14 October 2021
EMA/619305/2021 Corr.1[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zeposia

International non-proprietary name: ozanimod

Procedure No. EMEA/H/C/004835/II/0002/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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[1] 08.11.2021

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List of abbreviations

Abbreviation or Specialist Term	Definition
A3	Adenosine 3
Ab	Antibody
ADME	Absorption, Distribution, Metabolism, And Excretion
AKT	Protein Kinase B
ANOVA	Analysis Of Variance
AUC	Area Under The Plasma Concentration Time Curve
AUC_{0-24}	Area Under The Plasma Concentration Time Curve Over 24 Hours
cAMP	Cyclic Adenosine Monophosphate
CBC	Complete Blood Count
$CD4^+$	Cluster Of Differentiation 4 (Immune Cell Marker)
cf.	Confer (Latin), Compare
CHO	Chinese Hamster Ovary
Cmax	Maximum Plasma Concentration
CNS	Central Nervous System
DDI	Drug-Drug Interactions
DMSO	Dimethyl Sulfoxide
EAE	Experimental Autoimmune Encephalomyelitis
EC_{50}	Concentration At Which 50% Of Maximal Activity Is Observed
ECG	Electrocardiogram
Emax	Maximal Response Achieved Relative To The Internal Positive Control
ERK	Extracellular Signal-Regulated Kinase
FOB	Functional Observational Battery
FTY720	Fingolimod
FTY720-P	Fingolimod Phosphate

GABA	Gamma-Aminobutyric Acid
GLP	Good Laboratory Practice
GPCR	G Protein-Coupled Receptor
Gαi	Inhibitory G Protein
hERG	Human Ether-À-Go-Go-Related Gene
HCl	Hydrochloride
IA	Intrinsic Activity
IBD	Inflammatory Bowel Disease
IC50	Half Maximal Inhibitory Concentration
IFN-γ	Interferon Gamma
IL	Interleukin
IKr	Delayed Rectifier Potassium Channel
KD	Dissociation Constant
Ki	Inhibition Constant
MAO-A	Monoamine Oxidase A
MAO-B	Monoamine Oxidase B
MS	Multiple Sclerosis
MT1	Melatonin 1
NOEL	No Observed Effect Level
NR	No Response
NS	Not Significantly Diferente
PD	Pharmacodynamics
PIF	Photo Irritation Factor
PK	Pharmacokinetic
QD	Once Daily
RMS	Relapsing Multiple Sclerosis
S1P	Sphingosine 1-Phosphate

S1P1	Sphingosine 1-Phosphate Receptor Subtype 1
S1P2	Sphingosine 1-Phosphate Receptor Subtype 2
S1P3	Sphingosine 1-Phosphate Receptor Subtype 3
S1P4	Sphingosine 1-Phosphate Receptor Subtype 4
S1P5	Sphingosine 1-Phosphate Receptor Subtype 5
S1PR	Sphingosine 1-Phosphate Receptor
SCID	Severe Combined Immunodeficiency
SEM	Standard Error Of The Mean
Th1	T Helper Type 1 Cell
TK	Toxicokinetic
TNBS	2,4,6-Trinitrobenzenesulfonic Acid
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
[^{35}S]GTPγS	Guanosine 5-O-(3-[^{35}S]Thio)Triphosphate
5-HT	5-Hydroxytryptamine
5-HTP	5-Hydroxytryptophan

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 24 November 2020 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

C.I.6.a (Extension of indication)
Extension of indication to include the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent for Zeposia; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.2 and 5.1 of the SmPC and Annex IID are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes throughout the product information.

C.I.4
Update of sections 4.4 and 4.5 of the SmPC in order to update the current SmPC description about PK interaction with BCRP inhibitors based on the study report from a drug interaction study with cyclosporine l(RPC-1063-CP-001).

The group of variations requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) EMA/488493/2020 (P0383/2020) on the agreement of a paediatric investigation plan (PIP) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001710-PIP03-17-M02 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes   Co-Rapporteur: Martina Weise

Timetable	Actual dates
Submission date	24 November 2020
Start of procedure:	26 December 2020
CHMP Co-Rapporteur Assessment Report	18 February 2021
CHMP Rapporteur Assessment Report	8 March 2021
PRAC Rapporteur Assessment Report	26 February 2021
PRAC Outcome	11 March 2021
CHMP members comments	15 March 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 March 2021
Request for supplementary information (RSI)	25 March 2021
CHMP Rapporteur Assessment Report	27 June 2021
PRAC Rapporteur Assessment Report	25 June 2021
PRAC members comments	30 June 2021
Updated PRAC Rapporteur Assessment Report	1 July 2021
PRAC Outcome	8 July 2021
CHMP members comments	12 July 2021
Updated CHMP Rapporteur Assessment Report	19 July 2021
2nd Request for supplementary information (RSI)	22 July 2021
CHMP Rapporteur Assessment Report	21 September 2021
PRAC Rapporteur Assessment Report	17 September 2021
PRAC members comments	22 September 2021
Updated PRAC Rapporteur Assessment Report	23 September 2021
PRAC Outcome	30 September 2021
CHMP members comments	04 October 2021
Updated CHMP Rapporteur Assessment Report	07 October 2021
Opinion	14 October 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disorder that involves the surface mucosa, the crypt epithelium, and the submucosa of the colon. Patients with UC suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, fever, and an increased risk of colorectal cancer, which can have a profound impact on patients' quality of life.

State the claimed the therapeutic indication

The proposed indication is:

Ozanimod is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

The recommended dose is 0.92 mg ozanimod once daily.

The capsules can be taken with or without food.

The initial dose escalation regimen of ozanimod from Day 1 to Day 7 is required and shown below. Following the 7-day dose escalation, the once daily dose is 0.92 mg, starting on Day 8.

Table 1: Dose Escalation Regimen

Day of Treatment	Dosage
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

Epidemiology

UC prevalence is estimated to be 70-500 cases per 100.000 with peak age of onset between 15 and 25 years. Within Europe there is an east-west and north-south gradient, but the incidence appears to have increased in southern and eastern countries during recent years (ECCO guideline, 2017). In 15% of cases, UC is diagnosed in childhood and may present before school age. In general, mortality is not increased in UC but the disease may present as life-threatening acute severe colitis. Patients may live with a considerable symptom burden and high risk of disability despite medical treatment.

Biologic features

UC is a chronic, relapsing inflammatory bowel disease affecting the rectum and, in many instances, also part of/the entire 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.

Clinical presentation, diagnosis and stage/prognosis

Onset of disease most commonly occurs between 15 and 40 years of age. 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, and 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. Patients have a 10% cumulative risk of colectomy 5 years after diagnosis, and 15% at 10 years.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. 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.

Patients with UC may also experience extra-intestinal manifestations including primary sclerosing cholangitis or eye, joint, or skin manifestations. Improved intestinal disease activity in UC is associated with an improvement in some extra-intestinal manifestations.

Management

The pathology of UC is characterized by a life-long chronic course of remissions and exacerbations. Until a cure is found, the overall goal of treatment for patients with active UC is to induce and maintain remission and to induce and maintain mucosal healing. Despite the advancements in therapies available to patients with UC, there are still a significant number of patients with moderate to severe UC who do not respond, lose response or are intolerant to available therapies. There is a high unmet need for new efficacious treatments for patients with manageable safety and with the convenience of an oral administration.

The mainstay of therapy for mild to moderate UC is 5-aminosalicylic (5-ASA) agents. These agents are effective at inducing and maintaining remission in UC. The majority of patients with moderate to severe active UC benefit from topical, oral or parenteral glucocorticosteroids. Remission, however, cannot be maintained with steroids. Azathioprine (AZA) or mercaptopurine (MP) has been employed as glucocorticoid-sparing agents in patients unable to be weaned from glucocorticoids. Anti-tumour necrosis factor α (TNF) agents, integrin inhibitors and novel immunomodulatory agents (such as tofacitinib) are indicated for the treatment of UC patients refractory to standard treatment (as previously described). The biologic anti-TNF agents were the first newer-generation drugs to be approved for the treatment of UC, offering a treatment option for patients who had failed conventional therapy. In a systematic review of clinical trials, a high proportion of patients treated with anti-TNF therapy fail to achieve an initial response or remission to therapy. Within reported clinical trials, approximately 19% to 58% of patients are primary non-responders (ie, fail to achieve clinical response) to anti-TNF therapy. Gordon et al, 2015 also reported that between 17% to 22% of patients with UC experienced a secondary nonresponse (ie, loss of response after initial response).

Real world evidence supports that many patients with UC treated with biologic therapy frequently require dose increases or need to switch therapies in order to improve disease control. Using a database of chart information abstracted by selected gastroenterologists across the US and 5 European Union (EU) countries (France, Germany, Italy, Spain and the United Kingdom [UK]), treatment patterns of patients with moderate to severe UC with documented administration of biologic agents were examined (Armuzzi, 2020). Among patients using biologic therapy for greater than 3 months, the dose administered was

greater than the indicated dose or dose frequency (in the US: 37% for infliximab, 13% for adalimumab, 25% for vedolizumab). In this study, switching therapy was common. For the whole sample size (N = 1419), 69% of patients were on their second line of therapy and 34% were on their third line of therapy. Biologic agents were the most common second line (40%) and third-line therapies (57%). The primary reason (> 80%) for switching therapy was efficacy-related (eg, primary or secondary nonresponse).

Safety concerns related to using anti-TNF agents include serious infections leading to hospitalization or death, including tuberculosis, bacterial sepsis, invasive fungal infections, and infections due to opportunistic pathogens. Ustekinumab, which inhibits the IL-12/23 p40 subunit, is, like the anti-TNFs, also susceptible to loss of response due to anti-drug antibodies (ADAs) and is associated with serious and opportunistic infections (including reactivation of latent tuberculosis), malignancies, and skin cancers. Serious hypersensitivity reactions have also been reported. Vedolizumab is associated with safety concerns including injection-related reactions and hypersensitivity, infections including tuberculosis and progressive multifocal leukoencephalopathy (PML), and malignancies. Tofacitinib is the only oral immunomodulator approved for moderate to severe UC. While the oral route of administration advanced the treatment for patients with moderate to severe UC, tofacitinib is associated with greater risk of serious infections, opportunistic infections and herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous infections. In the EU, tofacitinib is to be used with caution in patients with known risk factors for venous thromboembolism (VTE), including prior VTE, major surgery, immobilization, myocardial infarction within the previous 3 months, heart failure, combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, or malignancy. Additional VTE risk factors such as age, obesity, diabetes, hypertension, and smoking status should be considered.

Surgery with colectomy is curative but can be associated with significant morbidity and is thus reserved for acute severe (fulminant) colitis or resistant cases and in some cases as cancer treatment or prevention. Intestinal continuity can be restored by construction of an ileo-anal pouch.

According to the CHMP UC guideline (2018), the goal of treatment of ulcerative colitis is achieving and maintaining symptomatic and endoscopic remission.

About the product

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 2 major active metabolites, CC112273 and CC1084037. Approximately 94% of circulating total active drug exposure is represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%).

Sphingosine-1-phosphate 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 multiple sclerosis (MS).

2.1.2. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek scientific advice (SA) from the CHMP for the development of the UC programme. SA was sought from the Swedish and UK agencies.

During development, the guidance document for medicinal products to treat patients with UC that was in effect at the time clinical program design was CHMP/EWP/18463/2006 dated 2008, prior to the recent 2018 revision (Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis CHMP/EWP/18463/2006 Rev.1). For this reason, the MAH justifies some post hoc analysis presented in the dossier.

2.1.3. General comments on compliance with GLP, GCP

All non-clinical pivotal safety pharmacology and toxicology studies were conducted in accordance with the requirements of the United States (US) Food and Drug Administration (FDA) Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies (21 CFR Part 58) and International Conference on Harmonization (ICH) guidelines. The United States is an Organization for Economic Co-operation and Development (OECD) Member Country and adheres to the OECD Mutual Acceptance of Data (MAD) program.

The clinical studies have been conducted in the USA (the phase I studies) as well globally, involving study sides within the EU, as well as outside the EU (North America, South America, Asia, Africa and Australia).

The applicant confirmed that the clinical trials included were performed in accordance with the principles of GCP, as defined by ICH and that the clinical trials carried out outside the EU meet the ethical requirements of the Directive 2001/20/EC.

2.2. Non-clinical aspects

2.2.1. Introduction

To support the use of Ozanimod in patients with UC in vivo pharmacodynamic studies in rodent models of colitis were submitted with this application. Furthermore, an in vitro radioligand binding pharmacodynamics (PD) PD-study is submitted which has not been previously assessed during the MAA procedure for the MS indication.

No further new non-clinical studies were submitted with this application. With regard to the non-clinical safety, pharmacokinetic and toxicology studies, the applicant refers to the studies submitted with the initial MAA for treatment of MS.

2.2.2. Pharmacology

Primary pharmacodynamic studies

An **in vitro assessment of radioligand binding affinity of ozanimod and metabolites at human S1P$_1$ and S1P$_5$** were performed (Report RP-PH-018). This study has not been previously submitted and assessed.

Binding affinity studies were performed in membranes from CHO cells stably expressing human cloned S1P$_1$ and S1P$_5$ whereby the ability of ozanimod and its metabolites (CC112273, CC1084037, RP101124,

RP101075, RP101988, RP101442, RP112289, and RP112509) to displace the binding of [³H]-ozanimod by 50% (IC$_{50}$) was measured. These IC$_{50}$ values were converted to inhibition constants (K$_i$ – concentration of competing ligand which would occupy 50% of the receptors) using the Cheng Prusoff equation and the determined dissociation constant for [³H]-ozanimod (K$_D$ – concentration of the radioligand which occupies 50% of the receptors at equilibrium). In all assays the endogenous ligand, S1P, was used as a reference control. Saturation binding analysis determined K$_D$ values for ozanimod to be 1.62 nM and 6.56 nM for S1P$_1$ and S1P$_5$, respectively. Using these K$_D$ values, the K$_i$ values were calculated from the inhibition curve IC$_{50}$'s and it was determined that all active metabolites had inhibition constants in the sub nM range for S1P$_1$. The major metabolites CC112273 and CC1084037 yielded S1P$_1$ K$_i$ values of 0.29 ± 0.08 nM and 0.11 ± 0.03 nM, respectively, both similar to ozanimod (0.29 ± 0.04 nM). In agreement with functional potencies, the K$_i$ values for S1P$_5$ were higher than for S1P$_1$ and in the 1 – 40 nM range with the major metabolites CC112273 and CC1084037 yielding S1P$_5$ K$_i$ values of 19.31 ± 1.11 nM and 1.99 ± 0.13 nM, respectively with ozanimod at 5.54 ± 0.35 nM (Table 5.2.2.1). RP101124 was unable to compete with [³H]-ozanimod at S1P$_1$ or S1P$_5$ (Table 5.2.2.1) suggesting it does not bind within the ozanimod binding pocket of S1P$_1$ or S1P$_5$, a clear explanation for its lack of functional activity as assessed using [³⁵S]GTPγS binding. Sphingosine 1- phosphate was also competitive with [³H]-ozanimod suggesting that ozanimod binds to the orthosteric binding site for the endogenous ligand of S1P$_1$ and S1P$_5$.

Table 2: Human Sphingosine 1-phosphate Receptor 1 and 5 Radioligand Binding of Ozanimod and its Eight 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

IC$_{50}$ = concentration at which 50% of the [³H]-ozanimod was displaced; K$_i$ = 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; S1P$_1$ or S1P$_5$ = 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.**

The study results suggest that the active metabolites of ozanimod are able to compete for the same binding site as the parent molecule within S1P$_1$ and S1P$_5$ and that ozanimod and its active metabolites bind to the orthosteric binding site for the endogenous agonist, S1P.

The potency and intrinsic activity for S1P$_1$ internalization were assessed in response to treatment of S1P$_1$ expressing cells with ozanimod and downstream circulating active metabolites after multiple different

durations of compound exposure (Report RP-PH-013). The results showed that ozanimod and metabolites induced robust receptor internalization at all time points studied with a trend towards increased potency with longer duration of test compound exposure. The internalization of $S1P_1$ results in a functional antagonism due to the reduced availability of the receptor for further activation. This loss of $S1P_1$ from the cell surface contributes to the peripheral mechanism of action of ozanimod and its active metabolites and results in retention of lymphocytes in the peripheral lymphoid tissues since the cells can no longer sense and follow the S1P gradient between the lymphoid tissue and the systemic circulation. Metabolite RP101124 was inactive in that it did not cause $S1P_1$ internalization at any concentration or at any time point studied. Ozanimod did not cause internalization of $S1P_5$ with compound exposure for 60 minutes followed by immediate assessment, or upon assessment a further 23 hours later.

Ozanimod and metabolites CC112273 and RP101988 elicit robust intracellular signaling in astrocytes isolated from human, mouse, and rat cerebral cortex using AKT and ERK phosphorylation as the readout Report RP-PH-004; Report RP-PH-009; and Report RP-PH-012). The results confirm an effect of ozanimod on a CNS cell type pertinent to MS pathology. Pharmacological characterization using selective $S1P_1$ and $S1P_5$ agonists, including ozanimod, determined this signaling response to be mediated by $S1P_1$ and not $S1P_5$ (Report RP-PH-011).

In vivo pharmacology

A range of in vivo pharmacodynamic studies have been submitted to support the proposed extension of indication for treatment of UC. These studies are described and assessed in the following.

Efficacy of Ozanimod in Rodent Models of Inflammatory Bowel Disease

The objective of these studies was to assess the efficacy of ozanimod in two widely used rodent models of inflammatory bowel disease, namely naïve T-cell adoptive transfer in severe combined immunodeficiency (SCID) mice and TNBS-induced colitis in rats. The adoptive transfer of naïve CD4+CD45RB^{high} T lymphocytes from donor mice into SCID mice induces colonic inflammation that develops several weeks later. Intra-rectal administration of the hapten, TNBS initiates a mucosal immune response that induces colitis by a Th1-mediated immune response (Kiesler, 2015). The efficacy of the active metabolites of ozanimod was not directly assessed in either model.

A summary of the studies in rodent models of IBD is given in table 3.

Table 3: Summary of Findings from Preclinical Studies of Inflammatory Bowel Disease with Ozanimod

Study/Report Number	Model	RPC1063 Dose Regimen	Findings Relevant to RPC1063 (vs. Vehicle Controls)
MCD4-RPT-1	CD4+ adoptive transfer in SCID mice	1.2 mg/kg QD PO (d21-d41)	Improved body weight, colon weight (74%) and density (71%) Reduced colon edema (77%), inflammation (57%), gland loss (79%), hyperplasia (81%), neutrophil score (81%), mucosal thickness (75%), summed histopathology score (70%) Efficacy associated with reduced ALC (41% 24 hr post-dose) Comparable results to cyclosporine, TNF Ab positive controls
MCD4-RPT-3	CD4+ adoptive transfer in SCID mice	0.3, 0.6, 1.2 mg/kg QD PO (d21-d41)	Reduced colon density (40%; 1.2 mg/kg) Improved distal colon erosion (all doses; 80 – 90%) Reduced mucosal thickness (0.3 and 1.2 mg/kg; 45 – 49%) Reduced levels of multiple colon cytokines
MCD4-RPT-4	CD4+ adoptive transfer in SCID mice	1.2 mg/kg QD PO (d21-d48)	The positive control, cyclosporine did not significantly affect clinical or histopathological parameters. RPC1063 was without significant effect on clinical or histopathological parameters. The positive control's lack of effect classifies this as a failed study.
IBD-RPI-10	Rat TNBS	0.1, 0.3, 1 mg/kg QD PO (d0-d6)	Improved body weight and animal health/behavior Reduced total colonic score (1 mg/kg; 54%) Improved colon density (0.3, 1 mg/kg; ≤ 70%) Improved colon disease scores (0.3, 1 mg/kg; ≤ 54%)
IBD-RPI-11	Rat TNBS	1 mg/kg QD PO (d0-d6)	Improved body weight and animal health/behavior Improved colon length and weight Reduced total colonic score (50%) Return to normal bowel function by day 3

Ab = antibody; ALC = absolute lymphocyte count; d = study day; hr = hours; PO – per os (oral); QD = quaque die (once daily); TNBS = 2,4,6-Trinitrobenzenesulfonic acid; TNF = tumor necrosis factor.

Efficacy of Ozanimod in the Severe Combined Immunodeficient Mouse Adoptive Transfer Model of Inflammatory Bowel Disease

Female SCID mice were each injected intraperitoneally with approximately 4 x 105 splenic CD4+CD45RB^{high} T lymphocytes isolated from female BALB/c mice. Twenty-one days later, mice were randomized into groups of N = 10 based on body weight loss relative to day 0. Once daily oral dosing of vehicle (5% DMSO/5% Tween 20 in 0.1N HCl) or ozanimod formulated in vehicle commenced on study day 21 and continued for 21 consecutive days thereafter. The positive control, cyclosporine A was formulated in 1% carboxymethylcellulose and administered orally once daily. A hamster anti-mouse tumor necrosis factor (TNF) antibody (TN3-19.12) served as a non-mechanistic positive control and was administered at 300 µg per mouse (once-weekly, intraperitoneal). 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.

In study MCD4-RPT-1, ozanimod was assessed in mice at 1.2 mg/kg (orally administered), a dose which approximated the estimated effective dose of 1 mg/kg in mice based on a reduction of circulating lymphocyte counts. Figure 5.2.2.1 illustrates that the increase in colon density, indicative of inflammation in vehicle-treated mice, was attenuated significantly by 71% in ozanimod-treated mice. This effect was

numerically greater but statistically similar to cyclosporine and TNF-α positive controls (48% – 54% attenuation).

Figure 1: Colon Density Values for Severe Combined Immunodeficiency Mice with Adoptive Transfer Inflammatory Bowel Disease Treated with Ozanimod
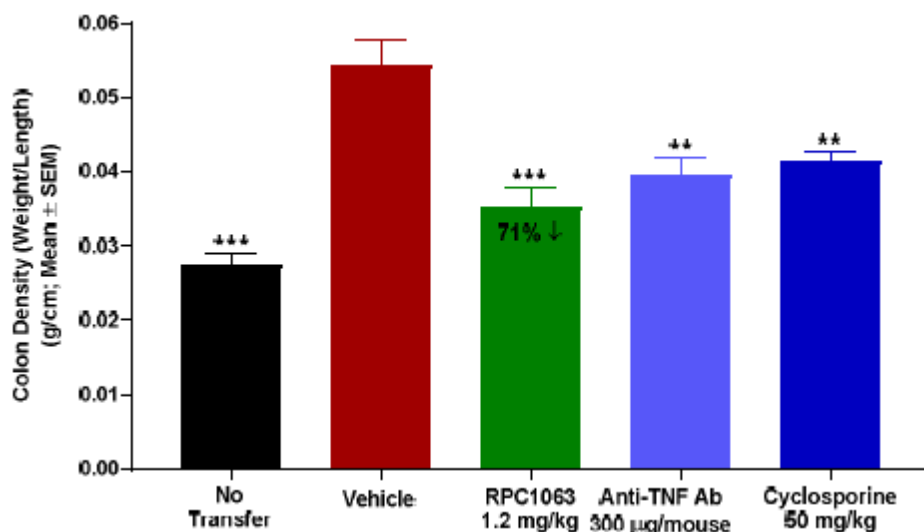
Ab = antibody; RPC1063 = ozanimod; SEM = standard error of the mean; TNF = tumor necrosis factor.

**, *** $p < 0.01$ and 0.001, respectively, compared to Vehicle (one-way analysis of variance [ANOVA] with Dunnett's multiple comparisons post-test); N = 10 except the no transfer group (N = 4).

This study also included statistical analysis of additional investigative compounds. RPC1063 and cyclosporine were administered by oncedaily oral gavage. The anti-TNF Ab was administered by once-weekly intraperitoneal injection. Group mean values are displayed with error bars denoting SEM.

In support of an anti-inflammatory effect consistent with engagement of $S1P_1$ pharmacology, mice treated with ozanimod exhibited decreased numbers of circulating lymphocytes 24 hours after the final dose that were similar to cyclosporine and TNF-α positive controls. Under these conditions, the 41% decrease in circulating lymphocytes observed with ozanimod-treated mice is consistent with that observed 24 hours post-final dose in EAE mice (Report 20091001-1d) and normal rats (Report RP-PH-005-1.0 Amendment 1) with a maximum decrease in mice at this dose of approximately 80% (Report RP-PK-002).

The individual and summed histological scores of inflammation, gland loss, hyperplasia, neutrophil score, and distal mucosal thickness that were all significantly attenuated by ozanimod and both positive controls were presented. The distal colon mucosal thickness in SCID mice with adoptive transfer was significantly reduced similar to no transfer and the cyclosporine and TNF-α positive controls.

Figure 2: Colon Histopathology Scores (A) and Distal Colon Mucosal Thickness (B) in Severe Combined Immunodeficient Mice with Adoptive Transfer Inflammatory Bowel Disease Treated with Ozanimod

A

B

Ab = antibody; RPC1063 = ozanimod; SEM = standard error of the mean; TNF = tumor necrosis factor.
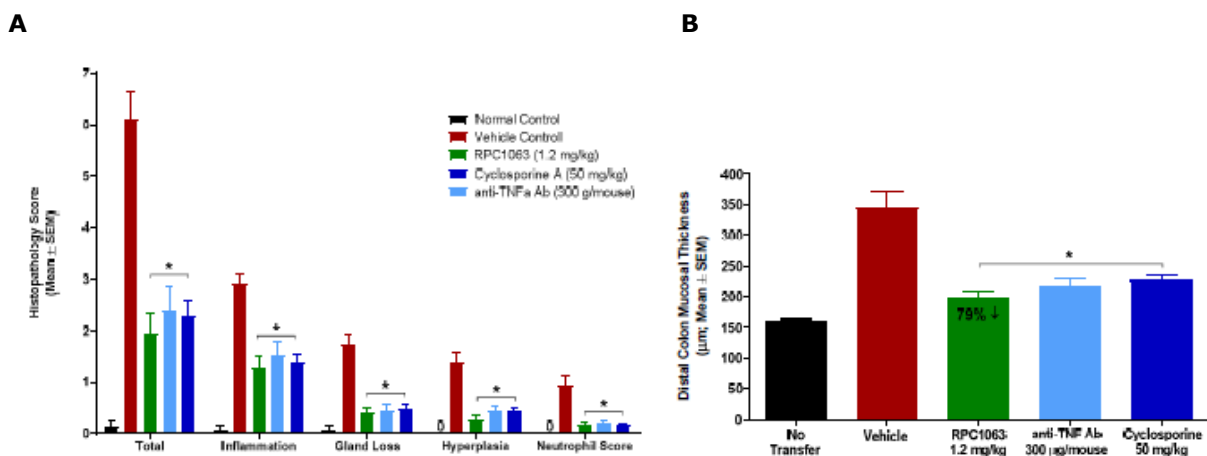
* $p < 0.05$ compared to Vehicle (one-way analysis of variance [ANOVA] with Dunnett's multiple comparisons posttest); N = 10 except the no transfer group (N = 4). This study also included statistical analysis of additional investigative compounds. RPC1063 and cyclosporine were administered by once-daily oral gavage. The anti- TNF Ab was administered by once-weekly intraperitoneal injection. Group mean values are displayed with error bars denoting SEM. Total score = sum of individual parameter scores for inflammation, gland loss, erosion and hyperplasia. '0' = score of 0 for the normal control group.

Two additional adoptive transfer inflammatory bowel disease studies were performed in SCID mice with ozanimod and are summarized below.

The dose-response effects of ozanimod (0.3, 0.6 and 1.2 mg/kg) are detailed in Report MCD4-RPT-3, a study performed under the same conditions as Report MCD4-RPT-1. Although the severity of disease was greater than in Report MCD4-RPT-1 (e.g., 3.125-fold vs. 2-fold increases in colon density values), 1.2 mg/kg ozanimod still reduced elevated colon density values significantly by 40% (cf. 71% in MCD4-RPT-1) comparable to cyclosporine positive control (49%). Although ozanimod at 0.3 mg/kg tended to reduce colon density (34%), this was not statistically significant, and the 0.6 mg/kg group did not exhibit a similar trend (5%). Erosion of the distal colon and elevated distal colon mucosal thickness were attenuated significantly by ozanimod at 0.3 and 1.2 mg/kg and levels of inflammatory mediators (IFN-γ, IL-12 p70, IL-1β, IL-6, IL-8, IL-10 and TNF-α) were also reduced significantly in colon homogenates, in a dose-dependent manner (**Table 4**) and consistent with attenuation of histological inflammation by ozanimod at 1.2 mg/kg.

Table 4: Cytokine Levels in Colon Homogenates from Severe Combined Immunodeficient Mice with Adoptive Transfer Inflammatory Bowel Disease Treated for 21 Days with Ozanimod

Group	IFN-γ	IL-10	IL-12 p70	IL-1β	IL-6	IL-8	TNF-α
No Transfer	1.10 ± 0.72 *	0.00 ± 0.00 *	0.00 ± 0.00 *	26.64 ± 3.84 *	1.39 ± 0.91 *	52.99 ± 3.31 *	0.09 ± 0.09 *
Vehicle	456.2 ± 38.95	17.36 ± 3.18	11.33 ± 4.96	6416 ± 468	230.8 ± 32.76	6482 ± 746.4	123.9 ± 13.75
Cyclosporine	154.1 ± 28.1 *	2.53 ± 1.30 *	0.00 ± 0.00 *	1307 ± 334.2 *	41.96 ± 8.86 *	1267 ± 478.6 *	23.44 ± 4.61 *
Ozanimod (0.3 mg/kg)	388.8 ± 75.96	4.84 ± 2.11 *	0.00 ± 0.00 *	2812 ± 449.2 *	137.5 ± 26.32 *	4515 ± 772.2	82.06 ± 15.07 *
Ozanimod (0.6 mg/kg)	398.97 ± 54.7	6.20 ± 3.27 *	0.00 ± 0.00 *	2241 ± 341.3 *	157.6 ± 43.81	3658 ± 618.4 *	58.48 ± 8.86 *
Ozanimod (1.2 mg/kg)	266.5 ± 43.6 *	0.00 ± 0.00 *	0.00 ± 0.00 *	802.6 ± 137.0 *	49.12 ± 8.49 *	3423 ± 650.6 *	± 3.89 *

IFN-γ = interferon-gamma; IL = interleukin, TNF-α = tumor necrosis factor-alpha.

Units: pg/mL (200 mg distal colon tissue sample), mean ± S.E.M.

* $P < 0.05$ ANOVA vs vehicle control; N = 10 per group

An additional adoptive transfer study (Report MCD4-RPT-4) was conducted under different conditions (mice from a different vendor, 49- vs. 42-day duration) and due to a lack of statistically significant protection by the positive control cyclosporine, is considered to be a failed study.

Efficacy of Ozanimod in the 2,4,6-Trinitrobenzenesulfonic Acid (TNBS) Rat Model of Inflammatory Bowel Disease

Male Sprague Dawley rats were fasted for 24 hours, weighed, and randomized into groups (N = 8). Inflammation was induced by instilling 64 mg/kg TNBS (5% v/v picrylsulfonic acid, 45% v/v aqueous TNBS, 50% v/v ethanol) intra-rectally into the colon under isoflurane anesthesia. Two hours after TNBS instillation, cohorts of rats were orally administered vehicle (5% DMSO/5%Tween 20 in 0.1N HCl), ozanimod at 0.1, 0.3, or 1 mg/kg formulated in vehicle or prednisolone 10 mg/kg (positive control) formulated in water. Animals were orally dosed once daily for 7 consecutive days. The doses of ozanimod were chosen to span the 0.3 mg dose that significantly lowered lymphocyte counts in rats. Body weight, clinical observations, and fecal pellets were assessed daily. 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. A composite "colon disease score" was derived for each rat via assessment of the number of adhesions and strictures, the number and size of ulcers, and the colon wall thickness (Report IBD-RPI-10).

During the study, two animals died in each of the TNBS cohorts treated with ozanimod 0.1 mg/kg and vehicle. This is not unexpected in this aggressive model with deaths often related to intestinal rupture as a result of severe TNBS-induced intestinal inflammation. Both deaths in the vehicle group were associated with intestinal rupture and whilst this was not the case for ozanimod at 0.1 mg/kg, both animals had lost approximately 30% of their starting body weight and were found dead immediately prior to scheduled sacrifice.

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 this was statistically significant at the 1 mg/kg dose. In contrast, body weight loss in the prednisolone positive control group was not different from the vehicle control. In addition to maintaining body weight, it is noteworthy that rats in the group treated with 1 mg/kg ozanimod were reported to exhibit improved spontaneous behaviors relative to the TNBS

vehicle controls. Moreover in these animals, and those dosed with 0.3 mg/kg, ozanimod significantly and dose dependently reduced the increased colon density (≤ 70%; **Figure 3**) and total colon disease (≤ 54%; **Figure 3**) scores induced by TNBS treatment.

Figure 3: Colon Density Values (A) and Scores (B) in Rats with TNBS-induced Inflammatory Bowel Disease Treated with Ozanimod
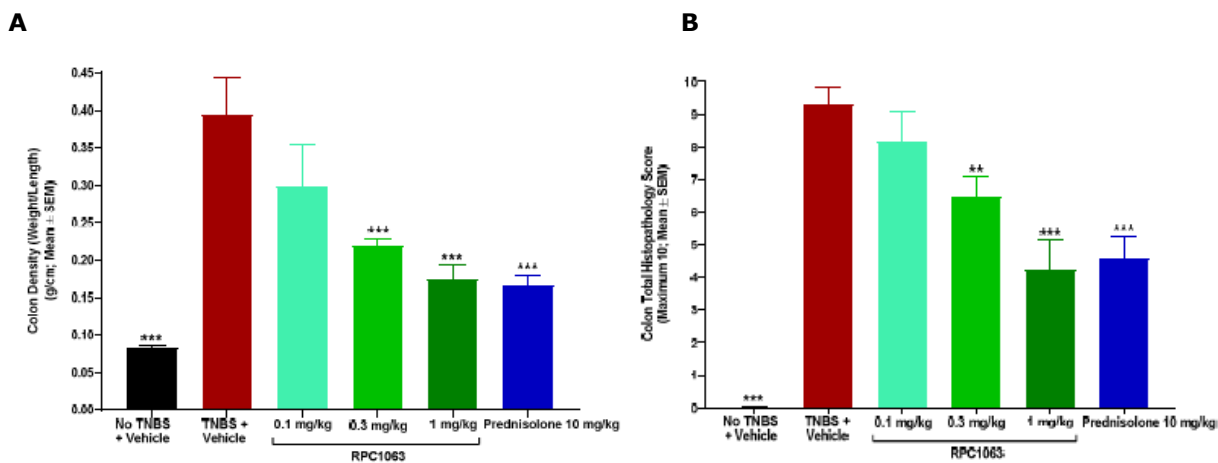
RPC1063 = ozanimod; SEM = standard error of the mean; TNBS = 2,4,6-trinitrobenzene sulfonic acid.

* $p < 0.05$ compared to TNBS Vehicle (Student's t-test); N = 8 except the TNBS vehicle group (N = 6). This study also included statistical analysis of additional investigative compounds. RPC1063 and prednisolone were administered by once-daily oral gavage. Group mean values are displayed with error bars denoting SEM.

Total colon disease score (maximum = 10) is the summed total of individual scores for adhesions (maximum 2), strictures (maximum 3), ulcers (maximum 3) and thickness (maximum 2).

Source: Report IBD-RPI-10.

An additional rat TNBS study was performed (Report IBD-RPI-11) in which the efficacy of ozanimod at 1 mg/kg in IBD-RPI-10 was replicated; for example, body weight loss was significantly attenuated (days 1 - 4, day 6), colon weight gain was reduced by 68% (cf. 50% in Report IBD-RPI-10), and total colon disease score was attenuated by 50% (cf. 54% in Report IBD-RPI-10). Furthermore, there was a return to normal bowel function by day 3 and similar observations of improved animal health and behavior.

Secondary pharmacodynamic studies

No new secondary pharmacodynamic studies were submitted this was considered acceptable by the CHMP.

Safety pharmacology programme

No new safety pharmacology studies have been submitted for this line extension. The safety pharmacology studies submitted in course of the initial MAA for the MS indication are considered sufficient.

Pharmacodynamic drug interactions

No studies have been submitted this is considered acceptable by the CHMP

2.2.3. Pharmacokinetics

No new pharmacokinetic studies have been performed for the proposed indication for treatment of UC and are not deemed necessary by the CHMP.

2.2.4. Toxicology

Single dose toxicity

No new studies were submitted this was considered acceptable by the CHMP.

Repeat dose toxicity

Both, MS and UC are immune mediated chronic diseases. As for treatment of MS, treatment of UC requires long-term treatment. The recommended doses and dosing regimen are the same for MS and UC. The ozanimod-induced reduction of lymphocytes migration into the CNS and intestine is suggested to be involved in the mechanism of its therapeutic effects in MS and UC. There are no meaningful differences in the pharmacokinetic parameters in patients with MS or UC.

Considering these points, the safety studies submitted for the MS indication is also relevant for the UC indication. Furthermore, the safety margins calculated for treatment of MS are also applicable for UC.

No further repeat-dose toxicity studies are considered necessary

Genotoxicity

The genotoxicity studies have been conducted and submitted for the initial MAA for the MS indication. These studies are also sufficient for the new proposed UC indication.

The information in section 5.3 of the SmPC is appropriate.

Carcinogenicity

The carcinogenicity studies have been conducted and submitted for the initial MAA for the MS indication. These studies are also sufficient for the new proposed UC indication.

The information in section 5.3 of the SmPC is appropriate.

Reproduction toxicity

No new data has been submitted in this application. Ozanimod induces embryolethality and teratogenicty in rats and rabbits at exposures with low or absent safety margin compared to the human exposure at the maximum dose of 0.92 mg ozanimd. Zeposia is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. The existing contraindication during pregnancy and in women of childbearing potential is also considered justified for the UC indication. There are alternative therapeutics with more experience and/or a better safety profile available for the treatment of UC during pregnancy. Therefore, the existing wording in section 4.6 is agreed also in view of the extension of indication for treatment of UC.

Toxicokinetic data

No new data were submitted this was considered acceptable by the CHMP.

Local tolerance

No new data were submitted this was considered acceptable by the CHMP.

Other toxicity studies

Immunotoxicity assessment identified the expected pharmacological action of decreased circulating lymphocyte count and also an inhibitory effect on primary and secondary T-dependent IgG antibody responses.

Ozanimod and metabolites were negative for in vitro signals of phototoxicity.

Juvenile

Repeated Dose Juvenile Toxicity Study in Rats

Ozanimod was administered via oral gavage to male and female rats at dosage levels of 0.3, 3, and 10 mg/kg/day for a period of at least 10 weeks beginning on PND 21 (Report 1840-011).

All animals survived to the scheduled necropsies. There were no changes that were considered test article-related in clinical observations, mean body weight, ophthalmoscopy examinations, sexual maturation, learning and memory (as measured by passive avoidance evaluations), coagulation times, fibrinogen concentration, urinalysis endpoints, bone length and density, or macroscopic observations at necropsy.

Ozanimod administration resulted in non-adverse treatment-related changes. These included decreased ease of removal from cage in males, decreased food consumption in males, increased mean basic movement, mean fine movement, and mean total distance in females, decreased circulating lymphocyte counts, increased chloride concentration, and decreased mean absolute spleen weights and thymus weights.

Histologic findings in this study were similar to adult rats (pulmonary alveolar histiocytosis, decreased corticomedullary ratio of the thymus and depletion of periarteriolar lymphocytes in the spleen). Similar to adult rats, the histologic changes partially to fully reversed following a 2-week non-dosing period. No new target organs were identified in the definitive juvenile rat toxicity study. In conclusion, the NOAEL was 10 mg/kg/day, the highest dose tested in this study.

Immunotoxicology

Repeated Dose Juvenile Immunotoxicology Study in Rats

Oral administration of ozanimod to juvenile Sprague-Dawley rats was initiated at 21 days of age with continued daily administration for 33 days (Report 73508) with 14-day recovery groups at doses of 0.3, 3, or 10 mg/kg/day. Keyhole Limpet Hemocyanin (KLH) at 1 mg/mL was administered subcutaneously for a total dose of 100 µg/animal/day split equally between 2 dorsal injection sites on Days 7 and 25.

A dose-dependent decrease in white blood cell counts driven mainly by a decrease in total lymphocytes was noted in all ozanimod dose groups. Both the primary and secondary T-cell dependent anti-KLH IgG antibody responses (TDAR) were inhibited in a statistically significant manner following ozanimod administration by oral gavage at doses of 3 and 10 mg/kg/day. A dose-related decrease in the absolute number of peripheral T and B lymphocytes was observed on Days 14 and 33 after administration of ozanimod. These returned toward the control values at the end of the recovery period (Day 47). Due to

decreased TDAR responses at 3 mg/kg/day, the low dose of 0.3 mg/kg/day was determined to be the NOAEL.

Repeated Dose Immunotoxicology Study in Adult Rats

Ozanimod was administered at dose levels of 0.2, 0.7, and 2 mg/kg/day for 33 consecutive days by oral gavage to Sprague-Dawley rats (Report 72864). Keyhole Limpet Hemocyanin (at 1 mg/mL) was administered subcutaneously to all TDAR animals at a volume of 700 μL/animal on Days 7 and 25.

An inhibitory effect on both the primary and secondary TDAR was present following administration of the test article at the two highest doses; however, there was no statistically significant inhibition observed at the lowest ozanimod dose level of 0.2 mg/kg/day. A dose related decrease (minimal at the low dose) in the absolute number of peripheral T and B lymphocytes was observed after administration of ozanimod. Slight to moderate increases in the number of circulating natural killer (NK) cells were noted in males while no changes were observed in females in response to ozanimod. Spleen weights were lower in the 2 mg/kg/day group. Due to the decreased TDAR responses at 0.7 mg/kg/day, the low dose of 0.2 mg/kg/day was determined to be the NOAEL.

2.2.5. Ecotoxicity/environmental risk assessment

The purpose of this type II variation is to extend the currently approved indication to include the treatment of adult patients with moderately to severely active ulcerative colitis (UC). The calculation of the Predicted Environmental Concentration (PEC) has been based on a systematic review of population-based studies to estimate the prevalence. The applicant calculated the prevalence as 285 per 100,000 population based on the highest prevalence measured in a European country and the proportion of patients (50%) with moderate and severe ulcerative colitis. This result has been established on a publication of Burisch (2019) where over the first 5-years disease the proportion of patients (Western Europe [n=591, 82%] and Eastern Europe [n=126, 18%) with moderate and severe disease decreased from 41% to 11% from year 1 to year 5. The PECSW value for UC is 0.0013 μg/L.

The updated PEC value has been amended regarding the sum of the PEC-values for the previously authorized indication RRMS and new proposed indication (UC). The calculated value (0.0060 μg/L) is below the action limit of 0.01 μg/L.

2.2.6. Discussion on non-clinical aspects

To support the use of Ozanimod in patients with UC, in vivo pharmacodynamic studies in rodent models of colitis were submitted with this application. Furthermore, an in vitro radioligand binding PD-study is submitted which has not been previously assessed.

No further new non-clinical studies were submitted with this application. With regard to the non-clinical safety, pharmacokinetic and toxicology studies, the applicant refers to the studies submitted with the initial MAA for treatment of MS.

The newly submitted in vitro radioligand binding affinity study was performed in membranes from CHO cells stabliy expressing human cloned $S1P_1$ and $S1P_5$. The results suggest that the metabolites of ozanimod are able to compete for the same binding site as the parent molecule and that ozanimod and its metabolites bind to the orthosteric binding site for the endogenous agonist, S1P. These data are consistent with those of the previously submitted in vitro studies in that they demonstrate a higher activity of ozanimod and metabolites for $S1P_1$ than for $S1P_5$ and show inactivity of the major human

metabolite RP101124. Furthermore, the study provides a deeper insight into the binding site and better understanding of the mechanism of action of ozanimod and metabolites.

The applicant has submitted a range of in vivo pharmacodynamics studies in rodent models of IBD to support the proposed indication for treatment of UC. These included studies in naïve T-cell adoptive transfer in SCID mice and TNBS-induced colitis in rats.

In the mouse model ozanimod showed effectiveness at a dose of 1.2 mg/kg/day as demonstrated by significant reduction in lymphocytes. Furthermore, histopathology parameters associated with IBD (inflammation, gland loss, hyperplasia, neutrophil score, and distal mucosal thickness) and tissue cytokine levels were all significantly attenuated by ozanimod at 1.2 mg/kg/day. In a dose response study no clear dose-response relationship has been shown. For most parameters the dose of 0.3 mg/kg was more effective than the dose of 0.6 mg/kg/day. However, the dose of 1.2 mg/kg/day showed significant effectiveness.

In the rat model ozanimod showed effectiveness at a dose of $\geq$0.3 mg/kg/day. Ozanimod significantly and dose dependently reduced the increased colon density ($\leq$ 70%) and total colon disease ($\leq$ 54%) scores induced by TNBS treatment. The dose of 0.3 mg/kg/day has also been shown to reduce lymphocytes in rats.

The studies in animal models of IBD in mice and rats have some limitations as only ozanimod has been investigated. No studies have been performed with the metabolites, especially the active human metabolites. Difference in the quantitative metabolic profile have been observed between human and rodents. For example, in rodents the two major human active metabolites CC112273 and CC1084037 were present at significantly lower levels than in humans. However, evaluation of the active metabolites (CC112273, RP101988, RP101075, and RP101442) in EAE mouse model of MS showed efficacy similar to that of ozanimod and was associated with a significant reduction (except for CC112273) in lymphocyte counts. Furthermore, in vitro studies also demonstrated that the active metabolites all have a similar activity profile to the parent compound in that they are potent robust agonists for $S1P_1$ and $S1P_5$ and that they are able to compete for the same binding site as the parent molecule within $S1P_1$ and $S1P_5$ by binding to the orthosteric binding site for the endogenous agonist, S1P. Therefore, it is highly likely that the active metabolites of ozanimod show similar efficacy in the rodent models of IBD.

No new pharmacokinetic studies have been performed for the proposed indication for treatment of UC and are not deemed necessary. There are no meaningful differences in the pharmacokinetic parameters in patients with MS or UC.

Further safety studies are also not considered necessary. Both, MS and UC are immune mediated chronic diseases. As for treatment of MS, treatment of UC requires long-term treatment and the recommended doses and dosing regimens are the same for both indications. The ozanimod-induced reduction of lymphocyte migration into the CNS and intestine is suggested to be involved in the mechanism of its therapeutic effects in MS and UC. Considering these points, the safety studies submitted for the MS indication are also relevant for the UC indication. Furthermore, the safety margins calculated for treatment of MS are also applicable for UC. The wording proposed for section 5.3 of the SmPC is agreed.

According to the SmPC, Zeposia is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Ozanimod induces embryolethality and teratogenicity in rats and rabbits at exposures with low or absent safety margin compared to the human exposure at the maximum dose of 0.92 mg ozanimd. The vascular findings (generalized edema (anasarca) in the rat and great vessel abnormalities in the rabbit) are likely mediated by the $S1P_1$ activity of ozanimod and its active metabolites. Therefore, these finding should be regarded as of human relevance. The contraindication during pregnancy and in women of childbearing potential is considered justified. There are alternative therapeutics with more experience and/or a better safety profile available for the

treatment of UC during pregnancy. Therefore, the wording proposed for section 4.6 is agreed also in view of the extension of indication for treatment of UC.

Zeposia is only indicated for treatment of adult patients with MS and UC. Therefore, the juvenile animal studies are currently of lower relevance. However, in these studies no effects different from those seen in adults were observed

Ozanimod HCl is not expected to pose a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

From a non-clinical point of view there are no objections against the approval of Zeposia for the indication "Treatment of patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or are intolerant to either conventional therapy or a biologic agent".

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Ozanimod.

Considering the above data, ozanimod is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The applicant is submitting new data both on clinical pharmacology, as well as safety and efficacy as indicated above. The clinical pharmacology studies newly submitted are displayed in the following overview table:

Table 5 : Clinical pharmacology studies submitted in support of the proposed variations

Protocol Number Indication Phase Regions	Study Title/Design	Study Population	Dosing Regimen(s)	Subject Exposure by Treatment/ Overall Demographics	Study Status/ Date CSR Completed/ Disposition	Location
RPC01-1915 NA Phase 1	A Phase 1, Multi-center, Extension Study to Further Evaluate the Safety, Pharmacodynamics and Pharmacokinetics of Ozanimod and Active Metabolites in Healthy Adult Subjects	From RPC01-1912 and RPC01-1914: healthy men and nonpregnant, nonlactating women, ages 18 to 55 years, inclusive From RPC01-1913, healthy men and nonpregnant, nonlactating women, ages 25 to 55 years, inclusive.	No IP (ozanimod) was administered in this study	Total 232 subjects: Parent protocol RPC01-1912: 100 subjects Parent protocol RPC01-1913: 79 subjects Parent protocol RPC01-1914: 53 subjects Refer to parent protocols for demographics	Completed CSR: 16 Sep 2019 Final disposition: Dosed = 0 Discontinued = 1 Completed = 231	5.3.3.4 Extrinsic Factor PK Study Reports
RPC-1063-CP-001 NA Phase 1	A Phase 1, Randomized, Parallel-group, Open-label Study to Evaluate the Effect of Cyclosporine on the Single-dose Pharmacokinetics of Ozanimod and Major Active Metabolites in Healthy Adult Subjects	Healthy men and nonpregnant, nonlactating women, ages 18 to 55 years, inclusive	Treatment Group A (reference): A single oral dose of ozanimod 0.46 mg Treatment Group B (test): A single oral dose of ozanimod 0.46 mg plus a single oral dose of cyclosporine 600 mg	20 subjects per treatment group were enrolled. Overall demographics: **Sex:** Male: 25 (62.5%); Female: 15 (37.5%) **Age (yrs):** Mean (SD): 39.3 (9.56); Min, Max: 19, 55 **Race:** Native American or Alaskan Native: 0 (0%) Asian: 1 (2.5%) Black: 16 (40.0%) White: 22 (55.0%) Other: 1 (2.5%)	Completed CSR: 22 Sep 2020 Final disposition: Dosed = 40 Discontinued = 1 Completed = 39	5.3.3.4 Extrinsic Factor PK Study Reports

CSR = clinical study report; IP = investigational product; Max = maximum; Min = minimum; NA = not applicable; PK = pharmacokinetic; SD = standard deviation; yrs = years.

The table does not include Study RPC01-1001 which is a supplemental analysis of a previously submitted study with the study title: "A Supplemental Biomarker Analysis to: A Phase 1, Multi-center, Randomized, 12-week, Open-label Study to Evaluate the Multiple Dose Pharmacokinetics and Pharmacodynamics of RPC1063 in Patients with Multiple Sclerosis."

