPC01-3101 Maintenance Period or through the open-label extension in study RPC01-3102) until Week 52.

[e] The following preferred terms were used to classify subjects with lung disease at baseline: asthma, bronchial hyperreactivity, bronchitis chronic, chronic obstructive pulmonary disease, asthma exercise induced, pulmonary sarcoidosis, bronchiectasis, idiopathic pulmonary fibrosis, pneumoconiosis, and interstitial lung disease.

Source: Sponsor

C. Study RPC01-3101: Randomized Comparisons of Pulmonary Function Results

Randomized Summary Comparisons from the Induction Phase:

Relying on the randomized comparison of the ozanimod group versus placebo from Cohort 1, subjects in Study RPC01-3101's IndP who received ozanimod experienced a mean change (decline) from baseline in FEV1 of 0.057 L (57 mL) compared to a mean change (decline) from baseline in FEV1 of 0.035 L (35 mL) among placebo subjects (see Table 7), resulting in a mean difference of 22 mL. These changes corresponded to changes in percent predicted FEV1 of unclear clinical significance (0.81%) in the studied population, since the mean baseline FEV1 for this group was normal. Similarly, subjects who received ozanimod experienced a mean change (decline) from baseline in FVC of 0.043 L (43 mL) compared to a mean change from baseline (improvement) from baseline in FVC or 0.001 L (1 mL) among placebo subjects, resulting in a mean differences of 44 mL, which also corresponded to changes in percent predicted FVC of unclear clinical significance (0.53%) in the studied population. The $DLCO_{Hgb}$ evaluation is limited due to a lack of complete baseline data and a further lack of complete follow-up data for the comparison.

> ***Reviewer's Comment****: In the opinion of this reviewer, the DLCO data provided for this comparison are of limited interpretability, given the smaller sample size overall and the added uncertainty created by the 24 of 85 subjects (28%) in the placebo group that did not have Week 10 data recorded.*

Table 7 RPC01-3101, Cohort 1 Induction Phase, Randomized Comparisons: Mean Change from Baseline in Pulmonary Function Measures

	Cohort 1					
	Ozanimod 1 mg (N = 429)			Placebo (N = 216)		
Parameter	n	Percent change (SD)	Absolute change (SD)	n	Percent change (SD)	Absolute change (SD)
FEV_1 (L)	388	-1.122 (10.777)	-0.057 (0.373)	183	-0.617 (8.313)	-0.035 (0.284)
FEV_1 PPN	389	-1.000 (10.525)	-1.574 (10.757)	184	-0.391 (9.220)	-0.764 (9.214)
FVC (L)	388	-0.653 (9.861)	-0.043 (0.408)	183	0.488 (8.861)	0.001 (0.366)
FVC PPN	389	-0.269 (9.935)	-0.760 (9.971)	184	0.315 (9.642)	-0.230 (9.723)
DLCOhgb[a] (mM/min/kPa)	146	-2.625 (186.655)	-0.475 (16.728)	61	-4.509 (19.565)	-0.847 (3.143)

$DLCO_{hgb}$: diffusion capacity of the lung for carbon monoxide corrected for hemoglobin; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; PPN: percent of predicted normal
Source: Sponsor

Randomized Threshold Comparisons from the Induction Phase:
While mean change from baseline allows for a convenient summary measure of the effect of ozanimod, some proportion of outlying subjects may have more exaggerated responses to S1PRM agents that may be better observed using a responder-analysis based on threshold changes in pulmonary function measures. While no threshold of pulmonary function change has been adequately validated for purposes of judging the pulmonary safety of UC drugs, threshold analyses based on a ≥200 mL change in either FEV1 or FVC (with or without an associated ≥12% change in percent predicted) were requested based on American Thoracic Society spirometry guidelines for bronchodilator responsiveness.

When these thresholds are applied to the randomized comparisons of ozanimod versus placebo in the IndP of Cohort 1from RPC01-3101 (see Table 8), the data suggest that a higher proportion of subjects in the ozanimod group experienced absolute changes in FEV1 ≥200 mL compared to subjects in the placebo group (26% versus 19%, respectively). Similarly, a higher proportion of subjects in the ozanimod group experienced absolute changes in FVC ≥200 mL compared to subjects in the placebo group (27% versus 20%, respectively). In addition, the proportion of subjects who met the combined threshold of an FEV1 decline of ≥200 mL and a decline of ≥12% in FEV1 percent predicted or the combined threshold of an FVC decline of ≥200 mL and a decline of ≥12% in FVC percent predicted also were both higher in the ozanimod group than in the placebo group. These data suggest that a higher proportion of subjects taking ozanimod may have larger and potentially clinically significant changes in pulmonary function, which justifies a description of pulmonary safety in labeling as well as wording that describes a need for further evaluation if clinically indicated.

> ***Reviewer's Comment***: *These threshold analyses suggest that some subjects with UC who receive ozanimod may experience declines in FEV1 and/or FVC that may potentially be clinically significant and require additional evaluation. Importantly, clinical decision-making surrounding the evaluation of absolute pulmonary function measures will require additional knowledge of a patient's comorbidities such as pre-existing respiratory disease. A 200 mL decline in FEV1 may not be perceived in a subject with normal lung function, for example, but could represent a highly clinically significant change in a subject with co-morbid severe COPD. These data and the nuance of clinical-decision-making justify the application of the pre-existing labeling wording of "assess pulmonary function (e.g., spirometry) if clinically indicated" for the UC indication as well.*

Table 8 RPC3101: Cohort 1, Induction Phase, Randomized Comparisons: Threshold Analyses of Pulmonary Function Measures

Parameter	Cohort 1	
	Ozanimod 1 mg (N = 429) n/m (%)	Placebo (N = 216) n/m (%)
FEV_1 decrease of ≥ 200 mL from Baseline	99/386 (25.6)	35/182 (19.2)
FEV_1 decrease of ≥ 200 mL and ≥ 12% from Baseline	35/386 (9.1)	9/182 (4.9)
FVC decrease of ≥ 200 mL from Baseline	103/386 (26.7)	37/183 (20.2)
FVC decrease of ≥ 200 mL and ≥ 12% from Baseline	32/386 (8.3)	10/183 (5.5)
DLCOhgb decrease of ≥ 10% from Baseline	42/139 (30.2)	21/59 (35.6)

$DLCO_{hgb}$: diffusion capacity of the lung for carbon monoxide corrected for hemoglobin; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; m: number of subjects with available data for analysis
Source: Sponsor

Comparisons from the Maintenance Phase:
Considering the initial randomized comparator groups from Cohort 1 (see Section IV A, above), Week 52 data from the MP relies only on Responder subjects that continued in RPC01-3101 or additional Responders that were randomized into the comparison groups from Cohort 2, and no longer represent randomized comparisons from baseline (i.e., before any exposure to ozanimod). The utility of these data is unclear. While comparisons between the ozanimod versus placebo group of these "re-randomized" subjects could provide a separate measure of change in pulmonary function for clinical Responder patients that may discontinue ozanimod, the relevance of this comparison to pulmonary safety is unclear. More importantly, this MP comparison is neither equivalent to a measure of reversibility of lung function changes nor a measure of progression of lung function changes, and the comparison cannot inform labeling for those topics.

> ***Reviewer's Comment****: Analyses of these MP comparator groups cannot be used to inform questions of progression or reversibility. Because of this, no labeling claims regarding reversibility or progression are supported by the current data. Wording previously used in the labeling to describe the MS population (i.e., "There is insufficient information to determine the reversibility of the decrease in FEV_1 or FVC after drug discontinuation") may be utilized in labeling to describe these situations.*

D. Studies RPC01-3101 and RPC01-3102: Exposure-Based Comparisons of Pulmonary Function Results

Exposure-Based Summary Comparisons from the Induction Phase and Maintenance Phase:
Non-randomized comparisons based on exposure group in the IndP and MP of Trial RPC01-3101 do not present additional clinically significant safety concerns (see Table 9).

In comparisons of the ozanimod-ozanimod group versus the placebo-placebo group during the IndP, the ozanimod-ozanimod group experienced a mean change (decline) from baseline in FEV1 of 0.032 L compared to a mean change (decline) from baseline in FEV1 of 0.012 L among placebo-placebo subjects at Week 10 (i.e., at the end of the IndP). Similarly, subjects in the ozanimod-ozanimod group experienced a mean change (decline) from baseline in FVC of 0.011 L compared to a mean change from baseline (improvement) from baseline in FVC or 0.018 L observed in subjects in the placebo-placebo group at Week 10. The mean FEV1 and FVC differences between the groups at Week 10 correspond approximately in direction and magnitude to those observed in the randomized comparisons above.

Comparisons of the ozanimod-ozanimod group versus the placebo-placebo group during the MP are further limited by additional subject dropout. Acknowledging the uncertainties created by these missing data in addition to the non-randomized exposure-based comparator groups and the inclusion of unblinded data in these analyses, available data from the MP (i.e., change from baseline at Week 52) show that the ozanimod-ozanimod group experienced a mean change (decline) from baseline in FEV1 of 0.048 L compared to a mean change (decline) from baseline in FEV1 of 0.076 L among placebo-placebo subjects at Week 52. Similarly, subjects in the ozanimod-ozanimod group experienced a mean change (decline) from baseline in FVC of 0.051 compared to a mean change from baseline (decline) from baseline in FVC or 0.061 L observed in subjects in the placebo-placebo group at Week 52.

> ***Reviewer's Comment***: *Given the uncertainties in interpretation of these exposure-based categories, caution should be exercised in interpreting them quantitatively for labeling purposes. In the opinion of this reviewer, these exposure-based categories represent the best available comparison of consistent ozanimod and placebo use from Baseline to Week 52, and are qualitatively somewhat reassuring regarding the severity of pulmonary function changes due to ozanimod. Despite the higher number of subjects in the ozanimod-ozanimod group, and despite the bias inherent in comparing this group to a placebo-placebo group that only included those Responder subjects with concurrent clinical improvement in their UC, the available pulmonary function data do not provide evidence for a larger or clinically significant difference between the groups at Week 52* (b) (4) *Also, as previously described, analyses of these MP comparator groups cannot be used to inform questions of progression or reversibility.*

As noted in the randomized comparisons, the $DLCO_{Hgb}$ evaluation is limited due to the small sample size for the placebo-placebo group, a lack of complete baseline data, and a further lack of complete follow-up data for the comparison at Week 10 and at Week 52.

Table 9 RPC01-3101 and RPC01-3102: Induction Phase and Maintenance Phase, Exposure-based Groupings: Mean Change from Baseline in Pulmonary Function Measures

	Placebo-Placebo[a] (3101 IP+MP) N = 69			Placebo-Ozanimod[b] (3101 IP + 3102) N = 120			Ozanimod-Placebo[c] (3101 IP+MP) N = 227			Ozanimod-Ozanimod[d] (3101 IP+MP, 3101 IP+3102) N = 466		
Parameter Visit	n	Percent change (SD)	Absolute change (SD)	n	Percent change (SD)	Absolute change (SD)	n	Percent change (SD)	Absolute change (SD)	n	Percent change (SD)	Absolute change (SD)
FEV_1 (L)												
Week 10	63	0.066 (8.889)	-0.012 (0.301)	113	-0.847 (8.137)	-0.044 (0.280)	214	-2.573 (10.648)	-0.102 (0.382)	439	-0.491 (9.915)	-0.032 (0.325)
Week 52	45	-0.862 (14.207)	-0.076 (0.529)	67	-2.634 (13.766)	-0.123 (0.448)	117	-0.182 (12.104)	-0.036 (0.423)	322	-0.874 (12.727)	-0.048 (0.410)
FEV_1 PPN (%)												
Week 10	63	0.151 (9.028)	-0.241 (9.722)	114	-0.546 (9.525)	-0.944 (9.147)	214	-2.602 (10.669)	-3.082 (11.170)	440	-0.486 (9.636)	-0.962 (9.518)
Week 52	45	-0.933 (14.081)	-1.799 (15.029)	67	-0.051 (13.239(	-0.775 (11.594)	117	-0.548 (12.505)	-1.198 (13.678)	322	-0.574 (11.350)	-1.243 (11.317)
FVC (L)												
Week 10	63	1.100 (9.170)	0.018 (0.392)	114	0.414 (8.740)	0.002 (0.353)	214	-1.513 (10.756)	-0.087 (0.444)	439	-0.067 (9.152)	-0.011 (0.375)
Week 52	45	0.681 (14.858)	-0.061 (0.689)	67	-1.790 (10.811)	-0.097 (0.436)	118	0.422 (12.995)	-0.033 (0.538)	322	-0.721 (10.881)	-0.051 (0.468)
FVC PPN (%)												
Week 10	63	1.403 (10.184)	0.795 (10.490)	115	-0.040 (9.414)	-0.585 (9.402)	214	-1.108 (10.781)	-1.666 (11.001)	440	0.444 (8.713)	0.059 (8.603)
Week 52	45	0.428 (14.856)	-0.474 (15.962)	67	-0.154 (10.177)	-0.659 (9.505)	118	-0.033 (13.161)	-0.679 (13.784)	322	0.268 (11.059)	-0.378 (11.239)
DLCOhgb[e] (mM/min/kPa)												
Week 10	12	-0.750 (12.224)	0.028 (0.904)	45	-4.275 (19.144)	-1.005 (3.478)	71	1.883 (260.541)	1.616 (15.507)	153	-4.192 (24.315)	-1.272 (11.664)
Week 52	8	-13.575 (28.269)	-4.563 (12.070)	23	4.818 (43.405)	-1.281 (7.111)	32	-63.363 (278.305)	-5.104 (23.571)	111	3.548 (47.130)	-1.136 (13.982)

DLCOhgb = diffusion capacity of the lung for carbon monoxide corrected for hemoglobin; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PPN = percent of predicted normal; SD = standard deviation.

[a] Subjects who were assigned to receive placebo until Week 10 and were assigned to receive placebo until Week 52 in Study RPC01-3101. Corresponds to "placebo" group in the RPC01-3101 Maintenance Period (NDA 209899/SN0063, M1.11.3, Table 4).

[b] Subjects who were assigned to receive placebo until Week 10 and then were assigned to receive ozanimod (ie, through the open label extension in study RPC01-3102) until Week 52.

[c] Subjects who were assigned to receive ozanimod (ie, as part of "Cohort 1" or "Cohort2") until Week 10 and then were assigned to receive placebo until Week 52. Corresponds to "Ozanimod 1 mg – Placebo" group in RPC01-3101 Maintenance Period (NDA 209899/SN0063, M1.11.3, Table 4).

[d] Subjects who were assigned to receive ozanimod until Week 10 (ie, as part of "Cohort 1" or "Cohort 2") and then were assigned to receive ozanimod (ie, either through the re-randomization in RPC01-3101 Maintenance Period or through the open-label extension in study RPC01-3102) until Week 52.

[e] Abbreviated as "DLCO" in the source tables.

Note: Baseline is defined as the RPC01-3101 Screening Visit pulmonary function testing. In cases where open-label extension data from RPC01-3102 are included, the Week 52 analyses utilize data from RPC01-3102 Week 46 pulmonary function testing.

Source: Sponsor

Exposure-Based Threshold Comparisons from the Maintenance Phase:

When the same ≥200 mL thresholds (with or without an accompanying ≥12% in percent predicted) for FEV1 change or FVC change are applied to the randomized comparisons of the ozanimod-ozanimod versus placebo-placebo group in the MP of RPC01-3101 (see Table 10), the data suggest that a higher proportion of subjects in the ozanimod-ozanimod group experienced absolute changes in FEV1 ≥200 mL compared to subjects in the placebo-placebo group at Week 52 (32% versus 22%, respectively). However, the proportion of subjects in the ozanimod-ozanimod group that experienced absolute changes in FVC ≥200 mL was similar compared to subjects in the placebo group (31% versus 29%, respectively). Similarly, the proportion of subjects who met the combined threshold of an FEV1 decline of ≥200 mL and a decline of ≥12% in FEV1 percent predicted or the combined threshold of an FVC decline of ≥200 mL and a decline of ≥12% in FVC percent predicted also were both similar across the ozanimod-ozanimod group and the placebo-placebo group. These data suggest that a higher proportion of subjects taking ozanimod may have larger and potentially clinically significant changes

in pulmonary function compared to placebo; while these details may not require separate labeling, they provide additional justification for a description of pulmonary safety in labeling as well as wording that describes a need for further evaluation if clinically indicated.

> ***Reviewer's Comment****: Again acknowledging the uncertainties in the interpretation of these exposure-based categories and relying on a qualitative assessment of the best available data at Week 52, these exposure-based analyses suggest that there could be a higher proportion of subjects with potentially clinically meaningful changes in FEV1 with ozanimod use compared to placebo use. However, given the limitations described, these analyses are not rigorous enough to definitively justify separate ruling of these threshold analyses. However, these results reinforce the need for labeling for UC that may encourage additional assessments of pulmonary function if clinically indicated.*

Table 10 RPC01-3101 and RPC01-3102, Induction Phase and Maintenance Phase, Exposure-Based Categories: Threshold Analyses of Pulmonary Function Measures

Parameter Visit	Placebo-Placebo[a] (3101 IP+MP) N = 69 n/m (%)	Placebo-Ozanimod[b] (3101 IP + 3102) N = 120 n/m (%)	Ozanimod-Placebo[c] (3101 IP+MP) N = 227 n/m (%)	Ozanimod-Ozanimod[d] (3101 IP+MP, 3101 IP+3102) N = 466 n/m (%)
FEV_1 decrease of ≥ 200 mL from Baseline				
Week 10	14/63 (22.2)	20/113 (17.7)	70/214 (32.7)	102/439 (23.2)
Week 52	10/45 (22.2)	30/67 (44.8)	25/117 (21.4)	104/322 (32.3)
FEV_1 decrease of ≥ 200 mL and ≥ 12% from Baseline				
Week 10	3/63 (4.8)	6/113 (5.3)	21/214 (9.8)	33/439 (7.5)
Week 52	5/45 (11.1)	14/67 (20.9)	11/117 (9.4)	42/322 (13.0)
FVC decrease of ≥ 200 mL from Baseline				
Week 10	11/63 (17.5)	24/114 (21.1)	75/214 (35.0)	108/439 (24.6)
Week 52	13/45 (28.9)	27/67 (40.3)	37/118 (31.4)	100/322 (31.1)
FVC decrease of ≥ 200 mL and ≥ 12% from Baseline				
Week 10	3/63 (4.8)	6/114 (5.3)	18/214 (8.4)	30/439 (6.8)
Week 52	6/45 (13.3)	8/67 (11.9)	9/118 (7.6)	40/322 (12.4)

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; m = number of subjects with available data for analysis.