Three further study reports are submitted investigating further the population PK and PK-PD relationship, as well as the specifics of dose-response with regard to the results of the phase 2 study. The data and data analyses are included in the studies CLG-Certara-UC-358-1, and CLG-Certara-UC-358-2, as well as in the additional Dose Estimation Report to study RPC01-202 (see below).

An overview on the clinical efficacy and safety studies submitted is given in the following tables:

Table 6: Clinical Studies Supporting the Efficacy of Ozanimod in Ulcerative Colitis

Protocol Number / Study Type / No. of Centers[a] / Location	Study Dates (Start–Completion)[b]	Study Design / Control Type	Study Population Randomized/ Completed/ Discontinued	Dosing Route and Regimen	Demographics	Primary Endpoint

RPC01-202
 	
Phase 2 Efficacy and Safety (parent study)
 	
No. of Centers: 57
 	
Regions: Europe, North America, and Asia-Pacific region
	IP and MP:
	26 Dec 2012 - 10 Mar 2015
	
	OLP:
	17 May 2013 - 29 Aug 2019
		Multicenter study comprising a randomized, double-blind, placebo-controlled parallel-group Core Period (IP and MP) and an OLP
		
		Core Period: Subjects who completed the 9-week IP and who were responders entered a 24-week MP.
		
		OLP: Subjects who were nonresponders 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 extended treatment with ozanimod.
			Adult subjects with moderately to severely active UC (Mayo score 6 to 12 inclusive with endoscopy subscore ≥ 2) confirmed by endoscopic and histologic evidence.
			IP:
			Randomized: 199
			Treated: 197
			Completed: 186
			Discontinued: 11
			MP:
			Entered: 103
			Completed: 91
			Discontinued: 12
			OLP:
			Enrolled: 170
			Completed: 14
			  Completed Week 56: 123
			  Completed Week 104: 102
			  Completed Week 152: 84
			  Completed Week 200: 71
			  Completed Week 248: 24
			Discontinued/withdrew consent: 156 (54 of these subjects rolled into Study RPC01-3102)
				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.
				IP (9 weeks):
				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.
				MP (24 weeks):
				Subjects continued same treatment received in IP for an additional 24 weeks.
				OLP (Week 33 onwards):
				Ozanimod 1 mg QD PO
					IP:
					Sex, n (%):
					Male: 115 (58.4)
					Female: 82 (41.6)
					Age (yrs):
					Mean (SD): 40.8 (11.82)
					Min, Max: 18, 73
					Race, n (%):
					White: 182 (92.4)
					Asian: 8 (4.1)
					Black: 4 (2.0)
					Other: 2 (1.0)
						IP:
						Proportion of subjects in clinical remission at Week 9 (4-component Mayo score)

Protocol Number / Study Type / No. of Centers[a] / Location	Study Dates (Start–Completion)[b]	Study Design / Control Type	Study Population Randomized/ Completed/ Discontinued	Dosing Route and Regimen	Demographics	Primary Endpoint
RPC01-3101 Phase 3 Efficacy and Safety (parent study) No. of Centers: 370 Regions: North America, Europe, Asia Pacific, South America, South Africa	IP and MP: 12 Aug 2015 - 27 Mar 2020	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 rerandomized to an additional 42 weeks of double-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 nonresponders 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.	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 (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 Assigned dose for 9 weeks following 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 assigned dose until end of Induction Period. 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 rerandomized 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.	IP Cohort 1 Sex, n (%): Male: 388 (60.2) Female: 257 (39.8) Age (yrs): Mean (SD): 41.6 (13.56) Min, Max: 18, 74 Race, n (%): White: 562 (87.1) Black or African American: 18 (2.8) Asian: 53 (8.2) Other: 12 (1.9) IP Cohort 2 Sex, n (%): Male: 214 (58.3) Female: 153 (41.7%) Age (yrs): Mean (SD): 42.1 (13.72) Min, Max: 18, 74 Race, n (%): White: 336 (91.6) Black or African American: 10 (2.7) Asian: 12 (3.3) Other: 9 (2.5)	IP: Proportion of subjects in clinical remission at Week 10 (3-component Mayo score) MP: Proportion of subjects in clinical remission at 52 weeks (3-component Mayo score)

Table 7: Clinical Studies Supporting the Efficacy of Ozanimod in Ulcerative Colitis (continued)

Protocol Number / Study Type / No. of Centers[a] / Location	Study Dates (Start–Completion)[b]	Study Design / Control Type	Study Population Randomized/ Completed/ Discontinued	Dosing Route and Regimen	Demographics	Primary Endpoint

RPC01-3102
 	
Phase 3 Safety (OLE)
 	
No. of Centers: 229
 	
Regions: Europe, North America, Asia Pacific, South Africa, South America
	02 Dec 2015 - ongoing (data cutoff 31 Mar 2020)	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
			Subjects who previously participated in a UC trial of ozanimod (ie, 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
				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 through end of study: ozanimod 1 mg QD PO
					Subjects from 3101:
					Sex, n (%):
					Male: 486 (59.2)
					Female: 335 (40.8)
					Age (yrs):
					Mean (SD): 41.7 (13.65)
					Min, Max: 18, 74
					Race, n (%):
					White: 731 (89.0)
					Black: 24 (2.9)
					Asian: 54 (6.6)
					Other: 12 (1.5)
					
					Subjects from 202:
					Sex, n (%):
					Male: 32 (59.3)
					Female: 22 (40.7)
					Age (yrs):
					Mean (SD): 42.4 (11.55)
					Min, Max: 18, 64
					Race, n (%):
					White: 48 (88.9)
					Black: 1 (1.9)
					Asian: 3 (5.6)
					Other: 2 (3.7)
						Long-term safety and efficacy

IP = Induction Period; max = maximum; min = minimum; MP = Maintenance Period; No. = number; OLE = Open-label Extension; OLP = Open-label Period; PO = orally or by mouth; QD = once daily; SD = standard deviation; UC = ulcerative colitis.
[a] Number of centers with subjects randomized (controlled studies) or enrolled (open-label studies).
[b] Start date = first subject's first visit date. Completion date = last subject's last visit date. Ongoing studies include data as of the indicated cutoff date.

Three ozanimod dosage strengths were prepared for clinical investigation: 0.25 mg ozanimod hydrochloride (HCl) (equivalent to 0.23 mg ozanimod), 0.5 mg ozanimod HCl (equivalent to 0.46 mg ozanimod), and 1 mg ozanimod HCl (equivalent to 0.92 mg ozanimod). For the ease of reading, doses applied in clinical studies are referred to as ozanimod 0.25 mg, 0.5 mg and 1 mg, respectively, in the efficacy and safety part of this Report.

2.3.2. Pharmacokinetics

Pharmacokinetic interaction studies

One PK interaction study was submitted as part of this variation. Study RPC-1063-CP-001 was conducted to assess the impact of cyclosporine, a breast cancer resistance protein (BCRP) inhibitor, on the PK of the major active metabolites, CC112273 and CC1084037. This study provided additional data to supplement the results from a previously conducted drug interaction study [RPC01-1903]. The study has been assessed previously by the CHMP. In this study, coadministration with cyclosporine did not alter ozanimod exposure, but caused an approximate 2-fold increase in RP101988 area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration (AUC0-last). The impact on downstream major metabolites CC112273 and CC1084037 was unknown. Both metabolites in vitro were determined to not be substrates of BCRP. However, to assess the potential for increased RP101988 concentrations to lead to changes in the exposure of these downstream metabolites, a second drug interaction study (RPC-1063-CP-001) with cyclosporine was conducted.

Study number: RPC-1063-CP-001

A Phase 1, Randomized, Parallel-group, Open-label Study to Evaluate the Effect of Cyclosporine on the Single-dose Pharmacokinetics of Ozanimod and Major Active Metabolites in Healthy Adult Subjects

First subject enrolled: *04 Oct 2019*

Last subject completed: *29 Dec 2019*

Date of report: *22 Sep 2020*

Objectives:

The primary objective was to evaluate the effect of cyclosporine, an index inhibitor of BCRP, on the single-dose PK of ozanimod and its major active metabolites, CC112273 and CC1084037, in healthy adult subjects. The assessment of safety and tolerability and of the effect of cyclosporine on the single-dose PK of ozanimod's minor active metabolite, RP101988, were secondary and exploratory objectives respectively.

Study design

This was a Phase 1, randomized, parallel-group, open-label study. 40 healthy male or female subjects ($\geq$ 18 and $\leq$ 55 years of age, at least 50 kg, body mass index (BMI) within the range of 18.0 to 30.0 kg/m2, non-smoking within preceding 3 months) were to be enrolled and were to be randomized into 1 of the 2 treatment groups, with 20 subjects in each treatment group (1:1 randomization, sex as a stratifying factor) as follows:

-        Treatment Group A (reference): A single oral dose of ozanimod 0.46 mg (one ozanimod 0.46 mg capsule)

-         Treatment Group B (test): A single oral dose of cyclosporine 600 mg (six cyclosporine 100 mg capsules) followed immediately by a single oral dose of ozanimod 0.46 mg (one ozanimod 0.46 mg capsule).

Table 8: Investigational Products used in Study RPC-1063-CP-001

Table 1:   Investigational Products

Investigational Product Name	Unit Dose	Dosage Form	Route of Administration	Manufacturer	Lot Number	Expiration Date
Ozanimod (formerly referred to as RPC1063)	0.46 mg (equivalent to ozanimod HCl 0.50 mg)	Ozanimod (expressed as the HCl salt) was blended with microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate in opaque hard-gelatin capsule shells	Oral	Patheon, Inc.	19F0541	Apr 2020
Cyclosporine, USP Modified	100 mg	Capsule	Oral	Teva Pharmaceuticals USA	100011483	Feb 2021

HCl = hydrochloride; mg = milligram; USP = United States Pharmacopeia.
Source: Appendix 16.1.6

The investigational drugs were to be taken with approximately 240 mL of nonrefrigerated, noncarbonated water (additional water allowed if required for the subject to complete dosing) following an overnight fast of at least 10 hours. Subjects remained fasted and upright (ie, not be allowed to lie down) for 4 hours after dosing.

Eligible subjects were to be domiciled in the clinical research unit from Day -1 until after the last PK sample (at 336 hours after ozanimod dosing) was collected. Serial PK blood samples were to be collected predose (within 1 hour before ozanimod dosing) and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96,

120, 144, 168, 192, 216, 240, 264, 288, 312, and 336 hours following ozanimod dosing. Allowable windows for PK sample collection relative to dosing were: ± 10 minutes through 24 hours postdose; and ± 15 minutes after 24 hours.

Physical examinations, 12-lead electrocardiograms (ECGs), vital sign measurements, and clinical laboratory tests were to be performed and adverse events (AEs) and concomitant medications were to be monitored throughout the study to assess safety. A whole blood deoxyribonucleic acid (DNA) sample was to be collected from all eligible subjects for pharmacogenomic analysis (if warranted).

Subjects were to be contacted by telephone 60 ± 5 days after the dose of ozanimod for a follow-up safety assessment.

Results:

For 990 primary samples and 988 duplicate samples received, a total of 990 study samples (no duplicates) were analysed for RPC1063, CC112273, CC1084037, and RP101988.

The results from calibration curve standards and quality control samples met the acceptance criteria, demonstrating acceptable performance of the methods throughout the sample analysis period for 15 out of 16 runs. Run 9 (Re-injection of Run 8 for instrument qualification) was accepted for CC112273, and CC1084037. QCs did not meet acceptance criteria for RPC1063, the instrument was not considered qualified.

Pharmacokinetic Variables

Plasma drug concentrations and PK parameters were to be summarized descriptively (including arithmetic mean, SD, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric coefficient of variation, where appropriate) by treatment group and nominal time point (where appropriate).

The following PK parameters were estimated: C_{max}, T_{max}, $AUC_{0-tlast}$, AUC_∞

For ozanimod and RP101988 only: CL/F

For ozanimod only: Vz/F, $t_{1/2}$

The primary PK parameters were C_{max} and AUC (AUC_∞ for ozanimod and RP101988 and AUC_{last} for CC112273 and CC1084037).

To evaluate the effect of cyclosporine on the PK of ozanimod and its major active metabolites, an analysis of variance (ANOVA) was performed on the natural log-transformed primary PK parameters (C_{max}, AUC_{last} or $AUC_{0-\infty}$) of ozanimod, CC112273, CC1084037, and RP101988 using the PK Population (excluding subjects with major protocol violations that would impact PK assessments). The model included treatment group as fixed effect. The least squares geometric means for ozanimod alone (Group A, reference) and ozanimod + cyclosporine (Group B, test) was estimated from the model. The ratio (test to reference) and the corresponding 90% confidence intervals (CIs) were provided.

Statistical methods

No formal hypothesis testing was planned. Sample size calculation was based on the inter-subject variability (coefficient of variation [CV]) of < 48% for C_{max} and AUC for ozanimod, CC112273 and CC1084037 (RPC01-1912), a sample size of 18 subjects per treatment group (total of 36 subjects) would provide estimation of geometric mean ratio (test to reference) of the PK parameters with a 90% CI of (0.77, 1.30) assuming the true ratio of 1.

To account for potential dropout, 20 subjects were to be enrolled within each treatment group.

Conduct of the study

According to the Applicant the study was designed and monitored in accordance with procedures of the Sponsor's representative, which comply with the ethical principles of Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki. The Applicant states that there were no notable departures regarding compliance with applicable international GCP standards or relevant Celgene International II Sàrl (CIS II) or representative policies and procedures. It was ensured that monitoring procedures were to be performed before, during, and after the study.

The actual timepoint for data collections were used for the PK analysis. The types of deviations noted included: Assessments performed in the incorrect order (vital signs/ECG), Assessments performed out of allowable time window (ECG, Vitals Heart Rate, 60 day follow up,), Assessments not performed (Lab Sample at Follow up,), Women not of childbearing potential were given pregnancy tests, Hemolyzed PK samples (n =39), Concomitant medication usage noted with no corresponding AE documented (Tylenol, n=1 subject). PK sample time deviations were noted in 12 instances (1 minute, not within 24 hours post dose +/- 10 minutes: n=1), ECG not evaluable due to lead reversal,

Results

Disposition of Subjects

Overall, 40 subjects (100%) completed treatment: 20 subjects (100%) in the ozanimod 0.46 mg group and 20 subjects (100%) in the ozanimod 0.46 mg + cyclosporine 600 mg group. All 40 subjects (100%) were included in the PK and Safety Populations.

1 subject discontinued from ozanimod + cyclosporin (withdrawal by subject).

Demographic and Baseline Characteristics (Safety Population) were as follows (overall):

Age: 39.3 (mean, 19 – 55 years), 25/15 male/female, 1 Asian, 16 Black or African American, 1 Native Hawaiian or other Pacific Islander, 22 White, weight: 74.77 (52.5 – 90.3 kg), height: 169.7 (154.2 – 181.5 cm), BMI 26.10 (19.3 – 29.9 kg/m2) with little differences between the groups.

No subject reported receiving prior medications. Two subjects receiving ozanimod 0.46 mg and 6 subjects receiving ozanimod 0.46 mg + cyclosporine 600 mg received concomitant medications during the study for AEs. In addition, one subject receiving ozanimod 0.46 mg received paracetamol for an unspecified indication.

Pharmacokinetic results:

Mean plasma ozanimod, CC112273, CC1084037, and RP101988 concentration-time profiles by treatment group are presented in the following figures:

Figure 4: Mean concentration-time profiles by treatment of ozanimod, CC112273, CC1084037 and RP101988

Figure 1: Mean (± SD) Plasma Concentration-time Profiles for Ozanimod Following Oral Administration of a Single Dose of Ozanimod 0.46 mg Alone and Ozanimod Coadministered with Cyclosporine – Linear and Semi-log Plots (PK Population)
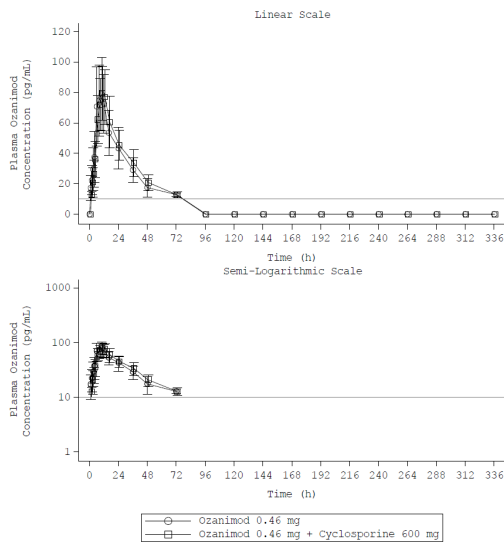
BLQ = below the limit of quantification; h = hours; LLOQ = lower limit of quantification; mg = milligram; ml = milliliter; pg = picogram; PK = pharmacokinetic; SD = standard deviation.
Notes: BLQ values were replaced with zero.
Solid line parallel to X-axis indicates the LLOQ (10.00 pg/mL) value.
Source: Figure 14.2.5.1.1

Figure 2: Mean (± SD) Plasma Concentration-time Profiles for CC112273 Following Oral Administration of a Single Dose of Ozanimod 0.46 mg Alone and Ozanimod Coadministered with Cyclosporine – Linear and Semi-log Plots (PK Population)

BLQ = below the limit of quantification; h = hours; LLOQ = lower limit of quantification; mg = milligram; ml = milliliter; pg = picogram; PK = pharmacokinetic; SD = standard deviation.
Notes: BLQ values were replaced with zero.
Solid line parallel to X-axis indicates the LLOQ (25.00 pg/mL) value.
Source: Figure 14.2.5.1.2

Figure 3: Mean (± SD) Plasma Concentration-time Profiles for CC1084037 Following Oral Administration of a Single Dose of Ozanimod 0.46 mg Alone and Ozanimod Coadministered with Cyclosporine – Linear and Semi-log Plots (PK Population)
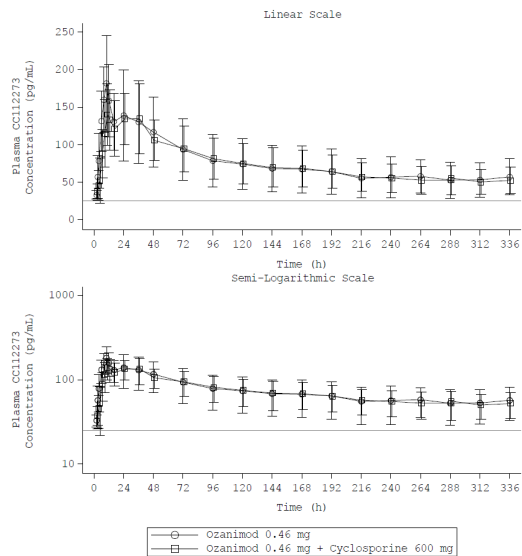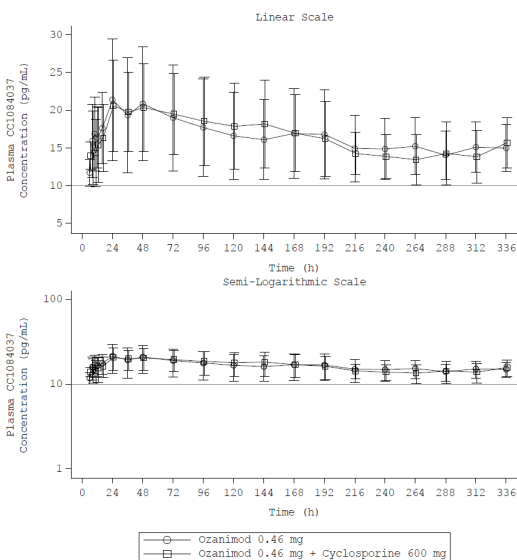

BLQ = below the limit of quantification; h = hours; LLOQ = lower limit of quantification; mg = milligram; ml = milliliter; pg = picogram; PK = pharmacokinetic; SD = standard deviation.
Notes: BLQ values were replaced with zero.
Solid line parallel to X-axis indicates the LLOQ (10.00 pg/mL) value.
Source: Figure 14.2.5.1.3

Figure 4: Mean (± SD) Plasma Concentration-time Profiles for RP101988 Following Oral Administration of a Single Dose of Ozanimod 0.46 mg Alone and Ozanimod Coadministered with Cyclosporine – Linear and Semi-log Plots (PK Population)
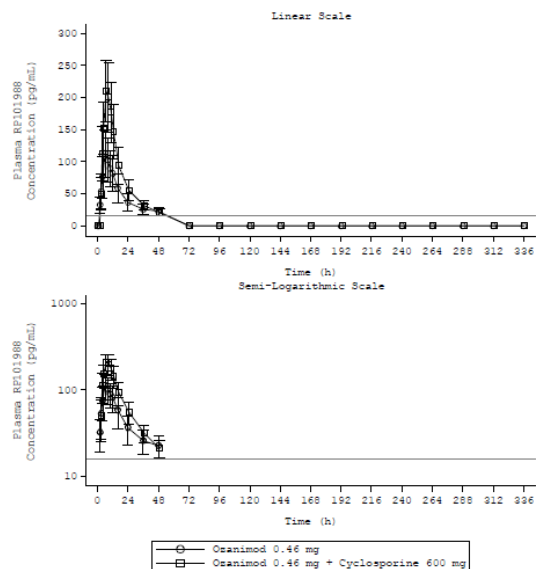
BLQ = below the limit of quantification; h = hours; LLOQ = lower limit of quantification; milligram = mg; ml = milliliter; pg = picogram; PK = pharmacokinetic; SD = standard deviation.
Notes: BLQ values were replaced with zero.
Solid line parallel to X-axis indicates the LLOQ (16.00 pg/mL) value.
Source: Figure 14.2.5.1.4

Summary statistics and the statistical analysis to assess the effect of cyclosporine on the PK of ozanimod and its metabolites are presented in the following tables.

Table 9: Summary Statistics of PK parameters for ozanimod and metabolites, single dose administration of 0.46 mg alone or co-administered with cyclosporine.

Table 4: Summary Statistics of Pharmacokinetic Parameters for Ozanimod and Metabolites Following Oral Administration of a Single Dose of Ozanimod 0.46 mg Alone or Coadministered with Cyclosporine (PK Population)

PK Parameter (unit)	Statistics	Ozanimod 0.46 mg	Ozanimod 0.46 mg + Cyclosporine 600 mg	CC112273 Ozanimod 0.46 mg	CC112273 Ozanimod 0.46 mg + Cyclosporine 600 mg	CC1084037 Ozanimod 0.46 mg	CC1084037 Ozanimod 0.46 mg + Cyclosporine 600 mg	RP101988 Ozanimod 0.46 mg	RP101988 Ozanimod 0.46 mg + Cyclosporine 600 mg
T_{max} (h)	n	20	20	20	20	20	19	20	20
	Median	10.0	10.0	10.0	20.0	24.0	36.0	6.00	6.00
	(Min, Max)	(6.00, 12.0)	(6.00, 12.0)	(8.00, 48.0)	(10.0, 36.0)	(10.0, 144)	(10.0, 72.0)	(6.00, 8.00)	(6.00, 10.0)
C_{max} (pg/mL)	n	20	20	20	20	20	20	20	20
	Mean (SD)	82.3 (24.6)	81.5 (17.8)	189 (62.7)	159 (40.8)	23.0 (7.58)	21.3 (7.59)	115 (37.5)	222 (46.7)
	CV%	29.9	21.9	33.1	25.6	32.9	35.6	32.5	21.0
AUC_{last} (pg*h/mL)	n	20	19	20	19	20	18	20	19
	Mean (SD)	2062 (679)	2195 (595)	24914 (10338)	24460 (7321)	4194 (2415)	4370 (2356)	1979 (741)	3415 (941)
	CV%	32.9	27.1	41.5	29.9	57.6	53.9	37.5	27.6
AUC_{inf} (pg*h/mL)	n	16	13	ND	ND	ND	ND	ND	ND
	Mean (SD)	2449 (796)	2837 (616)						
	CV%	32.5	21.7						
AUC_{0-168} (pg*h/mL)	n	ND	ND	ND	ND	15	16	ND	ND
	Mean (SD)					3061 (969)	2838 (1108)		
	CV%					31.7	39.0		
$t_{½}$ (h)	n	20	19	13	13	10	12	20	19
	Mean (SD)	19.2 (4.42)	20.6 (2.91)	285 (175)	282 (140)	272 (170)	390 (238)	15.3 (3.23)	13.1 (2.72)
	Median	18.0	21.0	245	268	214	326	14.7	13.6
	CV%	23.1	14.2	61.5	49.7	62.5	61.0	21.1	20.7

Table 4: Summary Statistics of Pharmacokinetic Parameters for Ozanimod and Metabolites Following Oral Administration of a Single Dose of Ozanimod 0.46 mg Alone or Coadministered with Cyclosporine (PK Population) (Continued)

PK Parameter (unit)	Statistics	Ozanimod 0.46 mg	Ozanimod 0.46 mg + Cyclosporine 600 mg	CC112273 Ozanimod 0.46 mg	CC112273 Ozanimod 0.46 mg + Cyclosporine 600 mg	CC1084037 Ozanimod 0.46 mg	CC1084037 Ozanimod 0.46 mg + Cyclosporine 600 mg	RP101988 Ozanimod 0.46 mg	RP101988 Ozanimod 0.46 mg + Cyclosporine 600 mg
CL/F (L/h)	n	16	13	NA	NA	NA	NA	NA	NA
	Mean (SD)	205 (59.1)	172 (51.9)						
	CV%	28.9	30.2						
V_z/F (L)	n	16	13	NA	NA	NA	NA	NA	NA
	Mean (SD)	5176 (1394)	4950 (1060)						
	CV%	26.9	21.4						

λ_z = terminal elimination rate constant; AUC = area under the plasma concentration-time curve; AUC_{0-168} = AUC from time 0 to 168 hours post dose ozanimod; AUC_{0-14d} = AUC from time 0 to 14 days postdose ozanimod; AUC_{inf} = AUC from time 0 to infinity; AUC_{last} = AUC from time 0 to last quantifiable concentration; CL/F = apparent oral clearance; C_{max} = maximum observed plasma concentration; CV% = percent coefficient of variation; Max = maximum; mg = milligram; Min = minimum; n = number of subjects in specified category or characteristic with non-missing observations; NA = not applicable; ND = not determined; PK = pharmacokinetic; R^2 = coefficient of determination; SD = standard deviation; $t_{½}$ = terminal elimination half-life; T_{last} = time to last measurable concentration; T_{max} = time to C_{max}; V_z/F = apparent volume of distribution associated with the terminal phase.
Notes: Mean is arithmetic mean. If the extrapolated AUC_{inf} > 20% or if ND due to R^2 < 0.80 or if there were < 3 points available for the determination of λ_z, then that subject's AUC_{inf} was not included in the analysis. If the subject only had 1 measurable concentration, then AUC_{last} was not included in the analysis. If T_{last} was less than 336 hours, then that subject's AUC_{0-14d} was not included in the analysis. If C_{max} = 0, then that subjects T_{max} was set to missing.
Major active metabolites of ozanimod: CC112273, CC1084037; minor active metabolite of ozanimod; RP101988
Source: Tables 14.2.5.2.1, 14.2.5.2.2, 14.2.5.2.3, 14.2.5.2.4, and Listing 16.2.6.8.2.1

Table 10: Statistical analysis to assess the effect of cyclosporine on the PK of ozanimod and metabolites

Table 5: Statistical Analysis to Assess the Effect of Cyclosporine on the PK of Ozanimod and Metabolites (PK Population)

Analyte	PK Parameter	Comparison	Number of Subjects		Geometric LS Means		Ratio of Geometric LS Means (Test to Reference)	90% CI for Geometric LS Mean Ratio of (Test to Reference)
			Test	Reference	Test	Reference		
Ozanimod	C_{max} (pg/mL)	Test vs Reference	20	20	79.0	78.31	1.008	(0.881, 1.153)
	AUC_{inf} (pg*h/mL)	Test vs Reference	13	16	2750	2305.7	1.193	(0.997, 1.427)
	AUC_{last} (pg*h/mL)	Test vs Reference	19	20	2107	1961.9	1.074	(0.916, 1.259)
CC112273	C_{max} (pg/mL)	Test vs Reference	20	20	152	176	0.865	(0.746, 1.003)
	AUC_{last} (pg*h/mL)	Test vs Reference	19	20	23184	22736	1.020	(0.850, 1.223)
CC1084037	C_{max} (pg/mL)	Test vs Reference	20	20	20.8	20.9	0.992	(0.865, 1.139)
	AUC_{last} (pg*h/mL)	Test vs Reference	18	20	3471	3129	1.109	(0.714, 1.724)
	AUC_{0-168} (pg*h/mL)	Test vs Reference	16	15	2771	2808	0.987	(0.847, 1.150)
RP101988	C_{max} (pg/mL)	Test vs Reference	20	20	220	113	1.956	(1.702, 2.249)
	AUC_{last} (pg*h/mL)	Test vs Reference	19	20	3305	1887	1.751	(1.466, 2.093)

λ_z = terminal elimination rate constant; AUC = area under the plasma concentration-time curve; AUC_{0-14d} = AUC from time 0 to 14 days postdose ozanimod AUC_{0-168} = AUC from time 0 to 168 hours postdose ozanimod; AUC_{inf} = AUC from time 0 to infinity; AUC_{last} = AUC from time 0 to last quantifiable

Since AUCinf was not reported for RP101988 in 13 out of 20 subjects in the ozanimod 0.46 mg group due to AUC%extra exceeding 20%, this parameter was excluded from the statistics.

Cmax, AUC 0- t, and AUC 0-inf

Coadministration with cyclosporine had no effect on the Cmax of ozanimod and resulted in a numerical increase of 19% in mean ozanimod AUCinf. Cyclosporine decreased the mean Cmax of CC112273 numerically by approximately 14% with little effect on the AUClast of CC112273 and on either the AUClast or Cmax of CC1084037.

The 90% CI for the ratio of geometric means for Cmax, AUC0-last, and AUC0-∞ encompasses 1 for ozanimod, CC112273, and CC1084037, indicating there was no statistically significant difference in exposure of ozanimod, CC112273, and CC1084037 with or without cyclosporine coadministration. Cyclosporine significantly increased Cmax and AUC0-last for RP101988 by 96% and 75%, respectively.

The median Tmax (10.0 hours) of ozanimod was similar between treatments. Mean ozanimod t½ (19 to 21 hours) and Vz/F (4950 to 5176 L) were similar between treatments and CL/F was slightly lower (172 L/h) when ozanimod was coadministered with cyclosporine than when administered alone (205 L/h). The median Tmax of CC112273 (20.0 vs 10.0 hours) and CC1084037 (36.0 vs 24.0 hours) was later following ozanimod coadministration with cyclosporine; however, the range of individual Tmax was similar for both treatments. The mean CC112273 t½ (282 to 285 hours) and CC1084037 (272 to 390 hours) were similar across treatments. The median Tmax (6.0 hours) of RP101988 was similar between treatments. The mean RP101988 t½ (13 to 15 hours) was also similar for both treatments.

Safety results:

Overall, 15 subjects (37.5%) had at least 1 TEAE. The majority of the TEAEs occurred in the ozanimod 0.46 mg + cyclosporine 600 mg group: 2 subjects (10.0%) in the ozanimod 0.46 mg group and 13 subjects (65.0%) in the ozanimod 0.46 mg + cyclosporine 600 mg group.

The majority of TEAEs related to ozanimod were reported by the ozanimod 0.46 mg + cyclosporine 600 mg group: 0 subjects in the ozanimod 0.46 mg group and 5 subjects (25.0%) in the ozanimod 0.46 mg + cyclosporine 600 mg group. Seven subjects (35.0%) in the ozanimod 0.46 mg + cyclosporine 600 mg group had at least 1 TEAE that was related to cyclosporine.

Eight subjects reported TEAEs that were not related to IP: 2 subjects (10.0%) in the ozanimod 0.46 mg group and 6 subjects (30.0%) in the ozanimod 0.46 mg + cyclosporine 600 mg group.

All TEAEs were mild or moderate in severity. There were no TEAEs that were considered SAEs, no SAEs related to IP, no TEAEs that led to discontinuation of IP or deaths.

The most commonly reported TEAEs in ≥ 2 subjects for the ozanimod 0.46 mg + cyclosporine 600 mg group were nausea, diarrhoea, feeling hot, and headache. In the ozanimod 0.46 mg group, no TEAE was reported by more than 1 subject.

Sporadic out-of-range chemistry and hematology laboratory parameters were reported but no trends in mean laboratory results were noted, no notable trends or changes from baseline in vital signs were observed, no physical examination findings were reported as AEs. No ECG results with abnormal clinically significant findings were reported.

A single oral dose of ozanimod 0.46 mg, administered alone or in combination with a single oral dose of cyclosporine 600 mg, was generally safe and well tolerated in healthy adult subjects.

2.3.3. Pharmacodynamics

Based on previously submitted data in healthy subjects, administration of increasing doses of ozanimod in healthy subjects was associated with dose dependent reductions in ALC, a PD biomarker of S1P1 modulation. Following once-daily administration of 0.3, 1, and 1.5 mg ozanimod for 28 days in healthy subjects, the median ALC reductions from baseline were 34%, 65%, and 68%, respectively (MS SCP). These data suggested that doses of 1 mg achieve near maximal ALC reduction.

The new data submitted concern a retrospective analysis of stored samples from a clinical pharmacology study with intensive sampling in patients with MS (RPC01-1001) which was analysed for differential changes to leukocyte subpopulations.

In addition, the applicant has submitted Study RPC01-1915, which is formally a Phase 1, Multi-center, Extension Study to Further Evaluate the Safety, Pharmacodynamics and Pharmacokinetics of Ozanimod and Active Metabolitesin Healthy Adult Subjects of which the primary objective was to obtain safety data up to 75 ± 10 days postdose from the Phase 1 protocols RPC01-1912, RPC01-1913, and RPC-1914. This study also includes information on PD during the recovery phase after repeated ozanimod dosing in healthy adult subjects relating to normalisation of lymphocyte counts.

Mechanism of action

Based on previously submitted data in healthy subjects, administration of increasing doses of ozanimod in healthy subjects was associated with dose dependent reductions in ALC, a PD biomarker of S1P1 modulation. Following once-daily administration of 0.3, 1, and 1.5 mg ozanimod for 28 days in healthy subjects, the median ALC reductions from baseline were 34%, 65%, and 68%, respectively (MS SCP). These data suggested that doses of 1 mg achieve near maximal ALC reduction.

Primary and secondary pharmacology

<u>Study RPC01-1001:</u>

Study RPC01-1001 was an open-label randomized PK and PD study evaluating administration of 0.5 mg (n = 13) and 1 mg (n = 11) ozanimod, following a 7-day dose escalation, for 12 weeks in patients with RMS. A supplementary analysis of this study is now submitted.

The results of this supplementary analysis are not included in the study report (which dates December 2017 and was included in the initial submission already), but are provided by a publication (Harris S et al: Effect of the sphingosine-1-phosphate receptor modulator ozanimod on leukocyte subtypes in relapsing MS; Neurol Neuroimmunol Neuroinflamm 2020;7:e839.)

Eligible participants in this study had no history of relapse with onset from 30 days before screening until randomization, were clinically stable during this period without systemic corticosteroid or adrenocorticotropic hormone treatment, and had documentation of positive varicella zoster virus (VZV) immunoglobulin G (IgG) antibody status or complete VZV vaccination at least 30 days before study entry. In addition, they were required to have an Expanded Disability Status Scale score of 0–6 and be generally healthy aside from RMS. Key exclusion criteria included active infection or history of chronic infections or immunodeficiency, recent live vaccination, previous lymphocyte-depleting or immunosuppressant therapy, and ALC <1.000 × 10^9/L or white blood cell count <3.500 × 10^9/L.

As a pre-specified pharmacodynamic analysis, the ALC was evaluated on days 1, 5, 8, 28, 56, and 85 (end of treatment). This analysis was included in the previously submitted study report as of 2017.

Two further analyses are included in the newly submitted literature data for the exploration of leucocyte subpopulation behaviour in this population, flow cytometry and epigenetic cell counting:

The flow cytometry panel was used to characterize circulating leukocyte subsets at baseline (day 1) and days 28, 56, and 85. Analyzed subsets included CD19+ B cells,CD3+ T cells, monocytes, natural killer (NK) cells, and natural killer T (NKT) cells, as well as the following T-cell subtypes: CD4+ and CD8+ central and effector memory T cells, CD4+ and CD8+ naive T cells, and CD8+ terminally differentiated effector T cells expressing CD45RA (TEMRA).

The epigenetic cell counting was performed using bisulfite-converted deoxyribonucleic acid from frozen whole blood samples as substrate for quantitative polymerase chain reaction assays for selected cell type-specific demethylated loci (B cells, T cells, CD8+ cytotoxic T cells, CD4+ T helper cells, Regulatory T cells, Th17 cells, Naïve CD8+ T cells, and PD1 cells).

Flow cytometry analysis of circulating leukocyte subsets indicated that the dose-dependent decreases in ALCs with ozanimod treatment were primarily due to decreases in circulating CD19+ B cells and CD3+ T cells as shown in the following figure. There were minimal to no decreases in monocytes, NK, and NKT cells.
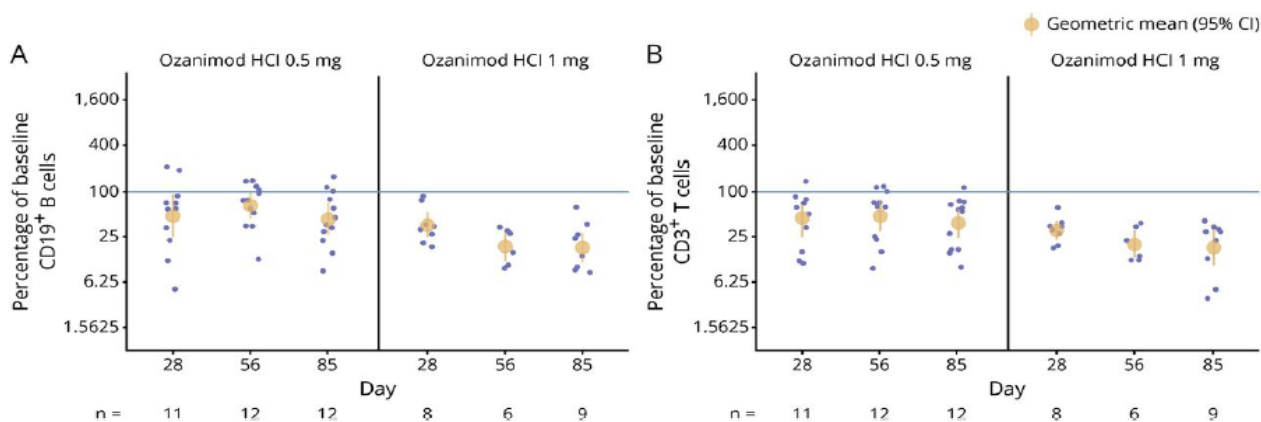
CI = confidence interval; RMS = relapsing multiple sclerosis.
Circulating levels of CD19+ B cells and CD3+ T cells were assessed as a percentage of baseline in patients with RMS treated with ozanimod HCl 0.5 or 1 mg/d, using flow cytometry.

Figure 5: Circulating Levels of B Cells (A) and T Cells (B) during Ozanimod Treatment

Further analysis of specific T-cell subtypes revealed greater decreases in CD4+ T-helper cells than CD8+ cytotoxic T cells in the ozanimod HCl 1 mg group, as well as greater decreases in both CD4+ and CD8+ central memory T cells versus effector memory T cells. By the end of treatment, ozanimod HCl 1 mg reduced mean CD4+ and CD8+ naïve T cells by ≥ 90%; ozanimod did not reduce circulating CD8+ TEMRA.

Study RPC01-1915:

This study is termed "A phase 1, multi-center, extension study to further evaluate the safety, pharmacodynamics, and pharmacokinetics of ozanimod and active metabolites in healthy adult subjects".

The primary objective was to obtain safety data up to 75 ± 10 days post-dose from the Phase 1 protocols RPC01-1912, RPC01-1913, and RPC-1914. The secondary objective was to collect additional data to further characterize the PD during the recovery phase after repeated ozanimod dosing in healthy adult subjects. The study reports of the three mentioned studies had been submitted with the initial application.

This study was to consist of 2 parts:

-        Mandatory data collection for safety: Subjects enrolled in the parent studies were to be consented to have data on adverse events (AEs), serious AEs (SAEs), pregnancy test results, and concomitant medications up to the 75 ± 10 days post-dose follow-up collected and reported in this study.

-        Optional sparse sampling for PK/PD: Eligible subjects from studies RPC01-1913 and RPC01-1914 were to be offered the opportunity to return to the clinical research unit (CRU) on 4 separate occasions for PK/PD sample collections up to the 75 ± 10 days postdose follow-up. After signing the ICF, eligible subjects were to be randomized to 1 of 3 sequences for sampling (see below). Subjects were to return to the CRU in the morning (between approximately 8 am and 11 am) once at each of the 4 time windows.

Table 11: RPC01-1915 Study Sequence

Sequence 1	Sequence 2	Sequence 3
Window a (10 to 13 days postdose)	Window b (14 to 20 days postdose)	Window c (21 to 27 days postdose)
Window c (21 to 27 days postdose)	Window d (28 to 34 days postdose)	Window e (35 to 41 days postdose)
Window f (42 to 48 days postdose)	Window g (49 to 55 days postdose)	Window h (56 to 64 days postdose)
Window i (65 to 85 days postdose)	Window i (65 to 85 days postdose)	Window i (65 to 85 days postdose)

A total of 232 subjects participated in the mandatory part of the study (Safety Population); 100 from parent study RPC01-1912, 79 from parent study RPC01-1913, and 53 from parent study RPC01-1914.

A total of 58 subjects (23 from parent study RPC01-1913 and 35 from parent study RPC01-1914) participated in the optional part of the study (Randomized Population) and were randomized to 1 of 3 sequences (as given above).

Results:

Overall, no new safety findings were observed in this extension study compared to the parent studies RPC01-1912, RPC01-1913, and RPC01-1914.

For the optional part of the study, 19, 18, and 21 patients were randomised in the three sequences. Patient groups were comparable for their mean demographic characteristics at study entry.

A total of 55 subjects (94.8%) in the optional part of the study (19 [100.0%], 17 [94.4%], and 19 [90.5%] subjects in Sequence 1, 2, and 3, respectively) were included in the Pharmacodynamic Population. A total of 3 subjects (5.2%) in the optional part of the study (1 subject [5.6%] in Sequence 2 and 2 subjects [9.5%] in Sequence 3) were excluded as they did not have at least 1 PD datum.

Spaghetti plots of ALC at baseline and up to 85 days after the last dose by treatment for RPC01-1913 and RPC01-1914 are presented in the following 2 figures. Baseline was the measurement prior to ozanimod/phenelzine/placebo dosing (Day 11) for parent study RPC01-1913 and the measurement on Day -2 for parent study RPC01-1914.

ALC = absolute lymphocyte count.
Note: Baseline was the measurement on Day 11 prior to dosing in the parent study RPC01-1913.

Figure 6: Spaghetti Plots of Absolute Lymphocyte Count at Baseline and up to 85 Days after the Last Dose by Treatment for Parent Study RPC01-1913 (Pharmacodynamic Population)

Figure 7: Spaghetti Plots of Absolute Lymphocyte Count at Baseline and up to 85 Days after the Last Dose by Treatment for Parent Study RPC01-1914 (Pharmacodynamic Population)

The following excerpts from the tables provided in the study report do give a more clear impression on the magnitude of changes over time. The evaluation of the data is complicated by the fact that not all samples in both studies were taken at the same time (due to the design of study 1913). Data are given for baseline of both studies, for the time period 28-34 days after end of treatment (study RPC01-1913 only), for the time period 49-55 days after the end of treatment (both studies) and for the last period (day 65 to 85).

Table 12: Summary Statistics of Observed, Change from Baseline, and Percent Change from Baseline for Absolute Lymphocyte Count at Baseline and up to 85 Days after the Last Dose of Ozanimod in Studies RPC01-1913 and RPC01-1914 (Pharmacodynamic Population)

	RPC01-1913			RPC01-1914[b]		
Window[a]	Observed Value	Change from Baseline	% Change from Baseline	Observed Value	Change from Baseline	% Change from Baseline
Baseline[c]						
N	9			16		
Mean (SD)	1.556 (0.3772)			1.980 (0.4694)		
Median	1.580			2.035		
Min, Max	1.09, 2.19			0.97, 2.74		
d (28 to 34 days)				Not collected		
N	3	3	3			
Mean (SD)	0.887 (0.5016)	-0.553 (0.2730)	-41.255 (0.2730)			
Median	0.840	-0.680	-46.835			
Min, Max	0.41, 1.41	-0.74, -0.24	-62.39, -14.55			
N	3	3	3	6	6	6
Mean (SD)	1.030 (0.4651)	-0.410 (0.3251)	-29.662 (0.3251)	1.690 (0.6113)	-0.410 (0.8466)	-15.070 (0.8466)
Median	0.840	-0.400	-36.697	1.640	-0.620	-29.894
Min, Max	0.69, 1.56	-0.74, -0.09	-46.84, -5.45	1.02, 2.76	-1.20, 1.15	-49.00, 71.43
N	8	8	8	16	16	16
Mean (SD)	1.306 (0.5855)	-0.278 (0.4529)	-18.266 (0.4529)	1.820 (0.5662)	-0.160 (0.4633)	-7.441 (0.4633)
Median	1.180	-0.255	-19.969	1.875	-0.190	-10.177
Min, Max	0.64, 2.45	-0.91, 0.39	-53.62, 18.93	0.78, 2.70	-1.06, 0.85	-46.00, 52.80

ALC = absolute lymphocyte count; Max = maximum; Min = minimum; N = number of subjects; SD = standard deviation.
[a] Windows are defined as intervals in days relative to post last dose of ozanimod in the parent studies.
[b] RPC01-1914 parent study did not have any samples collected until the 42 to 48 days postdose window following baseline.
[c] Baseline was the measurement on Day 11 prior to dosing for parent study RPC01-1913 and the measurement on Day -2 for parent study RPC01-1914.
Note: ALC was summarized when at least 3 subjects within a group had nonmissing data at the time point being summarized.

The applicant concludes that after multiple dosing of ozanimod 1.84 mg once daily for up to 28 days (preceded by the 10-day dose escalation of 0.23 mg for 4 days, 0.46 mg for 3 days, and 0.92 mg for 3 days), ALC appeared to return to near baseline by 65 to 85 days after the last dose of ozanimod.

CI = confidence interval.

Note: Circulating levels of (A) CD4⁺ central memory T cells, (B) CD4⁺ effector memory T cells, (C) CD8⁺ central memory T cells, and (D) CD8⁺ effector memory T cells during treatment with ozanimod HCl 0.5 or 1 mg/d, as assessed using flow cytometry.

Figure 8: Flow Cytometry Analysis of Circulating Levels of Central versus Effector Memory T Cells

In the epigenetic cell-counting analysis, total circulating leukocytes at Day 85 were reduced to 90% (95% CI: 78%, 104%) and 73% (95% CI: 55%, 97%) of baseline in the ozanimod HCl 0.5 mg and 1 mg groups, respectively. Results for specific leukocyte subsets were consistent with the flow cytometry results in showing dose-dependent decreases in total circulating B cells and T cells with ozanimod treatment, as well as decreases in CD4+ T-helper and CD8+ cytotoxic T cells and naive CD8+ T cells. This analysis also demonstrated greater reductions in Th17 cells than T regulatory cells or programmed cell death 1 (PD-1)+ cells.
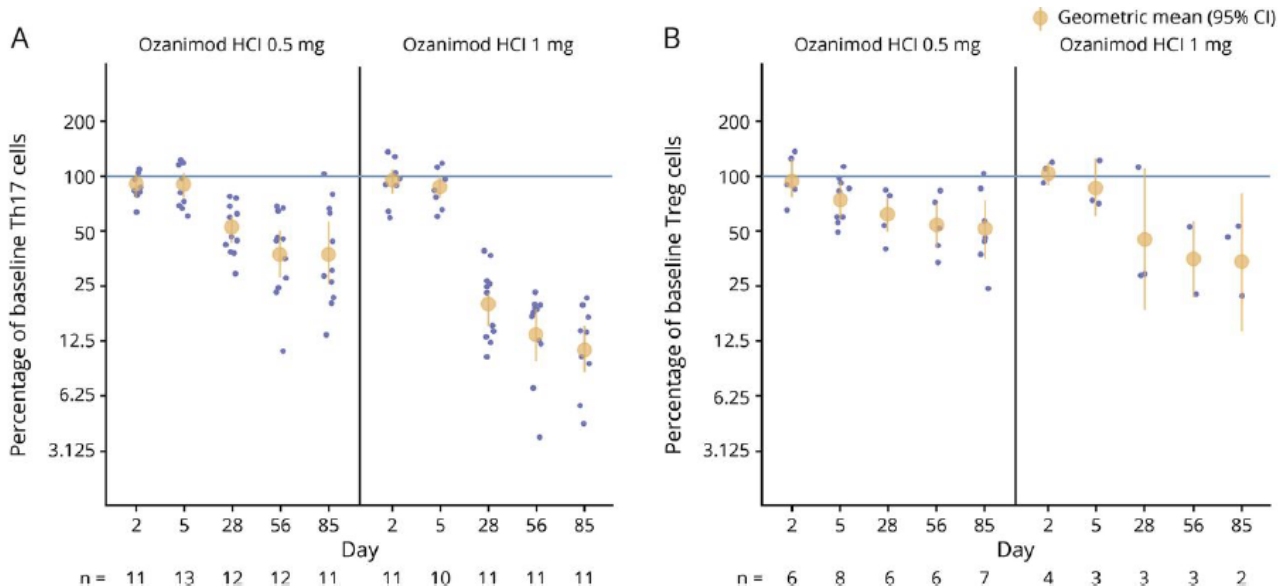
CI = confidence interval; Treg = T regulatory.

Note: Circulating levels of (A) Th17 cells and (B) Treg cells during treatment with ozanimod HCl 0.5 mg or 1 mg/d, as assessed using epigenetic cell counting.

Figure 9: Epigenetic Cell Counting: Circulating Levels of Th17 versus T Regulatory Cells

The applicant concludes that ozanimod dosed once daily induced differential changes to leukocyte subpopulations. Ozanimod caused greater reductions in CD4+ cells than CD8+ T cells, and greater decreases in central memory T cells versus effector memory T cells. In contrast, ozanimod had minimal impact on monocytes, NK, and NKT cells, which are important components of the innate immune response and maintenance of immunosurveillance.

Study RPC01-1915:

This study is termed "A phase 1, multi-center, extension study to further evaluate the safety, pharmacodynamics, and pharmacokinetics of ozanimod and active metabolites in healthy adult subjects".

The primary objective was to obtain safety data up to 75 ± 10 days post-dose from the Phase 1 protocols RPC01-1912, RPC01-1913, and RPC-1914. The secondary objective was to collect additional data to further characterize the PD during the recovery phase after repeated ozanimod dosing in healthy adult subjects. The study reports of the three mentioned studies had been submitted with the initial application.