[a] Subjects who were assigned to receive placebo until Week 10 and were assigned to receive placebo until Week 52 in Study RPC01-3101. Corresponds to "placebo" group in the RPC01-3101 Maintenance Period (NDA 209899/SN0063, M1.11.3, Table 4).

[b] Subjects who were assigned to receive placebo until Week 10 and then were assigned to receive ozanimod (ie, through the open label extension in study RPC01-3102) until Week 52.

[c] Subjects who were assigned to receive ozanimod (ie, as part of "Cohort 1" or "Cohort2") until Week 10 and then were assigned to receive placebo until Week 52. Corresponds to "Ozanimod 1 mg – Placebo" group in RPC01-3101 Maintenance Period (NDA 209899/SN0063, M1.11.3, Table 4).

[d] Subjects who were assigned to receive ozanimod until Week 10 (ie, as part of "Cohort 1" or "Cohort 2") and then were assigned to receive ozanimod (ie, either through the re-randomization in RPC01-3101 Maintenance Period or through the open-label extension in study RPC01-3102) until Week 52.

Note: Baseline is defined as the RPC01-3101 Screening Visit pulmonary function testing. In cases where open-label extension data from RPC01-3102 are included, the Week 52 analyses utilize data from RPC01-3102 Week 46 pulmonary function testing.

E. Study RPC01-3101: Respiratory Adverse Event Analyses

The Sponsor reports a similar incidence of TEAEs in the Respiratory, thoracic, and mediastinal disorders system organ class between the ozanimod treatment group and the placebo group (2.6% versus 1.4%, respectively). The Sponsor reports that none of the observed TEAEs in the Respiratory, thoracic, and mediastinal disorders system organ class was serious or led to treatment discontinuation in Study RPC01-3101.

Due to the lack of comparator groups that respect the original randomized treatment assignment throughout the IndP and MP, the evaluation of respiratory and related adverse events for subjects "re-randomized" in Study RPC01-3101's MP is limited.

> ***Reviewer's Comment***: *The reported AEs in the Respiratory, thoracic, and mediastinal disorders system organ class during the IndP do not suggest pulmonary safety signals that would warrant specific wording. The comparisons of AEs among "re-randomized" subjects in the MP are complicated by previous use of ozanimod among all subjects in both the placebo and ozanimod groups of the "re-randomized" comparisons. While these available MP data may have significant uncertainties in interpretation,* [redacted] (b) (4)

F. Studies RPC01-202 and RPC01-202olp: Comparisons of Pulmonary Function Results

The assessment of pulmonary function from Screening to Week 8 (i.e., the IndP) of Study RPC01-202 is conceptually analogous to the assessment of pulmonary function of Cohort 1 during the IndP of Study RPC01-3101. However, the following differences and uncertainties limit the ability of Study RPC01-202 to provide additional reliable data for labeling:

- Study RPC01-202 screened and randomized fewer subjects (approximately 65 per treatment group) leading to lower precision in summary measures.
- Study RPC01-202 includes dose levels of ozanimod 0.5 mg and ozanimod 1 mg; observed pulmonary function trends over the IndP in Study RPC01-202 do not appear to be strictly dose-dependent
    - The absolute decline in FEV1 is larger in the ozanimod 0.5 treatment group compared to placebo, and the percent predicted decline is larger in the ozanimod 1 mg treatment group compared to placebo. These observations suggest an overall similar trend to that seen in FEV1 analyses in RPC01-3101.
    - The Sponsor notes that analyses of FVC were skewed substantially by a supraphysiologic baseline value for FVC of 77 L reported in error, limiting reliable analyses of FVC.
- Analyses from the MP of Study RPC01-202 include uncertainties and limitations analogous to those described in Study RPC01-3101 over a shorter timeframe (i.e., 32 weeks). In addition, the lower overall sample size also leads to final comparator groups that may be too small for reliable evaluation
- While analogous exposure-based categorical analyses were requested for RPC01-202 and RPC01-202olp, the small sample size and baseline differences between the groups (e.g., in sex, age, race, previous smoking, FEV1, and FVC) limit reliable comparisons of pulmonary safety using these data.

> ***Reviewer's Comment***: *Taking all of the above factors into account, it is the opinion of this reviewer that the labeling of ozanimod for the UC indication should focus solely on analyses and data from Study RPC01-3101. The data from RPC01-202 and RPC01-202olp do not provide new clinically meaningful safety concerns, and these data are also not able to overcome or refute the safety concerns that warrant labeling from Study RPC01-3101.*

[redacted] (b) (4)

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/s/

ROBERT N BUSCH
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

DPHM PMR Memo

Date: 3/5/2021 **Date consulted:** 2/17/2021

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology (DG)

Drug: Zeposia (ozanimod) capsule

NDA: 209899

Sponsor: Bristol-Myers Squibb

Approved Indication(s): For the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Proposed Indication: For the treatment of moderately to severely active ulcerative colitis (UC) in adults.

Subject: Draft language for Post-Marketing Requirement (PMR)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 209899

- DG consult form for DPMH, DARRTS Reference ID 4747947

Consult Question: "DG requests MH reviewer assignment to assist with possible post-marketing requirement development. This application has orphan designation so these requirements would not be issued under PREA."

BACKGROUND

On November 30, 2020, the applicant (Bristol-Myers Squibb submitted an efficacy supplement to NDA 209899 for a new indication for the treatment of moderately to severely active ulcerative colitis (UC) in adults. The Division of Gastroenterology (DG) consulted the Division of Pediatric and Maternal Health (DPMH) on February 17, 2020, to assist with possible post-marketing requirement development.

Zeposia was approved on March 25, 2020 for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The PMR 3809-3, a pregnancy exposure registry, and PMR 3809-4, a complimentary study, were issued at the time of approval.

PMR 3809-3:

> Prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Zeposia (ozanimod) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Zeposia (ozanimod) before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR 3809-4:

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

Zeposia received European Commission approval in May 2020 for the treatment of multiple sclerosis.

<u>Current State of the Labeling</u>

- Approved labeling is in PLLR format.
- There is no boxed warning for this drug.

- There are contraindications for Zeposia which include:
    - In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure
    - Presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker
    - Severe untreated sleep apnea
    - Concomitant use of a monoamine oxidase inhibitor
- There is a warning under subsection 5.4 Fetal Risk

  There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm *[see Use in Specific Populations (8.1)]*. Because it takes approximately 3 months to eliminate ZEPOSIA from the body, women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA *[see Use in Specific Populations (8.1)]*.

Subsection 8.1 Pregnancy

There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women. In animal studies, administration of ozanimod during pregnancy produced adverse effects on development, including embryolethality, an increase in fetal malformations, and neurobehavioral changes, in the absence of maternal toxicity. In rabbits, fetal blood vessel malformations occurred at clinically relevant maternal ozanimod and metabolite exposures (see Data). The receptor affected by ozanimod (sphingosine-1-phosphate) has been demonstrated to have an important role in embryogenesis, including vascular and neural development.

Subsection 8.2 Lactation

There are no data on the presence of ozanimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Following oral administration of ozanimod, ozanimod and/or metabolites were detected in the milk of lactating rat at levels higher than those in maternal plasma. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEPOSIA and any potential adverse effects on the breastfed infant from ZEPOSIA or from the underlying maternal condition.

- There are 3 months contraception recommendations for women of childbearing potential.
- (b) (4)

Ulcerative Colitis and Pregnancy

In 2015, an estimated 1.3% of US adults (3 million) reported being diagnosed with IBD (b) (4) .[1] This was a large increase from 1999 (0.9% or 2 million adults).[2] Most people with IBD are diagnosed in their 20s and 30s.[3]
In patients with ulcerative colitis, active disease at conception is associated with increased risk of disease flare in pregnancy and poor pregnancy outcomes.[4] Pregnant females with IBD may be at increased risk for antepartum hemorrhage, low birth weight infants, and premature delivery.[5] However, the risk of congenital abnormalities does not appear to be increased.[6]

Reviewer comment:
Zeposia labeling contains a Warning for Fetal Risk in the labeling. There are several alternatives to treat moderate to severe ulcerative colitis without Warning and Precaution statement regarding fetal risk in the labeling.