This study was to consist of 2 parts:

-        Mandatory data collection for safety: Subjects enrolled in the parent studies were to be consented to have data on adverse events (AEs), serious AEs (SAEs), pregnancy test results, and concomitant medications up to the 75 ± 10 days post-dose follow-up collected and reported in this study.

-        Optional sparse sampling for PK/PD: Eligible subjects from studies RPC01-1913 and RPC01-1914 were to be offered the opportunity to return to the clinical research unit (CRU) on 4 separate occasions for PK/PD sample collections up to the 75 ± 10 days post dose follow-up. After signing the ICF, eligible subjects were to be randomized to 1 of 3 sequences for sampling (see below). Subjects were to return to the CRU in the morning (between approximately 8 am and 11 am) once at each of the 4 time windows.

Table 13: RPC01-1915 Study Sequence

Sequence 1	Sequence 2	Sequence 3
Window a (10 to 13 days postdose)	Window b (14 to 20 days postdose)	Window c (21 to 27 days postdose)
Window c (21 to 27 days postdose)	Window d (28 to 34 days postdose)	Window e (35 to 41 days postdose)
Window f (42 to 48 days postdose)	Window g (49 to 55 days postdose)	Window h (56 to 64 days postdose)
Window i (65 to 85 days postdose)	Window i (65 to 85 days postdose)	Window i (65 to 85 days postdose)

A total of 232 subjects participated in the mandatory part of the study (Safety Population); 100 from parent study RPC01-1912, 79 from parent study RPC01-1913, and 53 from parent study RPC01-1914.

A total of 58 subjects (23 from parent study RPC01-1913 and 35 from parent study RPC01-1914) participated in the optional part of the study (Randomized Population) and were randomized to 1 of 3 sequences (as given above).

Results:

Overall, no new safety findings were observed in this extension study compared to the parent studies RPC01-1912, RPC01-1913, and RPC01-1914.

For the optional part of the study, 19, 18, and 21 patients were randomised in the three sequences. Patient groups were comparable for their mean demographic characteristics at study entry.

A total of 55 subjects (94.8%) in the optional part of the study (19 [100.0%], 17 [94.4%], and 19 [90.5%] subjects in Sequence 1, 2, and 3, respectively) were included in the Pharmacodynamic Population. A total of 3 subjects (5.2%) in the optional part of the study (1 subject [5.6%] in Sequence 2 and 2 subjects [9.5%] in Sequence 3) were excluded as they did not have at least 1 PD datum.

Spaghetti plots of ALC at baseline and up to 85 days after the last dose by treatment for RPC01-1913 and RPC01-1914 are presented in the following 2 figures. Baseline was the measurement prior to ozanimod/phenelzine/placebo dosing (Day 11) for parent study RPC01-1913 and the measurement on Day -2 for parent study RPC01-1914.

Treatment Group = Ozanimod

Treatment Group = Phenelzine

Treatment Group = Placebo

ALC = absolute lymphocyte count.
Note: Baseline was the measurement on Day 11 prior to dosing in the parent study RPC01-1913.

Figure 10: Spaghetti Plots of Absolute Lymphocyte Count at Baseline and up to 85 Days after the Last Dose by Treatment for Parent Study RPC01-1913 (Pharmacodynamic Population)

Figure 11: Spaghetti Plots of Absolute Lymphocyte Count at Baseline and up to 85 Days after the Last Dose by Treatment for Parent Study RPC01-1914 (Pharmacodynamic Population)
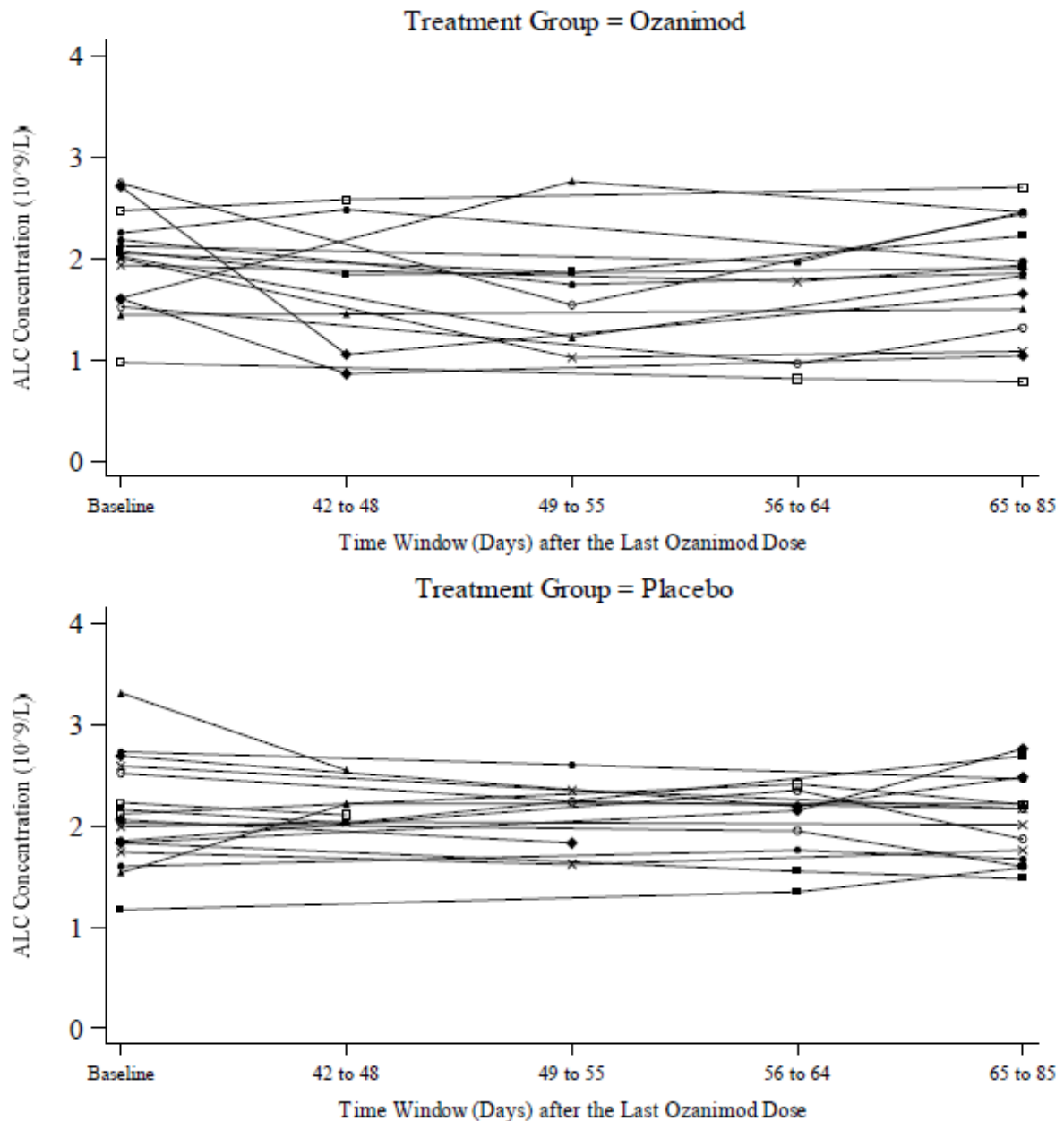
ALC = absolute lymphocyte count.

Note: Baseline was the measurement on Day -2 of the parent study RPC01-1914. Samples for subjects from parent study RPC01-1914 were not collected until the 42 to 48 days postdose window.

The following excerpts from the tables provided in the study report do give a more clear impression on the magnitude of changes over time. The evaluation of the data is complicated by the fact that not all samples in both studies were taken at the same time (due to the design of study 1913). Data are given for baseline of both studies, for the time period 28-34 days after end of treatment (study RPC01-1913 only), for the time period 49-55 days after the end of treatment (both studies) and for the last period (day 65 to 85).

Table 14: Summary Statistics of Observed, Change from Baseline, and Percent Change from Baseline for Absolute Lymphocyte Count at Baseline and up to 85 Days after the Last Dose of Ozanimod in Studies RPC01-1913 and RPC01-1914 (Pharmacodynamic Population)

Window[a]	RPC01-1913			RPC01-1914[b]		
	Observed Value	Change from Baseline	% Change from Baseline	Observed Value	Change from Baseline	% Change from Baseline
Baseline[c]						
N	9			16		
Mean (SD)	1.556 (0.3772)			1.980 (0.4694)		
Median	1.580			2.035		
Min, Max	1.09, 2.19			0.97, 2.74		
d (28 to 34 days)				Not collected		
N	3	3	3			
Mean (SD)	0.887 (0.5016)	-0.553 (0.2730)	-41.255 (0.2730)			
Median	0.840	-0.680	-46.835			
Min, Max	0.41, 1.41	-0.74, -0.24	-62.39, -14.55			
N	3	3	3	6	6	6
Mean (SD)	1.030 (0.4651)	-0.410 (0.3251)	-29.662 (0.3251)	1.690 (0.6113)	-0.410 (0.8466)	-15.070 (0.8466)
Median	0.840	-0.400	-36.697	1.640	-0.620	-29.894
Min, Max	0.69, 1.56	-0.74, -0.09	-46.84, -5.45	1.02, 2.76	-1.20, 1.15	-49.00, 71.43
N	8	8	8	16	16	16
Mean (SD)	1.306 (0.5855)	-0.278 (0.4529)	-18.266 (0.4529)	1.820 (0.5662)	-0.160 (0.4633)	-7.441 (0.4633)
Median	1.180	-0.255	-19.969	1.875	-0.190	-10.177
Min, Max	0.64, 2.45	-0.91, 0.39	-53.62, 18.93	0.78, 2.70	-1.06, 0.85	-46.00, 52.80

ALC = absolute lymphocyte count; Max = maximum; Min = minimum; N = number of subjects; SD = standard deviation.
[a] Windows are defined as intervals in days relative to post last dose of ozanimod in the parent studies.
[b] RPC01-1914 parent study did not have any samples collected until the 42 to 48 days postdose window following baseline.
[c] Baseline was the measurement on Day 11 prior to dosing for parent study RPC01-1913 and the measurement on Day -2 for parent study RPC01-1914.
Note: ALC was summarized when at least 3 subjects within a group had nonmissing data at the time point being summarized.

The applicant concludes that after multiple dosing of ozanimod 1.84 mg once daily for up to 28 days (preceded by the 10-day dose escalation of 0.23 mg for 4 days, 0.46 mg for 3 days, and 0.92 mg for 3 days), ALC appeared to return to near baseline by 65 to 85 days after the last dose of ozanimod.

2.3.4. PK/PD modelling

Two separate models were developed to analyse plasma concentrations of ozalimod and of the metabolite CC112273 over time using new data for UC patients, starting out from the existing models developed for healthy volunteers and RMS patients. The resulting Pop-PK-Model was used to develop a PK/PD model describing the correlations between metabolite concentration and ALC decrease over time using an Emax model. Further, an exposure-response model was developed describing how CC112273 AUC could be linked to Efficacy (Clinical remission) using logistic regression. Regarding safety, time-to-event analyses were conducted for the endpoints AST/ALT elevation and infections, analysing data separately for week 10 and week 52.

Population PK modeling

Also in the previous population PK analysis for patients with RMS, ozanimod and CC112273 were characterized by two separate models. The PK of CC112273 was described by a 2-compartment model with first order formation rate, a lag time and first order elimination. The evaluated full model included 45 covariate effects, and 12 of which were retained in the final model. The PK model developed for ozanimod was also a 2-compartment model with combined zero and first order absorption processes. Significant covariates included age and body weight on apparent clearance. The overall PK profiles were not expected to be different between RMS patients and UC patients. Hence, population PK analysis was performed for ozanimod, the parent drug, and CC112273, the most prominent circulating active moiety, using the models developed for RMS population, with evaluation of a disease effect to account for any differences between patients and healthy volunteers.

Subjects from 11 studies (Phase 1 to Phase 3) were included for the population PK analysis. PK population included healthy volunteers, RMS patients and UC patients. A total of 18901 PK concentrations from 2890 subjects were included in the PK analysis of CC112273 and 18834 PK concentrations from 2977 subjects were included in the PK analysis of ozanimod. Population PK analysis was performed on ozanimod and its most prominent metabolite CC112273 using 2-compartment models previously developed in RMS patients and adapted to the studied population. Sources of variability were explored, previously selected covariates were retained and a formal covariate analysis was performed using a full-model approach on new potential covariates. The final model was qualified using goodness-of-fit criteria, sampling importance resampling, and visual predictive check. Empirical individual Bayesian estimates of PK parameters were generated using the final population PK model. Based on individual parameter estimates, measures of ozanimod and CC112273 exposures were computed for each subject.

For the purpose of the analysis, included were two Phase 2 and Phase 3 UC studies (RPC01-202, RPC01-3101); three RMS studies for disease comparison (RPC01-1001, RPC01-201B and RPC01-301); and six Phase 1 clinical pharmacology studies in healthy volunteers that included analysis of the active major metabolite CC112273 (RPC01-1910, -1911, -1912, -1913, -1914 and -1915).

The analysis was performed using NONMEM (Version 7.4 or greater), with the first-order conditional estimation (FOCE) and the INTERACTION option. Perl-Speaks-NONMEM (PsN Version 4.6.0 or greater) and FORTRAN compiler (V4.6 or greater) were used during PK modeling evaluation, and the results were further analyzed by R® software (Version 3.6 or greater). Exploratory analyses were performed using R software (Version 3.6 or greater).

PPK Analysis of CC112273

A total of 3031 subjects with CC112273 PK samples were available in the PPK dataset of which total of 18901 (83.0%) concentrations were included in the PPK analysis of CC112273.

CC112273 concentrations were determined retrospectively in frozen plasma samples retained from all or subsets of the subjects who participated in Studies RPC01-1001, RPC01-201B, RPC01-301, RPC01-201, and RPC01-3101. For these studies, only concentration values within the long-term stability established in March 2020 (CC112273: 961 days) were included in this analysis. This is the reason for exclusion of 87.1% of the samples collected in UC study RPC01-202.

The PK population included 1257 (43.5%) male and 1633 (56.5%) female subjects. Median (range) age and body weight were 36.0 years (18.0 to 74.0 years) and 70.0 kg (37.8 to 173 kg), respectively. The subjects were primarily white (91.7%). The majority of subjects had normal hepatic and renal functions (90.7% and 69.9%, respectively). The population included 459 (15.9%) smokers. Overall, there were 259 (9.0%) healthy volunteers, 885 (30.6%) subjects with UC and 1746 (60.4%) subjects with RMS.

The overall approach for the development of the metabolite PPK model followed standard methods: The base model was based upon the previously developed model. The base model included the covariates previously determined to have a significant effect on model parameters. An interindividual variability (IIV) on the bioavailability (F1) parameter was added to the model. The disease effect on error was evaluated. The potential effect of additional covariates was assessed by a full model approach. A final model was determined by backward elimination of added covariates in the full model.

Table 15: Samples Included in the CC112273 PPK Analysis Dataset

Study	Total PK Samples	Predose BLQ	Postdose BLQ	Samples Excluded	Samples Included in Analysis (%[b])
RPC01-1910	3994 (16.2%)	56	137	0	3801 (96.5%)
RPC01-1911	3205 (13.0%)	69	197	0	2939 (93.7%)
RPC01-1912	2466 (10.0%)	79	229	493	1665 (69.8%)
RPC01-1913	502 (2.0%)	26	4	0	472 (99.2%)
RPC01-1914	1382 (5.6%)	28	90	0	1264 (93.4%)
RPC01-1001	867 (3.5%)	23	82	0	762 (90.3%)
RPC01-201B	3281 (13.3%)	0	32	1070	2179 (66.4%)
RPC01-301	4394 (17.9%)	767	98	271	3258 (89.8%)
RPC01-202	969 (3.9%)	0	20	824	125 (12.9%)
RPC01-3101	3554 (14.4%)	780	92	246	2436 (87.8%)
Total	24614 (100%)	1828 (7.4%[a])	981 (4.3%[b])	2904 (12.7%[b])	18901 (83.0%)

Abbreviations: BLQ = below the limit of quantification; PK = pharmacokinetic; PPK = population pharmacokinetic.
[a] Percentage of the total number of PK samples.
[b] Percentage of the total number of PK samples, excluding predose BLQ.
Note: Total PK samples include samples from PK analysis population.
Source: table_pk_samples_blq.R
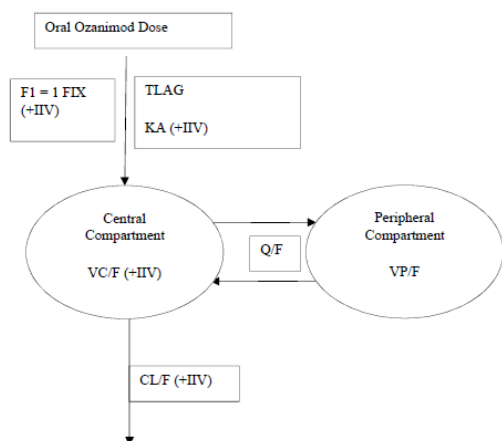
CL/F = apparent clearance; F1 = relative bioavailability; IIV = interindividual variability; KA = first order absorption rate constant; Q/F = apparent intercompartmental clearance; TLAG = lag time; VC/F = apparent volume of distribution of the central compartment; VP/F = apparent volume of distribution of the peripheral compartment.

Figure 12: Structural PK Model of CC112273

Natural-log-transformed concentration-time profiles of CC112273 were previously described by a first-order input with a fixed-length lag time (TLAG) and 2-compartment disposition. This structural model was used to describe the relationship between CC112273 concentrations and time.

The IIV was modeled as an exponential random-effect model in order to positively constrain the individual parameter values, which were thus assumed to follow a log-normal distribution.

Residual variability was described using statistical model with additive component. A disease effect (subjects with RMS or UC versus healthy subject) on residual variability was evaluated and significantly

improved the model predictions. Different residual error estimates were then added for the subjects with RMS/UC group and the healthy group.

Only the covariates that are deemed significant (ie, a decrease >6.63 in objective function value [OFV], p-value=0.01) 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. The list of covariates tested in the full model is presented in Table 17.

The final model was derived from the full model using stepwise backward elimination (p-value=0.001). For each step, a covariate that was deemed insignificant (ie, an increase >10.83 in OFV, p-value=0.001) was removed from the model for the following step. The final model was then derived from the full covariate and is considered to have the lowest OFV determined by backward elimination from the full model. However, as noted in the previous section, inferences on the magnitude of covariate effects were based on the full model.

Empirical Bayesian Estimate (EBE) PK parameters and summary exposure metrics were estimated from the final PPK model for each subject at a dose of 1mg of ozanimod. These parameters were summarized by disease type and presented in the table below for the primary PK parameters and for the secondary PK parameters.

Stepwise backward elimination was performed on the 3 added covariates (age and race on CL/F and disease status on KA), summarized in Table 16. All covariates were significant, and the final model remained similar to the full model. Parameter estimates of the full/final model and the SIR are presented below.

GOF plots of the final PPK model are presented in figures below.

Table 16: Summary Results of Final Model Selection

Model No.	Model Description	OFV	DF	ΔOFV	ΔDF
1	Full model	-33006.575	29	--	--
2	Full model - disease status on KA	-32960.315	27	46.260	-2
3	Full model - race on CL/F	-32973.110	28	33.465	-1
4	Full model - age on CL/F	-32983.570	28	23.005	-1

Abbreviations: ΔDF = difference in degrees of freedom; ΔOFV = difference in objective function value; CL/F = apparent clearance; DF = degrees of freedom; KA = first-order absorption rate constant; No. = number; OFV = objective function value.

Table 17: Covariate-PK Parameter Relationships to be evaluated in the Full CC112273 Model

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	-	-

Abbreviations: 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.
Note: √ = to be tested; X = included as part of the previous model.
Source: Appendix C

Geometric Mean (nmol*h/L)

Disease type	N	GM	%CV
Healthy	259	211	62.4
Relapsing multiple sclerosis	1769	152	73.7
Ulcerative Colitis	949	194	64.1

Geometric Mean (nmol/L)

Disease type	N	GM	%CV
Healthy	259	8.98	61.6
Relapsing multiple sclerosis	1769	6.58	72.3
Ulcerative Colitis	949	8.29	63.1
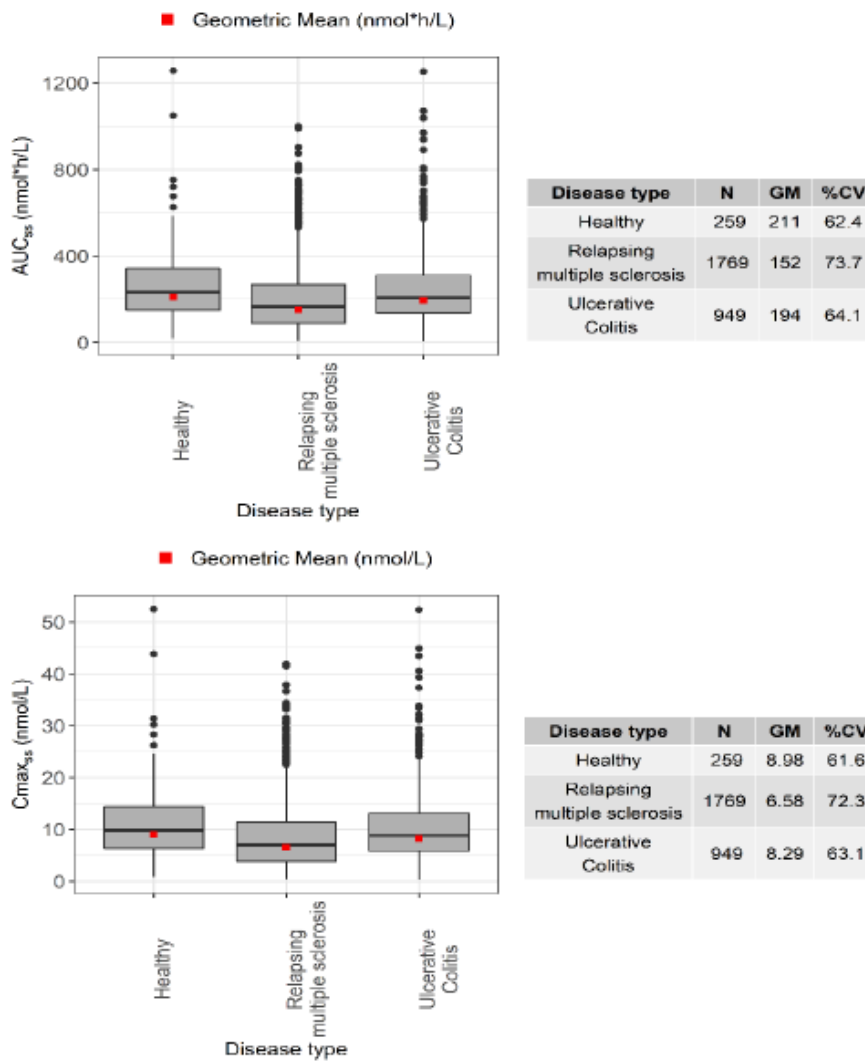
AUCss = area under the concentration-time curve at steady state; Cmaxss = maximum concentration at steady state; CV = coefficient of variation; GM = geometric mean; N = number of subjects.
Source: ModelApplication_11SEP2020.Rmd

Figure 13: Distribution of CC112273 Individual Bayesian Estimates of AUCss and Cmaxss by Disease Status (Ozanimod 1 mg).

Table 18: Summary of Primary PK Parameters by Disease Type

PK Parameter	Healthy Subjects N=259	Subjects With RMS N=1769	Subjects With UC N=949
CL/F (L/h)			
Mean (SD)	14.4 (11.7)	20.0 (18.8)	15.8 (21.7)
Median [Min, Max]	10.9 [1.75, 87.3]	13.9 [2.62, 245]	10.9 [1.92, 334]
VC/F (L)			
Mean (SD)	1240 (512)	1350 (905)	1490 (1150)
Median [Min, Max]	1180 [396, 3470]	1120 [278, 11500]	1180 [262, 14600]
Q/F (L/h)			
Mean (SD)	66.0 (0)	66.0 (0)	66.0 (0)
Median [Min, Max]	66.0 [66.0, 66.0]	66.0 [66.0, 66.0]	66.0 [66.0, 66.0]
VP/F (L)			
Mean (SD)	3910 (0)	3910 (0)	3910 (0)
Median [Min, Max]	3910 [3910, 3910]	3910 [3910, 3910]	3910 [3910, 3910]
KA (h^{-1})			
Mean (SD)	0.0804 (0.0444)	0.108 (0.0630)	0.111 (0.0855)
Median [Min, Max]	0.0706 [0.0178, 0.250]	0.0912 [0.0211, 0.797]	0.0878 [0.0256, 0.905]

Abbreviations: CL/F = apparent clearance; KA = first-order absorption rate constant; Q/F = apparent intercompartmental clearance; SD = standard deviation; VC/F = apparent volume of distribution of the central compartment; VP/F = apparent volume of distribution of the peripheral compartment.
Source: table_posthoc_summary.R

Table 19: Summary of Bayesian Estimates of CC112273 Secondary PK Parameter and Exposure Metrics from Simulations with Ozanimod 1 mg by Disease Type

PK Parameter	Healthy Subjects N=259	Subjects With RMS N=1769	Subjects With UC N=949
T_{max} (h)			
Mean (SD)	17.0 (3.88)	13.5 (2.01)	14.5 (2.53)
Median [Min, Max]	16.8 [8.67, 24.0]	13.3 [4.96, 24.0]	14.5 [4.38, 23.5]
C_{max} (nmol/L)			
Mean (SD)	0.794 (0.203)	0.806 (0.193)	0.780 (0.206)
Median [Min, Max]	0.780 [0.330, 1.53]	0.808 [0.196, 1.56]	0.771 [0.124, 2.00]
C_{avg} (nmol/L)			
Mean (SD)	0.611 (0.162)	0.637 (0.152)	0.615 (0.162)
Median [Min, Max]	0.601 [0.237, 1.20]	0.637 [0.149, 1.22]	0.606 [0.112, 1.49]
$HL\alpha$ (h)			
Mean (SD)	8.57 (2.95)	8.61 (4.09)	9.37 (4.60)
Median [Min, Max]	8.45 [2.70, 18.4]	7.78 [1.57, 30.5]	8.35 [0.799, 32.3]
$HL\beta$ (h)			
Mean (SD)	411 (259)	351 (243)	424 (262)
Median [Min, Max]	354 [76.0, 1910]	289 [52.8, 2360]	365 [49.9, 2070]
AUC_{ss} (nmol·h/L)			
Mean (SD)	257 (161)	201 (148)	240 (154)
Median [Min, Max]	232 [19.4, 1260]	165 [6.34, 999]	207 [4.36, 1250]
C_{maxss} (nmol/L)			
Mean (SD)	10.9 (6.69)	8.55 (6.18)	10.2 (6.42)
Median [Min, Max]	9.78 [0.929, 52.5]	7.03 [0.337, 41.9]	8.81 [0.248, 52.4]
C_{avgss} (nmol/L)			
Mean (SD)	10.7 (6.69)	8.37 (6.17)	10.0 (6.41)
Median [Min, Max]	9.67 [0.809, 52.4]	6.87 [0.264, 41.6]	8.64 [0.182, 52.2]
C_{minss} (nmol/L)			
Mean (SD)	10.5 (6.68)	8.07 (6.15)	9.73 (6.39)
Median [Min, Max]	9.50 [0.603, 52.2]	6.58 [0.171, 41.2]	8.31 [0.0964, 51.9]

Abbreviations: AUCss = area under the concentration-time curve at steady state; Cavg = observed time-average concentration; Cmax = maximum observed concentration; Cmaxss = maximum observed concentration at steady state; Cminss = minimum observed concentration at steady state; N = number of subjects; RMS = relapsing multiple sclerosis; SD = standard deviation; Tmax = time at maximum concentration; UC = ulcerative colitis.
Source: table_posthoc_summary.R
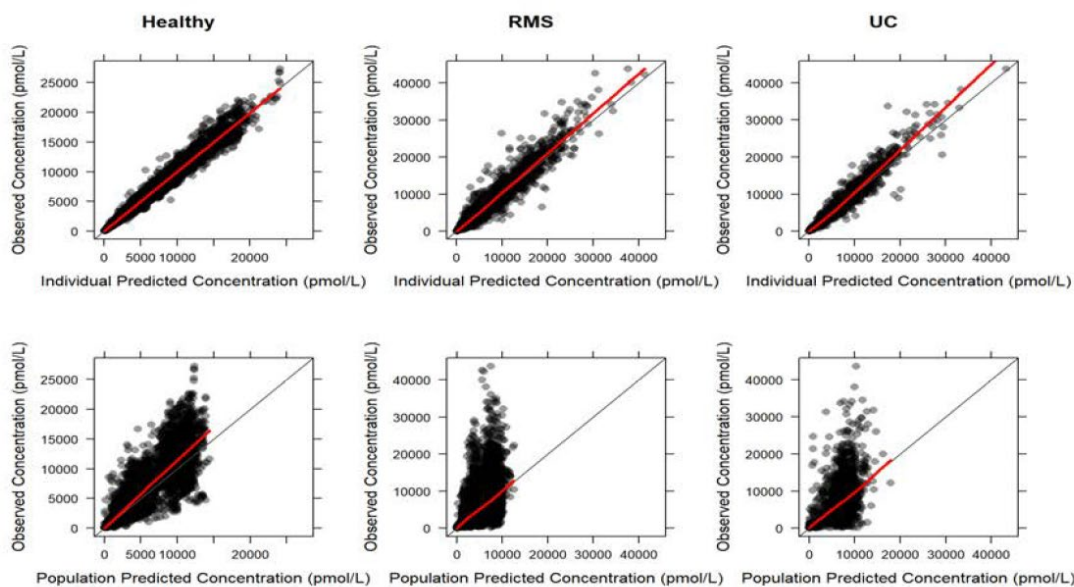
Figure 14: Diagnostic Plots from the Final PPK Model (by Disease Type)
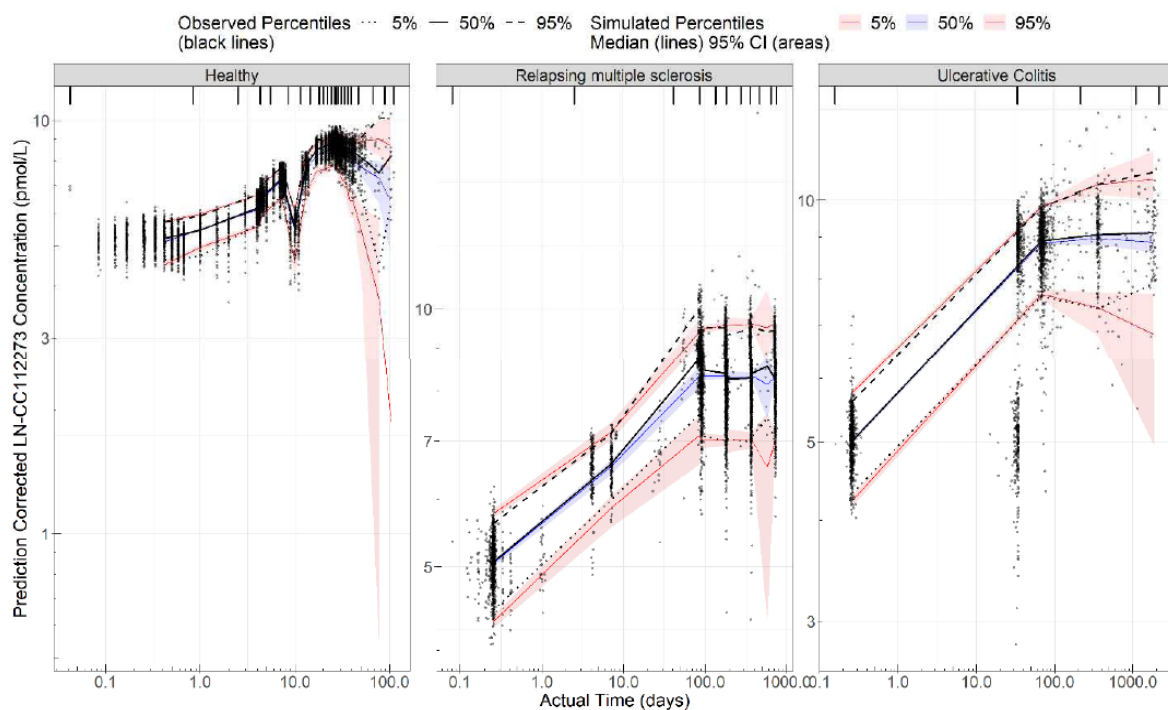
Figure 15: pcVPC Plot of All Concentrations Versus Actual Time after First Dose (Log-Scale)

Statistically significant covariates (95% CI excluded the null value) include body weight, age, bilirubin levels, sex, race, disease status, smoking status and hepatic impairment on CL/F, body weight, sex and hepatic impairment on VC/F and body weight, sex, disease status and hepatic impairment on KA. The overall apparent clearance of CC112273 in RMS population is slightly higher (<20%) than UC population, which resulted in slightly lower exposure (e.g. AUCss or Cmaxss) in RMS population than in UC population.

The most influential covariate on CL/F is smoking status. The smokers appear to have higher (~108%) apparent clearance of CC112273 than non-smokers. Although with limited number of non-white subjects (<10% of total subjects), the apparent clearance of CC112273 in non-white subjects is ~30% lower than

the white subjects. The apparent clearance of CC112273 in female subjects is moderately lower (~33%) than male subjects. The apparent clearance of CC112273 only slightly decreases with increasing age. The typical CL of a 57-year old subject accounts for about 90% of that of a 36-year subject. The apparent clearance of CC112273 also slightly decreases as body weight increases. The typical CL of a 102-kg subject accounts for about 85% of the CL in a 70-kg subject.

PPK Analysis of Ozanimod

The approach for model development of the ozanimod PPK was similar to the strategy used for the metabolite CC112273.

A total of 3057 subjects with ozanimod PK samples were available in the PPK dataset. Of these, 60 subjects did not have quantifiable post dose concentrations and 20 subjects were flagged for exclusion. These subjects were not considered in the descriptive statistics or the PPK analysis of ozanimod. Overall, 2977 subjects were included in the PPK analysis of ozanimod.

A total of 18834 (86.5%) concentrations were included in the PPK analysis of ozanimod. PK population for ozanimod analysis was slightly different from the PK population of CC112273 due to differences in samples availability and exclusions. More samples from study RPC01-202 (74.2 %) than for the metabolite model were included because there were no exclusions due to stability issues for ozanimod.

The previous model included the covariate effects of age and body weight on CL/F that were kept in the current structural model development. An IIV was estimated for KA, CL/F, VC/F, and D1. A disease effect (subjects with RMS or UC versus healthy subject as a reference) on residual variability was also evaluated and significantly improved the model predictions.

Model evaluation with GOF plots and VPCs demonstrated robust stability and predictive performance of the final PPK model. The typical CL/F and VC/F of ozanimod for a white, male, non-smoker, UC patients with a body weight of 70kg and an age of 36 years, bilirubin levels of 7 umol/L, ALT of 15 U/L, eGFR of 99.9 mL/min/1.73m2 were 174 L/h and 120 L, respectively.

Ozanimod concentration-time profiles are well characterized with a 2-compartment model with mixed zero and first order absorption and first order elimination rates. Statistically significant covariates include body weight, age, eGFR, bilirubin levels and disease status on CL/F, disease status on VC/F and body weight, sex and disease status on KA. The overall apparent clearance of ozanimod is lower in RMS population (<10%) than UC population, which resulted in similar exposures (e.g. AUCss and Cmaxss) in both populations. The most influential covariate on ozanimod apparent clearance is body weight. The typical apparent clearance of ozanimod in a 102-kg subject increases about 23% relative to a 70-kg subject. PPK final model parameter estimates are shown in the following table:

Table 20: PPK Final Model Parameter Estimates Ozanimod (Final Model)

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
DI[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

The typical terminal elimination half-life was 38.8 hours; with complete elimination expected after approximately 8 days. From the previous model developed, body weight and age were identified as statistically significant covariates of CL/F. Overall, 3 covariates indicated an important effect on PK parameter estimates, specifically the VC/F and CL/F. These include disease type, particularly the RMS group compared to the UC group, and the effect of age on VC/F and body weight on CL/F. The VC/F is expected to be lower in subjects with RMS compared to subjects with UC, and lower in younger subjects. Subjects with a lower body weight are also expected to have a lower CL/F.

Other covariates remained statistically significant following a stepwise backward elimination. These include an effect of eGFR and bilirubin on CL/F and an effect of body weight, sex, and disease type on KA. However, these have a very small exponent, indicative of a minor change in parameter estimates.

PK/PD modelling

The analyses consist of a population PK/PD analysis between CC112273 and absolute lymphocyte count (ALC); E-R analysis for clinical remission in the induction phase and maintenance phase as an efficacy endpoint; and E-R analysis for alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and infections as an efficacy endpoint.

Population PK-PD Analysis of Peripheral ALC

Subjects from 11 studies (Phase 1 to Phase 3) were included for the population PK-PD analysis. The analysis population included healthy volunteers, RMS patients and UC patients. A total of 34449 ALC measurements from 4122 subjects were included in the analysis. Population PK-PD analysis was

performed on ALC using post-hoc PK parameter estimates for the ozanimod metabolite CC112273 and a direct effect PK-PD model that was developed previously in RMS patients. Sources of variability were exploredusing standard methods. The final model was qualified using goodness-of-fit criteria and visual predictive checks (VPC).

The PK-PD analysis of ALC showed a maximum saturable decrease from baseline ALC between 68% and 85%, and the CC112273 concentration required to achieve 50% of the maximal decrease between 1.3 and 3.8 nmol/L. Females have a larger maximum effect (9.5%) than males. Compared to UC patients, healthy subjects and RMS patients have a larger (4.4%) and a smaller (-7.7%) maximum effect, respectively. A larger body weight was associated with a larger maximum effect, compared to a subject with median body weight of 69.9 kg.

The estimated parameters from the final model are presented in table below. The RSE% of the typical values are less than 6% and are less than 3% for the between subjects variability parameters. The only parameter that is not statistically significant is healthy on Emax (compared to UC), it was kept in the model because it was tested simultaneously as health status with RMS on Emax and it was statistically significant to keep both parameters in the final model.

Goodness-of-fit plots of the ALC final model by subject type are shown in **Figure 16**. The ALC prediction-corrected visual predictive check (pcVPC) plots are presented in **Figure 17** (versus CC112273 semi-logarithmic), and in **Figure 18** (versus time).

Figure 19 presents the typical ALC versus CC112273 concentrations for the subject types. Because both Emax and EC50 have disease as a covariate, a difference between the curves can be seen. Healthy subjects have the larger Emax, and RMS patients have the smaller Emax. RMS patients seem to have a smaller EC50, and healthy subjects, a larger EC50.

Table 21: ALC Final Model Parameters

Parameter	Point Estimate	RSE%	95% CI
Typical Values			
Baseline ALC (109/L)	1.76	0.482	1.74 – 1.78
Emax - Maximum Effect	0.740	1.83	0.713 – 0.766
EC50 - CC112273 with 50% reduction of maximum effect on ALC (pmol/L)	2832	5.70	2516 – 3149
Covariate Effects			
Sex on Emax (female)	0.0909	12.2	0.0692 – 0.113
Disease type on Emax (healthy)	0.0428 [a]	93.6	-0.0357 – 0.121
Disease type on Emax (relapsing multiple sclerosis)	-0.0800	26.2	-0.121 – -0.0390
Baseline body weight on Emax	0.0814	28.5	0.0359 – 0.127
Age on EC50	0.274	20.4	0.165 – 0.384
Smoking status on EC50 (smoker)	-0.333	13.4	-0.421 – -0.245
Disease type on EC50 (healthy)	0.232	46.7	0.0196 – 0.445
Disease type on EC50 (relapsing multiple sclerosis)	-0.475	15.2	-0.616 – -0.333
Baseline ALC on EC50	0.167	29.0	0.0720 – 0.262
Between Subject Variability			
On BALC	0.276	1.33	0.269 – 0.284
On Emax	0.181	2.56	0.171 – 0.190
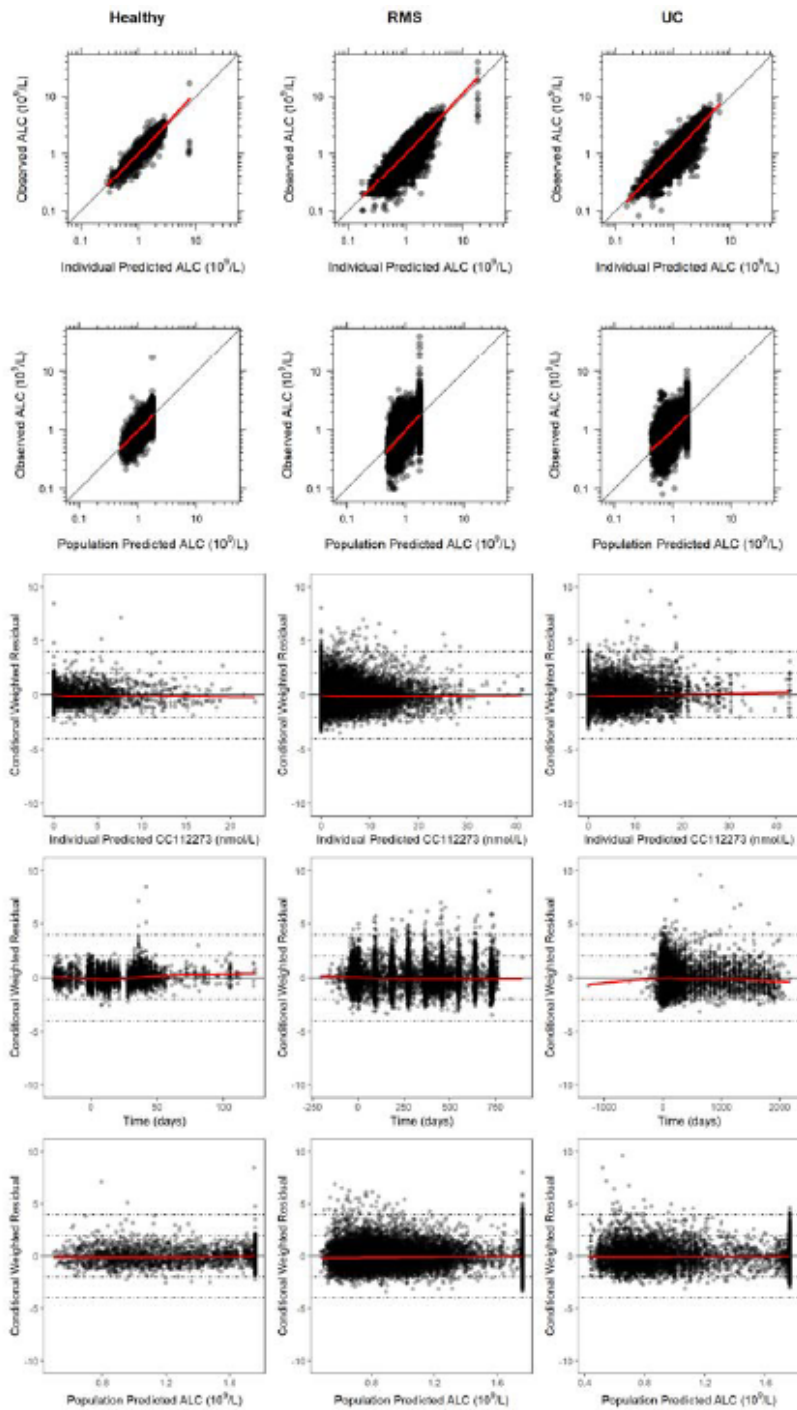
Abbreviations: ALC = absolute lymphocyte count; RMS = relapsing multiple sclerosis; UC = ulcerative colitis.
Note: Grey circles represent observed data. Overlapping grey circles appear as black circles. Black diagonal lines in plots in top row represent the line if unity (y = x). Red lines are the loess trend line for the data. Horizontal dashed lines in bottom row are at conditional weighted residual values of -4, -2, 2, and 4.
Source: FINALMODEL_results.html

Figure 16: ALC Final Model Goodness-of-Fit Plots by Subject Type
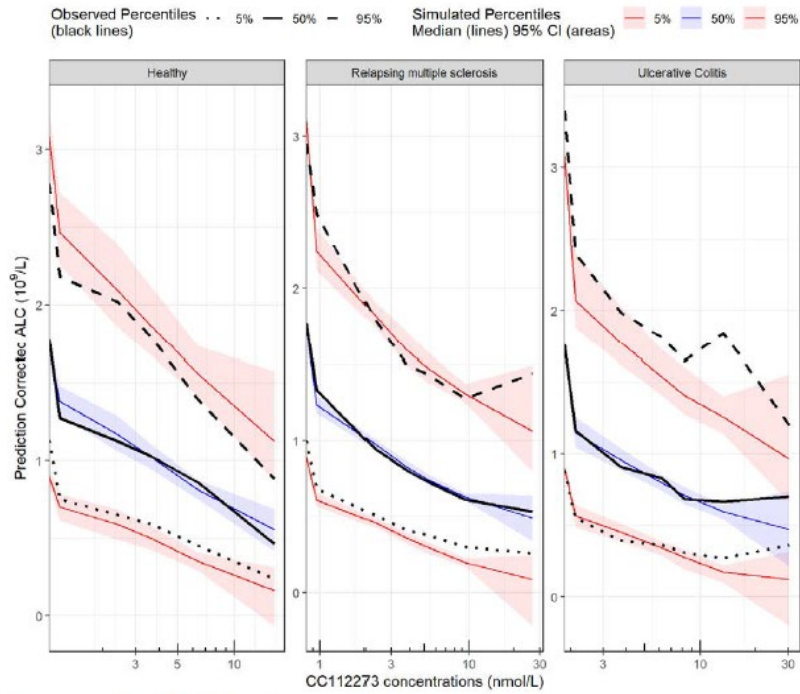
Abbreviations: ALC = absolute lymphocyte count; CI = confidence interval.
Source: FINALMODEL_vpc.html

Figure 17: Prediction-Corrected Visual Predictive Check Plot ALC Final Model versus CC112273 (Semi-Logarithmic) by Subject Type
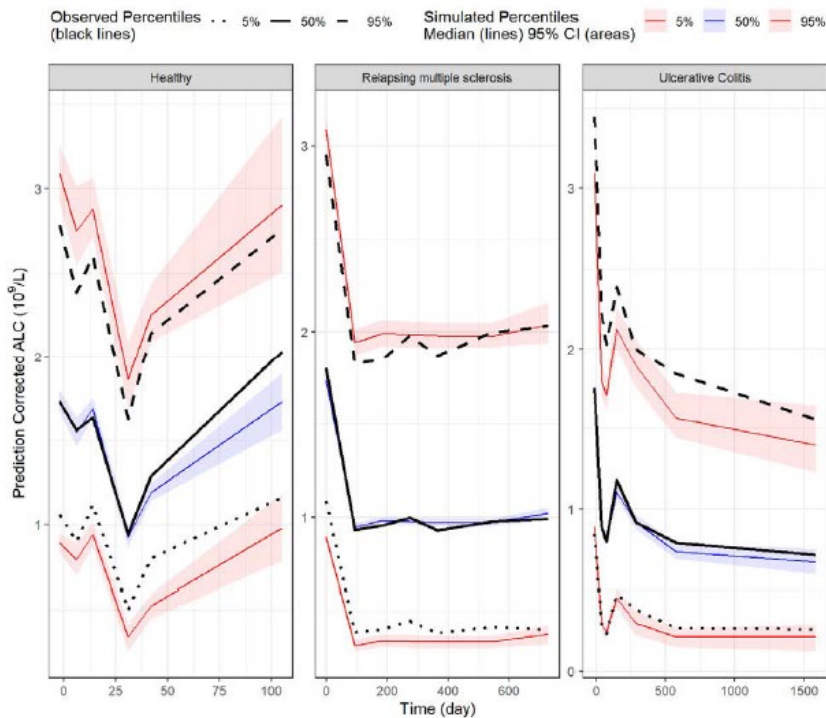
Abbreviations: ALC = absolute lymphocyte count; CI = confidence interval.
Source: FINALMODEL_vpc.html

Figure 18: Prediction-Corrected Visual Predictive Check Plot ALC Final Model versus Time
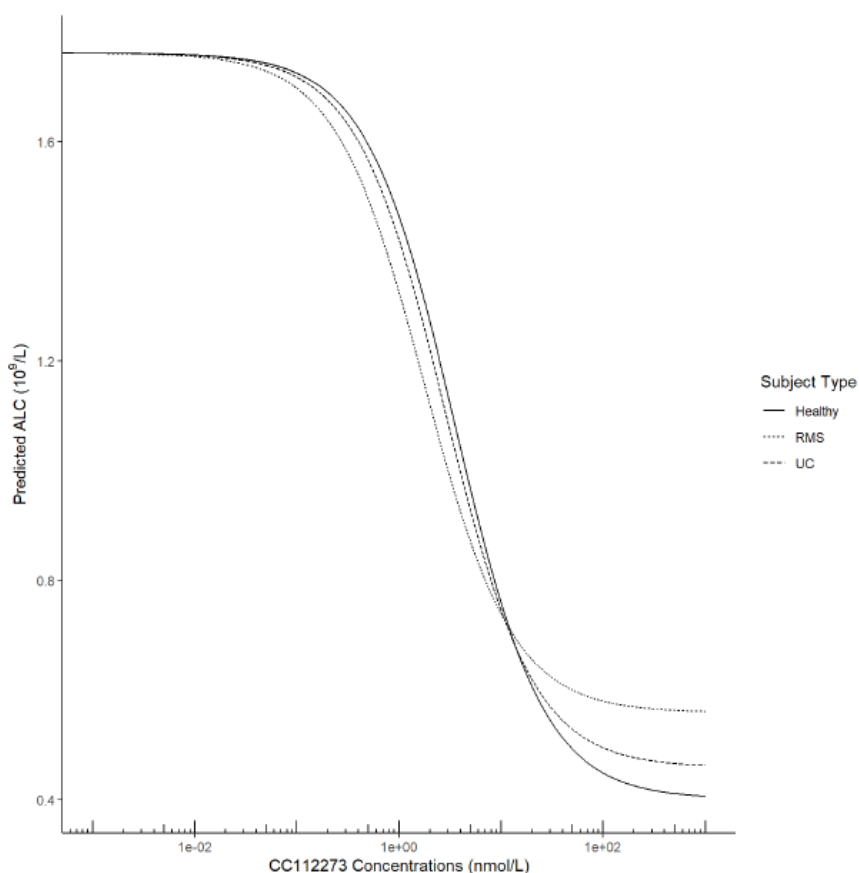
Figure 19: Predicted ALC versus CC112273 Concentrations by Typical Subject Type by Subject Type

<u>Exposure-Response Model – Efficacy (Clinical Remission)</u>

Subjects with ulcerative colitis (UC) from a single Phase 3 study were included for the Exposure-Response analysis of clinical remission. Separate evaluations of clinical remission was performed for the induction phase (Week 10) and the maintenance phase (Week 52). There were a total of 1012 subjects included in the induction phase and 526 subjects in the maintenance phase. Logistic regression analyses were performed to develop a model describing the relationship between the steady state exposure CC112273 (AUCss), and the probability of clinical remission at Week 10 or Week 52. The impact of other prognostic factors were evaluated using a full model approach with a stepwise backward deletion to arrive at a final model. The final model was qualified with visual predictive checks.

The efficacy E-R at Week 10 (or induction phase) showed a difference in clinical remission rate between subjects that received placebo and those that received ozanimod. However, the E-R was relatively flat across all exposure levels for subjects that received 1 mg ozanimod. The efficacy E-R at Week 52 (or maintenance phase) showed a clear difference in clinical remission rate between subjects that received placebo and those that received ozanimod. However, the E-R was relatively flat across all exposure levels for subjects that received 1 mg ozanimod.

Following elimination of nonsignificant predictors, the final model included CC112273 AUCss, baseline Mayo score, prior Anti-TNF use, and corticosteroid use as predictors of clinical remission. The reference individual has a baseline Mayo score of 9, no prior anti-TNF use, no corticosteroid use, and a steady-state CC112273 AUC of 204 nM*hr for subjects that received ozanimod. The probability of clinical remission for a reference individual receiving placebo is 15.1%, and for a reference individual receiving ozanimod is 43.3%.

The final model for Week 10 clinical remission exposure response showed a 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 1 mg ozanimod dose, the Week 10 clinical remission response rate was similar, with a slight trend toward greater response with higher exposure. The probability of clinical remission at Week 10 was 6% for a reference individual receiving placebo and 24.7% for a reference individual receiving ozanimod.

The final model for Week 52 clinical remission exposure response showed that across the range of exposures from the 1 mg ozanimod dose, the Week 52 clinical remission response rate was similar.

The response rate was lower in the placebo treatment group than the ozanimod treatment group. The probability of clinical remission at Week 52 was 15.1% for a reference individual receiving placebo and 43.3% for a reference individual receiving ozanimod.
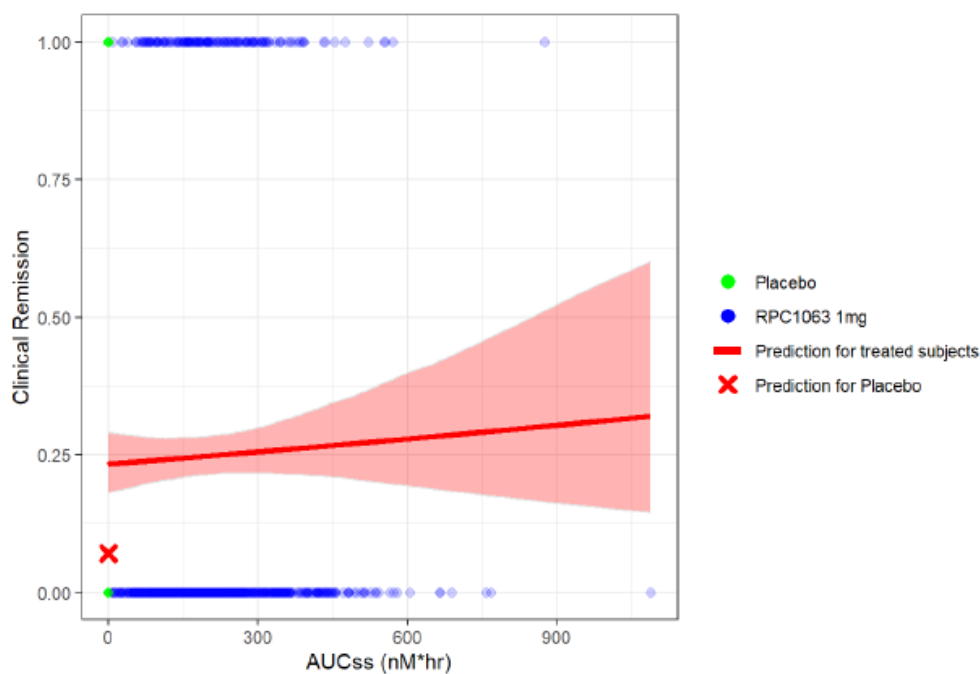
Figure 20: Observed and Model-Predicted Week 10 Clinical Remission (Induction Phase) for Placebo and Ozanimod-Treated Subjects

Table 22: Final Parameter Estimates for Week 10 Clinical Remission (Induction Phase) Logistic Regression

Parameter	Estimate	Odds Ratio	Standard Error of Estimate	95% CI of Odds Ratio
Intercept for Ozanimod-treated Subjects	-1.11	0.329	0.120	0.259, 0.414
Intercept for Placebo-treated Subjects	-1.47	0.230	0.305	0.121, 0.403
Effect of CC112273 AUCss for Ozanimod-treated Subjects	4.01e-04	1.00	7.24e-04	0.999, 1
Effect of Baseline Mayo Score	-0.320	0.726	6.24e-02	0.642, 0.820
Effect of Prior Anti-TNF Use	-0.707	0.493	0.213	0.321, 0.742
Effect of Use of Corticosteroids	-0.558	0.572	0.210	0.375, 0.857

Abbreviations: AUCss = area under the concentration-time curve at steady state; CI = confidence interval; TNF = tumor necrosis factor.
Note: The effects of CC112273 AUCss and baseline Mayo score are centered on the median values of 197 nM*hr and 9, respectively. The reference subject had the median value for baseline May score, no prior anti-TNF use, no corticosteroid use, and the median value for CC112273 AUCss for subjects treated with ozanimod. The intercept for a placebo patient is the sum of the Intercept for Ozanimod-treated Subjects and the Intercept for Placebo-treated Subjects. The odds ratio for a continuous variable corresponds to a change of one unit for that variable.
Source: CELG-1889-Efficacy-07OCT2020.html
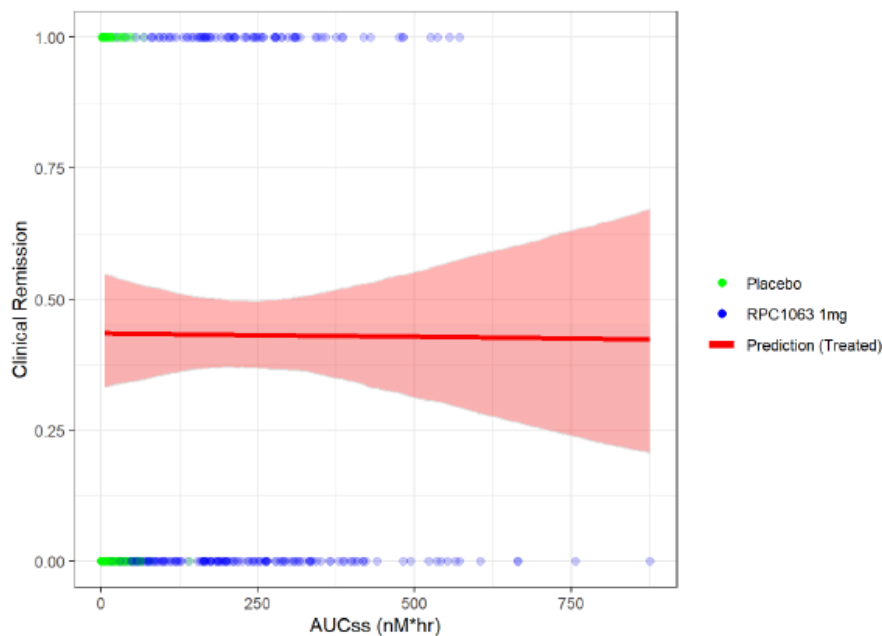
Figure 21: Observed and Model-Predicted Week 52 Clinical Remission (Maintenance Phase) for Placebo and Ozanimod-Treated Subjects

Table 23: Final Parameter Estimates for Week 52 Clinical Remission (Maintenance Phase) Logistic Regression

Parameter	Estimate	Odds Ratio	Standard Error of Estimate	95% CI of Odds Ratio
Intercept for Ozanimod-treated Subjects	-0.271	0.763	0.160	0.556, 1.04
Intercept for Placebo-treated Subjects relative to Ozanimod	-0.931	0.394	0.226	0.251, 0.611
Effect of CC112273 AUCss for Placebo-treated Subjects	1.93e-02	0.981	1.13e-02	0.958, 1.00
Effect of CC112273 AUCss for Ozanimod-treated Subjects	-5.32e-05	1.00	9.43e-04	0.998, 1.00
Effect of Use of Corticosteroids	-0.815	0.443	0.249	0.268, 0.713

Abbreviations: AUCss = area under the concentration-time curve at steady state; CI = confidence interval.
Note: The effects of CC112273 AUCss are centered on the median values of 15.8 nM*hr for placebo-treated subjects and 204 nM*hr for ozanimod-treated subjects. The reference placebo subject had no corticosteroid use, and a CC112273 AUCss of 15.8 nM*hr. The reference ozanimod subject had no corticosteroid use and a CC112273 AUCss of 204 nM*hr. The intercept for a placebo patient is the sum of Intercept for Ozanimod-treated Subjects and Intercept for Placebo-treated Subjects relative to Ozanimod. The odds ratio for a continuous variable corresponds to a change of one unit for that variable.
Source: CELG-1889-Efficacy-07OCT2020.html

Exposure-Response Analysis of Safety

Subjects from two Phase 2 studies (RMS patients) and one Phase 3 study (UC patients) were included for the exposure-response analysis of elevated ALT and/or AST levels and infections and infestations. Separate evaluations of each safety endpoint (ALT/AST and Infections/Infestations) was performed for the induction phase (Week 10) and the maintenance phase (Week 52). There were a total of 2750 subjects included in the induction phase (includes both RMS and UC) and 526 subjects in the maintenance phase (UC only). Time-to-event analyses were performed for the probability of first event for each endpoint. The impact of other prognostic factors were evaluated using a full model approach with a stepwise backward deletion to arrive at a final model. The final model was qualified with visual predictive checks.

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 in patients with UC or RMS.

The final model was derived from the full model using backward elimination (using Bayesian information criteria]).

Safety E-R of ALT and/or AST

A low incidence rate for both the induction and maintenance phases was shown, and across the range of CC112273 exposures from 0.5 mg to 1 mg ozanimod QD, the relative risk of AEs remained low. The ALT/AST endpoint was defined as the first observation of either an ALT or an AST value that exceeded 3 times the upper limit of normal.

Visual predictive checks of the time-to-event profiles for ALT/AST elevations during the induction phase (Week 10) were prepared for induction phase and maintenance phase (Figure 22 and Figure 23). There was an overprediction of the incidence rate from Day 300 through Day 650; however, the overall probability of an ALT/AST elevation was low (<15%).

The hazard ratios from the final model are presented in Table 24 for induction phase and in Table 25 for maintenance phase. The predicted probability of an ALT/AST elevation at Week 10 for UC patients across a range of steady-state CC112273 exposures is shown in **Figure 22Figure 24**, the corresponding predictions for the maintenance phase are shown in **Figure 23**.
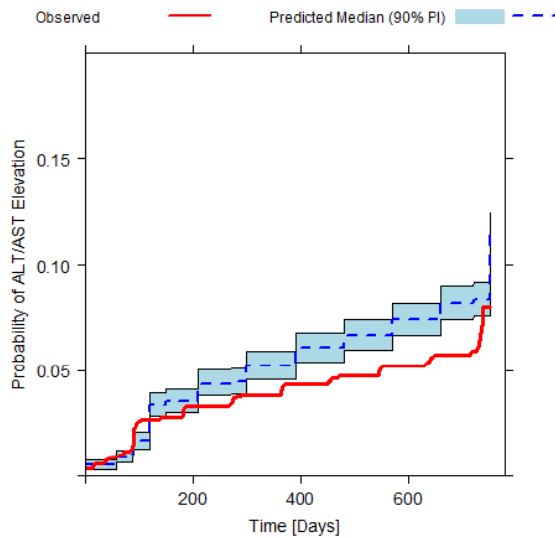
Figure 22: Visual Predictive Check for ALT/AST Endpoint for Induction Phase
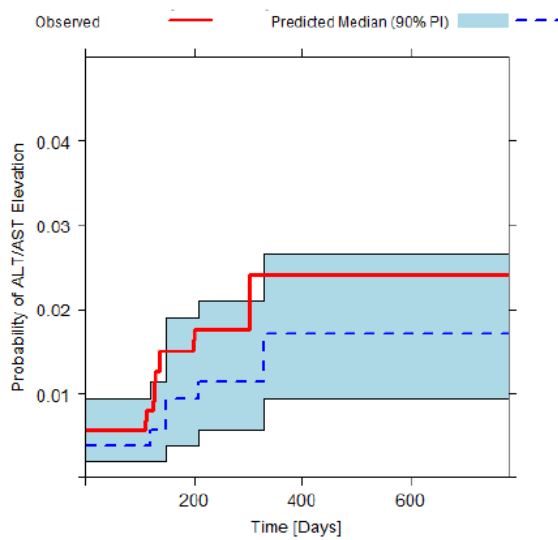
Figure 23: Visual Predictive Check for ALT/AST Endpoint for Maintenance Phase

Table 24: Hazard Ratios from Final Model for ALT/AST Endpoint for Induction Phase

Characteristic	Hazard Ratio	95% CI
Exposure (Ozanimod Treatment)		
5th Quantile AUCss (27 nM*hr)	1.08	1.04, 1.12
95th Quantile AUCss (396 nM*hr)	2.96	1.69, 5.19
Disease		
RMS	Reference	NA
UC	1.99	1.04, 3.82
Sex		
Female	Reference	NA
Male	2.37	1.59, 3.54

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUCss = area under the concentration-time curve; CI = confidence interval; RMS = relapsing multiple sclerosis; UC = ulcerative colitis.
Note: A reference individual had a CC112273 AUCss of 0 nM*hr, had RMS disease, and was female.
Source: Safety ER Analysis.R

Table 25: Hazard Ratios from Final Model for ALT/AST Endpoint for Maintenance Phase

Characteristic	Hazard Ratio	95% CI
Exposure (Ozanimod Treatment)		
5th Quantile AUCss (53 nM*hr)	1.18	1.0, 1.4
95th Quantile AUCss (538 nM*hr)	5.44	1.0, 29.56

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUCss = area under the concentration-time curve at steady state; CI = confidence interval.
Note: A reference individual had a CC112273 AUCss of 0 nM*hr.
Source: Safety ER Analysis.R
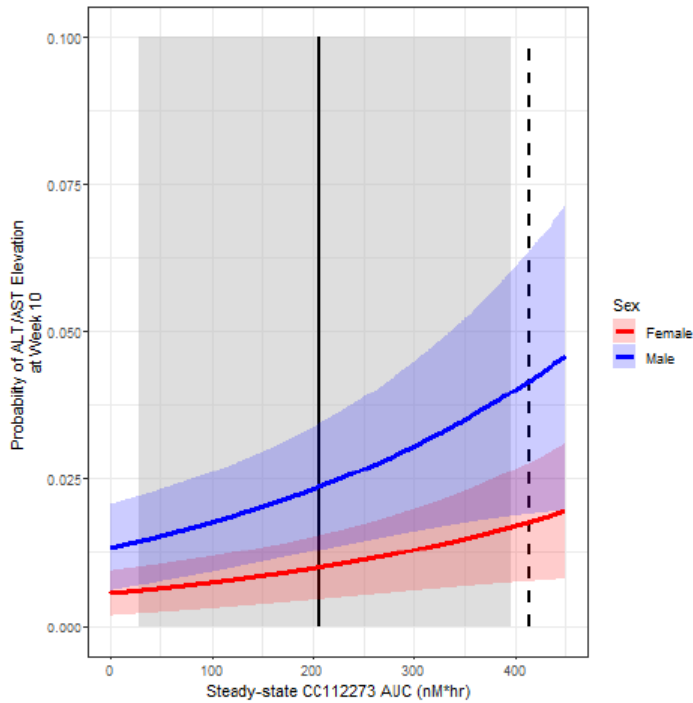
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the concentration-time curve; UC = ulcerative colitis.

Note: Shaded gray area represents the 5th to 95th quantile of model-predicted steady-state CC112273 exposure. The red and blue lines represent the predicted probability of an ALT/AST elevation for female and male UC patients, respectively, at Week 10 across the entire range of model-predicted steady-state CC112273 exposure from patients included in the analysis. The red and blue shaded areas represent the 95% confidence interval for female and male patients, respectively. Solid black vertical line is at CC112273 AUC of 207 nM*hr. Dashed black vertical line is at CC112273 AUC of 414 nM*hr.

Source: Safety ER Analysis.R

Figure 24: Predicted Probability of an ALT/AST Elevation at Week 10 in UC Patients Using the Final Model

Figure 25: Predicted Probability of an ALT/AST Elevation at Week 52 in UC Patients Using the Final Model

The safety E-R analysis of ALT and/or AST elevations showed that less than 4% of subjects experienced an elevation within the entire CC112273 exposure range (0.5 to 1 mg ozanimod QD) in the induction phase. Statistically significant predictors of ALT and/or AST elevations in the induction phase included

- steady-state CC112273 exposure (higher hazard ratio for higher exposure)

- disease type (higher hazard ratio UC relative to RMS)

- sex (higher hazard ratio for males).

The analysis of the maintenance phase, which included only UC subjects, also had a low incidence (<2%) of ALT and/or AST elevations for all CC112273 exposure levels. Statistically significant predictors of ALT and/or AST elevations in the maintenance phase included steady-state CC112273 exposure (hazard ratio = 5.44 at AUCss of 538 nM*hr relative to no exposure). The 95% confidence interval for the hazard ratio for the effect of steady-state CC112273 exposure included 1, or no effect.

Safety E-R of infections and infestations

Similar to the safety endpoint of ALT/AST elevation time to event-analyses were used to figure out significant predictors for infections as a possible adverse event under ozanimod treatment. Analysis was split into induction phase and maintenance phase.

The analysis of the induction phase showed, following the backward elimination process, that the remaining predictors were CC112273 AUCss, age, sex, baseline body weight, smoking status, and prior corticosteroid use. The impact of CC112273 AUCss was not statistically significant (p>0.10). The final model parameter estimates are presented in Table 26.

The analysis of the maintenance phase, which included only UC subjects, showed an incidence of infections of 17.5% for all CC112273 exposure levels. Statistically significant predictors of infections in the maintenance phase included baseline body weight (hazard ratio = 0.77 at 51 kg and 1.48 at 108 kg relative to 73 kg), and baseline albumin level (hazard ratio = 1.43 at 36 g/L and 0.78 at 48 g/L relative to 43 g/L). Steady-state CC112273 exposure was not a statistically significant predictor and the 95% confidence interval for the hazard ratio included 1.0 (hazard ratio = 1.55 at AUCss of 409 nM*hr relative to no exposure). The incidence of infections and infestations increased with increasing exposure, but the trend of increasing incidence of infections and infestations with increasing CC112273 exposure was not significant.

Hazard ratios for both models are listed in **Table 27** and **Table 28**. VPC plots are shown in Figure 26 and Figure 27, the resulting predicted probability of an infection is depicted in *Figure 28* and *Figure 29*.

Table 26: Final Model Parameter Estimates for Infection Endpoint for Induction Phase

Predictor	Estimate	Standard Error of Estimate	95% Confidence Interval
AUCss	0.000560	0.000343	-0.00011, 0.0012
Age	-0.0130	0.00388	-0.021, -0.0054
Sex (Male)	-0.404	0.0915	-0.58, -0.22
Baseline Body Weight	0.00783	0.00254	0.0028, 0.013
Smoking Status (Smoker)	0.152	0.0961	-0.036, 0.34
Corticosteroid Use (Yes)	0.209	0.0824	0.048, 0.37

Abbreviations: AUCss = area under the concentration-time curve at steady state.
Note: A reference individual had a CC112273 AUCss of 0 nM*hr, 37 years old, female, 70 kg body weight, not a smoker, and no corticosteroid use.
Source: Safety ER Analysis.R

Table 27: Hazard Ratios from Final Model for Infection Endpoint for Induction Phase

Characteristic	Hazard Ratio	95% CI
Exposure		
5th Quantile AUCss (27 nM*hr)	1.02	1.0, 1.03
95th Quantile AUCss (396 nM*hr)	1.25	0.96, 1.63
Age		
5th Quantile (22 year)	1.21	1.35, 1.08
95th Quantile (59 year)	0.75	0.63, 0.88
Sex		
Female	Reference	NA
Male	0.67	0.56, 0.8
Baseline Body Weight		
5th Quantile (49 kg)	0.85	0.94, 0.77
95th Quantile (102 kg)	1.28	1.1, 1.51
Smoker		
No	Reference	NA
Yes	1.16	0.96, 1.4
Prior Corticosteroid Use		
No	Reference	NA
Yes	1.23	1.05, 1.45

Abbreviations: AUCss = area under the concentration-time curve at steady state; CI = confidence interval; NA = no available.
Note: A reference individual had a CC112273 AUCss of 0 nM*hr, 37 years old, female, 70 kg body weight, not a smoker, and no corticosteroid use.
Source: Safety ER Analysis.R

Table 28: Hazard Ratios from Final Model for Infection Endpoint for Maintenance Phase

Characteristic	Hazard Ratio	95% CI
Exposure (Ozanimod Treatment)		
5th Quantile AUCss (53 nM*hr)	1.06	0.99, 1.13
95th Quantile AUCss (538 nM*hr)	1.77	0.92, 3.43
Baseline Body Weight		
5th Quantile (51 kg)	0.77	0.62, 0.96
95th Quantile (108 kg)	1.48	1.07, 2.07
Baseline Serum Albumin		
5th Quantile (36 g/L)	1.43	2.00, 1.02
95th Quantile (48 g/L)	0.78	0.61, 0.99

Abbreviations: AUCss = area under the concentration-time curve at steady state; CI = confidence interval.
Note: A reference individual had a CC112273 AUCss of 0 nM*hr, 73 kg body weight, and 43 g/L baseline albumin.
Source: Safety ER Analysis.R
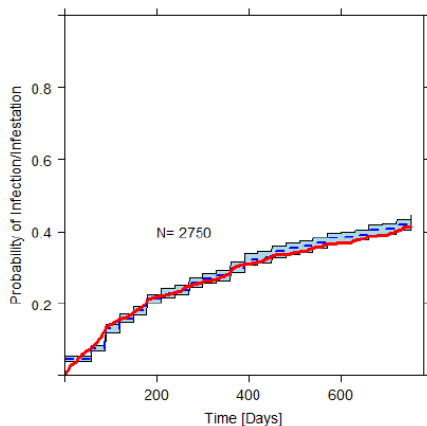
Abbreviations: N = number; PI = prediction interval.
Source: Safety ER Analysis.R

Figure 26: Visual Predictive Check for Infections Endpoint for Induction Phase
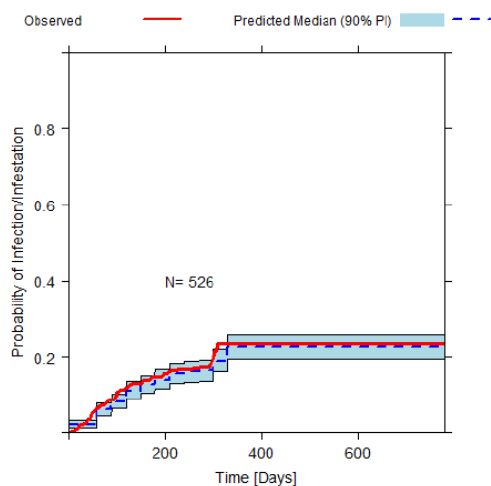
Abbreviations: N = number; PI = prediction interval.
Source: Safety ER Analysis.R

Figure 27: Visual Predictive Check for Infection Endpoint for Maintenance Phase
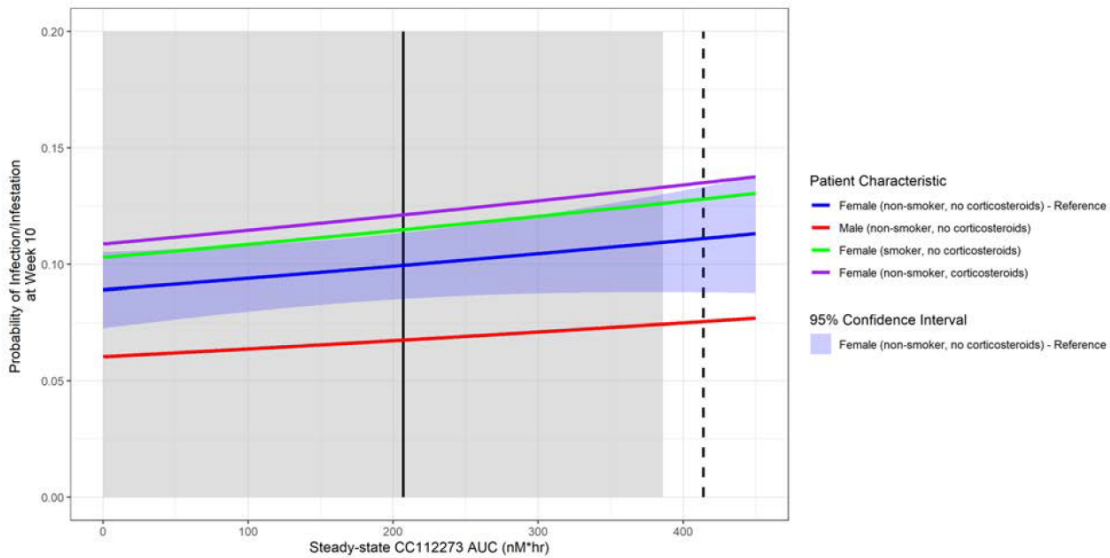
Abbreviations: AUC = area under the concentration-time curve; UC = ulcerative colitis.
Note: The shaded gray area represents the 5th to 95th quartile of model-predicted steady-state CC112273 exposure. The blue, red, green, and purple lines represent the predicted probability of an infection/infestation in UC patients at Week 10 across the entire range of model-predicted steady-state CC112273 exposure from patients included in the analysis. The blue shaded area represents the 95% confidence interval for the reference individual. The Solid black vertical line is at CC112273 AUC of 207 nM*hr. Dashed black vertical line is at CC112273 AUC of 414 nM*hr. Source: Safety ER Analysis.R

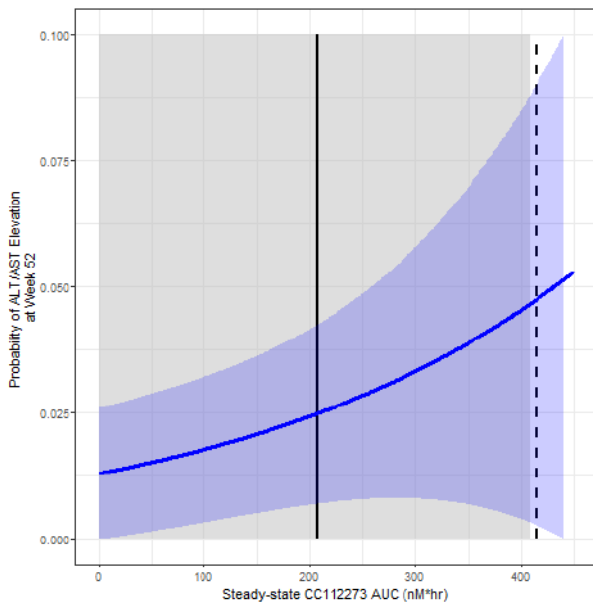**Figure 28: Predicted Probability of an Infection/Infestation at Week 10 in UC Patients Using the Final Model**
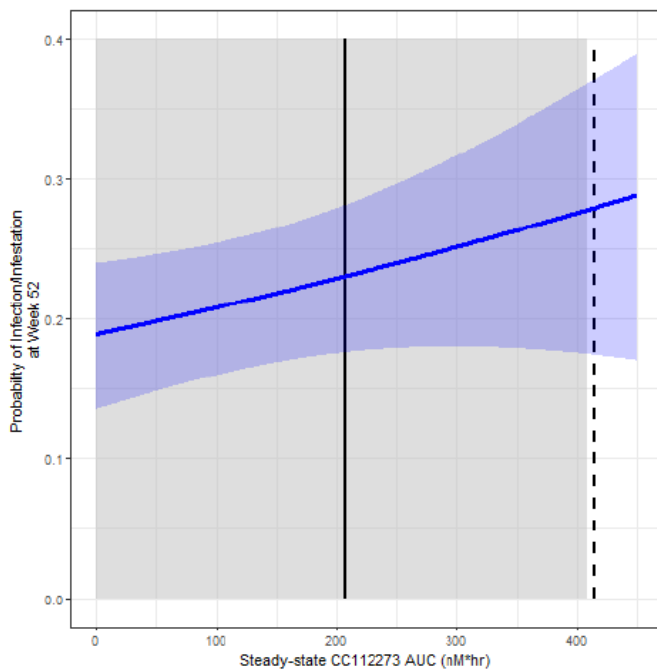
Figure 29: Predicted Probability of an Infection/Infestation at Week 52 in UC Patients Using the Final Model

2.3.5. Discussion on clinical pharmacology

Clinical Pharmacodynamics

Study RPC-1063-CP001 was conducted to evaluate the effect of cyclosporine, a probe drug for inhibition of BCRP on the plasma concentrations of ozanimod as well as its major active metabolites CC112273 and CC1084037, and revealed that the influence not only on the parent compound, but also on the main metabolites remain outside the range of potential clinical relevance. The proposed changes in the PI take adequately account of the results of the study. However, there is need for clarification on the adequacy of the information proposed for situations when other inhibitors (e.g. of CYP21C8) are administered concomitantly with inhibitors of BCRP.

The applicant has further submitted an extension study of a previous PK study (RPC01-1001) which evaluated the pharmacodynamic response to ozanimod on different sets of leukocyte subpopulations. There was a clear differential effect on different peripheral leucocyte populations, and it could be shown that populations referring to the innate immune response (such as NK and NKT-cells) were not relevantly affected and section 5.1 of the SmPC has been updated accordingly.

In addition, the applicant has submitted Study RPC01-1915, an extension study to further evaluate the safety, pharmacodynamics, and pharmacokinetics of ozanimod and active metabolites in healthy adult subjects further analysing the previous studies RPC01-1912, -1913, and -1914 in the context of the PK/PD documentation for the recovery from the peripheral leucocyte reduction. The study provided a good approximation of the recovery kinetics, which is thought to occur around 85 days post cessation of dosing. An amendment of the SmPC section 5.1 has been introduced to update the time to recovery of lymphocytes taking into account the variability observed.

Ozanimod has been demonstrated to be clinically effective with a benefit risk profile administered as 1 mg once daily in patients with Relapsing Remitting Multiple Sclerosis. To evaluate the appropriateness of 1 mg once daily in patients with UC, and to characterize the therapeutic window of ozanimod for patients with ulcerative colitis, an integrated PK assessment was made for ozanimod and the major metabolite CC112273, the PK/PD relationship with ALC reduction, dose-response and E-R relationships for efficacy, and E-R assessments for safety.

The PK-PD analysis of ALC on study CLG-Certara-UC-358-2 showed a maximum saturable decrease from baseline ALC between 68% and 85%, and the CC112273 concentration required to achieve 50% of the maximal decrease between 1.3 and 3.8 nmol/L.

A higher ALC baseline level was associated with a higher EC_{50}. The E_{max} and EC_{50} parameters in the final model are correlated, which is not unexpected given the relatively narrow dose range for ozanimod (0.25 mg to 2 mg) studied and large between subject variability in ALC response.

ALC simulations based on post hoc estimates of UC patients with ozanimod 0.5 mg and 1 mg daily were performed. The median times to recovery to 90% of baseline ALC after the patients stop the treatment were 52 and 67 days for ozanimod 0.5 mg and 1 mg daily, respectively. The median change from baseline was -46.8% and -57.8% for ozanimod 0.5 mg and 1 mg daily, respectively.

The dose dependence in recovery is consistent with the 0.5 mg having lower drug concentrations and ALC reduction than 1 mg, so recovery is more rapid. The mean simulated recovery of 32.8 days for 1 mg in UC is comparable to the 31.3 days in RMS, suggesting a similar recovery time across both disease states. The simulation results are comparable to the reported UC study results of approximately 35 days.

The evaluation of efficacy for ozanimod in the proposed indication is based on a pivotal Phase 3 study and a supportive Phase 2 study conducted in UC: Studies RPC01-3101 and RPC01-202. In this study, Fecal calprotectin, a biomarker of intestinal inflammation, was also measured.

In patients with UC, treatment with ozanimod resulted in a decrease in the inflammatory marker, faecal calprotectin (FCP) during the induction period, which was then maintained throughout the maintenance period (at 10 and 52 weeks).

A very thorough PK/PD analysis was performed regarding the Absolute Lymphocyte Count (ALC), with data also from the MS studies, however, in MS, ALC is the only PD biomarker available while in Ulcerative Colitis fecal calprotectin (FCP) is a much more common PD biomarker. Upon request from CHMP, the MAH conducted an exploratory analysis of the relationship between CC112273 exposure and FCP response in the Induction and Maintenance Periods of RPC01-3101 (CLG-Certara-UC-358-3). Although the results from the exploratory analysis of exposure-response between CC112273 and FCP were not quantitatively strong, qualitative results suggest a relation between ozanimod levels and FCP reduction. Additionally, although in the context of UC, ALC is a biomarker related to the mechanism of action, while fecal calprotectin (FCP) is a downstream biomarker of intestinal inflammation, efficacy results supersede the absence of a complete correlation of ozanimod and this PD biomarkers, therefore this issue was considered adequately addressed.

Clinical Pharmacokinetics

Two new Phase 1 studies were submitted. Study RPC01-1915, a Phase 1 extension study was conducted to provide data to further characterize the elimination kinetics of CC112273, and recovery kinetics of ALC in healthy subjects. Study RPC-1063-CP-001 was conducted to assess the impact of cyclosporine, a breast cancer resistance protein (BCRP) inhibitor, on the PK of the major active metabolites, CC112273 and CC1084037. This study provided additional data to supplement the results from Study RPC01-1903 and demonstrated that cyclosporine did not impact the PK of the major circulating metabolites CC112273 and CC1084037.

The population pharmacokinetics of ozanimod and CC112273 were previously characterized to support the original RRMS application. With the addition of data from the UC program, these population models were updated to incorporate the new data, and covariate assessments were revised and expanded. CC112273 PK parameters are predictive of the interconverting metabolite CC1084037 and CC112273 makes up the predominant circulating moiety. Additionally, CC1084037 and CC112273 time-matched concentrations were found to be highly correlated in a large dataset including Phase 1, 2, and 3 studies (correlation coefficient: 0.97). Therefore, PopPK analyses focused on quantifying concentrations of ozanimod and CC112273. Intrinsic and extrinsic factors associated with changes in CC112273 PK would be anticipated to apply similarly to the interconverting metabolite CC1084037.

Metabolite CC112273 Population pharmacokinetics were described with a 2-compartment disposition model and linear elimination. The rate of formation of the active metabolite was characterized using an absorption rate and fixed lag time describing the rate of appearance of CC112273 in the central compartment following dosed ozanimod in the drug depot, and relative bioavailability capturing the relative extent of metabolite formation. The most impactful covariates included a 108% increase in CL/F in smokers, and patients in the 95th percentile of body weight having a 179% increase in VC/F and 144% increase in KA.

The final CC112273 PopPK model also included statistically significant covariate effects of body weight, age, bilirubin, sex, race, disease type, and hepatic impairment on CL/F; sex and hepatic impairment for VC/F; and sex, hepatic impairment, and disease type for KA. Results indicate no clinically meaningful difference in the PK in elderly patients, and that no dose adjustments are needed in patients over 65 years.

Ozanimod population pharmacokinetics were described with a 2-compartment disposition model, a mixed zero-order and first order absorption rate, and linear elimination. The most impactful covariates on PK parameters were an increase in apparent clearance (CL/F) up to 23% for the 95th percentile of body weight, a 63.6% reduction in apparent central volume of distribution (VC/F) in RMS versus UC patients. The final ozanimod PopPK model included covariate effects of body weight, age, estimated glomerular filtration rate (eGFR), bilirubin and disease type on CL/F, disease type on VC/F, and body weight, sex, and disease type on first-order absorption rate constant (KA).

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology has been sufficiently characterised in patients with UC.

2.4. Clinical efficacy

Studies RPC01-202 and RPC01-3101 were designed to evaluate the treatment effect of ozanimod in patients with moderate to severe UC using different but complementary study designs (treat through versus randomized withdrawal). Both studies included an Induction Period and a Maintenance Period, with the objective to demonstrate efficacy at the end of each period.

According to the MAH, due to the study design features unique to each of these randomized, controlled studies, no formal data integration of efficacy results was performed, and results from the studies are presented individually.

The MAH assumed the term "statistically significant" refers to p-values ≤ 0.05 for treatment comparisons that were subject to hierarchical testing schemes predefined in the SAPs, which controlled for type I error at the 5% level of significance. The term "nominally significant" refers to p-values ≤ 0.05 for treatment comparisons that do not control for type I error at the 5% level of significance, either because the treatment comparison was not included in the hierarchy or because the treatment comparison was a post hoc analysis. To enhance clarity in this regard, statistically significant p-values are designated in tables using boldface type and nominally significant p-values are designated using italicized type.

2.4.1. Dose response study

No dose response studies were included for the development of ozanimod for UC. Study RPC01-202 used two doses in the induction period (0.5mg and 1mg vs placebo for 9 weeks) and supports the use of the 0.92mg (1mg/dose)

2.4.1.1. Study RPC01-02 – main study

Methods

Study RPC01-202 was a Phase 2, multi-center, parallel-group randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of ozanimod versus placebo in adults aged 18 to 75 years with moderately to severely active UC at screening, defined as a Mayo score of 6 to 12 inclusive with an endoscopy subscore of ≥ 2.

Study design:

Eligible subjects were randomized in a 1:1:1 ratio to receive 1 of 3 treatment regimens QD: placebo, ozanimod 0.5 mg, or ozanimod 1 mg. The Induction Period was 9 weeks, consisting of dose escalation over 7 days, followed by the assigned dose for 8 weeks. While the Study RPC01-3101 protocol included

the 7-day dose escalation in the determination of the length of the Induction and Maintenance Periods (see below), the Study RPC01-202 protocol did not. Therefore, the end of the Induction Period in Study RPC01-202 has been renamed Week 9 and the end of the Maintenance Period has been re-named Week 33 (termed Week 8 and Week 32, respectively, in the Study RPC01-202 clinical study report [CSR]) in order to ensure consistency between the studies in this SCE.

The overall study design is shown in the following figure:
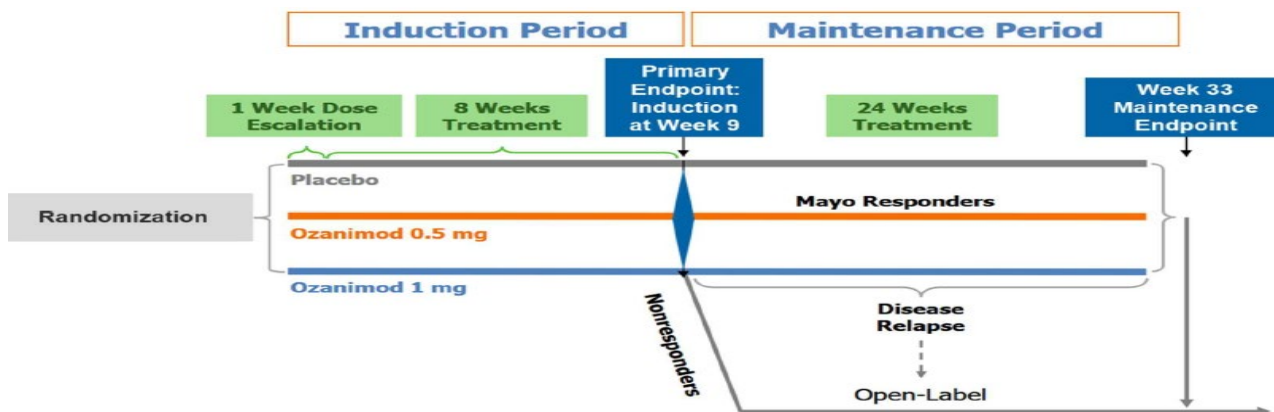
Figure 30: RPC01-202 Study Design Schematic

Subjects who completed the Induction Period and were responders at Week 9 (based on the 4-component Mayo definition) entered the 24-week Maintenance Period in which they continued to receive the same study treatment as during the Induction Period. Individual subject treatment remained blinded until all subjects reached the end of the Maintenance Period (Week 33). Subjects who completed the Induction Period and were non-responders at Week 9, and those who completed the Maintenance Period, and those who experienced disease relapse) during the Maintenance Period were eligible to enter the OLP

Study participants

To be enrolled, patients had to be receiving treatment with oral aminosalicylates or prednisone. Prior, but not concomitant, anti-TNF therapy was allowed, and randomization was stratified according to prior anti-TNF therapy experience (yes or no). Subjects with severe extensive colitis, a diagnosis of Crohn's disease or indeterminate colitis or the presence or history of a fistula consistent with Crohn's disease, or positive stool culture for pathogens were excluded.

Subjects who were receiving oral 5-ASA or oral corticosteroids at Screening were to keep their prescribed dose steady through the Induction Period.

All subjects in the OLP received daily study treatment with ozanimod 1 mg. All subjects, including those subjects who had received ozanimod 1 mg treatment in the Induction Period or Maintenance Period, underwent the dose escalation regimen to ensure blinding and to mitigate potential side effects of ozanimod when initiating treatment.

Subjects who did not show clinical improvement 8 weeks after initiation of the RPC01-202 OLP were to discontinue from the study. After completing 1 year of the OLP of Study RPC01-202, eligible subjects were able to immediately transition into the Phase 3 OLE Study RPC01-3102. The Sponsor stopped Study RPC01-202 in August 2019 in order to consolidate clinical studies; subjects had the opportunity to transition to the OLE Study RPC01- 3102 to continue treatment with investigational product.

Study Objectives:

The primary objective of the trial was to compare the efficacy of RPC1063 vs. placebo for induction of clinical remission at Week 8 in patients with moderately to severely active UC. The Secondary Study Objectives were to:

- Compare the efficacy of RPC1063 vs. placebo at Weeks 8 and 32 as measured by clinical response, clinical remission, and mucosal healing

- Compare the overall safety and tolerability of RPC1063 vs. placebo for the duration of the trial

Outcomes/ endpoints:

The following endpoints were used for the evaluation of efficacy in this study

Induction Period

- Primary endpoint (Week 9): Clinical remission (4-component Mayo)

- Key secondary endpoints (Week 9): Clinical response (4-component Mayo), Change from Baseline in Mayo score, Endoscopic improvement.

- Exploratory efficacy endpoints (Week 9): Clinical response, remission, or endoscopic improvement in subjects who previously received anti-TNF therapy or were refractory, lost response to, or intolerant of anti-TNF therapy, Histologic remission

Maintenance Period

No hierarchy of endpoints was introduced for the following:

- Clinical remission (4-component Mayo)

- Clinical response (4-component Mayo)

- Endoscopic improvement

In Study RPC01-202, endoscopic improvement was defined as an endoscopy subscore ≤ 1 (normal or inactive disease, or mild disease [erythema, decreased vascular pattern, mild friability]), and was termed "mucosal healing" in the RPC01-202 CSR. Since the definition (endoscopy subscore of ≤ 1 point) is the same as the definition for "endoscopic improvement" in Study RPC01-3101, "endoscopic improvement" is used throughout this SCE for consistency.

For the symptom scoring in this study, both RBS and SFS for a subject had to be available on the same day. The final scoring algorithm was using the last 14 days before the evaluation time-point. RBS and SFS were obtained from the subjects' paper diary entries (Mayo Diary Card). Sites then calculated RBS and SFS using the Mayo Score Worksheet. Endoscopy subscore was provided by a blinded central reader.

An interactive voice response system (IVRS) was used to stratify patients by prior anti-TNF treatment (yes or no) and to provide the treatment assignment for each patient. The randomisation scheme has been provided by the applicant in an appendix to the study report.

Blinding

During trial conduct through the time of data lock for the Induction Period, the Sponsor, patients, Investigators, and site personnel were blinded to treatment assignment. Placebo and active medication were of similar appearance.

Statistical methods

To control for Type 1 error due to multiple endpoints and two comparisons within each endpoint, a closed, sequential hierarchical procedure for testing endpoint and contrasts was specified in the SAP that ranked the 1 mg vs. placebo comparison above the 0.5 mg vs. placebo comparison within each of the primary and key secondary endpoints. As such, the hierarchy was specified in the following order of tests:

1. Proportion of patients in clinical remission at Week 8: 1 mg dose vs. placebo

2. Proportion of patients in clinical remission at Week 8: 0.5 mg dose vs. placebo

3. Proportion of patients in clinical response at Week 8: 1 mg dose vs. placebo

4. Proportion of patients in clinical response at Week 8: 0.5 mg dose vs. placebo

5. Change in Mayo score from baseline at Week 8: 1 mg dose vs. placebo

6. Change in Mayo score from baseline at Week 8: 0.5 mg dose vs. placebo

7. Proportion of patients with mucosal healing at Week 8: 1 mg dose vs. placebo

8. Proportion of patients with mucosal healing at Week 8: 0.5 mg dose vs. placebo

Each of the above endpoint/comparison combinations was tested in order following this hierarchy. If a test did not result in a p-value that was <0.05, then all subsequent tests in the hierarchy were to be considered exploratory and their resulting p-values were to be considered nominal.

In general, patients who were missing measures for response variables were analysed as non-responders for the primary analysis and patients who were missing measures for continuous variables had their last post-baseline value of the endpoint carried forward. If no post-baseline observation was available to carry forward, then the average score for the observed values within the same treatment group were used, rounded to the nearest integer.

The following analysis populations were defined:

The Safety Population included all patients who received at least one dose of study treatment, with treatment assignment based on the dose of RPC1063 actually received.

Two analysis populations were used for efficacy analyses:

The Intent-to-Treat (ITT) population consisted of all randomized patients who received at least one dose of study treatment, with treatment assignment designated according to randomized treatment. This was the primary population for the analysis of efficacy endpoints.

The Per-Protocol (PP) population consisted of the subset of the ITT population who did not have a major protocol violation and had treatment compliance for RPC1063/placebo within 80% to 120%. Supportive efficacy analyses were performed using the PP population.

Analysis of all efficacy endpoints were primarily based on the ITT population with treatment failure rules applied. The primary endpoint of proportion of patients in clinical remission at Week 8 was analysed using the Cochran-Mantel-Haenszel (CMH) test, stratified by prior anti-TNF therapy experience (yes or no). The primary analysis used the data from the 1 mg dose and placebo groups and compared the remission rates in these two groups using a two-sided test at the 0.05 level of significance.

The sample size was justified with respect to the comparison of remission rates at the end of the Induction Period between an RPC1063 group and the placebo group. Based on the use of a two-sided test at the alpha=0.05 level of significance, and assuming a placebo remission rate of 10%, a sample size of 60 patients per group will provide 80% power to detect an improvement in the remission rate of 21 percentage points or larger (i.e., an active group remission rate of 31% or larger).

The study was not powered for the exploratory Maintenance Period endpoints.

Results

Participants flow

A total of 199 subjects were enrolled in the study, including 67 subjects randomized to ozanimod 1 mg, 66 to ozanimod 0.5 mg, and 66 to placebo (Table 35). Of the 199 randomized subjects, 197 (99.0%) received investigational product and were included in the ITT Population. Overall, 186 (93.5%) of the randomized subjects completed the induction period, with similar completion rates across treatment groups (ozanimod 1 mg: 94.0%; ozanimod 0.5 mg: 95.5%; placebo: 90.9%). The reasons for discontinuation from the induction period were investigator decision (3.0% placebo), AE (3.0% ozanimod 0.5 mg, 1.5% placebo), consent withdrawal (4.5% ozanimod 1 mg, 1.5% placebo), subject choice to discontinue dosing (1.5% ozanimod 1 mg), and lack of efficacy (1.5% placebo).

Study conduct

The study was conducted in Europe (as well as in North America (USA and Canada) Asia (Korea, Israel) and Australia (Australia and New Zealand). The study has been conducted between 26 December 2012 and 10 March 2015 at 57 different sites.

Number analysed

The subject disposition for the short-term treatment period is shown in the following table:

Table 29: Subject Disposition in the Induction Period (All Randomized Subjects) – Study RPC01-202

Subject Disposition Category, n (%)	Ozanimod 1 mg (N = 67)	Ozanimod 0.5 mg (N = 66)	Placebo (N = 66)	Total (N = 199)
Who Entered/Dosed in Induction Period	67 (100)	65 (98.5)	65 (98.5)	197 (99.0)
Who Completed Induction Period	63 (94.0)	63 (95.5)	60 (90.9)	186 (93.5)
Who Discontinued from Induction Period	4 (6.0)	2 (3.0)	5 (7.6)	11 (5.5)
Primary Reason for Study Withdrawal				
Subject Withdrawal of Consent	3 (4.5)	0	1 (1.5)	4 (2.0)
Adverse Event/Intercurrent Illness	0	2 (3.0)	1 (1.5)	3 (1.5)
Investigator Decision	0	0	2 (3.0)	2 (1.0)
Lack of Efficacy/Worsening of Disease	0	0	1 (1.5)	1 (0.5)
Subject Choice to Discontinue Dosing	1 (1.5)	0	0	1 (0.5)

Approximately half (51.8%) of the randomized subjects entered the Maintenance Period, including, 62.7% with ozanimod 1 mg, 54.5%with ozanimod 0.5 mg, and 37.9% with placebo. Of those subjects who entered the Maintenance Period, completion rates were 95.2%, 83.3%, 84.0%, respectively. The most common reasons for discontinuation from the Maintenance Period were lack of efficacy/worsening of UC (2.4% with ozanimod 1 mg, 11.1% with ozanimod 0.5 mg, and 4.0% with placebo) and AE/intercurrent illness (2.8% with ozanimod 0.5 mg and 8.0% with placebo)

Table 30: Subject Disposition in the Maintenance Period (Randomized Subjects) – Study RPC01-202

Subject Disposition Category, n (%)	Ozanimod 1 mg (N = 67)	Ozanimod 0.5 mg (N = 66)	Placebo (N = 66)	Total (N = 199)
Maintenance Period (MP)				
Who Entered the MP	42 (62.7)	36 (54.5)	25 (37.9)	103 (51.8)
Who Were Dosed in the MP	41 (61.2)	36 (54.5)	25 (37.9)	102 (51.3)
Who Completed MP	40 (59.7)	30 (45.5)	21 (31.8)	91 (45.7)
Who Completed MP (of Entered MP)	40 (95.2)	30 (83.3)	21 (84.0)	91 (88.3)
Who Discontinued from MP (of Entered MP)	2 (4.8)	6 (16.7)	4 (16.0)	12 (11.7)
Primary Reason for Discontinuation				
Adverse Event/Intercurrent Illness	0	1 (2.8)	2 (8.0)	3 (2.9)
Noncompliance	0	0	1 (4.0)	1 (1.0)
Subject Withdrawal of Consent	1 (2.4)	1 (2.8)	0	2 (2.0)
Lack of Efficacy/Worsening Disease	1 (2.4)	4 (11.1)	1 (4.0)	6 (5.9)
Open-label Period (OLP)				
Who Entered the OLP	59 (88.1)	56 (84.8)	55 (83.3)	170 (85.4)

MP = Maintenance Period; OLP = Open-label Period.
Note: Denominators for reasons for discontinuation from the Maintenance Period are the number of subjects who entered the Maintenance Period. Unless otherwise indicated, denominators for all other percentages are the number of subjects randomized.