DATA REVIEW
Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Ozanimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood.

Review of Clinical Trials
Throughout the ozanimod clinical development program, pregnant and lactating females were excluded from study participation. A total of 55 pregnancies have been reported in the safety database in subjects treated with ozanimod across all indications (ulcerative colitis, (b) (4) and multiple sclerosis) and including one healthy volunteer (see table 1 below). All pregnancy exposures for study subjects occurred during the first trimester. Subjects discontinued study medication promptly except for those subjects who elected termination (n=12) and did not discontinue study medication. No teratogenicity was observed.

[1] Dahlhamer JM, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of inflammatory bowel disease among adults aged ≥18 years—United States, 2015. MMWR Morb Mortal Wkly Rep. 2016;65(42):1166–1169. https://www.cdc.gov/mmwr/volumes/65/wr/mm6542a3.htm.
(b) (4)
https://academic.oup.com/ecco-jcc/article/8/4/288/386357
[3] https://www.cdc.gov/ibd/data-statistics.htm Accessed 2/19/21
[4] Peppercorn MA, et al. Fertility, pregnancy, and nursing in inflammatory bowel disease. https://www.uptodate.com/contents/fertility-pregnancy-and-nursing-in-inflammatory-bowel-disease?search=ulcerative%20colitis%20pregnancy&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H6 Accessed 2/19/21.
[5] Peppercorn MA, et al. Fertility, pregnancy, and nursing in inflammatory bowel disease.
[6] Peppercorn MA, et al. Fertility, pregnancy, and nursing in inflammatory bowel disease.

Table 1. Applicant's Table of Pregnancy Outcomes in All Ozanimod-treated Subjects (safety population)

Outcome		Number of Outcomes		
	Subject with UC	[redacted] (b) (4)	Subject with MS	Healthy volunteer	Partner pregnancy
Pregnancies	7		**44**	**1**	**20**
Live birth without congenital abnormality	2		21[a]	0	7
Live birth with congenital abnormality	0		2	0	2[b]
Premature	0		3	0	5[c]
Ongoing	1		3	0	1
Spontaneous early loss	2		6[a]	0	1
Elective termination	2		9	1	0
No information expected	0		1	0	5

[redacted] (b) (4) MS = multiple sclerosis; UC = ulcerative colitis.
[a] 1 pregnancy was a set of twins that resulted in 1 normal birth and 1 vanishing twin.
[b] 1 case of Hirschsprung's disease and 1 case of congenital hydrocele
[c] 2 of the 5 partners' premature babies were a set of twins
Note: Pool D includes Studies RPC01-202, RPC01-3101, RPC01-3102, RPC01-1001, RPC01-201 Part A (Core), RPC01-201 Part A (Extension), RPC01-201 Part B, RPC01-301, RPC01-3001, [redacted] (b) (4)
Source: Safety database.

The incidence of congenital abnormality in subjects exposed to ozanimod in clinical trials was 2/55 (4%), which is consistent with background rate (3%) of major congenital malformation.[7] The incidence of spontaneous abortion in clinical trial subjects exposed to ozanimod is 8/55 (14.5%), which is consistent with expected incidence of early pregnancy loss in the general population (12% to 22%).[8]

Reviewer comment: Although there were four reports of congenital abnormalities, two of the reports of congenital abnormalities occurred in pregnancies where the male subject was exposed to ozanimod. One female subject with MS who took ozanimod during pregnancy had an infant with left kidney duplication and patent foramen ovale. The second malformation was not clear from the applicant's submission.

As of March 31, 2020, there have been 29 live births and 6 ongoing pregnancies in clinical trial subjects treated with ozanimod.

DISCUSSION/CONCLUSIONS

Ulcerative colitis occurs in females of reproductive potential, therefore ozanimod is likely to be used during pregnancy. There is an existing pregnancy registry and a database study on Zeposia

[7] Update on Overall Prevalence of Major Birth Defects --- Atlanta, Georgia, 1978—2005. MMWR Jan 11, 2008/57(01);1-5.
[8] García-Enguídanos, 2002

in pregnant females with multiple sclerosis. DPMH recommends issuing new postmarketing requirements, including a pregnancy registry study and complementary database study, to evaluate the use of Zeposia in pregnant patients.

RECOMMENDATIONS

1a. An international, prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of females exposed to Zeposia (ozanimod) during pregnancy with two other groups, including females exposed to other therapies approved to treat ulcerative colitis and an unexposed control population. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. This study can be conducted as part of the ongoing study under NDA 209899 PMR 3809-3.

1b. A pregnancy outcomes study using a different study design than provided for in PMR XXXX-X (for example, a retrospective cohort study using claims or electronic medical record data) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in females exposed to Zeposia (ozanimod) during pregnancy compared to an unexposed control population. This study can be conducted as part of the ongoing study under NDA 209899 PMR 3809-4.

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

/s/

WENJIE SUN
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Center for Drug Evaluation and Research

Division of Cardiology and Nephrology

Date:	22 JAN 2021
From:	Fred Senatore, MD, PhD, FACC, Clinical Team Leader, DCN
Through:	Mary Ross Southworth, PharmD, Deputy Division Director, Safety, DCN
	Norman Stockbridge, MD, PhD, Division Director, DCN
To:	Jay Fajiculay, Pharm D; Arushi deFonseka, MD, Tara Altepeter, MD, Division of Gastroenterology
NDA/IND	sNDA-209899 (Ulcerative Colitis); (b) (4) IND-115243 (Ulcerative Colitis)
Sponsor:	Bristol-Myers Squibb
Subject:	Cardiac Effects of Zeposia (ozanimod): Sphingosine 1-phosphate (SIP) receptor modulator
Material:	EDR Location: \\CDSESUB1\evsprod\NDA209899\0058 View EDR: View submission in docuBridge

This consult is in response to a request from the Division of Gastroenterology to address potential cardiac issues with ozanimod (sphingosine 1-phosphate (SIP) receptor modulator). We were tasked with the following two requests:

1) "Please review the cardiac safety data that were submitted with this sNDA in UC patients and comment on whether or not the findings appear consistent with the safety profile as demonstrated for this drug in MS, or if you identify any relevant differences for this new patient population that should warrant new information included in the prescribing information or differential safety monitoring or other considerations for the UC population. If new or differential concerns, further input on NDA labeling or necessary steps will be appreciated. Please plan to attend midcycle meeting if possible."

2) (b) (4)

(b) (4)

Consultation Review Strategy

To adequately address the questions posed to us in this consult, the following strategic approach was implemented: 1) a review of another SIP_1 agonist from an antecedent consultation was summarized to ascertain the possibility of a class effect; 2) the multiple sclerosis indication and associated cardiovascular contraindications and warnings were evaluated; 3) the cardiovascular safety data from sNDA 209899 was evaluated to ascertain whether additional risk is uncovered that would lead to the recommendation of additional risk mitigation; (b) (4)

Scientific Background

Ozanimod hydrochloride (RPC1063; hereafter referred to as "ozanimod") is a small molecule compound that selectively and potently activates the sphingosine 1-phosphate (S1P)-1 receptor ($S1P_1$) and the S1P-5 receptor ($S1P_5$), although it is more selective towards $S1P_1$ over $S1P_5$.

The $S1P_1$ receptor regulates lymphocyte recirculation between lymphoid tissue and blood. Binding of a small molecule agonist to the $S1P_1$ receptor is postulated to cause $S1P_1$ internalization within the lymphoid tissue, thus reducing peripheral lymphocyte count and consequently reducing availability for recruitment to sites of inflammation.

$S1P_1$ agonism causes activation of G-protein coupled inwardly rectifying potassium (GIRK) channels that regulate cardiac pacemaker activity. Influx of potassium through GIRK channels has a negative chronotropic effect (i.e., reduced frequency of contraction) on the sino-atrial node and a negative dromotropic effect (i.e., reduced conduction speed) on the atrio-ventricular node. The selective SIP_1 agonist is therefore thought to reduce heart rate during the time period between $S1P_1$ activation and $S1P_1$ internalization. Once internalized, GIRK channels are no longer activated. Potassium inflow through the GIRK channels therefore decreases, thus attenuating the negative chronotropic and negative dromotropic effects.

The $S1P_1$ receptor is highly expressed in atrial, septal, and ventricular cardiomyocytes. It is also expressed in the endothelial cells of cardiac vessels and in other endothelial and vascular smooth muscle cells, where it contributes to the regulation of endothelial barrier function and peripheral vascular tone. The modulation of the receptor could thus lead to vasoconstriction causing an increase in blood pressure .

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Ozanimod: sNDA 209899

To support an indication for the treatment of moderate to severe ulcerative colitis, the applicant conducted a phase 3, multicenter, randomized-withdrawal, double-blind, placebo-controlled trial of ozanimod administered as induction and maintenance therapy. The trial was conducted in 250 sites and enrolled 1012 subjects.