Of the 199 subjects who were randomized and entered the Induction Period in Study RPC01- 202, 170 entered in the OLP. Of these, the majority of subjects (72.4%) completed the Week 56 visit and the Week 104 visit (60.0%). Half (49.4%) of the subjects completed the Week 152 visit and 41.8% completed the Week 200 visit. Approximately 60% of subjects discontinued from the OLP. The most frequently reported reasons for discontinuation were withdrawal of consent, lack of efficacy, and subject choice to discontinue dosing (15.3% each). Three additional subjects did not have a study completion or discontinuation record (1 subject withdrew from the study due to a serious adverse event of erysipelas and 2 subjects withdrew consent). The Sponsor terminated the study in August 2019 in order to consolidate clinical studies.

Baseline characteristics

Demographic of subjects in Study RPC01-202 were generally similar across treatment groups. The overall ITT Population was 58.4% male and 92.4% white with mean age at Baseline of 40.8 years. The ozanimod 1 mg treatment group had a greater proportion of males (71.6%) than the placebo treatment group (53.8%). Results are shown in the following table:

Table 31: Demographics in the Induction Period (ITT Population) – Study RPC01-202

Parameter	Ozanimod 1 mg (N = 67)	Ozanimod 0.5 mg (N = 65)	Placebo (N = 65)	Total (N = 197)
Sex, n (%)				
Male	48 (71.6)	32 (49.2)	35 (53.8)	115 (58.4)
Female	19 (28.4)	33 (50.8)	30 (46.2)	82 (41.6)
Age (years)				
Mean (SD)	41.8 (11.01)	38.8 (12.06)	41.9 (12.30)	40.8 (11.82)
Min, Max	19, 64	18, 66	18, 73	18, 73
Race, n (%)				
White	62 (92.5)	59 (90.8)	61 (93.8)	182 (92.4)
Black	1 (1.5)	1 (1.5)	2 (3.1)	4 (2.0)
Asian	3 (4.5)	3 (4.6)	2 (3.1)	8 (4.1)
Other	1 (1.5)	1 (1.5)	0	2 (1.0)
Ethnicity, n (%)				
Hispanic or Latino	0	1 (1.5)	2 (3.1)	3 (1.5)
Not Hispanic or Latino	67 (100.0)	64 (98.5)	63 (96.9)	194 (98.5)
Weight (kg)				
Mean (SD)	77.4 (16.25)	72.3 (16.94)	72.6 (14.86)	74.2 (16.14)
Min, Max	45, 114	47, 128	45, 121	45, 128
Body Mass Index (kg/m²)				
Mean (SD)	25.8 (4.92)	24.3 (4.67)	24.8 (4.70)	25.0 (4.79)
Min, Max	18, 39	18, 44	17, 42	17, 44
Ever Smoked Tobacco, n (%)				
Yes	15 (22.4)	12 (18.5)	17 (26.2)	44 (22.3)
No	52 (77.6)	53 (81.5)	48 (73.8)	153 (77.7)
Current Smoker				
Yes	4 (6.0)	4 (6.2)	3 (4.6)	11 (5.6)
No	11 (16.4)	8 (12.3)	14 (21.5)	33 (16.8)

ITT = intent-to-treat; max = maximum; min = minimum; SD = standard deviation.
Note: denominators for percentages are N, the total number of subjects

The baseline UC disease history of subjects in Study RPC01-202 was consistent across treatment groups. The mean duration of time since UC diagnosis 6.2 years. The median 4- component Mayo score at Baseline was 8, and approximately half of the subjects had a 4- component Mayo score > 8. All, but 2 subjects, who were randomized in error, had Mayo endoscopy scores of 2 or 3. The evaluation is shown in the following table:

Table 32: Baseline Disease Characteristics in the Induction Period (ITT Population) – Study RPC01-202

Parameter	Ozanimod 1 mg (N = 67)	Ozanimod 0.5 mg (N = 65)	Placebo (N = 65)	Total (N = 197)
Age at UC Diagnosis (years)				
Mean (SD)	35.2 (12.08)	33.1 (11.29)	35.8 (13.03)	34.7 (12.15)
Min, Max	12, 63	12, 61	9, 67	9, 67
Years Since UC Diagnosis				
Mean (SD)	6.7 (6.76)	5.9 (5.44)	6.1 (5.46)	6.2 (5.91)
Min, Max	1, 29	0, 25	0, 24	0, 29
Extent of Disease, n (%)				
Limited to Left Side of Colon	41 (61.2)	41 (63.1)	41 (63.1)	123 (62.4)
Extensive	26 (38.8)	24 (36.9)	24 (36.9)	74 (37.6)
4-Component Mayo Score (Central Reader) at Baseline				
Mean (SD)	8.5 (1.61)	8.3 (1.45)	8.6 (1.51)	8.5 (1.52)
Median	8.0	8.0	8.0	8.0
Min, Max	6, 12	5[a], 11	6, 12	5[a], 12
4-Component Mayo Score (Central Reader) at Baseline Category, n (%)				
≤ 8	34 (50.7)	34 (52.3)	33 (50.8)	101 (51.3)
> 8	33 (49.3)	31 (47.7)	32 (49.2)	96 (48.7)
Rectal Bleeding, n (%)				
0 – No blood seen	5 (7.5)	6 (9.2)	4 (6.2)	15 (7.6)
1 – Streaks of blood with stool less than half the time	26 (38.8)	25 (38.5)	27 (41.5)	78 (39.6)
2 – Obvious blood with stool most of the time	33 (49.3)	32 (49.2)	28 (43.1)	93 (47.2)
3 – Blood alone passes	3 (4.5)	2 (3.1)	6 (9.2)	11 (5.6)
Stool Frequency, n (%)				
0 – Normal number of stools	0	2 (3.1)	0	2 (1.0)
1 – 1-2 stools more than normal	13 (19.4)	11 (16.9)	9 (13.8)	33 (16.8)
2 – 3-4 stools more than normal	20 (29.9)	28 (43.1)	25 (38.5)	73 (37.1)
3 – 5 or more stools more than normal	34 (50.7)	24 (36.9)	31 (47.7)	89 (45.2)

Table 33: Baseline Disease Characteristics in the Induction Period (ITT Population) – Study RPC01-202 (Continued)

Parameter	Ozanimod 1 mg (N = 67)	Ozanimod 0.5 mg (N = 65)	Placebo (N = 65)	Total (N = 197)
Physician's Global Assessment, n (%)				
0 – Normal	0	0	0	0
1 – Mild	2 (3.0)	2 (3.1)	2 (3.1)	6 (3.0)
2 – Moderate Disease	53 (79.1)	50 (76.9)	50 (76.9)	153 (77.7)
3 – Severe Disease	12 (17.9)	13 (20.0)	13 (20.0)	38 (19.3)
Mucosal Appearance (Endoscopy Subscore) by Central Reader, n (%)				
0 – Normal or Inactive Disease	0	0	0	0
1 – Mild Disease	2 (3.0)[b]	0	0	2 (1.0)[b]
2 – Moderate Disease	26 (38.8)	29 (44.6)	32 (49.2)	87 (44.2)
3 – Severe Disease	39 (58.2)	36 (55.4)	33 (50.8)	108 (54.8)
Any Prior UC Medication Use, n (%)				
5-ASA	67 (100)	63 (96.9)	63 (96.9)	193 (98.0)
Systemic Corticosteroids	52 (77.6)	49 (75.4)	52 (80.0)	153 (77.7)
Anti-metabolites (Immunomodulators)	22 (32.8)	24 (36.9)	17 (26.2)	63 (32.0)
Azathioprine	19 (28.4)	23 (35.4)	17 (26.2)	59 (29.9)
6-Mercaptopurine	5 (7.5)	1 (1.5)	2 (3.1)	8 (4.1)
Methotrexate	0	1 (1.5)	1 (1.5)	2 (1.0)
Other Immunomodulators	3 (4.5)	5 (7.7)	6 (9.2)	14 (7.1)
Anti-TNFs	15 (22.4)	12 (18.5)	10 (15.4)	37 (18.8)
Topical Medication	0	0	3 (4.6)	3 (1.5)
UC Medication Use at Screening, n (%)				
5-ASA	53 (79.1)	53 (81.5)	56 (86.2)	162 (82.2)
Systemic Corticosteroids	26 (38.8)	22 (33.8)	21 (32.3)	69 (35.0)
Azathioprine	0	0	1 (1.5)	1 (0.5)

5-ASA = 5-aminosalicylic acid; ITT = intent-to-treat; max = maximum; min = minimum; PP = Per Protocol; SD = standard deviation; TNF = tumor necrosis factor; UC = ulcerative colitis.

[a] One subject in the ozanimod 0.5 mg group was randomized with a baseline Mayo score < 6, a violation of Inclusion Criteria #4. This subject was not included in the PP Population.

[b] Two subjects in the ozanimod 1 mg group were randomized with Mayo endoscopy subscores < 2, a violation of Inclusion Criterion #4. These subjects were not included in the PP Population.

Prior and concomitant UC medications were generally similar across treatment groups. In the overall ITT Population, nearly all subjects had previously been treated with 5-ASA (98.0%) and 82.2% of subjects continued using 5-ASA at Screening. Approximately 78% of subjects had been previously treated with corticosteroids, and ~35% of subjects continued using systemic corticosteroids at Screening. Only about 20% of the patients were previously using anti-TNF medication.

Outcomes and estimation

The key efficacy results for the induction as well as "maintenance" period of the study are shown in the following table:

Table 34: Key Efficacy Results in the Induction and Maintenance Periods (ITT Population, Non-responder Imputation) – Study RPC01-202

Proportion of subjects in:	Week 9			Week 33		
	Ozanimod 1 mg (N = 67) n (%)	Ozanimod 0.5 mg (N = 65) n (%)	Placebo (N = 65) n (%)	Ozanimod 1 mg (N = 67) n (%)	Ozanimod 0.5 mg (N = 65) n (%)	Placebo (N = 65) n (%)
Clinical remission (4-component)[a]	Primary Analysis					
	11 (16.4) p = 0.0482	9 (13.8) p = 0.1422	4 (6.2)	14 (20.9) p = 0.0108	17 (26.2) p = 0.0021	4 (6.2)
Clinical response (4-component)[b]	38 (56.7) p = 0.0207	35 (53.8) p = 0.0648	24 (36.9)	34 (50.7) p = 0.0002	23 (35.4) p = 0.0571	13 (20.0)
Change from Baseline in Mayo Score	Mean: -3.4 p = 0.0042	Mean: -2.6 p = 0.1415	Mean: -2.0	Mean: -3.4 p = 0.0004	Mean: -2.2 p = 0.1932	Mean: -1.6
Endoscopic improvement[c]	23 (34.3) p = 0.0023	18 (27.7) p = 0.0348	8 (12.3)	22 (32.8) p = 0.0046	21 (32.3) p = 0.0064	8 (12.3)
Histologic remission[d]	15 (22.4) p = 0.0705	9 (13.8) p = 0.6294	7 (10.8)	21 (31.3) p = 0.0006	15 (23.1) p = 0.0164	5 (7.7)
Post Hoc Analyses						
Clinical remission (3-component)	22.4% p = 0.0263	16.9% p = 0.2099	9.2%	25.4% p = 0.0046	26.6% p = 0.0053	7.7%
Clinical response (3-component)	53.7% p = 0.0017	53.8% p = 0.0032	27.7%	49.3% p < 0.0001	33.8% p = 0.0156	15.4%

CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; RBS = rectal bleeding subscore; SCE = Summary of Clinical Efficacy; SFS = stool frequency subscore; TNF = tumor necrosis factor.

[a] Clinical remission (4-component) was defined as 4-component Mayo score ≤ 2 points with no individual subscore of >1 point. Primary endpoint as prespecified for statistical analysis.

[b] Clinical response (4-component) was defined as reduction in the 4-component Mayo score of ≥ 3 points and ≥30% from Baseline, with a decrease in the RBS of ≥1 point or an absolute RBS of ≤ 1 point.

[c] Endoscopic improvement is defined as endoscopy subscore of ≤ 1 point. This endpoint was termed "mucosal healing" in the Study RPC01-202 protocol. Since the definition (endoscopy subscore of ≤ 1 point) is the same as the definition for "endoscopic improvement" in Study RPC01-3101, "endoscopic improvement" is used throughout this document for consistency.

[d] Histologic remission was defined as Geboes 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: Mayo scores were calculated based on central endoscopy reading. Subjects with missing Mayo scores or Geboes scores were classified as nonresponders. P-value for comparison between the active and placebo groups are based on the CMH test, stratified by prior anti-TNF use (yes or no). P-values in bold are considered statistically significant; p-values in italics are ≤ 0.05 and considered nominally significant, because no multiplicity adjustment was applied.

Similar remission rates and statistical significance were found for the ITT Population using observed cases or LOCF imputation and for the Per-Protocol Population.

The primary analysis used Mayo scores with endoscopy sub-scores from central endoscopy reading, with adjudication if needed. As sensitivity analyses, other endoscopy reading methods were examined. Using the endoscopy sub-score from the original (single) central endoscopy reading (prior to adjudication) the results were similar to the primary analysis with the proportion of patients in clinical remission

statistically significantly higher for RPC1063 1 mg (17.9%) compared with placebo (4.6%, p=0.0114) but not for RPC1063 0.5 mg compared with placebo (13.8%, p=0.0698). Using the endoscopy subscore from Investigator's reading (i.e., local reading), clinical remission rates were higher in both RPC1063 groups (0.5 mg 18.5%; 1 mg 17.9%) compared with placebo (7.7%) but the differences did not reach statistical significance (p=0.0702 and p=0.0600, respectively).

The applicant has also evaluated the PD marker "reduction of lymphocyte count" and the following results were achieved:

Absolute lymphocyte count (ALC) was decreased in both RPC1063 treatment groups at all post-baseline visits. The steepest decrease occurred from baseline to Week 4. The following mean (SD) ALC values and percentage changes from baseline were observed at the end of the Induction Period (Week 8) and Maintenance Period (Week 32), respectively:

- Placebo group: Week 8 (n=61) and Week 32 (n=20):

- 1.93 (0.74) and 2.04 (0.84) cells x 10^9/L reflecting a change from baseline +16.6 (106.0)% and +4.8 (30.5)%

The mean percentage increase in the placebo group is influenced by one patient with 800% increase in ALC from baseline to Week 4 and Week 8. Median changes at these timepoints were +9% and +3%, respectively.

- RPC1063 0.5 mg group: Week 8 (n=61) and Week 32 (n=29):

- 1.19 (0.53) and 1.12 (0.54) cells x 10^9/L reflecting a change from baseline -32.3 (30.5)% and -32.3 (50.7)%

- RPC1063 1 mg group: Week 8 (n=60) and Week 32 (n=40)

- 0.97 (0.57) and 0.73 (0.45) cells x 10^9/L reflecting a change from baseline -49.2 (27.1)% and -60.8 (22.1)%

The overall results are shown in the following figure:
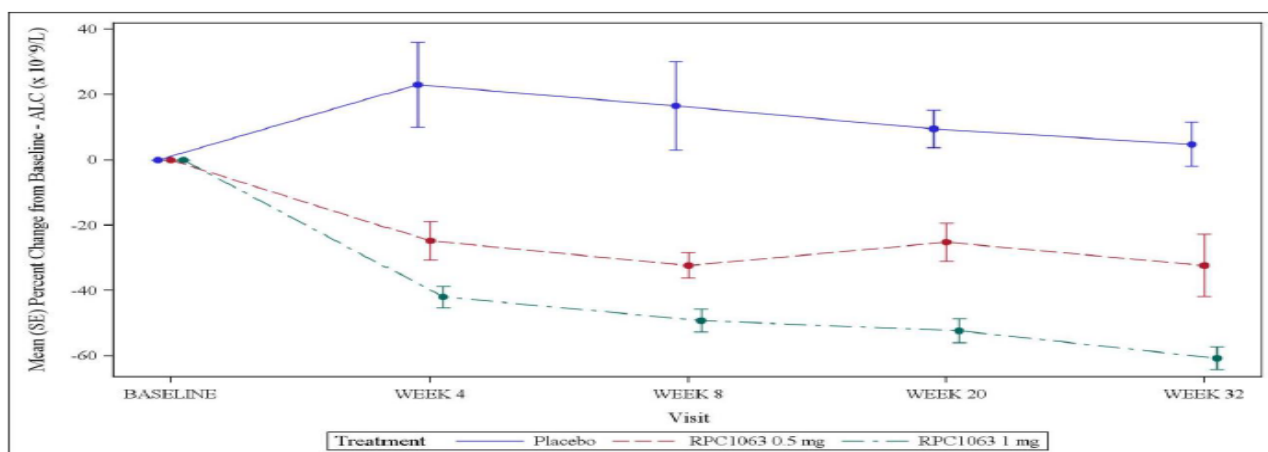
Figure 31: Mean (SE) Percent Change from Baseline in Absolute Lymphocyte Count (Safety Population)

Subgroup evaluation:

The applicant has investigated the consistency of results across a variety of subgroups:

	Diff	LCL	UCL	p-value
Overall	0.108	0.003	0.214	0.0482
Prior anti-TNFa use Yes				
No	0.131	0.004	0.258	0.0482
Age <median	0.221	0.053	0.388	0.0129
>=median	0.021	-0.113	0.156	0.7597
Sex Female	0.068	-0.125	0.261	0.4725
Male	0.146	0.025	0.266	0.0364
Disease localization Left Side	0.15	0.013	0.287	0.0375
Extensive	0.04	-0.124	0.204	0.6358
Baseline Mayo Score <=8	0.065	-0.104	0.235	0.4554
>8	0.154	0.033	0.275	0.0196
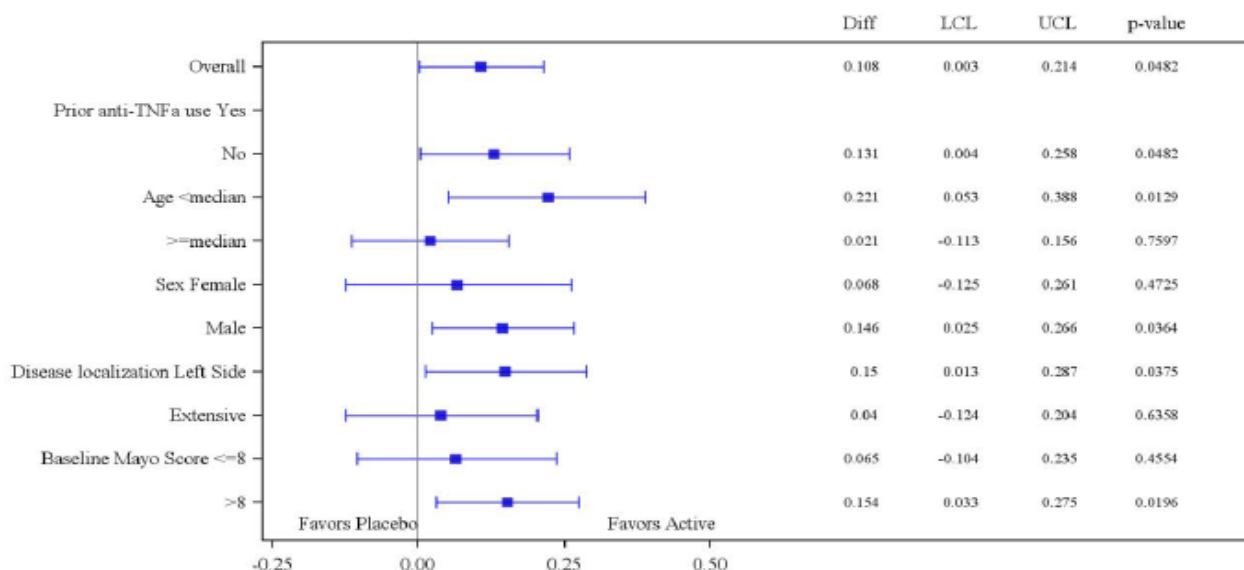
Source: Figure 14.2.2.1 and Listing 16.2.6.1.
Abbreviations: Diff, difference in proportion of patients in remission (RPC1063 1 mg – placebo); LCL, lower confidence limit; TNFa, tumor necrosis factor alpha; UCL, upper confidence limit
Notes: Endoscopy subscores were calculated based on central endoscopy reading. Patients with missing Mayo scores are classified as non-responders. Data are mean (95% confidence interval) difference in proportion of patients in remission. No patient with prior anti-TNF use achieved clinical remission. As such, the treatment difference, associated confidence interval, and p-value could not be estimated for the subgroup with prior anti-TNFα use.

Figure 32: Forest Plot of Clinical Remission at Week 8 by Subgroups (ITT Population, Non-Responder Imputation) - RPC1063 1.0 mg vs. Placebo

2.4.1.2. Long-term extension phase of study RPC01-202

The open-label period of the study was reported with a separate study report and only relevant results are summarised here.

Study participants

Subjects who completed the Induction Period and were non-responders at Induction Period Week 8 and those that completed the Maintenance Period or experienced disease relapse during the Maintenance Period had the option to enter the OLP. All subjects in the OLP (placebo group, ozanimod 0.5 mg group, and ozanimod 1 mg group from Core Period) received daily study treatment with ozanimod 1 mg. There was an 8-day dose escalation regimen consisting of 4 days of treatment with ozanimod 0.25 mg, followed by 3 days of treatment with ozanimod0.5 mg, followed by ozanimod 1 mg. All subjects, including those subjects who received ozanimod 1 mg treatment in the Induction Period or Maintenance Period, underwent the dose escalation regimen to ensure blinding. Subjects who did not show clinical improvement 8 weeks after initiation of the OLP were to discontinue from the study. The Sponsor stopped Study RPC01-202 in August 2019 and subjects had the opportunity to transition to the open-label extension Study RPC01-3102 to continue treatment with study drug.

Efficacy measurements

The efficacy measurements were summarized by Core Period treatment group at each OLP visit in the ITT population. The efficacy analyses are also presented by Responder (R) and non-responder (NR), which are defined by clinical response and reflect response status at OLP Baseline (i.e., last response status measured prior to first dose of ozanimod in OLP). Non responder imputation (NRI) was used as the primary method for addressing missing binary outcomes.

Number analysed

A total of 170 subjects were enrolled in the OLP. Of the 170 subjects who entered the OLP, the majority of subjects (123 subjects [72.4%]) completed the Week 56 visit and the Week 104 visit (102 subjects [60.0%]). There were 84 subjects (49.4%) who completed the Week 152 visit and 71 subjects (41.8%) who completed the Week 200 visit. There were 99 subjects (58.2%) who discontinued from the OLP. Reported primary reasons for discontinuation were withdrawal of consent, lack of efficacy, and subject choice to discontinue dosing (26 subjects each, 15.3%). There were 3 subjects who did not have a study completion or discontinuation record. Of these 3 subjects, 1 subject (Subject 202-412- 2002) withdrew from the study due to an SAE of erysipelas and 2 subjects withdrew consent.

The following table shows the subject disposition at enrolment:

Table 35: Subject Disposition (Enrolled Population)

Disposition Category	Total (N = 170) n (%)
Subjects who Consented to the OLP Study	170 (100)
Response Status at OLP Baseline	
Responder [a, b]	66 (38.8)
Non-Responder [a]	104 (61.2)
Subjects Who Completed the OLP Study[c]	14 (8.2)
Who Completed Week 56 Visit	123 (72.4)
Who Completed Week 104 Visit	102 (60.0)
Who Completed Week 152 Visit	84 (49.4)
Who Completed Week 200 Visit	71 (41.8)
Who Completed Week 248 Visit	24 (14.1)
Primary Reason for Study Withdrawal[d]	
Adverse Event	14 (8.2)
Pregnancy	1 (0.6)
Non-Compliance	2 (1.2)
Investigator Decision	2 (1.2)
Withdrawal of Consent	26 (15.3)
Lost to Follow-Up	2 (1.2)
Sponsor Termination of the Study or Suspension of the Study (ie, rollover to Study RPC01-3102)[c]	54 (31.8)
Lack of Efficacy/Worsening disease	26 (15.3)
Patient choice to discontinue dosing	26 (15.3)

OLP = Open-label Period; ITT = intent-to-treat.
[a] Clinical response (Four-component Mayo): Reduction from baseline in complete Mayo score of ≥ 3 points and reduction from baseline in complete Mayo score of ≥ 30%, and (reduction in rectal bleeding subscore of ≥ 1 point or a rectal bleeding subscore of ≤ 1 point).
[b] Three subjects (1 subject in the placebo group and 2 subjects in the ozanimod 0.5 mg group) were responders in the Induction Period, entered the Maintenance Period with no efficacy assessment at the end of the Maintenance Period, and their Induction Period response was carried onto OLP baseline.
[c] Subjects who transitioned to Study RPC01-3102 were not considered to have completed the OLP.
[d] Three subjects did not have a study completion or discontinuation record. One subject withdrew from the study due to a serious adverse event, and 2 subjects withdrew consent.

Baseline characteristics

Demographic characteristics for subjects who entered the OLP were assessed at the Core Period baseline. For subjects who entered the OLP, the mean age at Core Period baseline was 40.4 years, the mean weight was 74.2 kg, and the majority of subjects (157 subjects [92.4%)]) were White. The demographic characteristics for subjects who entered the OLP were similar to the overall population enrolled in the Core Period (data not shown).

Ulcerative colitis disease history for subjects who entered the OLP was assessed at the Core Period baseline. There were no notable differences in baseline disease characteristics across Core Period treatment groups for subjects in the ITT Population who entered the OLP.

Results

Outcome and estmation

The observed cases of clinical remission (based on the four-component, the three-component, or partial Mayo) at Week 56 and Week 104 (regardless of core study treatment assignment and status of remission at the end of core study) are presented in the following table. Overall, 39.5% of subjects were in clinical remission (four-component Mayo) starting from Week 56 and 41.4% of subjects were in clinical remission at Week 104. Using NRI, 54.7% of subjects were in clinical remission (partial Mayo) starting from Week 56 and 45.9% of subjects were in clinical remission at Week 104.

Table 36: Summary of Clinical Remission - Observed Cases (ITT Population)

Endpoint	Visit (OLP)	Total (N = 170) n1/n2 (%)
Clinical Remission (Four-component Mayo)[a]	Week 56	32/81 (39.5)
	Week 104	36/87 (41.4)
Clinical Remission (Three-component Mayo)[b]	Week 56	36/81 (44.4)
	Week 104	32/87 (36.8)
Clinical Remission (Partial Mayo)[c]	Week 56	93/140 (66.4)
	Week 104	78/107 (72.9)

ITT = intent-to-treat; OLP = Open-label Period.
[a] Clinical remission (Four-component Mayo): Complete Mayo score of ≤ 2 points with no individual subscore of > 1 point.
[b] Clinical remission (Three-component Mayo): Rectal bleeding subscore = 0 and stool frequency subscore ≤ 1 (and a decrease of ≥ 1 point from the baseline stool frequency subscore), and endoscopy subscore ≤ 1.
[c] Partial Mayo clinical remission: Partial Mayo score of ≤ 2 points with no individual subscore of > 1 point.
Note: n1=number of subjects who met the endpoint criterion; n2=number of subjects with endpoint assessed in OLP and is the denominator for all percentages.

Using a non-responder imputation for the ITT population, the following results are reported:

Table 37: Summary of Clinical Remission Based on Partial Mayo Score – Non-responder Imputation (ITT Population)

Endpoint	Visit (OLP)	Total (N = 170) n1/n2 (%)
Clinical Remission (Partial Mayo)[a]	Week 56	93/170 (54.7)
	Week 104	78/170 (45.9)

ITT = intent-to-treat; OLP = Open-label Period.
[a] Partial Mayo clinical remission: Partial Mayo score of ≤ 2 points with no individual subscore of > 1 point.
Note: n1=number of subjects who met the endpoint criterion; n2=number of subjects in OLP ITT population and is the denominator for all percentages.

A line plot of the actual values in Complete Mayo score over time is presented below.

Overall, there was a decrease in complete Mayo score from baseline to Week 56 and the decreased complete Mayo score was maintained over the OLP.
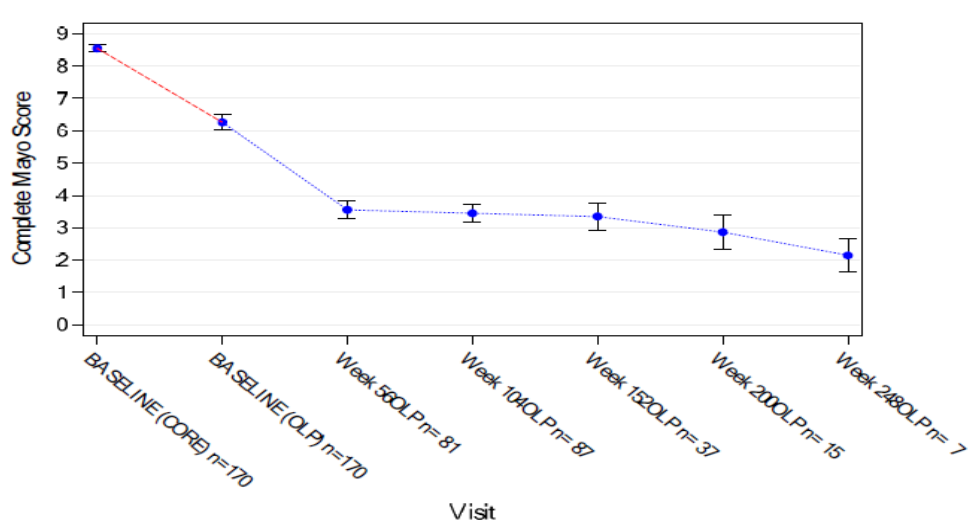
ITT= Intent-to-treat; OLP = Open-label Period; SE = standard error
Note: Baseline (Core) is defined as the last assessment prior to first dose of investigational drug in Core Period. Baseline (OLP) is defined as the last assessment prior to/on first dose date in the OLP. The time period between the Baseline (Core) and Baseline (OLP) was variable.

Figure 33: Line Plot of Actual Values (Mean and SE) in Complete Mayo Score Over Time in the OLP – Observed Cases (ITT Population)

Because the schedule of endoscopies performed beyond Week 104 was variable the number of endoscopies performed at later timepoints was small, which limits interpretation of results. Approximately 50% of subjects who had an endoscopy at Weeks 56 and 104 had endoscopic improvement (endoscopy subscore of ≤ 1 point) and approximately 37% and 30% of subjects had mucosal healing (alternative definition; endoscopy subscore of ≤ 1 point and a Geboes score < 2.0) at Weeks 56 and 104, respectively. Overall, approximately half of subjects were in histologic remission starting from Week 56 and throughout the OLP. The results are shown in the following table:

Table 38: Summary of Endoscopic Improvement, Mucosal Healing, and Histologic Remission in OLP Using Core Period Baseline (OLP ITT Population; Observed Cases) – Study RPC01-202 OLP

Endpoint	Visit (OLP)	Total (N = 170) n1/n2 (%)
Endoscopic Improvement[a]	Week 56	39/84 (46.4)
	Week 104	40/86 (46.5)
Mucosal Healing (Alternative Definition)[b]	Week 56	23/62 (37.1)
	Week 104	23/78 (29.5)
Histologic remission[c]	Week 56	31/67 (46.3)
	Week 104	30/78 (38.5)

ITT = intent-to-treat; OLP = Open-label Period; SCE = Summary of Clinical Efficacy.
[a] Endoscopic improvement: Endoscopy subscore of ≤ 1 point. This endpoint was termed "mucosal healing" in the Study RPC01-202 OLP protocol. Since the definition (endoscopy subscore of ≤ 1 point) is the same as the definition for "endoscopic improvement" in Study RPC01-3101, "endoscopic improvement" is used throughout this SCE for consistency.
[b] Mucosal healing (alternative definition): Endoscopy subscore of ≤ 1 point and a Geboes 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) in the same subject.
[c] Histologic remission: Geboes 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: Baseline was defined as the last assessment prior to the first dose date of investigational product in Core Period.
n1 = number of subjects who met the endpoint criterion; n2 = number of subjects with endpoint assessed in OLP and is the denominator for all percentages.

2.4.1.3. Dose-response report (Study RPC01-202 efficacy results and dose estimation for clinical response at week 32)

A report was provided to estimate the dose of ozanimod for assessing long term efficacy in subjects with moderate to severe ulcerative colitis. Dose estimation was conducted through modeling and simulation results based on a post-hoc analysis using clinical response at Week 32 utilizing the 3-component Mayo score from study RPC01-202. This endpoint was selected since there were enough events to allow for reliable model estimation in making distributional assumptions for conducting simulations when estimating dose. Another important assumption is that after 32-weeks clinical response should be stable and representative of the week 52 assessment planned for Study RPC01-3101.

A logistic regression model with treatment and prior TNF exposure as covariates was applied to the clinical response data at week 32. After initially fitting this model to that data, estimates and their standard errors for each treatment group were obtained on the logit scale using PROC GENMOD with the LS MEANS option in SAS. Since the estimators for each of the treatment groups on the logit scale have the property of being distributed as a normal with mean μ_i and variance σ_i^2 for i=1 (placebo), 2 (ozanimod 0.5 mg), and 3 (ozanimod 1.0 mg), data can be simulated under these distributional assumptions and a simple linear regression model with dose as a dependent variable (0 if placebo, 0.5 if ozanimod mg, and 1 if ozanimod 1 mg) can be fitted for each simulated case. Moreover, this will provide a distribution for dose using inverse prediction as the linear regression is a 1-to-1 function. Hence, if the desired response of some function f(x) is known where x is dose, then we can find the dose that maps back into that function via f-1(x). The targeted probability response is an absolute increase in clinical response of 0.30 above the placebo response which was estimated to be 0.128.

A linear regression was fitted to each simulation set such that 10,000 intercepts, slopes, and targeted doses through inverse prediction were created to construct their respective empirical distributions.

In the simulations, the targeted dose on average was 0.96 mg with a 95% empirical confidence interval of [0.70 mg, 1.42 mg].

2.4.1. Main study(ies)

2.4.1.1. Study RPC01-3101

RPC01-3101: "A phase 3, multi-centre, randomised, double-blind, placebo-controlled trial of oral RPC1063 as induction and maintenance therapy for moderate to severe ulcerative colitis"

Methods

The study consisted of two periods, and two cohorts in the first period:

In the Induction Period, subjects in Cohort 1 were randomized 2:1 to ozanimod 1 mg (N = 429) or placebo (N = 216) and subjects in Cohort 2 received open-label ozanimod 1 mg (N = 367). Subjects treated with ozanimod 1 mg who completed the Induction Period and who had achieved clinical response at Week 10 were eligible to be randomized 1:1 to receive either ozanimod 1 mg (N = 230) or matching placebo (N = 227) for an additional 42 weeks in the Maintenance Period. Subjects who were treated with placebo (Cohort 1) and who showed a clinical response at Week 10 continued to receive placebo in the Maintenance Period (N = 69). Total treatment duration in Study RPC01-3101 (including both the Induction and Maintenance Periods) was 52 weeks. Upon completion of 52 weeks of treatment, subjects were eligible to continue in OLE Study RPC01-3102 (up to a total treatment period of 5 years).
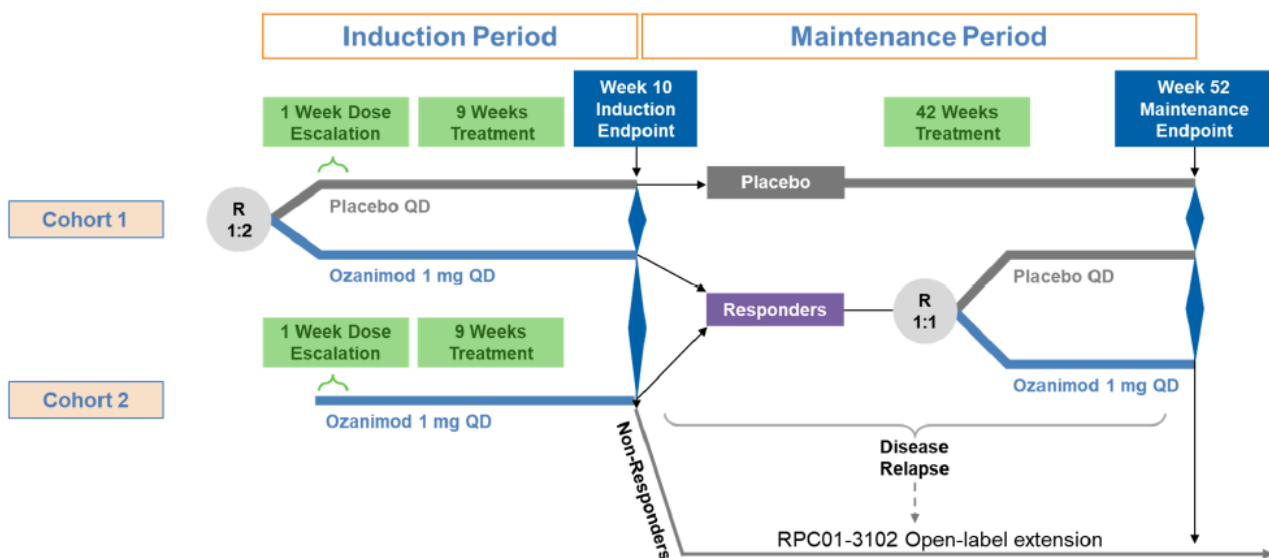
Figure 34: RPC01-3101 Study Design Schematic for Cohort 1 and Cohort 2

Study participants

The following most relevant in- and exclusion criteria were defining the patient population for the induction phase:

- Age range between 18 and 75 (at screening)

-        UC diagnosed at least 3 months before first intake of the investigational drug with confirmation of the diagnosis by clinical, endoscopic and histolopathological evidence (histology and/or endoscopy could be performed at screening also.

-        Minimal extension of UC ≥15 cm from the anal verge (as determined by baseline endoscopy)

-        Active UC of moderate to severe intensity defined as total Mayo score of 6-12, with an endoscpic subscore of 2 or more, rectal bleeding and stool frequency score of 1 or more.

-        Must be currently receiving treatment with at least one of the following medications: oral aminosalicylates (dose of 2.4 g or higher) with at least stable dose for 3 weeks prior to screening, prednisone at doses similar or smaller to 20 mg/day (or equivalent) at a stable dose for at least 2 weeks prior to screening or budesonide Multi Matrix (MMX) therapy receiving a stable dose for at least 2 weeks prior to screening endoscopy.

-        Could have received corticosteroids at doses ≥ 30 mg or budesonide MMX ≥ 9 mg or intravenous corticosteroids for at least 2 weeks and/or aminosalicylates at a dose of at least 2.4 g for 8 weeks and have failed treatment or have inadequate response.

-        Could have received biologics/anti TNF therapy prior to screening with an at least 8 week (or 5 elimination half-live) time distance and have inadequate response to this treatment after at least 4 weeks of treatment (either as primary non-response, or secondary non-response, or as intolerance to this treatment). Biologics were not allowed during treatment. Patients with an inadequate response or failure with more than 2 biologics were excluded as were those with a primary non-response to two or more biologics. Primary nonresponse was defined as signs and symptoms of persistently active disease despite an adequate trial of induction treatment with an anti-TNF agent (per country's approved label)

-        Could have received "conventional" immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) but have failed or inadequate response after an at least 8 week treatment (doses of AZA ≥ 1.5 mg/kg or 6-MP ≥ 0.75 mg/kg or MTX ≥ 12.5 mg/week), or intolerance. Immunosuppressant were not allowed during treatment.

-        Patients having previously received D-penicillamine, leflunomide, or thalidomide, natalizumab, fingolimod or etrasimod were excluded.

-        Availability of historical endoscopy (e.g. for cancer surveillance), highly active contraception.

-        Patients with severe extensive colitis, a history of fulminant colitis, toxic megacolon or imminent colectomy were also excluded.

-        Further exclusion criteria comprised a diagnosis of Crohn's disease, the presence of positive testing for C. difficile and other pathogens (ova, parasites, bacteria) within the last 60 days, and the presence of clinically relevant concomitant hepatic, neurological, pulmonary, phythamological, endocrine, psychiatric, and cardiovascular conditions making implementation of the protocol or interpretation of the study difficult or that would put the subject at risk by participating in the study, presence of type I diabetes, or any uncontrolled diabetes, history of uveitis, presence of any clinically relevant infection (Tbc, Hepatitis)

For the inclusion into the maintenance period, patients would need to have a "clinical response" either based on the total Mayo Score, or the three component Mayo Score (excluding physician's judgement). Subjects rerandomized in the Maintenance Period were stratified prior to randomization by clinical remission status (by either 3-component or 4-component Mayo Score) at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no). Clinical response (also used as endpoint in the induction period) for the inclusion into this phase) was defined as follows:

<u>Four-component Mayo</u>: A reduction from Baseline in the Complete Mayo score of $\geq$ 3 points and $\geq$ 30%, and a reduction from Baseline in the Rectal Bleeding subscore of $\geq$ 1 point or an absolute Rectal Bleeding subscore of $\leq$ 1 point.

<u>Three-component Mayo</u>: A reduction from Baseline in the 9-point Mayo score of $\geq$ 2 points and $\geq$ 35%, and a reduction from Baseline in the Rectal Bleeding subscore of $\geq$ 1 point or an absolute Rectal Bleeding subscore of $\leq$ 1 point

As mentioned, the study was conducted on all continents with most centers located at academic (tertiary care) specialised gastroenterology of IBD centers, but also at secondary care ambulatory (private practice) centres. No primary care centres were involved.

Treatments

Cohort 1: On Induction Day 1, subjects were randomly assigned in a 2:1 ratio to initiate investigational drug in accordance with a 7-day dose escalation regimen starting with:

- On Days 1 to 4, ozanimod 0.25 mg or matching placebo once daily (one 0.25 mg capsule)

- On Days 5 to 7, ozanimod 0.5 mg or matching placebo once daily (two 0.25 mg capsules)

- On Day 8, subjects received ozanimod 1 mg or matching placebo once daily for 9 weeks (one 1 mg capsule)

Cohort 2: On Induction Day 1, all subjects initiated investigational drug in accordance with a 7-day dose escalation regimen starting with the similar schedule as mentioned above with active treatment only.

On Maintenance Day 1, subjects from Cohort 1 or Cohort 2 with clinical response to ozanimod during the Induction Period were randomly assigned 1:1 to:

- Ozanimod 1 mg once daily for 42 weeks (one 1 mg capsule), or

- Matching placebo; a single capsule once daily for 42 weeks

Subjects from Cohort 1 who had been randomized to receive placebo and showed a clinical response at Week 10 continued to receive placebo in the Maintenance Period in a double-blind manner.

Objectives

The primary objective of the study was to demonstrate the efficacy of ozanimod versus placebo on induction of clinical remission in adults (for the induction therapy period), and to demonstrate the efficacy of ozanimod versus placebo on the maintenance therapy. These were defined as separate objectives.

The secondary objectives in the induction phase were as follows:

- Demonstrate the efficacy of ozanimod versus placebo on induction of clinical response in adults

- Demonstrate the efficacy of ozanimod versus placebo on achieving endoscopic improvement in adults

- Demonstrate the efficacy of ozanimod versus placebo on achieving histologic remission in adults

- Demonstrate the safety and tolerability of ozanimod induction therapy in all subjects

The secondary objectives in the maintenance phase were the following:

- Demonstrate the efficacy of ozanimod versus placebo in maintaining clinical response in adults

- Demonstrate the efficacy of ozanimod versus placebo on achieving endoscopic improvement in adults

- Demonstrate the efficacy of ozanimod versus placebo on maintaining clinical remission among subjects who achieved remission during induction therapy in adults

- Demonstrate the efficacy of ozanimod versus placebo in achieving corticosteroid-free remission in adults

- Demonstrate the efficacy of ozanimod versus placebo on durability of clinical remission in adults

- Demonstrate the safety and tolerability of ozanimod maintenance therapy in all subjects

Outcomes/endpoints

The main part of the evaluation of efficacy was based on the Mayo score, which is shown in the following table:

Table 39: "Original" Mayo Score (Schroeder 1987)

Stool frequency*
- 0 = Normal no. of stools for this patient
- 1 = 1–2 stools more than normal
- 2 = 3–4 stools more than normal
- 3 = 5 or more stools more than normal

Rectal bleeding†
- 0 = No blood seen
- 1 = Streaks of blood with stool less than half the time
- 2 = Obvious blood with stool most of the time
- 3 = Blood alone passed

Findings of flexible proctosigmoidoscopy
- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment‡
- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

_____

*Each patient served as his or her own control to establish the degree of abnormality of the stool frequency.

†The daily bleeding score represented the most severe bleeding of the day.

‡The physician's global assessment acknowledged the three other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

The following definitions were used for the chosen endpoints

Term	Definition
Mayo Score	
3-component Mayo score	The sum of the Rectal Bleeding subscore (RBS), Stool Frequency subscore (SFS), and the endoscopy subscore. Each subscore has a range of 0 to 3 points and the 3-component Mayo score has a range of 0 to 9 points.
	Throughout the trial, the endoscopy score 1 (mild disease) was used excluding the friability criterion).

Term	Definition
4-component Mayo score	The sum of the RBS, SFS, endoscopy, and Physician Global Assessmen (PGA) subscore. The 4-component Mayo score has a range of 0 to 12 points.
Partial Mayo score	The sum of the RBS, SFS, and PGA. The partial Mayo score has a range of 0 to 9 points
Clinical Remission	
3-component Mayo definition	RBS = 0 and SFS ≤ 1 (and a decrease of ≥ 1 point from the baseline SFS) and endoscopy subscore ≤ 1 without friability
Clinical Response	
3-component Mayo definition	A reduction from baseline in the 3-component Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point
Durable Clinical Remission	Clinical remission at Week 10 and at Week 52 in all subjects who entered the Maintenance Period
Maintenance of Remission	Clinical remission at Week 52 in the subset of subjects who are in remission at Week 10
Corticosteroid-free Remission	Clinical remission while off corticosteroids for ≥ 12 weeks at week 52
Endoscopic Improvement	Endoscopy subscore ≤ 1 without friability
Mucosal Healing	Endoscopic improvement with histologic remission (endoscopy subscore ≤ 1 without friability and a Geboes score < 2.0)
Histologic Remission	Geboes score < 2.0 (no neutrophils in the epithelial crypts or lamina propria, no increase in eosinophils in the lamina propria, and no crypt destruction, erosions, ulcerations, or granulation tissue)
Disease Relapse:	**occurred when all of the following criteria were met:**
	An increase in UC disease activity as defined by an increase in partial Mayo score of ≥ 2 points compared to the Week 10 partial Mayo score with an absolute partial Mayo score ≥ 4 points
	- An endoscopic subscore of ≥ 2 points
	- Exclusion of other causes of an increase in disease activity unrelated to underlying UC (eg, infections, change in medication)

5-ASA = 5-aminosalicylic acid; PGA = physician global assessment; RBS = rectal bleeding subscore; SFS = stool frequency subscore; TNF = tumor necrosis factor; UC = ulcerative colitis.

Induction phase endpoints:

The following endpoints were then used:

Primary Efficacy Endpoint:

- The proportion of adult patients in clinical remission at Week 10

Key Secondary Efficacy Endpoints:

- The proportion of adult patients with a clinical response at Week 10

- The proportion of adult patients with endoscopic improvement at Week 10

- The proportion of adult patients with mucosal healing at Week 10

Other Efficacy Endpoints:

- Change in complete Mayo score, partial Mayo score, 9-point Mayo score from Baseline to Week 10

- Proportion of adult patients with histologic remission at Week 10

- The proportion of adult patients in clinical remission (Four-component Mayo) at Week 10

- The proportion of adult patients with a clinical response (Four-component Mayo) at Week 10

- The proportion of adult patients with clinical response, remission, or endoscopic improvement at Week 10 in adult patients who previously received anti-TNF therapy

- Change in the SF-36 and the EQ-5D from Baseline to Week 10

- Health resource utilization at Week 10

- Work productivity at Week 10

The two-component endpoint for remission (symptoms from the Mayo score) was defined as post-hoc endpoint and included the following requirements: RBS = 0 and SFS $\leq$ 1 (and a decrease from Baseline of $\geq$ 1).

For cohort 2, similar endpoints were evaluated, however, with descriptive methods only, owing to the nature of the trial, being single-arm open label.

Maintenance phase endpoints:

The following endpoints were used:

Primary Efficacy Endpoint:

- The proportion of subjects in clinical remission at Week 52

Key Secondary Efficacy Endpoints:

- The proportion of subjects with a clinical response at Week 52

- The proportion of subjects with endoscopic improvement at Week 52

- The proportion of subjects in clinical remission at Week 52 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 at Week 52

- The proportion of subjects with durable clinical remission

Other Efficacy Endpoints:

- Change in 3-component Mayo score, 4-component Mayo score, and partial Mayo score from Baseline to Week 52

- The proportion of subjects with histologic remission at Week 52

- The proportion of subjects in clinical remission (4-component Mayo) at Week 52

- The proportion of subjects with a clinical response (4-component Mayo) at Week 52

- The proportion of subjects with clinical response, remission, or endoscopic improvement at 52 weeks in subjects who previously received anti-TNF therapy

- The proportion of subjects in remission at 52 weeks while off corticosteroids for any length of time

- Change in the SF-36 and the EQ-5D from Baseline to Week 52

- Health resource utilization at 28 weeks, 40 weeks, and at Week 52

- Work productivity at 28 weeks, 40 weeks, and at Week 52

The following "treatment failure rules were set up:

Subjects were considered to have failed treatment if any of the following occurred:

- Any protocol-prohibited change in medications including:

  o Post-Baseline initiation of, or increase in total daily dose level higher than the maximum dose taken between the Screening and Baseline visits in:

    ▪ Corticosteroids or 5-ASA dose to treat UC

    ▪ Prolonged course of systemic corticosteroids > 14 days for treatment of disease other than UC

  o Initiation of an immune suppressing therapy including 6-MP, azathioprine, anti- TNF agents, vedolizumab or tofacitinib

- A colectomy (partial or total) or an ostomy

- Discontinuation of investigational drug for lack of therapeutic effect before the Week 10 or Week 52 efficacy evaluations-

Subjects meeting criteria for treatment failure were treated as non-responders using NRI for statistical analyses of efficacy.