The trial design is shown in **Figure 1**. It was composed of 2 periods: induction and maintenance. The Induction Period was composed of 2 cohorts in which subjects in both cohorts were treated for a total 10 weeks and evaluated for a clinical response/remission:

- Cohort 1: subjects were randomized in a 2:1 ratio to receive either ozanimod 1 mg or placebo once daily in double-blind fashion. The subjects were stratified by steroid use at screening and prior anti-TNF therapy.
- Cohort 2: subjects received open-label ozanimod 1 mg once daily.

The intent of this open-label cohort was to provide a sufficient number of responders to ozanimod 1 mg to allow re-randomization of an adequate sample size for the Maintenance Period.

All subjects (both cohorts) initiated investigational drug in accordance with a 7-day dose escalation regimen starting with ozanimod 0.25 mg or matching placebo (matching placebo for Cohort 1 only) on Days 1 to 4 and ozanimod 0.5 mg once daily or matching placebo on Days 5 to 7. On Day 8, subjects received ozanimod 1 mg once daily or matching placebo for a total of 9 weeks (up to Week 10).

Subjects from Cohort 1 or Cohort 2 with clinical response (by either 3-component or 4-component Mayo definition) at the end of the Induction Period proceeded to the Maintenance Period. Subjects who completed the Induction Period and did not have a clinical response could participate in an optional Open-label Extension.

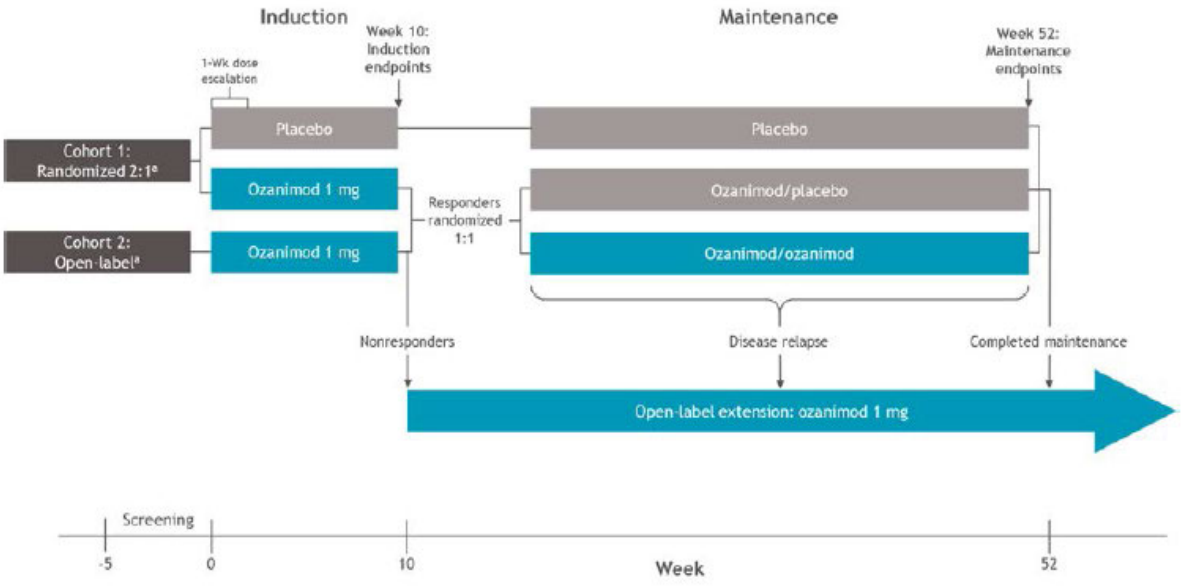
In the Maintenance Period, the clinically responding subjects were randomized to receive either ozanimod 1 mg or matching placebo (1:1 ratio) in a blinded fashion. Subjects who were randomized to placebo in the Induction Period and had at least a clinical response at Week 10 continued to receive placebo in the Maintenance Period in a double-blind manner.

Subjects rerandomized in the Maintenance Period were stratified prior to randomization by clinical remission status (by either 3-component or 4-component Mayo definition) at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no). Subjects were evaluated for disease activity/efficacy at Week 52 of the Maintenance Period.

Subjects who completed the Maintenance Period, or those who experienced disease relapse during the Maintenance Period, had the option to enter a separate Open-label Extension study (RPC01-3102).

Of a total of 1012 subjects enrolled in the Induction Period, 429 were randomized to ozanimod 1 mg and 216 were randomized to placebo in Cohort 1; 367 were allocated to Cohort 2. In the Maintenance Period, 69 subjects were allocated to placebo (originally on placebo during the Induction Period but had a clinical response), 227 were randomized to ozanimod-placebo image, and 230 were randomized to ozanimod 1 mg.

Figure 1: Phase 3 Trial Design



Source: NDA 209899 CSR (page 33/223)

In the safety population, cardiovascular system organ class (SOC) adverse events are shown in Table 1. This table contains a conglomeration of cardiovascular safety data from various tables in the body of the CSR and in the appendix.

The only notable finding was the expected bradycardia events in the induction period (5 in the ozanimod arms and 0 in the placebo arm). Other cardiovascular events were sporadic and did not point to a safety signal. The hypertension events noted in the maintenance period were evenly distributed between the ozanimod arm and the placebo arms.

Narratives of the 5 subjects who experienced bradycardia are found in the appendix (see Bradycardia Cases Reported on Study Day 1 and

Bradycardia Cases Reported after Study Day 1, respectively). The narratives indicated heart rate drops from 76 bpm to 46 bpm at Hour 6 on Day 1 in the setting of a left anterior fascicular block and left axis deviation on ECG (b) (6); from 56 bpm to 43 bpm at Hour 2 on Day (b) (6) with normal ECG (b) (6); from 59-63 bpm range to unknown heart rate at Hour 6, week 5 with pre-dose 1st degree atrioventricular block (b) (6) from 61 bpm to 50 bpm at unknown hour on Day (b) (6) with no ECG report (b) (6), and from 60 bpm to 45 bpm at unknown hour after 7 weeks with 1st degree atrioventricular block (b) (6)

There was a cardiovascular TEAE described as a "non-serious hypertensive crisis" in a subject on ozanimod in Cohort 1. The subject narrative was available [see Hypertensive Crisis in Cohort 1 (classified as nonserious)]. In this (b) (6) the baseline blood pressure was 138/100 mmHg and rose to 151/98 mmHg at Hour 3. The blood pressure resolved at Hour 6 (129/94 mmHg).

In the maintenance period, the two hypertensive crises events (1 on ozanimod and 1 on placebo) were categorized as serious. Narratives were available [see Hypertensive Crises (classified as serious adverse events)].

- (b) (6) randomized to placebo had a history of arterial hypertension. During the crisis occurring on Day (b) (6), study drug was interrupted. A diastolic blood pressure of 100 mmHg was recorded (systolic blood pressure was not reported). Baseline blood pressure was not reported. Study medication was resumed on Day (b) (6).
- (b) (6) randomized to ozanimod also had a history of arterial hypertension who experienced a blood pressure of 170/90 mmHg on Day (b) (6). No action was taken with study drug. The hypertensive crisis resolved on Day (b) (6) (blood pressure 130/80 mmHg).

Table 1: Treatment Emergent Adverse Events by Cardiovascular System Organ Class

Period	Cardiac Preferred Term	Cohort 1		Cohort 2
		Ozanimod 1 mg	Placebo	Ozanimod 1 mg
		N= 429	N = 216	N= 367
		n (%)	n (%)	n (%)
Induction	Angina Pectoris[1]	0	0	1
Induction	Coronary Artery Stenosis[1,4]	0	0	1
Induction	Bradycardia[2,3,4]	1[6]	0	3
Induction	Sinus Bradycardia[2,4]	0	0	1
Induction	Hypertension[5]	0	0	1
Induction	Non serious Hypertensive Crisis[8]	1	0	0
		Rerandomized		
		Ozanimod 1 mg	Placebo	Continued Placebo
Maintenance	Arrhythmia[7]	1	0	1

Maintenance	Unstable Angina[7]	0	0	1
Maintenance	Chronic Heart Failure[7]	1	0	0
Maintenance	Pericarditis[7]	1	0	0
Maintenance	Atrial Tachycardia[7]	0	0	1
Maintenance	Hypertension[7]	4	3	1
Maintenance	Hypertensive Crisis[7]	1	1	0
Maintenance	Ventricular Extrasystoles[6]	0	1	0

Sources from CSR: [1]Table 48 (Severe TEAE-Induction Period), [2]Table 54 (Adverse Events of Special Interest-Induction Period). Two of these bradycardia events led to study drug discontinuation (Table 60). [3]Note that Table 50 (events considered drug related TEAE- Induction Period) contains 2 events of bradycardia which are apparently reproduced in Table 54; [4]Note that Table 58 (TEAEs leading to study drug interruption-Induction Period) contains 1 event each of bradycardia, coronary artery stenosis, and sinus bradycardia which are apparently also listed in Table 54; [5]Table 58 (TEAEs leading to study drug interruption-Induction Period); [6] Located in CSR AE-listing 16.2.7.1 (page 26/263); [7]Table 14.3.1.2B (page 1262 and 1264/1838); [8]Narrative found on CSR page 175/223 and in Listing 16.2.7.6 (page 20/263).