For the endoscopies, in order to ensure quality data and standardization, the same endoscopist was used throughout the study wherever possible. Endoscopy videos were obtained during each endoscopy and were sent for central reading and determination of the Mayo endoscopy subscore. A detailed video review charter from the central reading laboratory outlined the endoscopic procedures, video recordings and equipment.

A clear biopsy protocol was implemented for the evaluation of the presence of disease as well as disease activity with taking one biopsy pair to be taken from the most inflamed area of the left colon.

For the subjective parts of the Mayo score, (stool frequency and rectal bleeding components of the Mayo score) and the clinician-reported Physician's Global Assessment (PGA) were collected in an electronic diary. Subjects completed the stool frequency and rectal bleeding subscores daily from the first screening visit for the subject throughout the study, except for the 90-day Safety Follow-up Visit.

Subjects were instructed on the use and completion of questions on the electronic diary. The subjects' normal number of stools was recorded on the first day of screening. This was defined as the number of stools the subject passed in a 24-hour period prior to having UC or when the subject was in remission.

The diary entries were reviewed by site personnel during screening (prior to dosing, if applicable) and during all study visits, except for the 90-day Safety Follow-up Visit. The stool frequency and rectal bleeding diary entries 2-weeks prior to each study visit were used to calculate the 3-component, 4-component, and partial Mayo score.

For the evaluation of the RBS and SFS items, different scoring algorithms were used:

Both RBS and SFS for a subject had to be available on the same day. Two different scoring algorithms (A and B) with 2 different timeframes (7-day or 14-day) were used. The stool frequency and rectal bleeding diary entries within the 7-day period prior to each study visit were used to calculate RBS and SFS used for the primary analyses (7-day scoring algorithm A).

While per the RPC01-3101 Induction Period statistical analysis plan (SAP) version (v)1.0, it was originally planned to use the same 14-day scoring algorithm for the primary analysis as was used for Study RPC01-202, the algorithm was changed to the 7-day algorithm in the RPC01-3101 Induction Period SAP v4.0 based on health authority feedback (FDA response letter [dated 15 Jun 2019]).

In order to show similarity in derivation of clinical remission and clinical response despite differences in the 2 scoring algorithms, a sensitivity analysis was conducted using the 14-day scoring algorithm A. An additional sensitivity analysis using the 14-day scoring algorithm B was also conducted. Algorithm B required at least 2 consecuteive days in which bltoh RBS and SFS assessments were made on the same day within the 14-day time-frame, while for algorithm A, days did not have to be consecutive. The algorithms and their use are shown in the following table:

Table 40: Mayo scoring algorithm used in study RPC01-3101

Mayo Scoring Algorithm	Study RPC01-3101
Primary Analysis	• Based on 7-day scoring algorithm (A) using the "3 allowable days". • Source data: RBS and SFS were obtained from electronic diary entries completed by the subject. • Endoscopy subscore was provided by a blinded central reader. • Scoring window: up to 7-day
Sensitivity Analysis Using Alternative Scoring Algorithm	14-day scoring algorithm (A) • 14-day scoring algorithm using the "3 allowable days" and a 14-day scoring window. 14-day scoring algorithm (B) • 14-day scoring algorithm using the "3 allowable days" (at least 2 of the "3 allowable days" needed to be consecutive) and a 14-day scoring window.

RBS = rectal bleeding subscore; SFS = stool frequency subscore.

Note: A day was considered as an allowable day if it satisfied the following criteria:
- has non-missing RBS and SFS data and is not excluded due to endoscopy procedure requirements. The determination of "3 allowable days" was to be in the following order:
1. If there are 3 consecutive days with non-missing stool frequency and rectal bleeding data, then use the 3 consecutive days closest to the visit date.
2. If there are only 2 consecutive days with non-missing stool frequency and rectal bleeding data, then use the 2 consecutive days closest to the visit date plus 1 day with non-missing stool frequency and rectal bleeding closest to the visit date.
3. If there are 3 days with non-missing stool frequency and rectal bleeding data, but they are not consecutive, then use the 3 days closest to the visit date.
If there are no 3 days with both non-missing stool frequency and rectal bleeding data, then the subscores will be set to missing.

Because the colonoscopy/flexible sigmoidoscopy preparations can interfere with the assessment of other clinical parameters, diary entries used to calculate the 4-component Mayo Score and Partial Mayo Score did not correspond to day(s) of bowel preparation or endoscopy.

Sample size

The protocol (latest version No. 7) included the following reflections about the sample size:

Cohort 1 (adult patients): Based on results from a previous Phase 2 induction trial of RPC1063 1 mg, it is anticipated that at least 16% of patients in the RPC1063 group and approximately 6% of patients in the placebo group will be in clinical remission at the end of the IP. Based on a 2-sided Fisher's exact test at alpha = 0.05, a sample size of approximately 600 patients randomized in a 2:1 ratio in Cohort 1 (400 RPC1063 1 mg and 200 placebo) will provide at least 90% power to detect this difference of 10 percentage points.

Cohort 2 (adult patients): Based on the same Phase 2 trial, it is anticipated that at least 60% of patients treated with RPC1063 will have a clinical response at the end of the IP. In order to ensure that there are approximately 420 patients with a clinical response to RPC1063 for potential enrolment of approximately 400 patients into the MP (assuming a 5% dropout rate), it will be necessary to enrol approximately 900 adult patients overall into the IP, of which 700 will receive treatment with RPC1063. Therefore, approximately an additional 300 patients receiving RPC1063 1 mg will be enrolled into Cohort 2.

Maintenance period: The placebo remission rate at Week 42 (52 weeks total treatment) is assumed to be 16% in a randomized withdrawal trial in UC patients who have previously had a clinical response to induction therapy (Feagan et al, 2013). Based on a 2-sided Fisher's exact test at alpha = 0.05, a sample size of 400 patients (200 patients per treatment group) will provide 90% power to detect a statistically significant improvement in the remission rate of 14 percentage points or larger (i.e., an active group remission rate of 30% or higher). To account for a 5% rate of patients who had a clinical response to induction therapy with RPC1063 not entering the MP, approximately 420 patients with a clinical response to RPC1063 will be required at the end of the IP.

The placebo remission rate at Week 42 (52 weeks total treatment) in the subset of patients who are in remission at Week 10 is assumed to be 16% (remission-in-remitters). Based on a 2-sided Fisher's exact test at alpha = 0.05, a sample size of 120 patients (60 per treatment group) will provide approximately 80% power to detect a statistically significant improvement in the remission-in-remitters rate of 24 percentage points or larger (ie, an active group remission-in-remitter rate of 40% or higher). As Cohort 2 is open-label, the ongoing remission rate at Week 10 from this cohort will be tracked and if it becomes evident that there will be fewer than 66 remitters from Cohort 2 entering MP, the sample size of Cohort 2 will be increased in proportion to the number of remaining remitters necessary to achieve approximately 66, which may in turn increase the number of patients from Cohort 2 qualifying to enter MP. To ensure adequate powering for the MP and a total of approximately 110 remitters, it may be necessary to increase the number of patients in Cohort 2 and therefore the total number of patients in the study.

Of note is the fact that the protocol also included recruitment of a cohort 3 referring to adolescent patients (which was implemented into the protocol per amendment and at request of the FDA). The study did, however, finally not recruit any adolescents. Therefore, this aspect of the trial is not further reported (however: see protocol amendments).

The final sample sizes were 429 and 216 in cohort 1 (treated with active and placebo, respectively) and 367 in the cohort 2. The maintenance study included finally 227 and 230 patients in the active and placebo groups.

Randomisation

The protocol foresaw the following for randomisation:

Consented/assented patients meeting all eligibility criteria will be assigned to treatment/randomized using the Interactive voice /web-based activated response system (IXRS).

Randomisation for cohort 1 in the induction phase was done using a 2:1 ratio (active:placebo) and using a 1:1 ratio in the maintenance phase. Cohort 2 was, of course not randomised.

Stratification factors were prior use of biologics/Anti-TNFs (yes/no) and use of corticosteroids (yes/no) for the induction period.

For the maintenance phase, patients were stratified by clinical remission status at Week 10 (yes or no) and corticosteroids use at Week 10 (yes or no).

Blinding (masking)

The study was conducted double-blind in cohort 1 and for the maintenance phase. Neither the investigator nor the patients were aware of treatment assignment until the end of the study period (last patient out).

Ozanimod and placebo capsules were identical in physical appearance. The treatment each subject received was not disclosed to the investigator, site staff, subject, Sponsor, or the clinical staff at the Contract Research Organization (CRO) involved with study conduct or data collection/analysis. Access to treatment assignments was strictly limited to groups directly involved with drug distribution, preparation of unblended output for the DSMB, safety personnel unblinded to treatment for SAE cases, and personnel involved in the conduct of PK assays.

Statistical methods

Data were analysed separately for the Induction Period and Maintenance Period according to their respective SAPs (SAP v4.0 for the Induction Period and SAP v4.1 for the Maintenance Period). Both periods were evaluated independently (regarded as independent studies). Changes to the planned statistical analyses plans were made prior to study unblinding.

All subject populations were defined and documented prior to database lock. The following analysis populations were used in the statistical analysis:

- Intent-to-Treat (ITT) populations:

- Induction Period ITT Population: (Cohort 1) All randomized subjects from Cohort 1 of the Induction Period of the study who received at least 1 dose of investigational drug (ozanimod or placebo); and (Cohort 2) all enrolled subjects from Cohort 2 of the Induction Period of the study who received at least 1 dose of investigational drug (ozanimod)

- Maintenance Period ITT Population: All randomized subjects who received at least 1 dose of investigational drug (ozanimod or placebo) in the Maintenance Period

The ITT populations were used as the primary population for all efficacy parameters.

- Per Protocol (PP) populations: The PP populations consists of all subjects in the ITT populations who adhered to the protocol. These populations were used in sensitivity analyses of the primary and key secondary endpoints to evaluate the influence of major protocol violators and protocol deviators on the primary results. Subjects were excluded from these populations if they violated the eligibility criteria or significantly deviated from the study plan. Specific reasons for warranting exclusion from these populations were documented prior to database lock and included, but were not limited to, investigational drug noncompliance > 20%, receiving incorrect investigational drug for more than 1 week in the

Induction Period or more than 1 month in the Maintenance Period, and missing more than 2 visits while still on the study.

-        Safety populations: The Safety populations consist of all subjects who received at least 1 dose of investigational drug. These populations were used for all summaries of safety data. Subjects randomized to placebo who received any amount of ozanimod were to be summarized in the ozanimod 1 mg group. Subjects randomized to ozanimod who received only placebo for all doses were to be summarized in the placebo group, otherwise they were to be summarized in the ozanimod 1 mg group.

Statistical tests:

- Induction period:

The primary analysis of proportion of subjects in clinical remission (3-component Mayo definition, 7-day scoring algorithm) at Week 10 was carried out on the ITT population using a two-sided Cochran-Mantel-Haenszel (CMH) test at the 5% level of significance, stratified by corticosteroid use at screening (yes or no), and prior anti-TNF use (yes or no). Number of subjects in remission, remission percentages, weighted difference in remission percentages, odds ratio, and associated 95% confidence intervals (CIs) and p-values are reported. Subjects who met the criteria for treatment failure were imputed using Non-Responder Imputation (NRI)

The primary analysis was repeated on the PP population and on key subgroups of the ITT population including, but not limited to, subjects with and without prior anti-TNF experience and subjects with and without prior corticosteroid use. These were considered sensitivity/supportive analyses only and are not subject to family-wise Type I error control.

The alternative definitions of remission were evaluated as sensitivity analysis (not subject to type I error control).

Starting from the primary endpoint, the 3 key secondary endpoints (clinical response, mucosal response and mucosal healing) were subsequently tested in order using a hierarchical testing procedure in order to control the overall Type I error rate for multiple endpoints. If the primary endpoint was statistically significant, the proportion of subjects with a clinical response (3-component Mayo definition, 7-day scoring algorithm) at Week 10 was tested at the 5% level of significance. This testing procedure continued through each of the 3 key secondary endpoints until an endpoint failed to reach statistical significance.

All secondary and other efficacy endpoints expressed as proportions of subjects were tested using the same type of CMH test as specified for the primary endpoint. All efficacy endpoints expressed as changes from Baseline were analysed with an analysis of covariance (ANCOVA) model adjusted for Baseline response parameter of interest, corticosteroid use at Screening, and prior anti-TNF use. The unadjusted mean changes from Baseline and SDs, adjusted least squares (LS) means and standard errors (SEs) with 95% CIs for both mean changes from Baseline and difference in the mean changes from Baseline, and p-values are provided.

- Maintenance Period:

The primary analysis of proportion of subjects in clinical remission (3-component Mayo definition, 7-day scoring algorithm) at Week 52 was carried out on the Maintenance Period ITT population using a 2-sided CMH test at the 5% level of significance, stratified by clinical remission status at Week 10 (3- or 4-component Mayo definition) of the Induction Period (yes or no), and corticosteroid use at Week 10 of the Induction Period (yes or no). Results were expressed as number of subjects in remission, remission percentages, weighted difference in remission percentages, odds ratio, and associated 95% CIs and p-values. Subjects who met the criteria for treatment failure were imputed using NRI

The primary analysis was repeated on the PP population and on key subgroups of the ITT population including, but not limited to, subjects with and without prior anti-TNF experience, subjects with and without prior corticosteroid use, and subjects with and without clinical remission at Week 10 of the Induction Period. These are considered sensitivity/supportive analyses only and are not subject to family-wise Type I error control.

In addition to the primary analysis of Maintenance Period clinical remission at Week 52 using the 3-component Mayo definition, the following alternative definitions of remission were explored as sensitivity analyses:

- Alternative definition 1: Rectal Bleeding Subscore ≤ 1 point and Stool Frequency Subscore ≤ 0 point (same or improved) and Endoscopy Subscore ≤ 1 point

- Alternative definition 2: Rectal Bleeding Subscore = 0 point and Stool Frequency Subscore ≤ 1 point and Endoscopy Subscore ≤ 1 point

- Alternative definition 3: Partial Mayo Score of ≤ 2 points with none of the associated 3 subscores > 1 point

- Alternative definition 4: Geboes index score ≤ 1.1 ignoring Geboes 2A (eosinophil score)

Stool frequency and rectal bleeding subscores derived using two 14-day scoring algorithm were also applied to the Mayo score calculation. Sensitivity analysis of the primary endpoint based on 14-day scoring algorithm was performed to support its primary analysis.

The 6 key secondary endpoints were tested in order using a hierarchical testing procedure (as ordered in Section 8.2.1.4) in order to control the overall Type I error rate for multiple endpoints. If the primary endpoint was statistically significant, the proportion of subjects with a clinical response (3-component Mayo definition) at 52 weeks was tested at the 5% level of significance.

If that endpoint was significant, then the proportion of subjects with endoscopic improvement at 52 weeks was tested at the 5% level of significance. This testing procedure continued through each of the 6 key secondary endpoints until an endpoint failed to reach statistical significance, after which all subsequent key secondary endpoints were considered exploratory. Endpoints listed as other secondary endpoints were tested in a non-hierarchical fashion without adjustments for multiplicity.

Handling of Missing Data

For proportion-based primary and key secondary efficacy endpoints, subjects with missing Week 10 efficacy data for the Induction Period and/or subjects with missing Week 52 efficacy data for Maintenance Period were considered non-responders using non-responder imputation (NRI). Sensitivity analyses around missing data could include tipping-point analysis, missing data imputed using multiple imputation (MI) and analysing observed cases with no imputation.

These missing data handling methods are detailed in the two SAPs. Conducting these sensitivity analyses using the proposed missing data handling methods (NRI, tipping point and multiple imputation) is to support that the comparisons of the 2 treatment groups in clinical remission at Week 10 and Week 52 are robust under different missing data imputation methods. For continuous efficacy endpoints, missing data analysis was performed using an MI method and observed cases with no imputation.

For cohort 2, no inferential testing was carried out.

Subgroup analyses were performed for the endpoints of clinical remission and clinical response only using the three-component Mayo score based on a 7-day scoring algorithm. The following were the pre-defined subgroups for the Induction Period as well as for the maintenance period:

1. Corticosteroid use at screening (yes vs no)

2. Prior anti-TNF use (yes vs no)

3. Baseline complete Mayo score ($\leq$ 9 vs > 9)

4. Extent of colitis (left-sided vs extensive)

5. Sex (female vs male)

6. Age at screening ($\leq$ median vs > median)

7. Baseline fecal calprotectin ($\leq$ 250 vs > 250 mg/kg)

8. Baseline ALC ($\leq$ 1,500 vs > 1,500 10^6/L)

9. Years since initial UC diagnosis ($\leq$ 4 vs > 4 years)

10. Region (North America, Eastern Europe, Western Europe, Asia Pacific)

11. Baseline partial Mayo score ($\leq$ median vs > median)

12. Baseline partial Mayo score ($\leq$ 7 vs > 7)

13. Baseline endoscopy subscore (2 vs 3)

14. Moderate UC status at Baseline (4-component Mayo score 6 to 10; yes versus no)

In addition, for the maintenance period, subgroup analyses were also performed for the criteria clinical remission status at week 10 (yes/no), and corticosteroids use at week 10 (yes/no).

In the Summary of Clinical Efficacy, the applicant takes note of the fact that the planning of the study (and the plans for evaluation) were drawn up at the time before the finalisation of the ICH-E9 addendum as well as the UC guideline were published or came into force. The applicant explains that the proposed evaluation strategy would implicitly correspond to a composite analysis strategy.

For treatment failure event number 1 (prohibited change in background medication), all potential treatment failure events were programmatically identified using a predefined search algorithm using WHO DD drug class and blinded data transfers. A manual review by the Sponsor team was conducted to confirm these potential treatment failures in a blinded manner prior to DBL. Based on the confirmed treatment failures, subjects had their efficacy data censored if collected on or after the date on which the treatment failure event took place and were considered non-remitters or non-responders for clinical remission or clinical response, respectively.

For treatment failure event number 2 (colectomy of other UC surgery), events were observed prior to unblinding of Study RPC01-3101 and subjects with events were considered non-remitters or non-responders for clinical remission or clinical response, respectively.

For treatment failure event number 3 (discontinuation due to lack of effect), subjects were encouraged to stay in the study for safety purposes if they stopped study treatment due to lack of therapeutic effect during the Induction Period; however, collection of efficacy data was discouraged by the Sponsor. In the Maintenance Period, if subjects relapsed, they were offered an opportunity to enrol into the OLE Study RPC01-3102, in which future efficacy data would not be available for analysis. If a subject discontinued the study due to relapse, then no efficacy data would be available and this would fall under the handling of missing data, in which NRI would apply (i.e., all missing data would be non-remitter or non-responder for clinical remission or clinical response, respectively).

Sensitivity estimand analyses that were outlined in the SCE SAP only included the treatment failure number 1 (except prolonged course of systemic corticosteroids > 14 days for treatment of disease other than UC) as intercurrent events (ICE) and did not involve treatment failures numbers 2 or 3.

The following table gives a description of the primary and "sensitivity estimand analyses" conducted:

Table 39: Description of primary and sensitivity estimand analyses

Study Period	Analysis/Endpoint Description	Intercurrent Event (ICE) Description	Estimand Analysis Strategy
Induction	***Primary analysis**/ Clinical Remission & Clinical Response at Week 10 (7-day scoring algorithm)*	*Treatment failure numbers 1, 2, and 3[a]*	*Composite*
Induction	Sensitivity/ Clinical Remission & Clinical Response at Week 10 (7-day scoring algorithm)	Treatment failure number 1[b]	Treatment Policy
Maintenance	***Primary analysis**/ Clinical Remission & Clinical Response at Week 52 (7-day scoring algorithm)*	*Treatment failure numbers 1, 2, and 3[a]*	*Composite*
Maintenance	Sensitivity/ Clinical Remission & Clinical Response at Week 52 (7-day scoring algorithm)	Treatment failure number 1[b]	Composite

5-ASA = 5-aminosalicylic acid; FDA = Food and Drug Administration; ICE = intercurrent events; SAP = statistical analysis plan; SCE = Summary of Clinical Efficacy; UC = ulcerative colitis.
[a] Treatment failure was defined prospectively in the Study RPC01-3101 protocol and SAPs in agreement with the FDA.
[b] Treatment failure number 1 (except prolonged course of systemic corticosteroid > 14 days for treatment of disease other than UC). SCE SAP-defined ICE subset as initiation or increase of corticosteroids/5-ASA/protocol-prohibited medications after first dose (Table 2). Failure to initiate corticosteroid taper for the Week 52 assessment could not be implemented due to data limitations.

Results

Participant flow

Of a total of 370 sites, 285 sites in 30 countries screened at least one subject for the trial. A total of 250 sites enrolled subjects. A total of 1831 subjects were screened, of which 819 failed screening criteria. The most common reasons for screen failure were not meeting the total Mayo score requirements (6-12) or the RBS and SFS in 18.1%, the presence of Varizella antibodies (or vaccination within 30 days prior to randomisation) in 5.7%, and inability to provide written informed consent and be compliant with the schedule of assessments in 4.6%.

There were 1012 subjects enrolled in Study RPC01-3101, including 645 subjects in Cohort 1 (429 randomized to ozanimod 1 mg and 216 to placebo) and 367 subjects in Cohort 2 (all treated with ozanimod 1 mg).
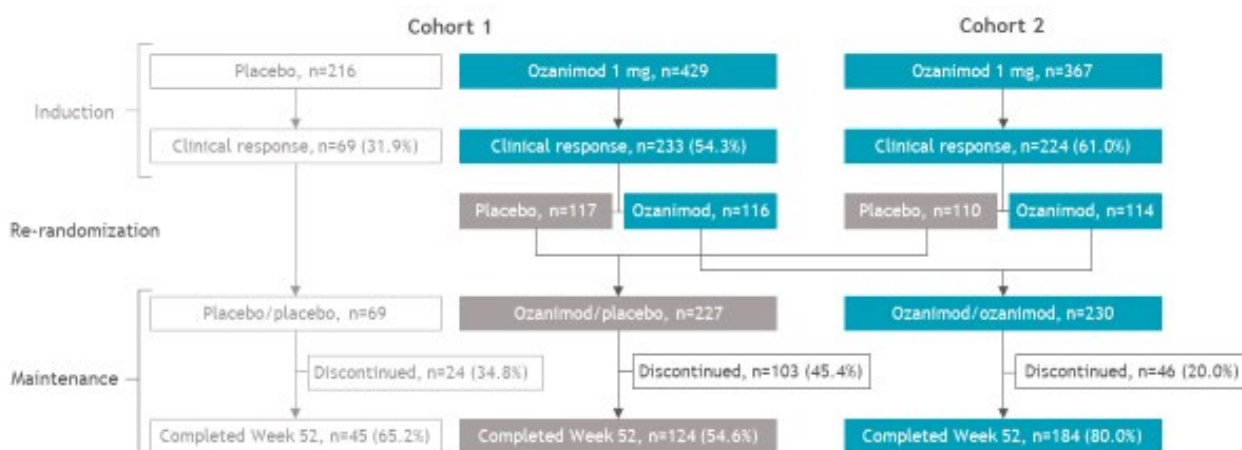
Figure 35: Disposition of Subjects (Study RPC01-3101)

Table 40: Subject Disposition – Induction period (randomised subjects' cohorts 1, and cohort 2)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429) n (%)	Placebo (N = 216) n (%)	Ozanimod 1 mg (N = 367) n (%)
Subjects Dosed[a]	429 (100.0)	216 (100.0)	367 (100.0)
Subjects Who Completed Induction Period[b]	401 (93.5)	192 (88.9)	324 (88.3)
Completed Induction Week 10, continuing into Maintenance Period[b, c]	233 (54.3)	69 (31.9)	224 (61.0)
Completed Induction Week 10, enrolled into open-label extension study[b]	159 (37.1)	120 (55.6)	79 (21.5)
Completed Induction Week 10, but discontinued study participation and did not enroll in open-label extension study[b]	9 (2.1)	3 (1.4)	21 (5.7)
Subjects Discontinued from Induction Period[b, d]	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 subject	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[e]	1 (0.2)	0	0
Physician Decision	0	0	1 (0.3)

[a] Percentages are based on the number of subjects in the Randomized population (Cohort 1) / Enrolled population (Cohort 2).
[b] Percentages are based on the number of subjects dosed.
[c] Subjects were required to be in clinical response by 3- or 4-component Mayo to continue into the Maintenance Period.
[d] Subjects discontinued from Induction Period are withdrawn from the study.
[e] Other reason includes: leaving the country.

A total of 526 subjects were treated during the Maintenance Period of the study, including 457 in the randomised part, of which 230 were re-randomised to ozanimod 1 mg, and 227 who re-randomized from ozanimod 1 mg to placebo, and 69 who continued on placebo. The numbers as well as discontinuations from the study with reasons are given in the following table.

The completion rate for the Maintenance Period was 80% in subjects continuously treated with ozanimod, ~55% in subjects rerandomized from ozanimod 1 mg to placebo, and ~65% in subjects continuously treated with placebo.

In total, 824 of 1012 subjects (~81%) enrolled in RPC01-3101 went on to enrol in the OLE study, RPC01-3102.

Table 41: Subject Disposition – Maintenance period (randomised subjects, placebo-placebo cohort)

n (%)	Placebo – Placebo (N = 69)	Rerandomized Subjects	
		Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects Dosed[a]	69 (100.0)	227 (100.0)	230 (100.0)
Subjects Who Completed Maintenance Period[b]	45 (65.2)	124 (54.6)	184 (80.0)
Completed Maintenance Week 42 (Week 52 of Study), enrolled into open-label extension study[b]	42 (60.9)	116 (51.1)	171 (74.3)
Completed Maintenance Week 42 (Week 52 of Study), but discontinued study participation and did not enroll in open-label extension study[b]	3 (4.3)	8 (3.5)	13 (5.7)
Subjects 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 open-label extension study	2 (2.9)	3 (1.3)	3 (1.3)
Withdrawal by subject	1 (1.4)	13 (5.7)	7 (3.0)
Other[c]	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)

[a] Percentages are based on the number of subjects in the Enrolled Population.
[b] Percentages are based on the number of subjects dosed.
[c] Other reason includes: subject lost to follow up, sponsor withdrew subject due to prolonged breast cancer chemotherapy. Early term visit was 90 days after last dose, so 90-day follow-up visit is not needed, wife wanted to get pregnant.

Recruitment

The study recruited the first patient on 12 August 2015. The date of the last visit for the induction period was 21 May 2019. The last subject visit for the maintenance period was 27 March 2020.

Conduct of the study

There are 4 protocols (originals all dated 30 Mar 2015): the main protocol (version 1.0), the region protocol (for regions implementing contraception methods to aligned with the "Recommendations related to contraception and pregnancy testing in clinical trials" [15 Sep 2014] by the Clinical Trial Facilitation Group), the protocol for Germany, and the protocol for Italy. The protocol for Italy was amended 8 times, the main protocol was amended 7 times, and the region protocol and protocol for Germany were amended twice to address local and regional requirements prior to the current versions.

The main features of the protocol amendments are given in the following:

- Amendment 1 (June 2016):

PK analyses were amended to add a third metabolite to the analysis (based on the results of study RPC01-1901), definitions of maintenance of remission, mucosla and histologic remissioin were updated, as well as descriptions of Mayo 3-component and 4-component scores added, clarifications to the in- and exclusion criteria were included, details regarding the colonic biopsies were revised, and the time periods for collection of SF and RB diary entries were further defined, revision of the description of the primary efficacy analysis (odds ratio instead of relative risk), and addition of treatment failure rules.

- Amendment 2 (June 2017)

Proportion of patients who could have previously received anti-TNF therapy from less or equal to 30% amended to approximately 35% to reflect increasing use of the product(s), removal of several prohibited concomitant medications due to new PK data becoming available

- Amendment 3 (December 2017):

Proportion of subject in Cohort 1 and Cohort 2 adjusted to reinstate the original limit of $\leq$ 30% of subjects who have received anti-TNF, limit of $\leq$ 50% was established for Cohort 2. These limits were established based on ongoing development programs in UC that have confirmed that subjects with anti-TNF experience achieved limited clinical response.

- Amendment 4 (May 2018):

A 75-day (± 10 days) Safety Follow-up Visit added to ensure adequate collection of AEs that could be associated with the investigational drug, additional assessment of ALC for subjects who had a confirmed ALC below the 200 cells/μL limit and permanently discontinued in order to evaluate the rebound effect after long-term exposure to ozanimod, visit windows for visits during the maintenance phase increased, BCRP inhibitors, CYP2C8 inzhibitors or inducers and MAO inghibitors added to the list of medications that were prohibited during the study, analysis method from the last observation carried forward (LOCF) method changed to the NRI method.

- Amendment 5 (November 2018):

Adolescent subjects included (FDA request) via a separate cohort (Cohort 3) utilizing 2:1 randomization. Adolescent subjects 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. Subsequent changes for efficacy measures and statistical evaluation for this cohort were also implemented.

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 PGA from the calculation of the 4-component Mayo.

- Amendment 6 (May 2019):

75-day (±10 days) Safety Follow-up Visit was changed to a 90-day (±10 days) Safety Follow-up Visit, revision of the requirements for female contraception and removal of the male requirements for contraception, revised Treatment Failure Rules: Added tofacitinib to the list of prohibited medications changes and updated prolonged use of systemic corticosteroids to > 14 days.

Baseline data

The baseline demographic characteristics of subjects in the Induction Period were generally well balanced between groups and consistent with a population of subjects with moderate to severe UC, with the exception of a higher percentage of male subjects in the placebo group as compared to the ozanimod group and as compared to the cohort 2 subjects. The majority of patients were white and from the Eastern European region (with additional 10-16% from Western Europe) with other

ethnicities/races/decent under 10% of the total with the exception of region being North America which was around 25%.

The baseline demographics are shown in the following table:

Table 41 Demographics - Induction Period (ITT Population), Study RPC01-3101

	Cohort 1		Cohort 2
	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)			
Mean (SD)	41.4 (13.54)	41.9 (13.64)	42.1 (13.72)
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)
≤ Median Age (40.0)[a]	217 (50.6)	114 (52.8)	184 (50.1)
> Median Age (40.0)[a]	212 (49.4)	102 (47.2)	183 (49.9)
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)

Table 42: Demographics - Induction Period (ITT Population), Study RPC01-3101 (continued)

Weight (kg)			
n	429	216	366
Mean (SD)	74.4 (18.25)	75.0 (16.28)	76.4 (18.59)
Min, Max	38, 173	40, 126	38, 156
Body Mass Index (kg/m²)			
n	428	216	366
Mean (SD)	25.40 (5.492)	25.11 (4.477)	25.88 (5.796)
Min, Max	16.3, 51.8	17.0, 38.9	15.3, 49.2
Tobacco/Nicotine Use, n (%)			
Current	26 (6.1)	15 (6.9)	16 (4.4)
Former	124 (28.9)	62 (28.7)	94 (25.6)
Never	279 (65.0)	139 (64.4)	257 (70.0)
Region, n(%)			
North America	107 (24.9)	60 (27.8)	80 (21.8)
Eastern Europe[b]	215 (50.1)	112 (51.9)	200 (54.5)
Western Europe[c]	62 (14.5)	21 (9.7)	60 (16.3)
Asia Pacific	36 (8.4)	20 (9.3)	27 (7.4)
South America	3 (0.7)	0	0
South Africa	6 (1.4)	3 (1.4)	0

ITT = Intent-to-Treat; SD = standard deviation.
[a] Median is derived based on the ITT population from Cohort 1.
[b] Eastern European countries include Belarus, Bulgaria, Croatia, Czech Republic, Georgia, Greece, Hungary, Latvia, Republic of Moldova, Poland, Romania, Russian Federation, Serbia, Slovakia, and Ukraine.
[c] Western European countries include Austria, Belgium, Germany, Italy, the Netherlands, and the United Kingdom.

The subjects continuing in the placebo group in the Maintenance Period continued to have a higher proportion of males (66.7%) compared to subjects rerandomized to placebo (53.7%) and subjects rerandomized to ozanimod (50.9%). The subjects continuing in the placebo group in the Maintenance Period had a higher proportion of subjects from Eastern Europe (71.0%) compared to subjects rerandomized to placebo (59.9%) and subjects rerandomized to ozanimod (52.6%).

The results are shown in the following table.

Table 43: Demographics – Maintenance Period (ITT Population), Study RPC01-3101

		Rerandomized Subjects	
	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)			
Mean (SD)	44.1 (14.72)	43.0 (13.71)	42.4 (13.53)
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)
≤ median age (42.0)[a]	34 (49.3)	112 (49.3)	126 (54.8)
> median age (42.0)[a]	35 (50.7)	115 (50.7)	104 (45.2)
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	0	4 (1.8)	3 (1.3)
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)
Weight (kg)			
n	69	227	229
Mean (SD)	76.3 (17.02)	75.4 (17.76)	74.8 (19.38)
Min, Max	51, 126	41, 173	38, 156

Table 21: Demographics – Maintenance Period (ITT Population), Study RPC01-3101 (continued)

	Placebo (N = 69)	Rerandomized Subjects	
		Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Body Mass Index (kg/m²)			
n	69	227	228
Mean (SD)	25.45 (4.868)	25.83 (5.408)	25.65 (5.803)
Min, Max	17.1, 38.9	15.3, 51.8	16.3, 49.5
Tobacco/Nicotine Use, n (%)			
Current	3 (4.3)	9 (4.0)	13 (5.7)
Former	14 (20.3)	61 (26.9)	55 (23.9)
Never	52 (75.4)	157 (69.2)	162 (70.4)
Region, n(%)			
North America	13 (18.8)	49 (21.6)	56 (24.3)
Eastern Europe[b]	49 (71.0)	136 (59.9)	121 (52.6)
Western Europe[c]	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)

ITT = Intent-to-Treat; SD = standard deviation.
[a] Median is derived based on the ITT population from Cohort 1.
[b] Eastern European countries include Belarus, Bulgaria, Croatia, Czech Republic, Georgia, Greece, Hungary, Latvia, Republic of Moldova, Poland, Romania, Russian Federation, Serbia, Slovakia, and Ukraine.
[c] Western European countries include Austria, Belgium, Germany, Italy, the Netherlands, and the United Kingdom.

The mean duration of UC symptoms at the beginning of the Induction Period for Cohort 1 was approximately 8 years, with a mean time since UC diagnosis of approximately 7 years. The mean 3-component Mayo score at baseline was 6.6 and the mean 4-component Mayo score was approximately 9. Approximately 35% of subjects had a 4-component Mayo score > 9 at baseline. Approximately 38% of subjects had disease extent proximal to the left side of the colon. The median baseline CRP was slightly lower at 4.0 mg/L in the Cohort 1 ozanimod group and 5.0 mg/L in the placebo and Cohort 2 ozanimod groups. The median faecal calprotectin (FCP) was approximately 1080 mg/kg in the Cohort 1 ozanimod group, 1350 mg/kg in the placebo group, and 1260 mg/kg in the Cohort 2 ozanimod group.

The baseline characteristics are shown in the following tables.

Table 44: Ulcerative Colitis Baseline Disease Characteristics – Induction Period (ITT Population), Study RPC01-3101

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N=367)
Age at UC Symptom Onset (years)			
n	429	216	366
Mean (SD)	33.7 (13.04)	34.6 (13.52)	33.7 (13.51)
Min, Max	10, 70	11, 70	3, 73
Age at UC Diagnosis (years)			
Mean (SD)	34.6 (13.22)	35.3 (13.60)	34.5 (13.43)
Min, Max	10, 70	12, 70	3, 73
Years since UC Symptom Onset			
Mean (SD)	7.9 (7.17)	7.6 (7.08)	8.65 (7.759)
Min, Max	0.0, 49	0, 40	0.0, 41.2
Years since UC Diagnosis			
Mean (SD)	6.9 (6.61)	6.8 (7.04)	7.91 (7.365)
Min, Max	0, 39	0, 39	0.2, 41.2
Extent of Disease, n (%)			
Limited to Left Side of Colon	268 (62.5)	134 (62.0)	237 (64.6)
Extensive	161 (37.5)	82 (38.0)	130 (35.4)
3-Component Mayo Score[a] (Central Reader) at Baseline			
Mean (SD)	6.6 (1.21)	6.6 (1.15)	6.8 (1.26)
Median	7.0	7.0	7.0
Min, Max	3, 9	4, 9	4, 9
4-Component Mayo Score[b] (Central Reader) at Baseline			
Mean (SD)	8.9 (1.47)	8.9 (1.35)	9.1 (1.49)
Median	9.0	9.0	9.0
Min, Max	6, 12	6, 12	6, 12
4-Component Mayo Score[b] (Central Reader) at Baseline Category - n (%)			
≤ 9	280 (65.3)	140 (64.8)	205 (55.9)
> 9	149 (34.7)	76 (35.2)	162 (44.1)
Mucosal Appearance at Endoscopy (Central Reader)[c] – n (%)			
2 – Moderate Disease	179 (41.7)	86 (39.8)	138 (37.6)
3 – Severe Disease	250 (58.3)	130 (60.2)	229 (62.4)

Table 45: Ulcerative Colitis Baseline Disease Characteristics – Induction Period (ITT Population), Study RPC01-3101 (continued)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N=367)
Fecal Calprotectin (mg/kg)			
Mean (SD)	2508.96 (4526.182)	3440.42 (6351.629)	2970.56 (5558.118)
Median	1079.48	1349.79	1259.85
Min, Max	3.8, 40525.0	3.8, 44709.3	5.9, 37128.7
C-Reactive Protein (mg/L)			
Mean (SD)	8.0 (13.42)	11.1 (18.09)	9.4 (13.62)
Median	4.0	5.0	5.0
Min, Max	1, 115	1, 123	1, 111

ITT = Intent-to-Treat; SD = standard deviation; UC = ulcerative colitis.
[a] 3-Component Mayo score is the sum of the Rectal Bleeding subscore, Stool Frequency subscore, and the Endoscopy subscore.
[b] 4-Component Mayo Score is the sum of the Rectal Bleeding subscore, Stool Frequency subscore, Physician Global Assessment subscore, and the Endoscopy subscore.
[c] Derived from Robarts data.

The mean duration of UC symptoms was slightly longer in subjects re-randomized to ozanimod (approximately 9.2 years) compared to subjects-re-randomized to placebo (approximately 8.2 years). The median 4-component Mayo score was 9.0 at screening for all subjects in the Maintenance Period. Of the subjects who remained on ozanimod, 41.3% had a 4-component Mayo score > 9 at baseline, compared with 27.8% who were re-randomized to placebo. The median baseline FCP was 1077.59 mg/kg in subjects who were re-randomized to placebo and 1208.98 mg/kg in subjects who remained on ozanimod.

Table 46: Ulcerative Colitis Baseline Disease Characteristics – Maintenance Period (ITT Population), Study RPC01-3101

		Rerandomized Subjects	
	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 (13.29)	35.1 (13.48)	33.4 (13.02)
Min, Max	15, 65	5, 73	8, 64
Age at UC Diagnosis (years)			
Mean (SD)	36.5 (13.69)	36.0 (13.44)	34.4 (13.01)
Min, Max	15, 65	5, 73	8, 66
Years since UC Symptom Onset			
Mean (SD)	8.47 (8.415)	8.21 (7.789)	9.24 (7.882)
Min, Max	0.5, 39.7	0.0, 37.6	0.0, 49.1
Years since UC Diagnosis			
Mean (SD)	7.75 (8.025)	7.23 (7.186)	8.36 (7.336)
Min, Max	0.3, 38.7	0.2, 37.6	0.2, 38.6
Extent of Disease, n (%)			
Limited to Left Side of Colon	41 (59.4)	157 (69.2)	152 (66.1)
Extensive	28 (40.6)	70 (30.8)	78 (33.9)
3-Component Mayo Score[a] (Central Reader)			
Mean (SD)	6.4 (1.17)	6.4 (1.24)	6.7 (1.31)
Median	7.0	7.0	7.0
Min, Max	4, 9	3, 9	4, 9
4-Component Mayo Score[b] (Central Reader)			
Mean (SD)	8.6 (1.37)	8.6 (1.42)	8.9 (1.57)
Median	9.0	9.0	9.0
Min, Max	6, 11	6, 12	6, 12
4-Component Mayo Score[b] (Central Reader) Category - n (%)			
≤ 9	52 (75.4)	164 (72.2)	135 (58.7)
> 9	17 (24.6)	63 (27.8)	95 (41.3)
Mucosal Appearance at Endoscopy (Central Reader)[c] – n (%)			
2 – Moderate Disease	33 (47.8)	111 (48.9)	98 (42.6)
3 – Severe Disease	36 (52.2)	116 (51.1)	132 (57.4)

Table 47: Ulcerative Colitis Baseline Disease Characteristics – Maintenance Period (ITT Population), Study RPC01-3101 (continued)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Fecal Calprotectin (mg/kg)			
n	69	225	226
Mean (SD)	2481.47 (5436.442)	2987.32 (5832.422)	2284.32 (3911.768)
Median	858.02	1077.59	1208.98
Min, Max	3.8, 32023.3	3.8, 37128.7	6.0, 27598.1
C-Reactive Protein (mg/L)			
Mean (SD)	7.2 (12.08)	6.8 (10.15)	6.8 (10.67)
Median	3.0	4.0	3.0
Min, Max	1, 70	1, 84	1, 86

ITT = Intent-to-Treat; SD = standard deviation; UC = ulcerative colitis.
[a] 3-Component Mayo score is the sum of the Rectal Bleeding subscore, Stool Frequency subscore, and the Endoscopy subscore.
[b] 4-Component Mayo Score is the sum of the Rectal Bleeding subscore, Stool Frequency subscore, Physician Global Assessment subscore, and the Endoscopy subscore.
[c] Derived from Robarts data.

With regard to the <u>medical history</u>, disease states reported in more than 10% of the participants were the following:

- In the induction period:

Haemorrhoids (13.1% of subjects in the Cohort 1 ozanimod group, 11.6% of subjects in the placebo group, and 8.7% of subjects in the Cohort 2 ozanimod group)

Anaemia (17.9% of subjects in the Cohort 1 ozanimod group, 13.4% of subjects in the placebo group, and 15.3% of subjects in the Cohort 2 ozanimod group)

Hypertension (12.1% of subjects in the Cohort 1 ozanimod group, 13.4% of subjects in the placebo group, and 14.2% of subjects in the Cohort 2 ozanimod group)

- In the maintenance period:

Hypertension (18.8% of subjects who remained on placebo, 13.7% of subjects who were re-randomized to placebo, and 14.3% of subjects who remained on ozanimod)

Anaemia (10.1% of subjects who remained on placebo, 18.1% of subjects who were re-randomized to placebo, and 13.5% of subjects who remained on ozanimod)

Haemorrhoids (13.0% of subjects who remained on placebo, 11.9% of subjects who were re-randomized to placebo, and 10.4% of subjects who remained on ozanimod)

Chronic gastritis (13.0% of subjects who remained on placebo, 7.9% of subjects who were re-randomized to placebo, and 7.0% of subjects who remained on ozanimod)

Gastroesophageal reflux disease (7.2% of subjects who remained on placebo, 10.6% of subjects who were re-randomized to placebo, and 8.7% of subjects who remained on

ozanimod)

Concomitant medication at baseline:

For the Induction Period, prior commonly used medications included medications used for endoscopic procedures (ie, fentanyl, propofol, midazolam). Other most common (ie, used by ≥ 15% of subjects in any group) prior medications for subjects in the Induction Period included ascorbic acid/potassium/sodium chloride/sodium sulfate and macrogol 4000, and macrogol 3350 (for bowel preparation)

Almost all the subjects in Cohort 1 had had been previously treated with 5-ASAs (~97%), most of whom failed to respond (~75%) or were intolerant (~9%) (Table 14.1.8.2.1A). Approximately 75% of subjects had used corticosteroids, including ~46% who failed to respond, ~12% who were intolerant, and ~25% who were steroid-dependent. Approximately 41% of subjects had failed to respond and/or were intolerant to immunomodulators (primarily AZA or 6-MP).

Additionally, patients failed or were intolerant to biologics, including anti-TNF and other biologics (such as vedolizumab). In Cohort 1, approximately 30% of subjects had an inadequate response, loss of response, or intolerance to anti-TNF use (as randomized). Of these subjects, 70/195 (~36%) failed to ever respond to at least 1 anti-TNF (primary nonresponse) and 126/195 (~65%) lost response to an anti-TNF (secondary nonresponse; 123/195 (~63%) had received 2 or more biologics and 91/195 (~47%) had received an integrin receptor blocker (ie, vedolizumab). Prior and concomitant treatment were similar for Cohort 2 with higher prior use of anti-TNF blocker use (43%) and vedolizumab in patients with prior anti-TNF blocker use (55.3%).

The data on prior medication are shown in the following table for the safety population:

Table 48: Prior Ulcerative Colitis Medication – Induction Period (Safety Population)

Prior UC Medication Preferred Name Response Category	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429) n (%)	Placebo (N = 216) n (%)	Ozanimod 1 mg (N = 367) n (%)
Corticosteroids	322 (75.1)	162 (75.0)	286 (77.9)
Failed to respond	200 (46.6)	96 (44.4)	168 (45.8)
Intolerant	50 (11.7)	28 (13.0)	28 (7.6)
Corticosteroid dependent	106 (24.7)	56 (25.9)	104 (28.3)
Oral aminosalicylic acids	418 (97.4)	210 (97.2)	362 (98.6)
Failed to respond	313 (73.0)	162 (75.0)	269 (73.3)
Intolerant	36 (8.4)	22 (10.2)	29 (7.9)
Immunomodulators	174 (40.6)	93 (43.1)	166 (45.2)
Failed to respond	118 (27.5)	70 (32.4)	121 (33.0)
Intolerant	58 (13.5)	34 (15.7)	55 (15.0)
Azathioprine	145 (33.8)	74 (34.3)	136 (37.1)
Failed to respond	94 (21.9)	50 (23.1)	95 (25.9)
Intolerant	50 (11.7)	24 (11.1)	46 (12.5)
Mercaptopurine	33 (7.7)	22 (10.2)	28 (7.6)
Failed to respond	23 (5.4)	16 (7.4)	23 (6.3)
Intolerant	12 (2.8)	10 (4.6)	9 (2.5)
Methotrexate	10 (2.3)	11 (5.1)	13 (3.5)
Failed to respond	8 (1.9)	8 (3.7)	11 (3.0)
Intolerant	1 (0.2)	3 (1.4)	2 (0.5)
Anti-TNF	130	65	159
Primary non-responder[a]	49 (37.7)	21 (32.3)	60 (37.7)
Secondary non-responder[a]	84 (64.6)	42 (64.6)	109 (68.6)
Intolerant[a]	27 (20.8)	17 (26.2)	26 (16.4)
Non-anti-TNF biologics	80 (18.6)	44 (20.4)	106 (28.9)
Primary non-responder	24 (5.6)	9 (4.2)	25 (6.8)
Secondary non-responder	49 (11.4)	33 (15.3)	75 (20.4)
Intolerant	10 (2.3)	4 (1.9)	12 (3.3)

TNF = tumor necrosis factor; UC = ulcerative colitis.

The most commonly used (i.e., used by >15% of subjects in any group) prior biologics medications for subjects in the Induction Period included:

- Adalimumab (11.9% of subjects in the Cohort 1 ozanimod group, 18.5% of subjects in the placebo group, and 19.3% of subjects in the Cohort 2 ozanimod group)

- Infliximab (22.6% of subjects in the Cohort 1 ozanimod group, 21.8% of subjects in the placebo group, and 34.1% of subjects in the Cohort 2 ozanimod group)

- Vedolizumab (16.6% of subjects in the Cohort 1 ozanimod group, 17.6% of subjects in the placebo group, and 25.3% of subjects in the Cohort 2 ozanimod group).

For the Maintenance Period, prior commonly used medications included medications used for endoscopic procedures (quite similar to the induction period). Prior treatments for UC included 5-ASA in nearly all subjects (98%) corticosteroids in ~72%, immunomodulators in ~38%, anti-TNFs (as randomized) in ~31%, and other biologics in ~16%. The table is not reproduced here and percentages are largely similar to the induction period.

Concomitant medication

Common concomitant medications for subjects in the Induction Period included medications used for endoscopy (e.g., propofol, midazolam, macrogol 4000).

Subjects enrolling in the study were required to be treated with other concomitant therapies including aminosalicylates (eg, mesalazine 71% of total subjects; sulfasalazine 13% of total subjects). The most commonly used substances were:

- Mesalazine (69.5% of subjects in the Cohort 1 ozanimod group, 65.3% of subjects in the placebo group, and 74.9% of subjects in the Cohort 2 ozanimod group)

- Sulfasalazine (15.6% of subjects in the Cohort 1 ozanimod group, 14.4% of subjects in the placebo group, and 9.8% of subjects in the Cohort 2 ozanimod group)

Concomitant corticosteroids for systemic use were used in 27.7% of subjects in the Cohort 1 ozanimod group, 32.4% of subjects in the placebo group, and 33.8% of subjects in Cohort 2 ozanimod group. In total, ~31% of subjects in the Induction Period were on concomitant oral corticosteroids.

The most commonly used corticosteroid for subjects in the Induction Period was prednisone (18.1% of subjects ozanimod total, 16.1% of subjects in the Cohort 1 ozanimod group, 17.6% of subjects in the placebo group, and 20.4% of subjects in the Cohort 2 ozanimod group). Budesonide was used concomitantly by 4.4% of subjects in the Cohort 1 ozanimod group, 6.0% of subjects in the placebo group, and 6.3% of subjects in the Cohort 2 ozanimod group.

Concomitant medication during the maintenance phase showed a tendency for lower rates of using these medications, with no substantial qualitative differences.

Treatment compliance was generally high during the study with approximately 100% across treatment groups during the Induction Period and approximately 98% to 99% across treatment groups during the Maintenance Period.

Numbers analysed

In the ITT Population of the Induction Period, there were a total of 429 subjects in the Cohort 1 ozanimod group, 216 subjects in the placebo group, and 367 subjects in the Cohort 2 ozanimod group. Reasons for exclusion from the PP Population of the Induction Period included treatment deviation, randomization procedure, excluded concomitant medication use, and selection criteria not met.

Table 49: Analysis Populations – Induction Period

| | Cohort 1 | | Cohort 2 |
	Ozanimod 1 mg n	Placebo n	Ozanimod 1 mg n
ITT Population	429	216	367
Safety Population	429	216	367
PP Population	422	214	361

ITT = Intent-to-Treat; PP = Per Protocol.

In the ITT population of the Maintenance Period, there were a total of 69 subjects in the placebo group, 227 subjects rerandomized to placebo, and 230 subjects rerandomized to ozanimod. Reasons for exclusion from the PP Population of the Maintenance Period included excluded concomitant medication use and selection criteria not met.

Table 50: Analysis Populations – Maintenance Period

| | | Rerandomized Subjects | |
	Placebo – Placebo n	Ozanimod 1 mg – Placebo n	Ozanimod 1 mg – Ozanimod 1 mg n
ITT Population	69	227	230
Safety Population	69	227	230
PP Population	67	221	224

ITT = Intent-to-Treat; PP = Per Protocol.

Protocol deviations:

A protocol deviation was defined as a deviation from the approved protocol version (valid at that time for that particular subject). Non-compliance with the study protocol, whether subject- or procedure-related, was classified into two categories, major and minor. A major protocol deviation was defined as a deviation that may impact the safety, health, and well-being of subjects; or the integrity and validity of the clinical study data. Major deviations could include items such as not signing the most recent version of the ICF, or administration of investigational product outside storage conditions, in addition to items such as receiving prohibited medications and missing assessments. In Cohort 1 of the Induction Period, 7 (1.6%) subjects in the ozanimod 1 mg arm and 2 (0.9%) subjects in the placebo arm were excluded from the Per Protocol Population due to at least 1 major protocol deviation (see above)). Reasons for exclusion included treatment deviation, incorrect randomization procedure, use of excluded concomitant medications, and selection criteria not met.

The following tables display the total number of major protocol deviations from the induction as well as the maintenance period:

Table 51: Summary of Major Protocol Deviations - Induction Period (ITT Population)

Protocol Deviation, n (%)	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Subjects with at least 1 major protocol deviation	182 (42.4)	96 (44.4)	126 (34.3)
Excluded concomitant medication	29 (6.8)	26 (12.0)	24 (6.5)
Informed consent[a]	30 (7.0)	16 (7.4)	16 (4.4)
Other/GCP issue	2 (0.5)	0	0
Randomization procedure	9 (2.1)	3 (1.4)	7 (1.9)
Selection criteria not met[b]	52 (12.1)	17 (7.9)	30 (8.2)
Serious adverse event reporting[c]	2 (0.5)	2 (0.9)	1 (0.3)
Study procedure	75 (17.5)	37 (17.1)	46 (12.5)
Treatment deviation[e]	48 (11.2)	21 (9.7)	26 (7.1)
Visit scheduling	9 (2.1)	9 (4.2)	5 (1.4)

ET = early termination; GCP = Good Clinical Practice; ITT = Intent-to-Treat.
[a] Common deviations included subjects not signing the most recent version during screening visits.
[b] Common deviations included selection criteria being confirmed after randomization and subjects taking excluded medications within the screening window
[c] Serious adverse event not reported within 24 hours.
[d] Common deviations included assessment not done at ET visit; assessment not done or done out of window on Day 1; cardiac or extended cardiac monitoring not done on Day 1; safety follow up visit not done.
[e] Study drug bottles not returned; subject took an extra dose; subject did not undergo dose escalation.

Table 52: Summary of Major Protocol Deviations - Maintenance Period (ITT Population)

Protocol Deviation	Placebo – Placebo (N = 69)	Rerandomized Subjects	
		Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects with at least 1 major protocol deviation	21 (30.4)	48 (21.1)	58 (25.2)
Excluded concomitant medication	6 (8.7)	5 (2.2)	7 (3.0)
Informed consent[a]	6 (8.7)	5 (2.2)	19 (8.3)
Other/GCP issue	0	0	1 (0.4)
Selection criteria not met	1 (1.4)	1 (0.4)	0
Serious adverse event reporting	3 (4.3)	6 (2.6)	0
Study procedure	9 (13.0)	20 (8.8)	19 (8.3)
Treatment deviation	1 (1.4)	17 (7.5)	20 (8.7)
Uncoded	1 (1.4)	0	0
Visit scheduling	2 (2.9)	5 (2.2)	4 (1.7)

GCP = Good Clinical Practice; ICF = informed consent form; ITT = Intent-to-Treat.
[a] Common deviations included failure to reconsent new ICF version during site visits.

Outcomes and estimation

Induction Period – Week 10: Primary Efficacy Endpoint

A highly statistically significantly higher proportion of subjects in the Cohort 1 ozanimod group (18.4%) achieved clinical remission using the 3-component Mayo definition, 7-day scoring algorithm compared to the placebo group (6.0%) at Week 10 of the Induction Period using NRI. The Cohort 2 ozanimod group

had a similar rate of remission (21.0%) to the Cohort 1 ozanimod group. The results are shown in the following table

Table 53: Proportion of Subjects in Clinical Remission (3-component Mayo Definition Using 7-day Scoring Algorithm) at Week 10 - Induction Period (ITT Population, Non-Responder Imputation)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Subjects in clinical remission, n (%)[a]	79 (18.4)	13 (6.0)	77 (21.0)
Odds ratio (95% CI)[b]	3.586 (1.938, 6.636)		-
Difference in proportions (95% CI)[b]	0.124 (0.075, 0.172)		-
p-value[b]	< 0.0001		-

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DBL = database lock; ITT = Intent-to-Treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore; TNF = tumor necrosis factor.

[a] Clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and Endoscopy subscore ≤ 1 point without friability.

[b] Odds ratio (active/placebo), treatment difference, and 2-side 95% Wald CI and p-value for comparison between the Cohort 1 ozanimod and placebo group are based on the CMH test, stratified by corticosteroid use at Screening and prior anti-TNF use (yes or no).

Note: Subjects with any of RBS, SFS, and endoscopy subscores missing at Week 10 are classified as non-remitters.

Results from all sensitivity analyses, including analysis of the Induction PP Population, analyses using alternative missing data handling methods and analyses using 4-component Mayo and additional alternative definitions of clinical remission, were consistent with the primary analysis using NRI with the 7-day scoring algorithm and support the robustness of the results.

Regarding the tipping point analysis of clinical remission at Week 10, the area marked as "Not Significant" is about $[(12 \times 28)/2] / (27 \times 45) = 13.8\%$ of the entire area, while the area marked as "Significant: RPC treatment favored over Placebo" is about 86.2% of the entire area. Most of the results in this tipping point sensitivity analysis being consistent with the primary analysis of clinical remission at Week 10 demonstrates the robustness of the primary analysis. The same conclusion can be reached for the tipping point analysis of clinical response at Week 10.

Table 54: Alternative Definitions of Clinical Remission at Week 10 of Total Treatment (Induction ITT Population, Nonresponder Imputation) – Study RPC01-3101

Analysis Method	Number (%) of Subjects		Treatment Comparison		
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Difference in Proportions (95% CI)[a]	Odds Ratio (95% CI)[a]	P-value[a,b]
Primary Analysis with Different Scoring Algorithms					
3-component Mayo Definition[c] with 14-day Scoring Algorithm A	80 (18.6)	15 (6.9)	0.117 (0.067, 0.167)	3.102 (1.737, 5.540)	< 0.0001
3-component Mayo Definition[c] with 14-day Scoring Algorithm B	80 (18.6)	15 (6.9)	0.117 (0.067, 0.167)	3.102 (1.737, 5.540)	< 0.0001
Alternative Definitions of Clinical Remission					
4-component Mayo Definition[d] with 7-day Scoring Algorithm	50 (11.7)	10 (4.6)	0.070 (0.029, 0.111)	2.718 (1.351, 5.467)	0.0037
Alternative Definition 1[e] with 7-day Scoring Algorithm	97 (22.6)	18 (8.3)	0.143 (0.089, 0.196)	3.262 (1.910, 5.571)	< 0.0001
Alternative Definition 2[f] with 7-day Scoring Algorithm	93 (21.7)	15 (6.9)	0.147 (0.096, 0.199)	3.772 (2.121, 6.711)	< 0.0001
Alternative Definition 3[g] with 7-day Scoring Algorithm	148 (34.5)	39 (18.1)	0.164 (0.097, 0.232)	2.448 (1.632, 3.671)	< 0.0001
Alternative Definition 4[h] with 7-day Scoring Algorithm	87 (20.3)	16 (7.4)	0.129 (0.077, 0.180)	3.218 (1.832, 5.650)	< 0.0001
Alternative Definition 4[h] with 14-day Scoring Algorithm A	88 (20.5)	17 (7.9)	0.126 (0.074, 0.178)	3.043 (1.757, 5.270)	< 0.0001
Alternative Definition 4[h] with 14-day Scoring Algorithm B	88 (20.5)	17 (7.9)	0.126 (0.074, 0.178)	3.043 (1.757, 5.270)	< 0.0001

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore; TNF = tumor necrosis factor.
[a] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI, and p-value for comparison between the active and placebo groups are based on the CMH test, stratified by corticosteroid use at Screening and prior anti-TNF use (yes or no).
[b] P-values in italics are ≤ 0.05 and considered nominally significant, because no multiplicity adjustment was applied.
[c] 3-component Mayo score definition: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and endoscopy subscore ≤ 1 point without friability.
[d] 4-component Mayo definition: 4-component Mayo score of ≤ 2 points and with no individual subscore of > 1 point.
[e] Alternative definition 1: RBS ≤ 1 point and SFS ≤ 1 point and endoscopy subscore ≤ 1 point

Maintenance Period – Week 52: Primary Efficacy Endpoint

A highly statistically significantly higher proportion of subjects who were rerandomized toozanimod (ozanimod 1 mg – ozanimod 1 mg treatment group) (37.0%) achieved clinical remission using the 3-component Mayo definition, 7-day scoring algorithm compared to subjects rerandomized to placebo (ozanimod 1 mg – placebo treatment group) (18.5%) at Week 52 of the Maintenance Period using NRI (p < 0.0001). Among subjects continuously treated with placebo, 24.6% were in clinical remission at Week 52. The results are displayed in the following table:

Table 55: Proportion of Subjects in Clinical Remission (3-component Mayo Definition Using 7-day Scoring Algorithm) at Week 52 of Total Treatment - Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects in clinical remission, n (%)[a]	17 (24.6)	42 (18.5)	85 (37.0)
Odds ratio (95% CI)[b]	-	2.755 (1.767, 4.294)	
Difference in proportions (95% CI)[b]	-	0.186 (0.108, 0.264)	
p-value[b]	-	< 0.0001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore; TNF = tumor necrosis factor.

[a] Clinical remission is defined as: RBS = 0 point and SFS $\leq$ 1 point (and a decrease of $\geq$ 1 point from the Baseline SFS) and Endoscopy subscore $\leq$ 1 point without friability.

A statistically significantly higher proportion of subjects in clinical remission at Week 52 in the re-randomized ozanimod group compared to the re-randomized placebo group was also observed when sensitivity analyses were performed using observed cases (p = 0.0050) and multiple imputation (p< 0.0009), as well as using Induction Cohort stratification (i.e., Cohort 1 or Cohort 2; p< 0.0001;) and the PP Population (p< 0.0001).

Supplementary analyses showed that a higher proportion of subjects re-randomized to ozanimod also achieved clinical remission compared to the re-randomized placebo group when using the 14-day scoring algorithm A (p< 0.0001) and 14-day scoring algorithm B (p< 0.0001, when using the 4-component Mayo definition and when using alternative definition 1, alternative definition 2 (p< 0.0001) and alternative definition 3 (p< 0.0001), and when excluding 9 subjects from Site 677.

A high percentage of missing data at Week 52 in ozanimod 1 mg-placebo arm (43.2%, 98/227) versus 26.5% (61/230) in the ozanimod 1 mg-ozanimod 1 mg arm, and a high percentage of subjects in ozanimod 1 mg-placebo arm who discontinued early due to "maintenance disease relapse" (74.8%, 77/103) limits the ability to reach a meaningful conclusion from the tipping point analysis of clinical remission based on missing data.

The results of some of these sensitivity analyses are shown in the following table:

Table 56: Alternative Definitions of Clinical Remission at Week 52 of Total Treatment (Maintenance ITT Population, Nonresponder Imputation) – Study RPC01- 3101

Analysis Method	Number (%) of Subjects		Treatment Comparison		
	Ozan 1 mg – Ozan 1 mg (N = 230)	Ozan 1 mg – Placebo (N = 227)	Difference in Proportions (95% CI)ª	Odds Ratio (95% CI)ª	P-valueª,ᵇ
Primary Analysis with Different Scoring Algorithms					
3-component Mayo Definitionᶜ with 14-day Scoring Algorithm A	92 (40.0)	46 (20.3)	0.199 (0.118, 0.279)	2.778 (1.807, 4.271)	*< 0.0001*
Primary Analysis with Different Scoring Algorithms					
3-component Mayo Definitionᶜ with 14-day Scoring Algorithm B	92 (40.0)	46 (20.3)	0.199 (0.118, 0.279)	2.778 (1.807, 4.271)	*< 0.0001*
Alternative Definitions of Clinical Remission					
4-component Mayo Definitionᵈ with 7-day Scoring Algorithm	88 (38.3)	42 (18.5)	0.199 (0.120, 0.278)	2.876 (1.854, 4.461)	*< 0.0001*
Alternative Definition 1ᵉ with 7-day Scoring Algorithm	93 (40.4)	52 (22.9)	0.176 (0.095, 0.258)	2.404 (1.582, 3.653)	*< 0.0001*
Alternative Definition 2ᶠ with 7-day Scoring Algorithm	93 (40.4)	50 (22.0)	0.185 (0.105, 0.266)	2.569 (1.679, 3.930)	*< 0.0001*
Alternative Definition 3ᵍ with 7-day Scoring Algorithm	125 (54.3)	80 (35.2)	0.193 (0.105, 0.280)	2.294 (1.557, 3.379)	*< 0.0001*
Alternative Definition 4ʰ with 7-day Scoring Algorithm	91 (39.6)	49 (21.6)	0.181 (0.100, 0.262)	2.509 (1.641, 3.837)	*< 0.0001*
Alternative Definition 4ʰ with 14-day Scoring Algorithm A	95 (41.3)	50 (22.0)	0.194 (0.113, 0.275)	2.627 (1.725, 4.002)	*< 0.0001*
Alternative Definition 4ʰ with 14-day Scoring Algorithm B	95 (41.3)	50 (22.0)	0.194 (0.113, 0.275)	2.627 (1.725, 4.002)	*< 0.0001*

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; ozan = ozanimod; RBS = rectal bleeding subscore; SFS = stool frequency subscore.

ª Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI, and p-value for comparison between the active and placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).

ᵇ P-values in italics are ≤ 0.05 and considered nominally significant, because no multiplicity adjustment was applied.

Induction Period – Week 10: "Key Secondary" Efficacy Endpoints

As mentioned above, the so-called "key secondary endpoints" included into a strict testing hierarchy to control the type I error. In the induction phase, there were 3 of these endpoints, including "clinical

response", "endoscopic improvement", and "mucosal healing" (defined as endoscopic improvement with histologic remission". The results for these three endpoints are shown in the following tables:

Table 57: Proportion of Subjects With a Clinical Response (3-component Mayo Definition using 7-day Scoring Algorithm) at Week 10 - Induction Period (ITT Population, Non-Responder Imputation)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Subjects in clinical response, n (%)[a]	205 (47.8)	56 (25.9)	193 (52.6)
Odds ratio (95% CI)[b]	2.670 (1.858, 3.836)		-
Difference in proportions (95% CI)[b]	0.219 (0.144, 0.293)		-
p-value[b]	< 0.0001		-

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore; TNF = tumor necrosis factor.
[a] Clinical response is defined as: A reduction from Baseline in the 3-component Mayo score of $\geq$ 2 points and $\geq$ 35%, and a reduction from Baseline in the RBS of $\geq$ 1 point or an absolute RBS of $\leq$ 1 point.
[b] Odds ratio (active/placebo), treatment difference, and p-value for comparison between the Cohort 1 ozanimod and placebo group are based on the CMH test, stratified by corticosteroid use at Screening and prior anti-TNF use (yes or no).
Note: Subjects with any of RBS, SFS, and endoscopy subscores missing at Week 10 are classified as non-responders.

Table 58: Proportion of Subjects with Endoscopic Improvement at Week 10 - Induction Period (ITT Population, Non-Responder Imputation)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367
Subjects with endoscopic improvement, n (%)[a]	117 (27.3)	25 (11.6)	100 (27.2)
Odds ratio (95% CI)[b]	2.876 (1.802, 4.591)		-
Difference in proportions (95% CI)[b]	0.157 (0.097, 0.217)		-
p-value[b]	< 0.0001		-

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; TNF = tumor necrosis factor
[a] Endoscopic improvement is defined as: Endoscopy subscore of $\leq$ 1 point.
[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI, and p-value for comparison between the Cohort 1 ozanimod and placebo group are based on the CMH test, stratified by corticosteroid use at Screening and prior anti-TNF use (yes or no).
Note: Subjects with missing endoscopy subscore at Week 10 are classified as non-responders.
Note: The source table for the Cohort 1 analysis erroneously states that dummy data were used in the generation of the output; this was a footnote from the dry run which was inadvertently not removed in the final run. Actual treatment data, not dummy data, were applied in the analysis.
Note: In the Cohort 1 sensitivity analysis for endoscopic improvement at Week 10 using the June 2020 DBL, there was 1 additional subject in the placebo group who was categorized as achieving endoscopic improvement.

Table 59: Proportion of Subjects with Mucosal Healing at Week 10 - Induction Period(ITT Population, Non-Responder Imputation)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Subjects with mucosal healing, n (%)[a]	54 (12.6)	8 (3.7)	42 (11.4)
Odds ratio (95% CI)[b]	3.767 (1.759, 8.068)		-
Difference in proportions (95% CI)[b]	0.089 (0.049, 0.129)		-
p-value[b]	< 0.001		-

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; TNF = tumor necrosis factor.

[a] Mucosal healing is defined as: Endoscopy subscore of ≤ 1 point without friability and 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).

[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI, and p-value for comparison between the Cohort 1 ozanimod and placebo group are based on the CMH test, stratified by corticosteroid use at Screening and prior anti-TNF use (yes or no).

Note: Subjects with missing endoscopy subscore or Geboes index score at Week 10 are classified as non-responders.

Maintenance Period – Week 52: "Key Secondary" Efficacy Endpoints

There were 6 "key secondary" endpoints in the maintenance phase, which were the following: The proportion of subjects with a clinical response at Week 52, the proportion of subjects with endoscopic improvement at Week 52, the proportion of subjects in clinical remission at Week 52 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 at Week 52, and the proportion of subjects with durable clinical remission. Results for these endpoints are shown in the following tables:

Table 60: Proportion of Subjects With a Clinical Response (3-component Mayo Definition Using 7-day Scoring Algorithm) at Week 52 of Total Treatment - Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects in clinical response, n (%)[a]	27 (39.1)	93 (41.0)	138 (60.0)
Odds ratio (95% CI)[b]	-	2.266 (1.542, 3.331)	
Difference in proportions (95% CI)[b]	-	0.192 (0.104, 0.280)	
p-value[b]	-	< 0.0001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore.

[a] 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 RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.

[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 and corticosteroid use at Week 10 (yes or no).

Note: Subjects with any of RBS, SFS, and endoscopy subscores missing at Week 52 are classified as non-responders.

Table 61: Proportion of Subjects with Endoscopic Improvement at Week 52 of Total Treatment - Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects with endoscopic improvement, n (%)[a]	20 (29.0)	60 (26.4)	105 (45.7)
Odds ratio (95% CI)[b]	-	2.476 (1.650, 3.716)	
Difference in proportions (95% CI)[b]	-	0.194 (0.110, 0.277)	
p-value[b]	-	< 0.001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat.
[a] Endoscopic improvement is defined as: Endoscopy subscore of ≤ 1 point without friability.
[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).
Note: Subjects with missing endoscopy subscore at Week 52 are classified as non-responders.

Table 62: Proportion of Subjects with Clinical Remission (3-component Mayo Definition Using 7-day Scoring Algorithm) at Week 52 of Total Treatment in Subset of Subjects in Remission at Week 10 - Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 12)	Ozanimod 1 mg – Placebo (N = 75)	Ozanimod 1 mg – Ozanimod 1 mg (N = 79)
Subjects in clinical remission, n (%)[a]	5 (41.7)	22 (29.3)	41 (51.9)
Odds ratio (95% CI)[b]	-	2.881 (1.447, 5.738)	
Difference in proportions (95% CI)[b]	-	0.239 (0.091, 0.386)	
p-value[b]	-	0.0025	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore.
[a] Clinical remission at Weeks 10 and 52 is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and Endoscopy subscore ≤ 1 point without friability.
[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by corticosteroid use at Week 10 (yes or no).
Note: Subjects with any of RBS, SFS, and endoscopy subscores missing at Week 52 are classified as non-remitters.

In the observed cases analysis for this endpoint, no difference in the proportion of subjects in clinical remission at Week 52 in the subset of subjects in clinical remission at Week 10 was observed between subjects rerandomized to ozanimod compared to the re- randomized placebo group (p=0.11)

Table 63: Proportion of Subjects with Corticosteroid-free Remission (3-component Mayo Definition Using 7-day Scoring Algorithm) at Week 52 of Total Treatment - Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects in corticosteroid-free remission, n (%)[a]	17 (24.6)	38 (16.7)	73 (31.7)
Odds ratio (95% CI)[b]	-	2.557 (1.598, 4.093)	
Difference in proportions (95% CI)[b]	-	0.152 (0.078, 0.226)	
p-value[b]	-	< 0.001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore.

[a] Corticosteroid-free remission is defined as: Clinical remission (which is defined as RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and Endoscopy subscore ≤ 1 point) at 52 weeks while off corticosteroids for ≥ 12 weeks.

[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI, and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).

Note: Subjects with any of RBS, SFS, and endoscopy subscores missing at Week 52 are classified as non-remitters.

Table 64:   Proportion of Subjects with Mucosal Healing at Week 52 of Total Treatment - Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects with mucosal healing, n (%)[a]	7 (10.1)	32 (14.1)	68 (29.6)
Odds ratio (95% CI)[b]	-	2.643 (1.642, 4.256)	
Difference in proportions (95% CI)[b]	-	0.156 (0.082, 0.229)	
p-value[b]	-	< 0.001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat.

Table 65: Proportion of Subjects with Durable Clinical Remission (3-component Mayo Definition Using 7-day Scoring Algorithm) at Week 52 of Total Treatment - Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects in durable clinical remission, n (%)[a]	5 (7.2)	22 (9.7)	41 (17.8)
Odds ratio (95% CI)[b]	-	2.646 (1.384, 5.061)	
Difference in proportions (95% CI)[b]	-	0.082 (0.028, 0.136)	
p-value[b]	-	0.0030	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore.

[a] Durable clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and Endoscopy subscore ≤ 1 point without friability at Weeks 10 and 52.

[b] Odds ratio (active/placebo), treatment difference, 2-sided Wald CI, and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).

Note: Subjects with any of RBS, SFS, and endoscopy subscores missing at Week 10 or Week 52 are classified as non-remitters.

Induction Period – Week 10: Other Secondary Efficacy Endpoints

The other secondary endpoints included the (numerical) change in complete Mayo score, partial Mayo score, 9-point Mayo score from Baseline to Week 10, the proportion of adult patients with histologic remission at Week 10, the proportion of adult patients in clinical remission (Four-component Mayo) at Week 10, the proportion of adult patients with a clinical response (Four-component Mayo) at Week 10, the proportion of adult patients with clinical response, remission, or endoscopic improvement at Week 10 in adult patients who previously received anti-TNF therapy, the Change in the SF-36 and the EQ-5D from Baseline to Week 10, Health resource utilization at Week 10, and Work productivity at Week 10.

- Change in Mayo Scores:

In Cohort 1, subjects in the ozanimod 1 mg group showed nominally significant decreases in 3-component (-2.4 versus -1.4) and 4-component (-3.2 versus -1.7) Mayo score from Baseline to Week 10 compared with those in the placebo group (p < 0.001 for each analysis; RPC01-3101). Nominally significant decreases in partial Mayo score from Baseline to Week 5 (-2.3 versus -1.5) and from Baseline to Week 10 (-2.7 versus -1.5) were also observed for subjects treated with ozanimod versus those treated with placebo (p < 0.001 for each analysis).

- Histological Remission.

The definition of histological remission was Geboes Score < 2.0, indicating no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions ulcerations or granulation tissue). The results are shown in the following table:

Table 66: Proportion of Subjects with Histologic Remission at Week 10 – Induction Period (ITT Population, Non-Responder Imputation)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Subjects with histologic remission, n (%)[a]	78 (18.2)	16 (7.4)	64 (17.4)
Odds ratio (95% CI)[b]	2.803 (1.593, 4.934)		
Difference in proportions (95% CI)[b]	0.108 (0.058, 0.158)		
p-value[b]	< 0.001		

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; TNF = tumor necrosis factor.
[a] 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).
[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI, and p-value for comparison between the Cohort 1 ozanimod and placebo group are based on the CMH test, stratified by corticosteroid use at Screening and prior anti-TNF use (yes or no).
Note: Subjects with missing Geboes index score at Week 10 are classified as non-remitters.

- Clinical Remission (4-point Mayo)

Table 67: Proportion of Subjects in Clinical Remission (4-component Mayo Definition using 7-day Scoring Algorithm) at Week 10 - Induction Period (ITT Population, Non-Responder Imputation)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Subjects in clinical remission, n (%)[a]	50 (11.7)	10 (4.6)	62 (16.9)
Odds ratio (95% CI)[b]	2.718 (1.351, 5.467)		
Difference in proportions (95% CI)[b]	0.070 (0.029, 0.111)		
p-value[b]	0.0037		

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; TNF = tumor necrosis factor.
[a] Clinical remission is defined as: 4-component Mayo score of ≤ 2 points and with no individual subscore of > 1 point.
[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the Cohort 1 ozanimod and placebo group are based on the CMH test, stratified by corticosteroid use at Screening and prior anti-TNF use (yes or no).

- Clinical response (4-point Mayo)

Table 68: Proportion of Subjects With a Clinical Response (4-component Mayo Definition Using 7-day Scoring Algorithm) at Week 10 - Induction Period (ITT Population, Non-Responder Imputation)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Subjects with a clinical response, n (%)[a]	222 (51.7)	55 (25.5)	209 (56.9)
Odds ratio (95% CI)[b]	3.213 (2.232, 4.626)		
Difference in proportions (95% CI)[b]	0.263 (0.189, 0.337)		
p-value[b]	< 0.0001		

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; RBS = rectal bleeding subscore; TNF = tumor necrosis factor.

[a] Clinical response is defined as: A reduction from Baseline in the 4-component Mayo score of ≥ 3 points and $\geq 30\%$, and a reduction from Baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.

[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the Cohort 1 ozanimod and placebo group are based on the CMH test, stratified by corticosteroid use at Screening and prior anti-TNF use (yes or no).

Note: 4-component Mayo score (0-12): Sum of the RBS, Stool Frequency subscore, Physician Global Assessment subscore, and the Endoscopy subscore. Subjects with any of the Mayo subscores missing at Week 10 are classified as non-responders.

- Subgroup analysis with regard to anti-TNF experience patients:

The following table shows the endpoints for the patients being TNF experienced vs. those not experienced:

Table 69: Proportion of Subjects with Clinical Remission, Clinical Response, Endoscopic Improvement, or Mucosal Healing by Prior Anti-TNF Use – Induction Period (ITT Population, Non-responder Imputation)

| Endpoint Subgroup | Number (%) of Subjects | | Treatment Comparison[a] | | |
	Ozanimod 1 mg	Placebo	Difference in Proportions (95% CI)[a]	Odds Ratio (95% CI)[a]	Nominal P-value[a, b]
Subjects in Clinical Remission at Week 10[c]					
No prior anti-TNF	N = 299 66 (22.1)	N = 151 10 (6.6)	0.154 (0.092, 0.215)	4.029 (1.998, 8.121)	< 0.0001
Prior anti-TNF	N = 130 13 (10.0)	N = 65 3 (4.6)	0.054 (-0.018, 0.126)	2.321 (0.634, 8.491)	0.1947
Subjects in Clinical Response at Week 10[d]					
No prior anti-TNF	N = 299 157 (52.5)	N = 151 44 (29.1)	0.233 (0.141, 0.325)	2.688 (1.769, 4.084)	< 0.0001
Prior anti-TNF	N = 130 48 (36.9)	N = 65 12 (18.5)	0.185 (0.060, 0.310)	2.618 (1.267, 5.410)	0.0084
Subjects with Endoscopic Improvement at Week 10[e]					
No prior anti-TNF	N = 299 97 (32.4)	N = 151 18 (11.9)	0.205 (0.131, 0.279)	3.539 (2.045, 6.123)	< 0.001
Prior anti-TNF	N = 130 20 (15.4)	N = 65 7 (10.8)	0.046 (-0.051, 0.144)	1.512 (0.603, 3.791)	0.378
Subjects with Mucosal Healing (Endoscopic Improvement with Histologic Remission) at Week 10[f]					
No prior anti-TNF	N = 299 47 (15.7)	N = 151 6 (4.0)	0.117 (0.065, 0.169)	4.486 (1.874, 10.740)	< 0.001
Prior anti-TNF	N = 130 7 (5.4)	N = 65 2 (3.1)	0.023 (-0.034, 0.080)	1.814 (0.362, 9.084)	0.465

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore. TNF = tumor necrosis factor.

[a] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the active and placebo groups are based on the CMH test, stratified by corticosteroid use at Screening and prior anti-TNF use (yes or no).

[b] P-values < 0.05 are considered nominally significant, because no multiplicity adjustment was applied.

[c] Clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and Endoscopy subscore ≤ 1 point without friability.

[d] Clinical response is defined as a reduction from Baseline in the 9-point Mayo score of ≥ 2 points and ≥ 35%, and a reduction from Baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.

[e] Endoscopic improvement is defined as a Mayo endoscopic score ≤ 1 without friability.

[f] Mucosal healing is defined as a Mayo endoscopic score ≤ 1 point without friability and 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) in the same subject.

Note: In the Cohort 1 sensitivity analysis for endoscopic improvement at Week 10 using the June 2020 DBL, there was 1 additional subject in the placebo group (prior anti-TNF use = no) who achieved endoscopic improvement

- Change in SF-36

While scores on the SF-36 generally improved for subjects randomized to either ozanimod or placebo in Cohort 1 during the Induction Period, the Cohort 1 ozanimod group had nominally significantly improved scores on the Physical Component Summary (PCS; p < 0.001), but not Mental Component Summary (MCS; p = 0.105), at Week 10 relative to placebo.

Individual domain scores improved relative to placebo on all physical health components, including physical functioning (p = 0.003), role-physical (p < 0.001), bodily pain (p < 0.001), and general health (p < 0.001). Scores improved on mental health components versus placebo, including vitality (p = 0.003), social functioning (p < 0.001), and mental health (p = 0.022), but not role-emotional (p =

0.624). Scores also improved on the SF-36 global health (p < 0.001) and health utility score (p = 0.013;) for ozanimod versus placebo.

The minimum clinically important difference (MCID) for the SF-36 PCS and MCS scores was defined as a $\geq$ 5 point improvement in each summary score. For the SF-36 PCS, a nominally significantly greater proportion of subjects on ozanimod achieved an MCID compared to placebo (48.64% versus 33.68%; p = 0.0006). No difference in the proportion of subjects who achieved an MCID in the SF-36 MCS was observed.

- Change in EQ-5D

The Cohort 1 ozanimod group also had nominally significantly improved scores on the EQ-5D Summary Index (p = 0.003) and EQ-5D Visual Analogue Scale (p < 0.001) relative to placebo at Week 10.

- Health resource utilisation

A low overall number of doctor visits, emergency room visits, and hospitalizations in the Induction Period made inferring treatment group differences in health-resource utilisation difficult.

On the WPAI-UC, the Cohort 1 ozanimod group generally had fewer hours missed due to UC, lower degree UC affected work productivity and regular activities, less absenteeism and higher presenteeism, and less percentage of overall work and daily activity impairment due to UC relative to placebo

- Biomarkers (faecal calprotectin):

Ozanimod 1 mg reduced markers of intestinal inflammation. At Baseline, the mean FCP levels in Cohort 1 were approximately 2500 µg/g in the ozanimod 1 mg treatment group and 3400 µg/g inthe placebo treatment group. The mean change from Baseline at Week 10 was nominally significantly greater with ozanimod 1 mg compared with placebo (-470.231 µg/g versus 21.115 µg/g, respectively; p = 0.002).

In Cohort 1, nominally significantly greater proportions of subjects treated with ozanimod 1 mg had a decrease from Baseline FCP > 50 μg/g to $\leq$ 50 μg/g at Week 10, from a Baseline of> 100 μg/g to $\leq$ 100 μg/g at Week 10, and from a Baseline of > 150 μg/g to $\leq$ 150 μg/g at Week 10 compared with those treated with placebo (p < 0.001 for each analysis). A post hoc analysis also showed that a nominally significantly greater proportion of subjects treated with ozanimod 1 mg also had a decrease from Baseline FCP > 250 μg/g to FCP $\leq$ 250 μg/g at Week 10 compared with those treated with placebo (37.8% versus 15.0%; p < 0.0001).

Post Hoc defined endpoints:

Change from BL in RBS and SFS and symptomatic responder rates.:

In order to evaluate the onset of action of ozanimod, post hoc analyses were performed to assess symptomatic improvement in RBS and SFS over time. Symptomatic improvements in RBS and SFS appeared to separate with ozanimod 1 mg relative to placebo as early as Week 2 (ie, 1 week after completing the 7-day dose escalation) with a continuous increase in separation from placebo through Week 10 (Figure 3). In Cohort 1, significantly greater LS mean reduction from Baseline in RBS was observed with ozanimod 1 mg compared with placebo starting at Week 2 (LS mean estimate: -0.56 versus -0.40, respectively; estimated treatment difference -0.16, 95% CI: -0.298, -0.023;). While there was a trend toward separation in SFS at Week 2 with ozanimod 1 mg versus placebo (LS mean estimate: -0.36 versus -0.27, respectively; estimated treatment difference -0.09, 95% CI: -0.215, 0.045), a significant separation was observed starting at Week 5 (LS mean estimate: -0.65 versus -0.46, respectively; estimated treatment difference -0.19, 95% CI: -0.336, -0.047).

The results are displayed in the following two figures:

Figure 17: Least Square Mean Estimate of Change from Baseline in Rectal Bleeding Subscore (Panel A) and Stool Frequency Subscore (Panel B) in the Induction Period (Induction ITT Population, Observed Cases) – Study RPC01-3101
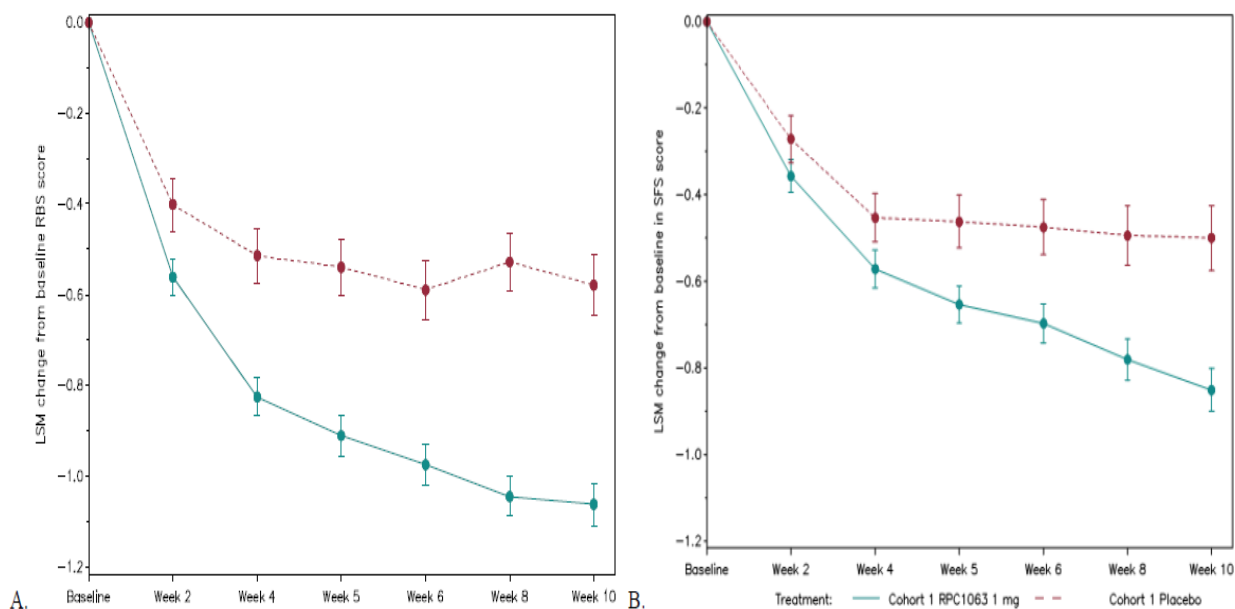
In addition to this "numerical" evaluation of the symptomatic scores, the applicant also defined a post-hoc responder definition for the two-component symptomatic remission. A nominally significantly greater proportion of subjects achieved symptomatic remission with ozanimod 1 mg than with placebo at Week 10 of the Induction Period (37.5% versus 18.5%; $p < 0.0001$).

Endoscopic normalisation:

Endoscopic normalization was defined as a Mayo endoscopy subscore of 0. In Cohort 1, a numerically greater proportion of subjects treated with ozanimod 1 mg met the criteria for endoscopic normalization at Week 10 compared with those treated with placebo, although the result did not reach nominal significance (6.1% versus 2.8%; $p = 0.0685$)

Maintenance Period – Week 52: Other Secondary Efficacy Endpoints

The endpoints defined as "other secondary are given in the following either as narrative, or with a short presentation in a table:

- Change in 3-component Mayo score, 4-component Mayo score, and partial Mayo score from Baseline to Week 52

Table 70: Change in Complete, Partial, and 3-component Mayo Score from Baseline to Week 52 - Maintenance Period (ITT Population, Observed Cases)

Endpoint Treatment Group		N	Baseline Mean (SD)	Change from Baseline LS Mean (SE)[a]	Treatment Difference Versus Placebo LSMD[a]	95% CI[a]	Nominal P-value[a]
3-component Mayo Score							
Rerandomized Subjects	Ozanimod 1 mg – Placebo	227	6.4 (1.24)	-4.0 (0.19)	-0.5	(-0.9, -0.1)	0.020
	Ozanimod 1 mg – Ozanimod 1 mg	230	6.7 (1.31)	-4.5 (0.16)			
4-component Mayo Score							
Rerandomized Subjects	Ozanimod 1 mg – Placebo	227	8.7 (1.41)	-5.3 (0.25)	-0.8	(-1.3, -0.2)	0.008
	Ozanimod 1 mg – Ozanimod 1 mg	230	9.0 (1.57)	-6.1 (0.21)			
Partial Mayo Score							
Rerandomized Subjects	Ozanimod 1 mg – Placebo	227	6.2 (1.18)	-4.3 (0.18)	-0.4	(-0.9, 0.0)	0.032
	Ozanimod 1 mg – Ozanimod 1 mg	230	6.4 (1.32)	-4.7 (0.15)			

ANCOVA = analysis of covariance; CI = confidence interval; ITT = Intent-to-Treat; LS = least squares; LSMD: least squares mean difference; SD = standard deviation SE = standard error.
[a] Based on ANCOVA for change from baseline adjusted for remission status at Week 10 (yes or no), corticosteroid use at Week 10 (yes or no), and the Baseline 4-component, partial, or 3-component Mayo score.
Notes: 4-component Mayo score (0-12): Sum of the Rectal Bleeding subscore, Stool Frequency subscore, Physician Global Assessment subscore, and the Endoscopy subscore.
Partial Mayo score (range of 0-9 points): Sum of the Rectal Bleeding subscore, Stool Frequency subscore, and the Physician Global Assessment subscore.
3-Component Mayo (range of 0-9 points): Sum of the Rectal Bleeding subscore, Stool Frequency subscore, and the Endoscopy subscore.
Baseline is derived from the latest subscores on or prior to the date of initial dose.

- The proportion of subjects with histologic remission at Week 52

Table 71: Proportion of Subjects with Histologic Remission at Week 52 – Maintenance Period (ITT Population, Non-Responder Imputation)

	Placebo (N = 69)	Rerandomized Subjects	
		Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects with histologic remission, n (%)[a]	10 (14.5)	37 (16.3)	77 (33.5)
Odds ratio (95% CI)[b]		2.684 (1.703, 4.229)	
Difference in proportions (95% CI)[b]		0.173 (0.096, 0.249)	
p-value[b]		< 0.001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; TNF = tumor necrosis factor.
[a] 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).
[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI, and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).
Note: Subjects with missing Geboes index score at Week 10 are classified as non-remitters.

- The proportion of subjects in clinical remission (4-component Mayo) at Week 52

Table 72: Proportion of Subjects in Clinical Remission (4-component Mayo Definition Using 7-day Scoring Algorithm) at Week 52 - Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects in clinical remission, n (%)[a]	17 (24.6)	42 (18.5)	88 (38.3)
Odds ratio (95% CI)[b]		2.876 (1.854, 4.461)	
Difference in proportions (95% CI)[b]		0.199 (0.120, 0.278)	
p-value[b]		< 0.0001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat.
[a] Clinical remission is defined as: 4-component Mayo score of ≤ 2 points and with no individual subscore of > 1 point.
[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).
Note: 4-component Mayo score (0-12): Sum of the Rectal Bleeding subscore, Stool Frequency subscore, Physician Global Assessment subscore, and the Endoscopy subscore. Subjects with any of the Mayo subscores missing at Week 52 are classified as non-remitters.

- The proportion of subjects with a clinical response (4-component Mayo) at Week 52

Table 73: Proportion of Subjects With a Clinical Response (4-component Mayo Definition Using 7-day Scoring Algorithm) at Week 52 - Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects with a clinical response, n (%)[a]	28 (40.6)	97 (42.7)	145 (63.0)
Odds ratio (95% CI)[b]		2.370 (1.615, 3.477)	
Difference in proportions (95% CI)[b]		0.205 (0.116, 0.293)	
p-value[b]		< 0.0001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; RBS = rectal bleeding subscore.
[a] Clinical response is defined as: A reduction from Baseline in the 4-component Mayo score of ≥ 3 points and ≥ 30%, and a reduction from Baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.
[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).
Note: 4-component Mayo score (0-12): Sum of the RBS, Stool Frequency subscore, Physician Global Assessment subscore, and the Endoscopy subscore. Subjects with any of the Mayo subscores missing at Week 52 are classified as non-responders.

- The proportion of subjects with clinical response, remission, or endoscopic improvement at 52 weeks in subjects who previously received anti-TNF therapy

Table 74: Proportion of Subjects with a Clinical Response, Remission, Endoscopic Improvement, Maintenance of Remission, Corticosteroid-free Remission, and Mucosal Healing in Subjects who Previously Received Anti-TNF Therapy

| Endpoint Subgroup | Number (%) of Subjects | | Treatment Comparison[a] | | |
	Ozanimod 1 mg	Placebo	Difference in Proportions (95% CI)[a]	Odds Ratio (95% CI)[a]	Nominal P-value[a,b]
Subjects in Clinical Remission at Week 52[c]					
No prior anti-TNF	N = 154 63 (40.9)	N = 158 35 (22.2)	0.185 (0.086, 0.283)	2.540 (1.523, 4.235)	0.0003
Prior anti-TNF	N = 76 22 (28.9)	N = 69 7 (10.1)	0.184 (0.062, 0.306)	3.737 (1.438, 9.714)	0.0053
Subjects in Clinical Response at Week 52[d]					
No prior anti-TNF	N = 154 96 (62.3)	N = 158 76 (48.1)	0.140 (0.033, 0.248)	1.800 (1.139, 2.845)	0.0119
Prior anti-TNF	N = 76 42 (55.3)	N = 69 17 (24.6)	0.304 (0.158, 0.451)	4.148 (1.959, 8.781)	0.0002
Subjects with Endoscopic Improvement at Week 52[e]					
No prior anti-TNF	N = 154 77 (50.0)	N = 158 48 (30.4)	0.194 (0.089, 0.298)	2.347 (1.461, 3.771)	< 0.001
Prior anti-TNF	N = 76 28 (36.8)	N = 69 12 (17.4)	0.189 (0.053, 0.324)	2.933 (1.302, 6.607)	0.009
Subjects with Clinical remission in Subset of Subjects in Remission at Week 10[f]					
No prior anti-TNF	N = 64 37 (57.8)	N = 58 19 (32.8)	0.250 (0.081, 0.419)	2.893 (1.364, 6.137)	0.0055
Prior anti-TNF	N = 15 4 (26.7)	N = 17 3 (17.6)	0.110 (-0.151, 0.370)	2.333 (0.306, 17.801)	0.4349

| Endpoint Subgroup | Number (%) of Subjects | | Treatment Comparison[a] | | |
	Ozanimod 1 mg	Placebo	Difference in Proportions (95% CI)[a]	Odds Ratio (95% CI)[a]	Nominal P-value[a,b]
Subjects with Corticosteroid-free Remission[g]					
No prior anti-TNF	N = 154 55 (35.7)	N = 158 31 (19.6)	0.161 (0.068, 0.255)	2.463 (1.437, 4.221)	< 0.001
Prior anti-TNF	N = 76 18 (23.7)	N = 69 7 (10.1)	0.129 (0.015, 0.244)	2.887 (1.076, 7.745)	*0.033*
Subjects with Mucosal Healing (Endoscopic Improvement with Histologic Remission) at Week 52[h]					
No prior anti-TNF	N = 154 51 (33.1)	N = 158 28 (17.7)	0.153 (0.058, 0.247)	2.323 (1.362, 3.963)	0.002
Prior anti-TNF	N = 76 17 (22.4)	N = 69 4 (5.8)	0.162 (0.055, 0.270)	4.781 (1.481, 15.440)	0.005
Subjects with Durable Remission at Week 52[i]					
No prior anti-TNF	N = 154 37 (24.0)	N = 158 19 (12.0)	0.115 (0.044, 0.187)	3.198 (1.547, 6.612)	0.002
Prior anti-TNF	N = 76 4 (5.3)	N = 69 3 (4.3)	0.005 (-0.059, 0.069)	1.130 (0.213, 5.986)	0.888

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; RBS = rectal bleeding subscore; SFS = stool frequency subscore. TNF = tumor necrosis factor.

[a] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the active and placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes/no), corticosteroid use at Week 10 (yes/no), and prior anti-TNF use (yes or no) at randomization.

[b] P-values < 0.05 are considered nominally significant, because no multiplicity adjustment was applied.

[c] Clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and Endoscopy subscore ≤ 1 point without friability.

[d] Clinical response is defined as a reduction from Baseline in the 9-point Mayo score of ≥ 2 points and ≥ 35%, and a reduction from Baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.

[e] Endoscopic improvement is defined as a Mayo endoscopic score ≤ 1 without friability.

[f] Percentage based on number of subjects in clinical remission at Week 10 (as shown).

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

[h] Mucosal healing is defined as a Mayo endoscopic score ≤ 1 point without friability and 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) in the same subject.

[i] Durable remission is defined as clinical remission at Week 10 and Week 52 in subjects who entered the Maintenance Period.

- The proportion of subjects in remission at 52 weeks while off corticosteroids for any length of time

Table 75: Proportion of Subjects in Clinical Remission While off Corticosteroids for any Length of Time at Week 52 – Maintenance Period (ITT Population, Non-Responder Imputation)

		Rerandomized Subjects	
	Placebo (N = 69)	Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects in clinical remission, n (%)[a]	17 (24.6)	38 (16.7)	73 (31.7)
Odds ratio (95% CI)[b]		2.557 (1.598, 4.093)	
Difference in proportions (95% CI)[b]		0.152 (0.078, 0.226)	
p-value[b]		< 0.0001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; MP = Maintenance Period; RBS = rectal bleeding subscore; SFS = stool frequency subscore TNF = tumor necrosis factor.

[a] Clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and Endoscopy subscore ≤1 point.

[b] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).

Note: 3-Component Mayo (range of 0-9 points): Sum of the RBS, SFS, and the Endoscopy subscore. Subjects with any of RBS, SFS, and endoscopy subscores missing at Week 52 are classified as non-remitters. A subject will be considered as off corticosteroids for any length of time if they never took corticosteroids during MP or stopped their corticosteroid dose on a date prior to the date of the Week 52 endoscopy or the date of the Week 52 clinic visit, whichever is earlier.

-      Post-hoc endpoint Endoscopic Normalisation:

A nominally significantly greater proportion of subjects continuously treated with ozanimod1 mg met the criteria for endoscopic normalization (Mayo endoscopy sub-score of 0) at Week 52 compared with those re-randomized to placebo at the start of the Maintenance Period (24.3% versus 11.9%; p = 0.0004).

Table 76: Proportion of Subjects with Endoscopic Normalization at Week 52 of Total Treatment (Maintenance ITT Population, Observed Cases) – Study RPC01- 3101

	Number (%) of Subjects		Treatment Comparison		
Parameter	Ozan 1 mg – Ozan 1 mg (N = 230)	Ozan 1 mg – Placebo (N = 227)	Difference in Proportions (95% CI)[a]	Odds Ratio (95% CI)[a]	P-value[a,b]
Endoscopic Normalization[c]	56 (24.3)	27 (11.9)	0.126 (0.058, 0.193)	2.484 (1.490, 4.140)	*0.0004*

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; ozan = ozanimod.

[a] Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI, and p-value for comparison between the active and placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).

[b] P-value in italics is ≤ 0.05 and considered nominally significant, because no multiplicity adjustment was applied.

[c] Endoscopic normalization was defined as an endoscopy subscore of 0.

- Change in the SF-36 and the EQ-5D from Baseline to Week 52

Scores on SF-36 generally improved during the Maintenance Period for subjects rerandomized to either ozanimod or placebo; however, the subjects re randomized to ozanimod had nominally significantly improved scores on the PCS (p = 0.016), but not MCS (p = 0.432), at Week 52 relative to those rerandomized to placebo.

Scores improved relative to placebo for the physical health components role-physical (p = 0.031) and general health (p = 0.002), but not physical functioning (p = 0.065), bodily pain (p = 0.338), while scores did not improve relative to placebo on the mental health components vitality (p = 0.216), social functioning (p = 0.166), role-emotional (p = 0.538), or mental health (p = 0.264). Scores improved on the SF-36 global health (p = 0.005), but not health utility score (p = 0.096).

For the SF-36 PCS, a nominally significantly greater proportion of subjects treated with ozanimod achieved an MCID (improvement of $\geq$ 5 points) compared to placebo at Week 52 (69.4% versus 57.5%; p = 0.03). No difference in the proportion of subjects achieving an MCID in the SF-36 MCS was observed.

The rerandomized ozanimod group also had nominally significantly improved scores on the EQ-5D Visual Analogue Scale (p = 0.005, but not the EQ-5D Summary Index (p = 0.428) relative to the group rerandomized to placebo, at Week 52.