Table 2 lists the number of subjects who required extended cardiac monitoring beyond the protocol-mandated 6-hour monitoring period, mostly for decreased heart rates (not clear how many were clinically bradycardic).

As expected, nadir heart rates relative to baseline were recorded at Hour 6 post treatment (16 in the ozanimod arms and 2 in the placebo arm). None of the heart rates fell below 45 bpm.

QTcF prolongations were evenly distributed amongst the arms; thus, no safety signal emerged.

Extended monitoring occurred in 6 subjects on ozanimod versus zero on placebo for unspecified reasons characterized as investigator discretion.

One subject in the Cohort 1 ozanimod treatment group and 1 subject in the Cohort 1 placebo treatment group in the Induction Period required a return to the clinic on Day 2 for extra monitoring because of QT prolongation. Although presumed, it was not clear if these 2 subjects were included in the QTcF line list in Table 2. Narratives on these subjects were available (see Extended Monitoring in Cohort 1 (Induction Period) Due to QT Prolongation).

- (b) (6) randomized to placebo had a baseline QTcF interval of 443 msec that asymptomatically increased to 452 msec at Hour 6. The QTcF interval decreased to 438 msec on Day (b) (6)
- (b) (6) randomized to ozanimod with a history of arterial hypertension and Wolff-Parkinson-White syndrome, on amiodarone, had a baseline QTcF interval of 426 msec that rose to 470 msec at Hour 6. The QTcF interval was reduced to 440 msec on Day (b) (6) The subject had mild dizziness on Day (b) (6) (hour unknown). The subject was reported to have overdosed on ozanimod (took 2 pills rather than 1). Blood pressure (120/80 mmHg) and heart rate (78 ←→64 bpm) were stable. No action was taken, and no treatment was required.

Table 2: Extended Cardiac Monitoring-Induction Period

Parameter[a], n (%)	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Subject Received Protocol-Mandated Extended Monitoring After 6 Hours	15 (3.5)	3 (1.4)	11 (3.0)
Primary Reason for Extended Monitoring			
HR < 45 bpm at Hour 6	0	0	0
HR Lowest Value at Hour 6 (and below baseline)	9 (2.1)	2 (0.9)	7 (1.9)
New Onset of AV Block (Second-degree or Higher)	0	0	0
Prolonged QTcF Interval (> 450 msec Males, > 470 msec Females)	2 (0.5)	1 (0.5)	2 (0.5)
Symptomatic bradycardia	0	0	0
Other[b]	4 (0.9)	0	2 (0.5)
Subject required overnight monitoring	0	0	1 (0.3)
Discharged but returned for monitoring on Day 2	1 (0.2)	1 (0.5)	0

AV = atrioventricular; HR = heart rate; QTcF = QT corrected by Fridericia's formula.
[a] All parameters are based on monitoring procedures in accordance with the protocol.
[b] Other reasons for extended monitoring were primarily investigator decision not due to adverse effect.
Source: Table 66, NDA 209899 CSR

ECG abnormalities at baseline, at Hour 6-Day 1, and at Week 10 are listed in the CSR Table 14.3.5.3.3A (*starting on page 853/1838-data not shown in entirety within this consult due to high volume*). Findings were generally evenly distributed between ozanimod and placebo arms. Some findings where the incidence of an ECG abnormality was higher in the ozanimod arm compared to the placebo arm have been extracted from the CSR table (*1st degree AV Block, Intraventricular Conduction defect, Atrial Arrhythmia defined as atrial premature complexes and ectopic atrial rhythm*) and are listed in Table 3. The differences between the arms for these events were evident at baseline without increasing the differences at Hour 6 Day 1 or Week 10. One subject in the Cohort 2 ozanimod group had second degree type I AV block. The narrative of this subject was available (see Atrio-Ventricular Blocks). None of these events were reported as an AE by the investigator. There were no reported cases of second degree type 2 or third-degree AV block.

Reviewer Comment: 2nd degree Mobitz 1 AV blocks are not clinically significant (i.e., would not require a pacemaker) unless symptomatic.

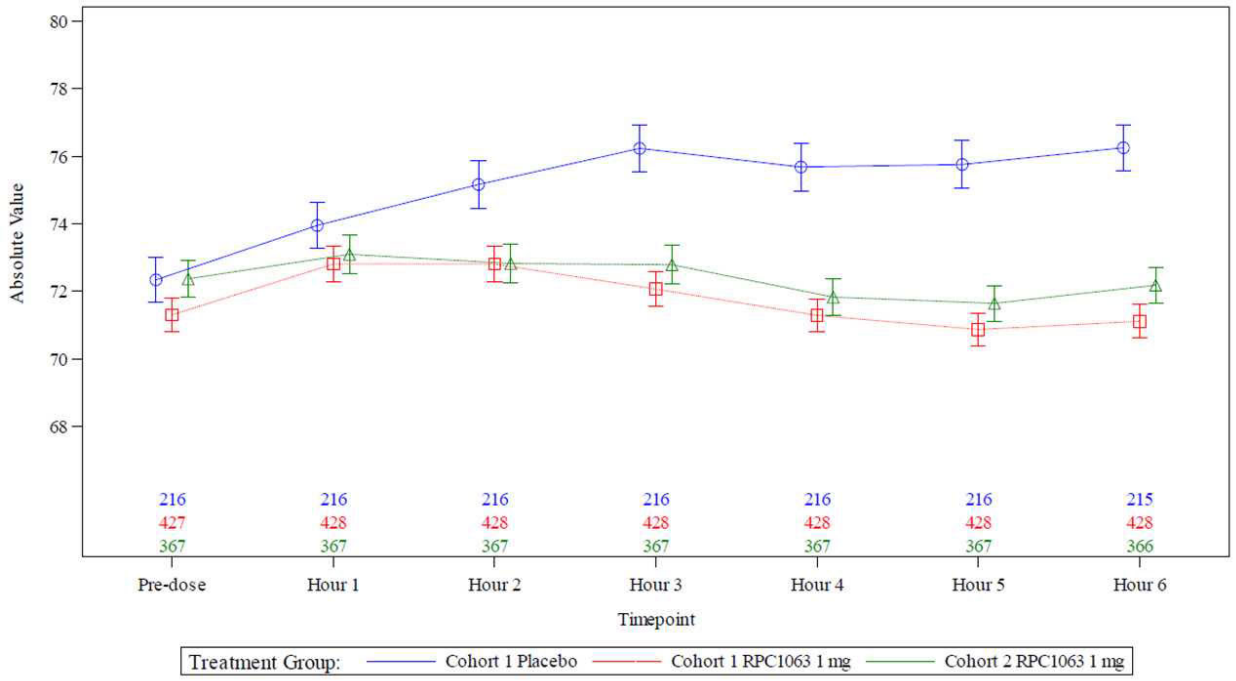
In the Maintenance Period, Heart Rate as a function of time in subjects in the placebo arm (continued placebo from the Induction Period), in the placebo arm after rerandomization, and ozanimod after rerandomization, are shown in Figure 2. Subjects on ozanimod had a tendency for a lower heart rate compared to the placebo arms, but the differences in heart rate (i.e., 70 bpm ←→ 72 bpm in the ozanimod arm, 71 bpm ←→ 75 bpm in the placebo arms) were not clinically significant.

Table 3: ECG Abnormalities

	Cohort 1		Cohort 2	Total
	Ozanimod 1 mg	Placebo	Ozanimod 1 mg	Ozanimod 1 mg
	N = 429	N = 216	N = 367	N = 796
	n (%)	n (%)	n (%)	n (%)
1st degree AVB				
-Baseline	19 (4.4)	2 (0.9)	16 (4.4)	35 (4.4)
-Day 1 Hour 6	21 (4.9)	4 (1.9)	16 (4.4)	37 (4.6)
-Week 10	16 (3.7)	1 (0.5)	12 (3.3)	28 (3.5)
2nd degree AVB, type 1				
-Baseline	0	0	0	0
-Day 1 Hour 6	0	0	0	0
-Week 10	0	0	1 (0.3)	1 (0.3)
IVCD				
-Baseline	11 (2.6)	4 (1.9)	15 (4.1)	26 (3.3)
-Day 1 Hour 6	15 (3.5)	4 (1.9)	13 (3.5)	28 (3.5)
-Week 10	12 (2.8)	3 (1.4)	11 (3.0)	23 (2.9)
Atrial Arrythmia				
-Baseline	6 (1.4)	3 (1.4)	7 (1.9)	13 (1.6)
-Day 1 Hour 6	6 (1.4)	2 (0.9)	6 (1.6)	12 (1.5)
-Week 10	8 (1.9)	1 (0.5)	3 (0.8)	11 (1.4)
Repolarization Abn				
-Baseline	14 (3.3)	3 (1.4)	7 (1.9)	21 (2.6)
-Day 1 Hour 6	16 (3.7)	4 (1.9)	8 (2.2)	24 (3.0)
-Week 10	14 (3.3)	3 (1.4)	6 (1.6)	20 (2.5)

Source: CSR Table 14.3.5.3.3A. Note: IVCD = Intraventricular Conduct Defect; Repolarization Abn = Repolarization Abnormality

Figure 2: Mean Heart rate Over Time During 6 Hours After First Dose-Induction Period



Source: Figure 21 NDA 209899 CSR: Circle = Cohort 1 Placebo; Square = Cohort 1 ozanimod 1 mg; Triangle = Cohort 2 ozanimod 1 mg. Error bars denote standard error

Section Summary:

- *The reported bradycardic events, AV blocks (1st degree and 2nd degree Mobitz 1), and variations of heart rate, were consistent with previous findings from the multiple sclerosis application. Other than bradycardia, the cardiovascular events reported in this sNDA were low in number and not significantly different from placebo. This review has not revealed any new cardiovascular safety signals.*
- *The effect of successively increased dosing on hemodynamic and cardiac conduction were not readily found in this sNDA and was not addressed in the multiple sclerosis program.*

(b) (4)

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Appendix

Cardiovascular Events in the Induction Period

Bradycardia Cases Reported on Study Day 1

- A 70-year-old male (b) (6) randomized to ozanimod with no relevant medical history or relevant concomitant medications, experienced a nonserious TEAE of bradycardia on Day (b) (6) Baseline HR was 76 bpm. The lowest HR during the 6-hour first dose observation period after the first dose of ozanimod 0.25 mg was 46 bpm at Hour 5 and it increased to 48 bpm at Hour 6. Nevertheless, the subject underwent extended monitoring. Prior to study entry, ECG findings variably included left anterior fascicular block, left-axis deviation, and HRs of 60 to 80 bpm. The Hour 6 ECG showed flat T-waves, left anterior fascicular block, left-axis deviation (-30 to -90 degrees), PR of 179 msec, and HR of 49 bpm. The Hour 8 ECG showed PR of 201 msec, HR of 45 bpm, which was the lowest HR documented, and normal T-wave morphology. The Hour 9 ECG showed HR of 49 bpm, PR of 196 msec, and normal T-wave morphology. No treatment was required, and no action was taken with the study drug. The event resolved on Day (b) (6) (unscheduled visit) with a HR of 58 bpm. The investigator assessed the relationship to study drug as probable.
- A 35-year-old male (b) (6) was enrolled in Cohort 2 with no relevant medical history or concomitant medications. After the first dose, the subject experienced headache, nausea,

and lightheadedness, which resolved on the same date. The lowest HR occurred at Hour 2 (43 bpm) and recovered to above baseline by Hour 5 (57 bpm; predose HR was 56 bpm). No treatment or extended monitoring was required for the events. ECG was normal at Hour 6.

Bradycardia Cases Reported after Study Day 1

- A 28-year-old male (b) (6) randomized to ozanimod experienced a nonserious TEAE of bradycardia. At screening, the subject's ECG was normal, and HR was 68 bpm. On Day (b) (6) the HR ranged from 59 to 63 bpm during first dose monitoring. The predose ECG showed first-degree AV block and left ventricular hypertrophy; at Hour 6, only left ventricular hypertrophy was still present. The subject reported at the Week 5 visit that on Day (b) (6), the subject experienced bradycardia; no HR value was available to report. No treatment was given, and the event was considered resolved/recovered on Day (b) (6) The subject continued on study medication until Day (b) (6) when it was stopped due to worsening UC. At the Early Termination visit (Day (b) (6)), the subject's HR was 68 bpm and the ECG showed nonspecific intraventricular conduction delay. At the 30-day safety follow-up visit, the subject's HR was 80 bpm. The investigator considered the event probably related to study medication.

- A 63-year-old female (b) (6) with a history of hypertension treated with perindopril was enrolled in Cohort 2. At baseline, the subject's predose HR was 61 bpm and BP was 123/70 mm Hg. On Day (b) (6) the subject was started on bisoprolol and increased the perindopril dose for hypertension. The physician conducted Holter monitoring on Day (b) (6) that showed nocturnal HR between 50 to 53 bpm. The TEAE was reported as "bradycardia due to bisoprolol use" and asthenia. Study drug was interrupted, and the bradycardia resolved on Day (b) (6). On Day (b) (6), the subject experienced hypertension (no documentation of high BP was provided) and sinus bradycardia; HR was 54 bpm and BP was 129/83 mm Hg. An ECG showed a HR of 53 bpm but was otherwise normal. No treatment was given for the events. The hypertension reportedly resolved the same day. The sinus bradycardia and asthenia resolved the next day. Ozanimod was restarted on Day (b) (6). On Day (b) (6), the subject experienced worsening hypertension, asthenia, and bradycardia; vital signs were not provided. The events were treated with meldonium and olmesartan. Ozanimod was discontinued on Day (b) (6). The hypertension resolved on Day (b) (6). On Day (b) (6), HR was 53 bpm and BP was 150/82 mm Hg. At the study termination visit 11 weeks after discontinuing ozanimod, asthenia had resolved, and bradycardia was ongoing; HR was 53 bpm and BP 132/81 mm Hg.

- A 67-year-old female (b) (6) was enrolled in Cohort 2. Baseline predose HR was 60 bpm and BP was 116/73 mm Hg. Baseline ECG showed first-degree AV block and PR of 212 msec. After 7 weeks of treatment, the subject noted lightheadedness and headaches in the evenings prior to sleep. The subject checked her HR and reported that at one time the pulse was down to 45 bpm. The subject was seen by a cardiologist in consultation and no clinically significant abnormalities were identified. The subject discontinued study treatment with the last dose at Week 9. An ECG at an unscheduled visit showed sinus rhythm, HR of 53 bpm, first-degree AV block, PR of 222 msec, and nonspecific ST segment abnormality with normal T-wave morphology. The bradycardia resolved 4 days after drug discontinuation with no corrective treatment. An ECG at the 30-day follow-up visit was normal. The subject had a relevant medical

history of arterial hypertension. No antihypertensive medication was documented as concomitant medication.

Hypertensive Crisis in Cohort 1 (classified as nonserious)

- A 31-year-old male [redacted], randomized to ozanimod with a medical history of ongoing hypertension and no documented prior or concomitant treatment with antihypertensives, experienced a nonserious TEAE of hypertensive crisis on Day [redacted] which resolved the same day. Baseline blood pressure on Day [redacted] was 138/100 mm Hg. The highest blood pressure measurement observed from cardiac monitoring during dose escalation was 151/98 mm Hg at Hour 3. At Hour 6, the blood pressure was 129/94 mm Hg. The subject was treated with one dose of oral enalapril 5 mg. No additional symptoms were reported, and no action was taken with study drug. The investigator assessed the event as unrelated to study drug.

Extended Monitoring in Cohort 1 (Induction Period) Due to QT Prolongation

- A 50-year-old male [redacted] randomized to placebo with no relevant medical history or relevant concomitant medications, experienced a nonserious TEAE of electrocardiogram QT prolonged on Day [redacted] which required Day [redacted] monitoring. Baseline ECG indicated a QTcF interval of 443 msec. Hour 6 ECG indicated a QTcF interval of 452 msec. The subject had no symptoms. No action was taken with the study drug and no treatment was required. An ECG on Day [redacted] indicated a QTcF interval of 438 msec and the event was considered resolved. The investigator assessed the event as related to study drug.

- A 41-year-old male [redacted] randomized to ozanimod with a medical history of moderate arterial hypertension and Wolff-Parkinson-White (WPW) syndrome and concomitant medications that included amlodipine for arterial hypertension, experienced nonserious TEAEs of electrocardiogram QT prolonged and dizziness (mild) after inadvertently taking 2 ozanimod pills on Day [redacted], which required Day [redacted] monitoring. At baseline, the subject's HR and blood pressure measurement were 78 bpm and 120/80 mm Hg, respectively, and the ECG indicated a QTcF interval of 426 msec. The lowest HR and blood pressure measurement on Day [redacted] was at Hour 4 (64 bpm and 120/80 mm Hg, respectively). Hour 6 ECG indicated a QTcF interval of 470 msec. The dizziness resolved on Day [redacted] and the event of electrocardiogram QT prolonged resolved on Day [redacted]. An ECG on Day [redacted] indicated a QTcF interval of 440 msec. No action was taken with study drug and no treatment was required. The investigator assessed the relationship to study drug as possible.

Atrio-Ventricular Blocks

- A 29-year-old male [redacted] with a medical history of deep vein thrombosis and pulmonary embolus 3 years prior to study entry, had a screening ECG that showed first-degree AV block with a PR interval of 250 msec. On Day [redacted], ECG findings included a baseline PR interval of 263 msec at baseline and a PR interval of 285 msec at Hour 6. At Week 10, the ECG showed second-degree AV block, Mobitz type 1 (the PR interval was 180 msec at cycle onset, lengthening with each beat until the 3rd or 4th beat was dropped). The subject reported no concurrent TEAEs and continued treatment in the maintenance period. Concomitant medications included prednisone 20 mg, aspirin, and vitamins. Four months later, the subject

experienced a UC relapse and entered the OLE study. An ECG at that time showed normal sinus rhythm without AV block; the PR interval was 188 msec.

Cardiovascular Events in the Maintenance Period

Hypertensive Crises (classified as serious adverse events)

- A 59-year-old male (b) (6) randomized to ozanimod/placebo with a medical history of arterial hypertension, coronary artery disease, obesity, and dyslipidemia and concomitant medications that included ramipril for arterial hypertension, experienced serious events of hypertensive crisis and vomiting on Study Day (b) (6) and was hospitalized. At the time of the event, the diastolic blood pressure was 100 mm Hg (systolic blood pressure was not available). Treatment of the events included ramipril and metoclopramide. Study drug was interrupted. The vomiting resolved on Study Day (b) (6) and the hypertensive crisis resolved on Study Day (b) (6) The subject was discharged on Study Day (b) (6) and study medication was resumed. The investigator assessed the relationship of the hypertensive crisis to study drug as unlikely, and the relationship of the vomiting to study drug as unrelated. The investigator reported that the subject's arterial hypertension had not generally worsened since the subject was under study, but the subject was hospitalized due to an arterial hypertension crisis.

- A 55-year-old male (b) (6) randomized to ozanimod/ozanimod with a medical history of arterial hypertension and concomitant medications that included perindopril for arterial hypertension, experienced a serious event of hypertensive crisis with a blood pressure of 170/90 mm Hg on Study Day (b) (6) and was hospitalized. An ECG was performed, but the results were not provided. On the same day, nonserious TEAEs of coronary heart disease, atherosclerotic cardiosclerosis (verbatim term), dyslipidemia, and chronic heart failure 1st degree (verbatim term) were reported. The subject experienced no signs or symptoms associated with the nonserious events. No action was taken with the study drug. Treatment for the event included amlodipine, indapamide, ramipril, betahistine, moxonidine, piracetam, vinpocetine, magnesium sulfate, and acetylsalicylic acid. The hypertensive crisis resolved on Study Day (b) (6) and the subject was discharged from the hospital with a blood pressure of 130/80 mm Hg. The investigator assessed the relationship of the hypertensive crisis to study drug as unrelated.

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Medical Officer's Review of (b) (4)
IND 115243 and NDA 209899/S001
Ophthalmology Consultant

(b) (4)
IND 115243
NDA 209899

Submission: 12/11/2020

Review completed: 12/29/2020

Name: Ozanimod

Sponsor: Celgene International II Sarl

Pharmacologic Category: Sphingosine 1-phosphate (S1P) receptor modulator

Indications: Multiple sclerosis

Requested:
1) Approved S1P modulators are associated with an increased risk of macular edema (ME). Ozanimod is currently approved for the treatment of MS. Please review the safety findings related to this issue within the UC application and comment on whether a similar increased risk of macular edema exists in association with use of this product in UC patients, and what ophthalmologic monitoring is indicated in UC patients if approved. Please comment on whether the recently approved labeling for MS is adequate to cover UC patients, or if you see a need for differential information to be included in the labeling.

(b) (4)

AESI Category Preferred Term, n (%)	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Macular edema	1 (0.2)	0	0

AESI Category Preferred Term, n (%)	Placebo (N = 69)	Re-randomized Subjects	
		Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg- Ozanimod 1 mg (N = 230)
Macular edema	0	0	1 (0.4)

In the Induction Period, 1 subject (0.2%) in the Cohort 1 ozanimod 1 group and no subjects in the placebo treatment group had a TEAE of macular edema. One subject (0.3%) in the Cohort 2 ozanimod 1 mg group had a TEAE of peri-macular edema (coded as macular edema; but was not macular edema on review). One subject (0.4%) re-randomized to the ozanimod group in the Maintenance Period had a TEAE of macular edema (Table 14.3.1.2B).

Brief descriptions of these cases are provided below:

- (b) (6) (Cohort 1 ozanimod treatment group) was a 56-year old White female with a medical history of Raynaud's phenomenon and systemic lupus erythematosus. The optical coherence tomography (OCT) results were normal at Screening. On Study Day (b) (6), the subject had a nonserious AE of vision alteration that recovered/resolved on Study Day (b) (6) with no change to study drug or treatment received. On Study Day (b) (6) the subject experienced macular edema (verbatim: right eye macular edema) which was considered moderate in intensity. On the same day, a non-serious AE of moderate detachment of retinal pigment epithelium and macular fibrosis was also reported OCT scan showed abnormal foveal thickness of 336 μm and 415 μm in the left and right eyes, respectively. The results from the vision test during the physical exam for the visit were normal (20/25 right eye and 20/40 left eye). No treatment was given for all the events. Study medication was discontinued on Study Day (b) (6) due to macular edema. The event of macular edema was considered recovered/resolved on Study Day (b) (6) with normal OCT results. The events of detachment of retinal pigment epithelium and macular fibrosis were considered not recovered/not resolved. The MERP reviewed the data and OCT images and determined that macular edema was present. The investigator considered the relationship of the event to the study medication possible.

Reviewer's Comments: *This subject did not have any predisposing factors for macular edema. The subject should have had an OCT on Day (b) (6) when the vision alteration was noted. It is not likely that the vision alteration resolved on Day (b) (6) but the subject was noted to have macular edema in both eyes on Day (b) (6)*

(b) (4)

- (b) (6) (Cohort 1 ozanimod treatment group) was a 63-year old, White male with a history of presbyopia and diabetes mellitus. On Study Day (b) (6), the subject reported decreased visual acuity, blurred distant vision, sensitivity to light, and sudden blindness lasting for a few seconds in duration. On Study Day (b) (6) the subject was diagnosed with macular edema which was considered mild in intensity. An ophthalmological examination showed a central foveal thickness of 325 µm in the OD, central foveal thickness of 265 µm in the OS, macular edema in both eyes, and non-proliferative hypertensive diabetic retinopathy. Visual acuity was 0.8 in the OD and 0.9 in the OS. Study medication was permanently discontinued on the same day; no treatment was provided for the event. On Study Day (b) (6) OCT showed substantial improvement of visual acuity; non-proliferative diabetic hypertensive retinopathy remained ongoing. The event of macular edema was considered recovered/resolved on Study Day (b) (6). On the same day, laboratory test results showed increased HbA1c (8.0%), and urinalysis was positive for glucose (1+). The MERP confirmed macular edema and diabetes was noted as a predisposing factor. The investigator considered the relationship of the event to the study medication possible.

Reviewer's Comments: *The subject had macular edema in both eyes. While the subject had diabetes, which can lead to macular edema, the macular edema in this case is not likely to be due to the diabetes because the HbA1c was at most 8.0%.*

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA209899Orig1s001

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

NDA 209899/S-001

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Celgene International II Sàrl
Attention: Petra Pavlickova, PhD, RAC
Associate Director, Regulatory Affairs
3033 Science Park Road, Suite 300
San Diego, CA 92121

Dear Dr. Pavlickova:

Please refer to your supplemental new drug application (sNDA) dated and received on November 30, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zeposia (ozanimod) capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR: 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is May 30, 2021.

We are reviewing your application according to the processes described in the draft guidance for industry *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*.[1] Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/ commitment requests by April 28, 2021.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

We request that you submit the following information by February 21, 2021:

Clinical Pharmacology

Reference is made to your population PK report CLG-Certara-UC-358-1 entitled "Population Pharmacokinetic Analyses of Ozanimod and Active Metabolite CC112273 in Ulcerative Colitis Patients". You have proposed to evaluate the effect of concomitant administration of prednisone or prednisolone on the PK of the major active metabolite of ozanimod (CC112273) through a population PK approach. We request the following additional information:

(1) Re-evaluate the impact of concomitant prednisone or prednisolone on the PK of major active metabolite of ozanimod (CC112273) as a time-dependent covariate. Specifically, if patients stop or start the concomitant medication during the PK sampling, this needs to be reflected in the corresponding covariate over time.

(2) Provide detailed dosing information for the concomitant prednisone or prednisolone, including the dose given, the time of drug administration, and time of drug discontinuation.

(3) Submit the results along with updated dataset and scripts for population PK analysis.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and PLLR Requirements for Prescribing Information[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents

[2] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

- A sample tool illustrating the format for Highlights and Contents

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the labeling issues in the attached Prescribing Information.

We request that you resubmit revised labeling that addresses these issues by February 19, 2021. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at FDA.gov.[4]

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed Prescribing Information (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

Do not submit launch materials until you have received our proposed revisions to the Prescribing Information (PI) and Medication Guide and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see FDA.gov.[6] If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug/biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call me at (301) 796-9007 or email me at jay.fajiculay@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, MMSc
Director
Division of Gastroenterology
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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