- Health resource utilization at 28 weeks, 40 weeks, and at Week 52

A low overall number of doctor visits, emergency room visits, and hospitalizations in the Maintenance Period made inferring treatment group differences in HRU difficult. The HRU score collects data on reported doctor visits, emergency room visits, and hospitalizations in the Maintenance Period. In order to examine the reasons for hospitalizations for UC within the trial, a post hoc analysis of subjects requiring hospitalizations during the Maintenance Period due to UC-related AEs (as defined by anemia, dehydration, worsening, flare, or relapse of UC) as reported by the investigator was conducted. The analysis demonstrated a lower proportion of subjects re-randomized to ozanimod (5/16, 31%) compared with those re-randomized to placebo (10/19, 53%) experienced hospitalizations due to UC.

- Work productivity at 28 weeks, 40 weeks, and at Week 52

On the WPAI-UC, the re-randomized ozanimod group generally had fewer hours missed due to UC, lower degree UC affected work productivity and regular activities, less absenteeism due to UC, and less percentage of overall work and daily activity impairment due to UC relative to the group re-randomized to placebo.

The following post-hoc analyses were conducted and reported in the study report:

Proportion of Subjects with Symptomatic Remission: A nominally significantly greater proportion of subjects re-randomized to ozanimod achieved symptomatic remission compared to subjects re-randomized to placebo at Week 52 of the Maintenance Period (51.3% versus 33.5%; p < 0.0001).

Time to Relapse

Relapse was defined as an increase in partial Mayo score of $\geq$ 2 points compared to the Week 10 partial Mayo score with an absolute partial Mayo score $\geq$ 4 points AND an endoscopic subscore of $\geq$ 2 points. A nominally significantly lower proportion of subjects re-randomized to ozanimod experienced relapse during the Maintenance Period compared to subjects re-randomized to placebo (81 [35.7%] subjects versus 31 [13.5%] subjects, p < 0.001). A Kaplan-Meier plot of time to relapse is shown in the following:
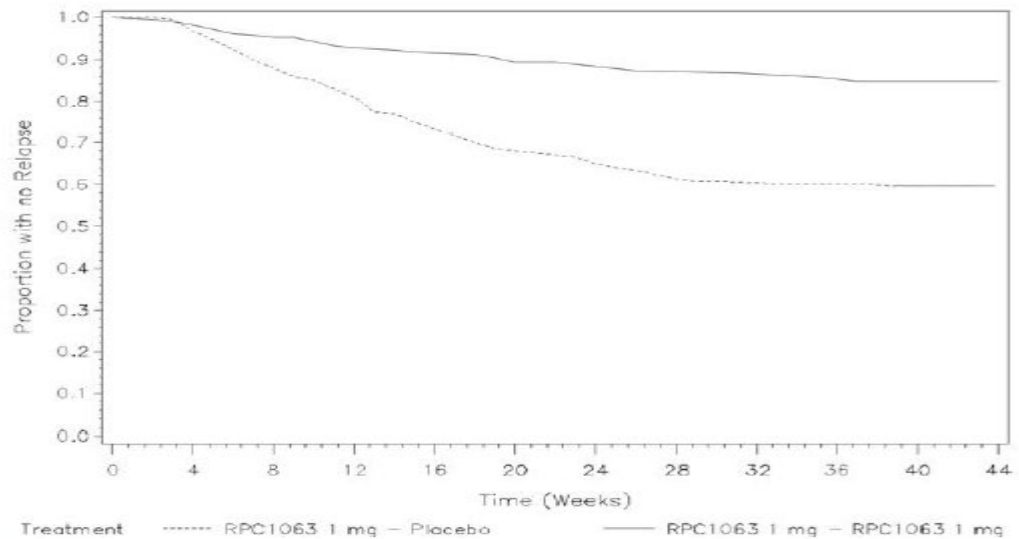
ITT = Intent-to-Treat.
Source: Post Hoc Figure 14.2

Figure 36: Kaplan-Meier Plot of Time to Relapse in Maintenance Period (ITT Population)

Ancillary analyses

The following subgroups were investigated, and reported for both, the induction as well as the maintenance periods: Corticosteroid use (yes/no), prior anti-TNF therapy (yes/no), moderate UC status at baseline (yes/no), baseline complete Mayo Score (>9/≤9), extent of colitis (left-sided/extensive), sex (male/female), age at screening (cut-off 40 years), level of faecal calprotectin (cut-off 250 mg/ml), ALCs at baseline (cut-off 1500 10^6/l), Region (North America, Western Europe/Eastern Europe/Asia Pacific/South America/South Africa), baseline partial Mayo Score (<median vs >median), and baseline endoscopic subscore (2 vs 3).

Subgroup analyses of the primary endpoint (clinical remission at Week 10) and key secondary endpoints (clinical response, endoscopic improvement, and mucosal healing at Week 10) demonstrated a consistent treatment effect in favour of ozanimod 1 mg over placebo across almost all subgroups analysed, underscoring the robustness of the efficacy data.

The results of the analyses on clinical remission and mucosal healing are shown in graphical form in the following two figures:

Subgroup	Diff.	LCL	UCL	p-value
Overall	0.12	0.075	0.172	<0.0001
Corticosteroids use at Screening: Yes	0.09	0.021	0.149	0.0326
No	0.14	0.078	0.208	0.0002
Prior anti-TNF use: Yes	0.05	-0.018	0.126	0.1947
No	0.15	0.092	0.215	<0.0001
Moderate UC Status at Baseline: Yes	0.13	0.079	0.187	<0.0001
No	0.07	0.006	0.133	0.1827
Baseline Complete Mayo Score: <=9	0.15	0.085	0.218	0.0001
>9	0.06	0.006	0.122	0.0746
Extent of Colitis: Extensive	0.09	0.015	0.166	0.0387
Left-Sided	0.15	0.083	0.208	0.0001
Sex: Female	0.14	0.047	0.230	0.0113
Male	0.11	0.051	0.161	0.0011
Age at Screening: <= Cohort 1 median (40 years)	0.11	0.052	0.167	0.0022
> Cohort 1 median (40 years)	0.14	0.067	0.220	0.0015
Baseline Fecal Calprotectin: <= 250 mg/kg	0.06	-0.075	0.189	0.4096
> 250 mg/kg	0.14	0.088	0.192	<0.0001

Favor Placebo — Favor RPC6013

Subgroup	Diff.	LCL	UCL	p-value
Baseline ALC: <= 1500 10^6/L	0.12	0.022	0.208	0.0239
> 1500 10^6/L	0.13	0.069	0.183	0.0004
Years Since Initial UC Diagnosis: <= 4 years	0.14	0.065	0.207	0.0017
> 4 years	0.11	0.046	0.178	0.0040
Region: North America	0.13	0.041	0.211	0.0141
Western Europe	0.02	-0.015	0.064	0.4819
Eastern Europe	0.15	0.074	0.234	0.0010
Asia Pacific	0.09	-0.006	0.182	0.1798
South America	NA	NA	NA	NA
South Africa	NA	NA	NA	NA
Baseline Partial Mayo Score: <= median (6)	0.15	0.085	0.224	0.0005
> median (6)	0.08	0.020	0.149	0.0274
Baseline Partial Mayo Score: <= 7	0.13	0.077	0.187	<0.0001
> 7	0.08	0.017	0.144	0.1320
Baseline Endoscopy Subscore: 2	0.19	0.096	0.288	0.0007
3	0.06	0.019	0.104	0.0198

Favor Placebo — Favor RPC6013

Figure 37: Forest Plots of Clinical Remission (3-component Mayo Definition using 7-day Scoring Algorithm) at Week <u>10</u> by Subgroup - Induction Period Cohort 1 (ITT Population, Non-Responder Imputation)

	Diff.	LCL	UCL	p-value
Overall	0.09	0.049	0.129	<0.001
Corticosteroids use at Screening: Yes	0.06	-0.001	0.116	0.103
No	0.10	0.052	0.157	0.001
Prior anti-TNF use: Yes	0.02	-0.034	0.080	0.465
No	0.12	0.065	0.169	<0.001
Moderate UC Status at Baseline: Yes	0.09	0.049	0.140	<0.001
No	0.06	-0.001	0.112	0.241
Baseline Complete Mayo Score: <=9	0.11	0.056	0.169	<0.001
>9	0.05	0.000	0.092	0.114
Extent of Colitis: Extensive	0.05	-0.015	0.118	0.167
Left-Sided	0.11	0.061	0.162	<0.001
Sex: Female	0.11	0.059	0.169	0.005
Male	0.08	0.022	0.130	0.014
Age at Screening: <= Cohort 1 median (40 years)	0.06	0.011	0.114	0.042
> Cohort 1 median (40 years)	0.12	0.059	0.181	0.002
Baseline Fecal Calprotectin: <= 250 mg/kg	0.07	-0.067	0.201	0.333
> 250 mg/kg	0.10	0.062	0.141	<0.001

Favor Placebo — Favor RPC6013

-1.0   -0.5   0.0   0.5

	Diff.	LCL	UCL	p-value
Baseline ALC: <= 1500 10^6/L	0.07	-0.007	0.147	0.094
> 1500 10^6/L	0.10	0.053	0.149	0.001
Years Since Initial UC Diagnosis: <= 4 years	0.09	0.021	0.153	0.024
> 4 years	0.08	0.035	0.134	0.006
Region: North America	0.07	0.007	0.138	0.070
Western Europe	0.01	-0.085	0.115	0.796
Eastern Europe	0.12	0.058	0.189	0.002
Asia Pacific	0.03	-0.026	0.092	0.398
South America	NA	NA	NA	NA
South Africa	NA	NA	NA	NA
Baseline Partial Mayo Score: <= median (6)	0.12	0.059	0.177	0.001
> median (6)	0.06	0.004	0.109	0.072
Baseline Partial Mayo Score: <= 7	0.10	0.052	0.145	<0.001
> 7	0.05	0.001	0.105	0.217
Baseline Endoscopy Subscore: 2	0.14	0.051	0.219	0.007
3	0.05	0.016	0.081	0.022

Favor Placebo — Favor RPC6013

-1.0   -0.5   0.0   0.5

ALC = absolute lymphocyte count; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Diff = treatment difference (ozanimod 1 mg versus placebo); ITT = Intent-to-Treat; LCL = lower 95% confidence limit; NA = not applicable; RBS = rectal bleeding subscore; SFS = stool frequency subscore; TNF = tumor necrosis factor; UC = ulcerative colitis; UCL = upper 95% confidence limit.

Notes: Subjects with any of the requisite subscores missing at Week 10 are classified as non-responders. For subgroups that are less than 5% of the ITT Population, "NA" is displayed for comparison statistics.

Figure 38: Forest Plots of Mucosal Healing (3-component Mayo Definition using 7-day Scoring Algorithm) at Week <u>10</u> by Subgroup **- Induction Period Cohort 1 (ITT Population, Non-Responder Imputation)**

Subgroup	Diff.	LCL	UCL	p-value
Overall	0.19	0.108	0.264	<0.0001
Clinical Remission at Week 10: Yes	0.23	0.085	0.379	0.0028
No	0.16	0.070	0.250	0.0007
Corticosteroids use at Week 10: Yes	0.14	0.016	0.267	0.0318
No	0.20	0.107	0.301	<0.0001
Corticosteroids use at Screening: Yes	0.18	0.067	0.299	0.0040
No	0.19	0.091	0.293	0.0003
Prior anti-TNF use: Yes	0.18	0.062	0.306	0.0053
No	0.18	0.086	0.283	0.0003
Moderate UC Status at Baseline: Yes	0.20	0.111	0.282	<0.0001
No	0.13	-0.059	0.325	0.2256
Baseline Complete Mayo Score: <=9	0.18	0.076	0.280	0.0007
>9	0.21	0.094	0.331	0.0017
Extent of Colitis: Extensive	0.19	0.060	0.330	0.0074
Left-Sided	0.18	0.089	0.281	0.0002
Sex: Female	0.23	0.114	0.346	0.0002
Male	0.15	0.040	0.253	0.0075
Age at Screening: <= median (42 years)	0.16	0.053	0.258	0.0040
> median (42 years)	0.23	0.111	0.347	0.0002

Favor Placebo — Favor RPC6013

Subgroup	Diff.	LCL	UCL	p-value
Baseline Fecal Calprotectin: <= 250 mg/kg	-0.02	-0.210	0.173	0.8495
> 250 mg/kg	0.24	0.151	0.320	<0.0001
Baseline ALC: <= 1500 10^6/L	0.20	0.058	0.337	0.0069
> 1500 10^6/L	0.17	0.079	0.269	0.0005
Years Since Initial UC Diagnosis: <= 4 years	0.10	-0.024	0.226	0.1112
> 4 years	0.24	0.134	0.338	<0.0001
Region: North America	0.25	0.094	0.406	0.0035
Western Europe	0.09	-0.095	0.283	0.3485
Eastern Europe	0.18	0.075	0.290	0.0012
Asia Pacific	0.05	-0.218	0.325	0.7136
South America	NA	NA	NA	NA
South Africa	NA	NA	NA	NA
Baseline Partial Mayo Score: <= median (6)	0.20	0.085	0.308	0.0006
> median (6)	0.19	0.076	0.294	0.0019
Baseline Partial Mayo Score: <= 7	0.19	0.104	0.277	<0.0001
> 7	0.18	0.012	0.357	0.0657
Baseline Endoscopy Subscore: 2	0.22	0.094	0.339	0.0006
3	0.16	0.064	0.266	0.0023

Favor Placebo — Favor RPC6013

ALC = absolute lymphocyte count; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Diff = treatment difference (ozanimod 1 mg versus placebo); ITT = Intent-to-Treat; LCL = lower 95% confidence limit; NA = not applicable; RBS = rectal bleeding subscore; SFS = stool frequency subscore; TNF = tumor necrosis factor; UC = ulcerative colitis; UCL = upper 95% confidence limit.

Notes: 3-Component Mayo (range of 0-9 points): Sum of the RBS, SFS, and the Endoscopy subscore. Subjects with any of RBS, SFS, and endoscopy subscores missing at Week 52 are classified as non-remitters. For subgroups that are less than 5% of the ITT Population, "NA" is displayed for comparison statistics.

Clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and Endoscopy subscore ≤ 1 point without friability.

Weighted difference, 2-sided 95% Wald CI and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no). If the subgroup is the stratification factor, the CMH test is not stratified by this subgroup factor.
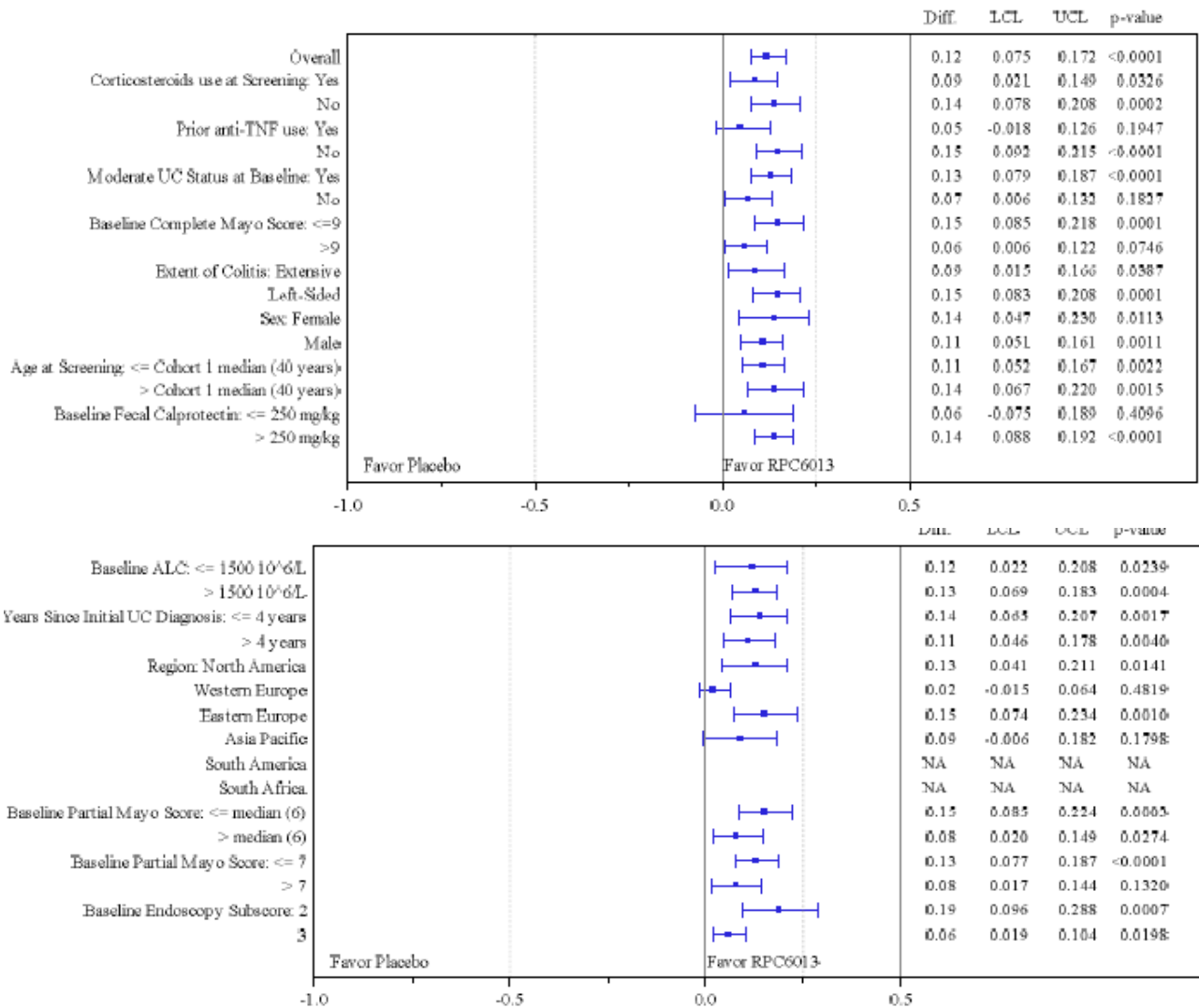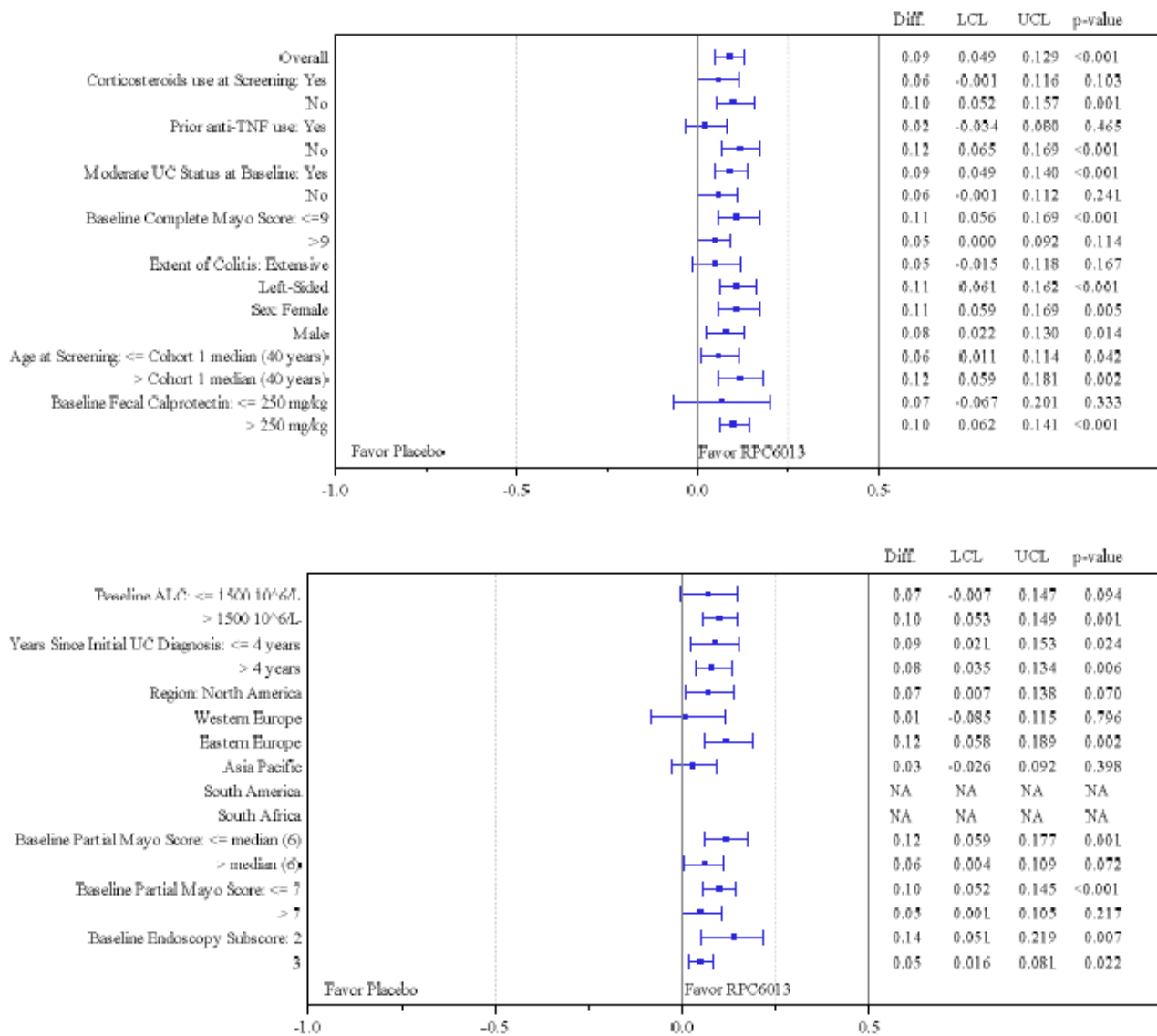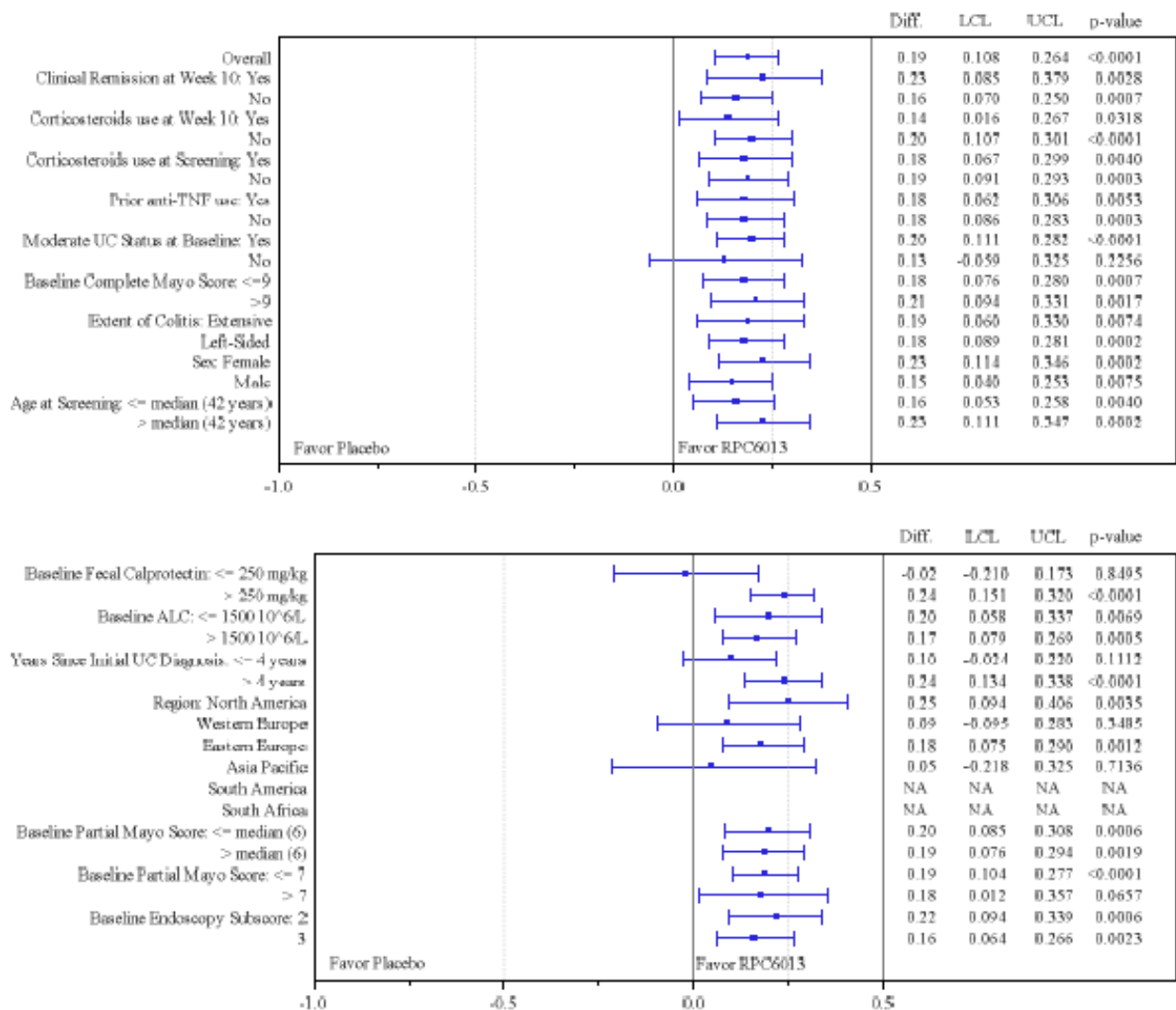
Figure 39: Forest Plot of Clinical Remission (3-component Mayo Definition using 7-day Scoring Algorithm) at Week 52 of Total Treatment by Subgroup – Re-randomized Maintenance Period (ITT Population, Non-Responder Imputation)

	Diff.	LCL	UCL	p-value
Overall	0.16	0.082	0.229	<0.0001
Clinical Remission at Week 10: Yes	0.21	0.070	0.347	0.0039
No	0.13	0.042	0.211	0.0039
Corticosteroids use at Week 10: Yes	0.10	-0.019	0.216	0.1062
No	0.18	0.088	0.270	0.0002
Corticosteroids use at Screening: Yes	0.13	0.018	0.234	0.0297
No	0.18	0.081	0.272	0.0004
Prior anti-TNF use: Yes	0.16	0.055	0.270	0.0053
No	0.15	0.058	0.247	0.0017
Moderate UC Status at Baseline: Yes	0.17	0.087	0.248	<0.0001
No	0.16	-0.013	0.325	0.1202
Baseline Complete Mayo Score: <=9	0.16	0.058	0.253	0.0017
>9	0.18	0.073	0.280	0.0035
Extent of Colitis: Extensive	0.19	0.063	0.309	0.0043
Left-Sided	0.14	0.053	0.236	0.0023
Sex: Female	0.20	0.094	0.300	0.0004
Male	0.12	0.013	0.222	0.0282
Age at Screening: <= median (42 years)	0.09	-0.001	0.187	0.0573
> median (42 years)	0.23	0.112	0.339	0.0002

Favor Placebo — Favor RPC6013

	Diff.	LCL	UCL	p-value
Baseline Fecal Calprotectin: <= 250 mg/kg	-0.01	-0.183	0.165	0.9195
> 250 mg/kg	0.20	0.116	0.278	<0.0001
Baseline ALC: <= 1500 10^6/L	0.14	0.002	0.272	0.0506
> 1500 10^6/L	0.16	0.077	0.253	0.0003
Years Since Initial UC Diagnosis: <= 4 years	0.05	-0.067	0.169	0.3894
> 4 years	0.22	0.129	0.312	<0.0001
Region: North America	0.26	0.100	0.420	0.0023
Western Europe	0.02	-0.095	0.127	0.7914
Eastern Europe	0.14	0.038	0.246	0.0077
Asia Pacific	0.11	-0.183	0.397	0.5031
South America	NA	NA	NA	NA
South Africa	NA	NA	NA	NA
Baseline Partial Mayo Score: <= median (6)	0.17	0.064	0.274	0.0015
> median (6)	0.15	0.043	0.248	0.0089
Baseline Partial Mayo Score: <= 7	0.17	0.084	0.249	<0.0001
> 7	0.14	0.000	0.285	0.0945
Baseline Endoscopy Subscore: 2	0.20	0.084	0.323	0.0009
3	0.12	0.028	0.210	0.0138

Favor Placebo — Favor RPC6013

Figure 40: Forest Plot of Mucosal Healing at <u>Week 52</u> of Total Treatment by Subgroup– Re-randomized Maintenance Period (ITT Population, Non-Responder Imputation)

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 77: Summary of efficacy for trial RPC01-3101 (induction phase)

Title:	A Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of oral RPC1063 as induction and maintenance therapy for moderate to severe ulcerative colitis

Study identifier	RPC01-3101 EudraCT number: 2015-000319-41		
Design	Parallel group, multinational, multicentre, randomised, double-blind placebo controlled trial for the induction of remission		
	Duration of main phase:	10 weeks	
	Duration of Run-in phase:	5 weeks screening	
	Duration of Extension phase:	not applicable (see further table below)	
Hypothesis	Superiority versus placebo		
Treatments groups	Ozanimod 1 mg/day	N=429	
	Placebo	N=216	
Endpoints and definitions	Primary endpoint	3-component Clinical remission	The proportion of adult patients in clinical remission at Week 10 with clinical remission defined as Rectal Bleeding subscore = 0 and Stool Frequency subscore ≤ 1 (and a decrease of ≥ 1 point from the Baseline Stool Frequency subscore) and Endoscopy subscore ≤ 1
	"Key" secondary (with type I error control)	Clinical Response	The proportion of adult patients with a clinical response at Week 10 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 ≤ 1 point
	"Key" secondary (with type I error control	Endoscopic improvement	The proportion of adult patients with endoscopic improvement at Week 10 defined as Endoscopy subscore of ≤ 1 point
	"Key" secondary (with type I error control	Mucosal Healing	The proportion of adult patients with mucosal healing at Week 10 defined as Endoscopy subscore of ≤ 1 point and a Geboes index score < 2.0
	Other Secondary: endpoint	Histologic remission	Proportion of adult patients with histologic remission at Week 10 defined as Geboes index score < 2.0
	Post-hoc CHMP guideline conform EP:	Symptomatic remission	Patients in symptomatic ("clinical") remission defined as RBS = 0 and SFS ≤ 1 (and a decrease from Baseline of ≥ 1)
Database lock	27 Mar 2020		

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat		
Descriptive statistics	Treatment group	Placebo	Ozanimod 1 mg

and estimate variability	Number of subject	216	429
	PEP: 3-component clinical remission	13(6.0%)	79 (18.4%)
	Clinical Response	56 (25.9%)	205 (47.8%)
	Endoscopic improvement	25 (11.6%)	117 (27.3%)
	Mucosal Healing	8 (3.7%)	54 (12.6%)
	Histologic remission	16 (7.4%)	78 (18.2%)
	Symptomatic remission	40 (18.5%)	161 (37.5%)

Effect estimate per comparison	Primary endpoint (3-component clinical remission)	Treatment difference	12.4% (7.5, 17.2)
		Odds ratio	3.586 (1.938, 6.636)
		p-value	< 0.0001
	Clinical Response	Treatment difference	21.9% (14.4, 29.3)
		Odds ratio	2.670 (1.858, 3.836)
		p-value	< 0.0001
	Endoscopic improvement	Treatment difference	15.7% (9.7, 21.7)
		Odds ratio	2.876 (1.802, 4.591)
		p-value	< 0.0001
	Mucosal Healing	Treatment difference	8.9% (4.9, 12.9)
		Odds ratio	3.767 (1.759, 8.068)
		p-value	<0.001
	Histologic remission	Treatment difference	10.8% (5.8, 15.8)
		Odds ratio	2.803 (1.593, 4.934)
		p-value	<0.001>
	Symptomatic remission	Treatment difference	19.0% (12.2, 25.8)
		Odds ratio	2.717 (1.821, 4.056)

		p-value	<0.0001
Notes	N/A		

Table 78: Summary of efficacy for trial RPC01-3101 (maintenance phase)

Title: A Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of oral RPC1063 as induction and maintenance therapy for moderate to severe ulcerative colitis			
Study identifier	RPC01-3101 EudraCT number: 2015-000319-41		
Design	Parallel group, multinational, multicentre, randomised, double-blind placebo controlled trial for the maintenance of remission		
	Duration of main phase:	42 weeks	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	not applicable	
Hypothesis	Superiority against placebo		
Treatments groups	Ozanimod 1 mg/day	N=230 for 42 weeks (for a total duration of 52 weeks)	
	Placebo	N=227 for 42 weeks (for a total duration of 52 weeks)	
Endpoints and definitions	Primary endpoint	3-component clinical remission	The proportion of subjects in clinical remission at Week 52 (definition see previous table)
	"Key" secondary (with type I error control)	Clinical Response	The proportion of subjects with a clinical response at Week 52 (definition see previous table)
	"Key" secondary (with type I error control)	Endoscopic improvement	The proportion of subjects with endoscopic improvement at Week 52 (definition: see previous table)
	"Key" secondary (with type I error control)	Maintenance of remission	The proportion of subjects in clinical remission at Week 52 in the subset of subjects who were in remission at Week 10
	"Key" secondary (with type I error control)	CS-free remission	The proportion of subjects with corticosteroid-free remission (with corticosteroid free defined as being off corticosteroids for at least 12 weeks)
	"Key" secondary (with type I error control)	Mucosal healing	The proportion of subjects with mucosal healing at Week 52 (definition see previous table)
	"Key" secondary (with type I error control)	Durable Remission	The proportion of subjects with durable clinical remission defined as clinical remission at Week 10 and at 52 weeks in all patients who entered the MP
	"Other" secondary endpoint	Histologic remission	The proportion of subjects with histologic remission at Week 52
	Post-hoc secondary endpoint	Symptomatic remission	Patients in symptomatic ("clinical") remission defined as RBS = 0 and SFS ≤ 1 (and a decrease from Baseline of ≥ 1)

	Post-hoc secondary endpoint"	Relapse	Proportion of patients with relapse during the 42 weeks treatment, with relapse defined as an increase in partial Mayo score of ≥ 2 points compared to the Week 10 partial Mayo score with an absolute partial Mayo score ≥ 4 points AND an endoscopic subscore of ≥ 2 points.
Database lock	27 Mar 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (time-point week 42 after randomisation; 52 weeks after start of induction treatment)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Ozanimod 1 mg
	Number of subject	N=227	N=230
	Primary endpoint 3-component clinical remission	42 (18.5%)	85 (37.0%)
	Clinical Response	93 (41.0%)	138 (60.0%)
	Endoscopic improvement	60 (26.4%)	105 (45.7%)
	Maintenance of remission	22/75 (29.3%)	41/79 (51.9%)
	CS-free remission	38 (16.7%)	73 (31.7%)
	Mucosal healing	32 (14.1%)	68 (29.6%)
	Durable Remission	22 (9.7%)	41 (17.8%)
	Histologic remission	37 (16.3%)	77 (33.5%)
	Symptomatic remission	76 (33.5%)	118 (51.3%)
	Relapse	81 (35.7%)	31 (13.5%)
	Primary endpoint 3-component clinical remission	Treatment difference (%; 95% CI)	18.6 (10.8, 26.4)
		Odds ratio (95% CI)	2.755 (1.767, 4.294)
		p-value	< 0.0001
	Clinical Response	Treatment difference (%; 95% CI)	19.2 (10.4, 28.0)
		Odds ratio (95% CI)	2.266 (1.542, 3.331)
		p-value	< 0.0001

		Treatment difference (%; 95% CI)	19.4 (11.0, 27.7)
	Endoscopic improvement	Odds ratio (95% CI)	2.476 (1.650, 3.716)
		p-value	< 0.001
		Treatment difference (%; 95% CI)	23.9 (9.1, 38.6)
	Maintenance of remission	Odds ratio (95% CI)	2.881 (1.447, 5.738)
		p-value	0.0025
		Treatment difference (%; 95% CI)	15.2 (7.8, 22.6)
	CS-free remission	Odds ratio (95% CI)	2.557 (1.598, 4.093)
		p-value	< 0.001
		Treatment difference (%; 95% CI)	15.6 (8.2, 22.9)
	Mucosal healing	Odds ratio (95% CI)	2.643 (1.642, 4.256)
		p-value	< 0.001
		Treatment difference (%; 95% CI)	8.2 (2.8, 13.6)
	Durable Remission	Odds ratio (95% CI)	2.646 (1.384, 5.061)
		p-value	0.0030
		Treatment difference (%; 95% CI)	18.0 (9.3, 26.7)
	Symptomatic remission	Odds ratio (95% CI)	2.191 (1.485, 3.234)
		p-value	< 0.0001
		Treatment difference (%; 95% CI)	17.3 (9.6, 24.9)
	Histologic remission	Odds ratio (95% CI)	2.684 (1.703, 4.229)
		p-value	<0.001
		Treatment difference (%; 95% CI)	N/A
	Relapse	Odds ratio (95% CI)	N/A
		p-value	< 0.001
Notes	The applicant has currently not evaluated the maintenance study according to the requirements of the CHMP UC guideline. These results need to be added once the response to the RSI has been evaluated.		

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled data have been submitted. This was considered acceptable by the CHMP.

Clinical studies in special populations

No studies in special populations are presented. Patients above the age of 65 were included to a marginal extent only and patients of the age of 75 or older were not included into the study. The SmPC reflects that data for >65 is scarce and not considered meaningful.

Supportive study(ies)

The applicant has additionally conducted a long-term open-label extension study which has of course, the primary objective of demonstrating safety. However, efficacy data from this trial will be reported in the following.

Study RPC01-3102:

Study RPC01-3102 is an ongoing Phase 3, multi-center, OLE study designed to evaluate the long-term safety and efficacy of ozanimod in subjects with moderately to severely active UC. Only subjects who had previously participated in Study RPC01-3101 or the OLP of Study RPC01-202 and met eligibility criteria were eligible for entry in this study. Subjects who entered the study from an open-label parent study or treatment period of ozanimod (i.e., from the OLP of Study RPC01-202 or Induction Period Cohort 2 of Study RPC01-3101) continued to receive ozanimod 1 mg QD. All subjects entering the study from a blinded parent study or treatment period of ozanimod (i.e., Induction Period Cohort 1 or the Maintenance Period of Study RPC01-3101) initiated ozanimod 1 mg treatment in accordance with the 7-day dose escalation regimen.

Subjects who had not achieved clinical response or remission at RPC01-3102 study entry were to be discontinued from ozanimod if they did not show clinical improvement from the Baseline visit of Study RPC01-3102 to Week 10.

Subjects remaining in the study will receive ozanimod 1 mg QD until the end of 2021 or until marketing authorization is obtained in their country, whichever comes first.

Results reported by the applicant are as of the data cut-off date of 31 Mar 2020.

A total of 878 subjects enrolled in this ongoing study, including 824 subjects from parent Study RPC01-3101 and 54 subjects from parent Study RPC01-202 OLP. These latter 54 patients did not have an efficacy evaluation as of the data-cut-off, and therefore are not included in the following tables.

As of the data cut-off date (31 Mar 2020), 52.4% of subjects in the RPC01-3101 total group completed the Week 46 Visit, while 38.7% of subjects withdrew from investigational product. The most frequently reported reasons for study treatment discontinuation were lack of efficacy (18.9% of subjects), withdrawal by subject (11.9% of subjects), and AE (3.4% of subjects). Subjects who had not achieved clinical response or remission at study entry were instructed to discontinue from the study if no clinical improvement from Study RPC01-3102 Baseline was observed by Week 10.

Table 79: Overall Disposition for Subjects Entering the Open-Label Extension (OLE Enrolled Population) – Study RPC01-3102

	Treatment Group in the Parent Study RPC01-3101			
	Placebo/ Placebo (N = 184) n (%)	Ozanimod 1 mg/ Placebo (N = 197) n (%)	Ozanimod 1 mg/ Ozanimod 1 mg (N = 443) n (%)	Total (N = 824) n (%)
Number of Subjects Consented but Never Treated	0	1 (0.5)	2 (0.5)	3 (0.4)[a]
Number of Subjects Included in the Intent-To-Treat Population	184 (100.0)	196 (99.5)	441 (99.5)	821 (99.6)
Number of Subjects[b]				
Who Completed the Week 22 Visit	142 (77.2)	145 (74.0)	300 (68.0)	587 (71.5)
Who Completed the Week 46 Visit	121 (65.8)	93 (47.4)	216 (49.0)	430 (52.4)
Who Completed the Week 94 Visit	65 (35.3)	39 (19.9)	82 (18.6)	186 (22.7)
Who Completed the Week 142 Visit	21 (11.4)	10 (5.1)	40 (9.1)	71 (8.6)
Who Withdrew from OLE Treatment	93 (50.5)	43 (21.9)	182 (41.3)	318 (38.7)
Primary Reason for Study Treatment Discontinuation				
Physician Decision	5 (2.7)	0	21 (4.8)	26 (3.2)
Non-compliance with Investigational Drug	1 (0.5)	0	0	1 (0.1)
Non-compliance with Protocol/Protocol Deviation	2 (1.1)	0	2 (0.5)	4 (0.5)
Adverse Event	9 (4.9)	4 (2.0)	15 (3.4)	28 (3.4)
Lack of Efficacy	45 (24.5)	22 (11.2)	88 (20.0)	155 (18.9)
Withdrawal by Subject	28 (15.2)	15 (7.7)	55 (12.5)	98 (11.9)
Pregnancy	1 (0.5)	1 (0.5)	1 (0.2)	3 (0.4)
Study Termination by Sponsor	0	0	0	0
Other[c]	2 (1.1)	1 (0.5)	0	3 (0.4)

OLE = open-label extension; UC = ulcerative colitis.

[a] Two subjects (Subjects 571-1005 and 600-1003) were included in the category "consented but never treated" in error in this interim report; the 2 subjects were consented and treated with study drug. Subject 430-1001 was consented but never dosed; the subject subsequently withdrew consent. These errors will be corrected later in the final clinical study report.

[b] Denominators for percentages are the number of subjects in the Intent-to-Treat Population. All subjects who receive at least one dose of investigational drug in this study will comprise both the Intent-To-Treat Population and the Safety Population. The subjects in the treatment group 'Placebo/Placebo' from RPC01-3101 include those subjects who were on Placebo, completed Cohort 1 induction period and entered the OLE (RPC01-3102). The subjects in the treatment group of 'Ozanimod 1 mg/Ozanimod 1 mg' from RPC01-3101 include those subjects who were treated with ozanimod 1 mg in Cohort 1 or 2 induction period and entered the OLE (RPC01-3102).

[c] Other reason includes: lost to follow-up and UC progression/flare.

The demographic characteristics for the parent study RPC01-3101 total group are presented in the following table. For subjects who entered the OLE, the mean age at parent study Baseline (last measurement collected on or prior to the date of the first dose in the parent study) was 41.7 years with a mean weight 74.78 kg of for the RPC01-3101 total group.

Table 80: Demographics for Subjects in the Open-label Extension Period (OLE ITT Population) – Study RPC01-3102

Parameter	Parent Study RPC01-3101 Total (N = 821)
Sex, n (%)	
Female	335 (40.8)
Male	486 (59.2)
Age (years)	
Mean (SD)	41.7 (13.65)
Min, Max	18, 74
Age Category (years) n (%)	
< 65	777 (94.6)
≥ 65	44 (5.4)
Race, n (%)	
White	731 (89.0)
Black	24 (2.9)
Asian	54 (6.6)
Other	12 (1.5)
Ethnicity, n (%)	
Hispanic or Latino	36 (4.4)
Not Hispanic or Latino	785 (95.6)
Weight (kg)	
n	820
Mean (SD)	74.78 (17.948)
Min, Max	37.8, 173.3
Body Mass Index (kg/m²)	
n	819
Mean (SD)	25.39 (5.390)
Min, Max	15.3, 51.8
Tobacco/Nicotine Usage, n (%)	
Never	559 (68.1)
Former	216 (26.3)
Current	46 (5.6)
Region, n (%)	
North America[a]	197 (24.0)
Eastern Europe[b]	464 (56.5)
Western Europe[c]	103 (12.5)
Asia Pacific[d]	47 (5.7)
South America[e]	3 (0.4)
South Africa	7 (0.9)

ITT = intent-to-treat; max = maximum; min = minimum; OLE = Open-label Extension; SD = standard deviation.
[a] Canada and United States
[b] Belarus, Bulgaria, Croatia, Czech Republic, Georgia, Greece, Hungary, Israel, Latvia, Republic of Moldova, Poland, Romania, Russian Federation, Serbia, Slovakia, and Ukraine.
[c] Belgium, Germany, Italy, Netherlands, and United Kingdom
[d] Australia, Republic of Korea, and New Zealand
[e] Argentina
Note: Baseline demographics are taken from the parent study.

Ulcerative colitis disease history for subjects who entered the OLE was assessed at the parent study Baseline. There were no notable differences in baseline disease characteristics across parent study treatment groups for subjects in the OLE ITT Population and the disease characteristics were consistent with the overall ITT Population of the parent study. For the RPC01-3101 total group, the mean (SD) and median 4-component Mayo score at Baseline was 8.9 (1.44) and 9.0, respectively, with 36.3% of subjects having a 4-component Mayo score (by central reader) at Baseline > 9. The mean (SD) and median 3-component Mayo score at Baseline was 6.7 (1.22) and 7.0, respectively. In total, 31.9% of subjects in the RPC01- 3101 total group were using systemic corticosteroids at screening and 33.7% had prior anti-TNF use at screening (based on the concomitant medication electronic case report form [eCRF]). 41.9% had a prior use of (conventional) immunosuppressants, and 97.7% had a prior use of aminosalicylates.

Given the number of different mechanisms by which subjects entered the OLE, there was a large range of exposure prior to entry into, as well as during the OLE. The mean (median) exposure to investigational product in the OLE for subjects in the RPC01- 3101 total group and subjects in the RPC01-202 OLP group was 1.17 (0.94) years and 0.85 (0.86) years, respectively. Of note, the 54 subjects who enrolled from Study RPC01-202 OLP had additional (up to 5.5 years) exposure to ozanimod 1 mg in the parent study. The mean (median) exposure to study drug overall (including parent study) for subjects in the RPC01-3101 total group and subjects in the RPC01-202 OLP group was 1.75 (1.60) years and 6.07 (6.04) years, respectively. The overall maximum duration of exposure (including parent study) was 4.6 years for subjects from parent study RPC01-3101 and 6.8 years for subjects from parent study RPC01-202 OLP.

There were 389 subjects (47.4%) in the RPC01-3101 total group and 5 subjects (9.3%) in the RPC01-202 OLP group who were treated with ozanimod for > 1 year in OLE Study RPC01- 3102 (RPC01-3102 CSR.

No efficacy data are available for the 54 subjects who enrolled from the parent Study RPC01-202 OLP, due to insufficient follow-up time for those subjects at the time of the Study RPC01-3102 data cutoff date.

Regardless of the duration of treatment in the parent study, of the 821 subjects in the RPC01- 3101 total group who completed all the assessments required for the efficacy endpoints (RBS, SFS, and endoscopy), 42.7% of subjects were in clinical remission and the majority of subjects (78.2%) had clinical response (3-component Mayo definition) at Week 46. Nearly half of subjects (49.9%) also met the criteria for endoscopic improvement and 40.9% had corticosteroid-free remission at Week 46.

Overall, long-term efficacy of ozanimod 1 mg was generally maintained at Weeks 94 and 142 for clinical remission (49.4% and 41.5%, respectively), clinical response (82.6% and 80.4%, respectively), endoscopic improvement (56.6% and 47.6%, respectively), and corticosteroid-free remission (48.1% and 35.8%, respectively). Of the subjects in the RPC01-3101 total group who achieved clinical remission or clinical response at RPC01-3102 study entry (responders by 3-component Mayo score using the 7-day algorithm), the majority of subjects generally maintained clinical remission (69.6% of subjects) and clinical response (93.9%), met the criteria for endoscopic improvement (71.8%), and had corticosteroid-free remission (68.7%). As with the overall population, long-term remission was generally maintained at Weeks 94 and 142 for subjects who were responders at study entry.

A summary of the results is given in the following table:

Table 81: Summary of Efficacy Endpoints in Open-label Extension for Parent Study RPC01-3101 Total Group (OLE ITT Population; Observed Cases) – Study RPC01-3102

Endpoint	Visit	Parent Study RPC01-3101 Total (N = 821) n1/n2 (%)
Clinical Remission[a]	Week 46	164/384 (42.7)
	Week 94	78/158 (49.4)
	Week 142	22/53 (41.5)
Clinical Response[b]	Week 46	294/376 (78.2)
	Week 94	128/155 (82.6)
	Week 142	41/51 (80.4)
Endoscopic Improvement[c]	Week 46	212/425 (49.9)
	Week 94	99/175 (56.6)
	Week 142	30/63 (47.6)
Corticosteroid-free Remission[d]	Week 46	157/384 (40.9)
	Week 94	76/158 (48.1)
	Week 142	19/53 (35.8)

ITT = intent-to-treat; OLE = Open-label Extension; RBS = rectal bleeding subscore; SFS = stool frequency subscore.

[a] Clinical remission (3-component Mayo): RBS = 0 and SFS $\leq$ 1 (and a decrease of $\geq$ 1 point from the Baseline SFS), and endoscopy subscore $\leq$ 1 without friability. The 7-day scoring algorithm was used.

[b] Clinical response (3-component Mayo): Reduction from Baseline in the 3-component Mayo score of $\geq$ 2 points and reduction from Baseline in the 3-component Mayo score $\geq$ 35%, and reduction from Baseline in the RBS of $\geq$ 1 point or a RBS of $\leq$ 1 point. 3-component Mayo score is defined as the sum of RBS, SFS, and the endoscopy subscore. The 7-day scoring algorithm was used.

[c] Endoscopic improvement: Endoscopy subscore of $\leq$ 1 point without friability.

[d] Clinical remission while off corticosteroids for $\geq$ 12 weeks.

Note: For efficacy data, Baseline was defined as the last measurement collected on or prior the date of first dose in the parent study.

n1 = number of subjects who met the endpoint criterion; n2 = number of subjects with endpoint assessed at visit and is the denominator for all percentages.

The applicant has also analysed these long-term efficacy data for the patient group with prior anti-TNF use, and the results are shown in the following table:

Table 82: Summary of Efficacy Endpoints in Open-label Extension in Subjects Who Had Previously Received Anti-TNF Therapy (OLE ITT Population, Observed Cases) – Study RPC01-3102

Endpoint	Visit	Parent Study RPC01-3101
		Prior Anti-TNF Use (N = 284) n1/n2 (%)
Clinical Remission[a]	Week 46	31/114 (27.2)
	Week 94	19/38 (50.0)
	Week 142	7/15 (46.7)
Clinical Response[b]	Week 46	78/112 (69.6)
	Week 94	30/37 (81.1)
	Week 142	12/14 (85.7)
Endoscopic Improvement[c]	Week 46	41/124 (33.1)
	Week 94	24/41 (58.5)
	Week 142	11/19 (57.9)
Corticosteroid-free Remission[d]	Week 46	29/114 (25.4)
	Week 94	18/38 (47.4)
	Week 142	7/15 (46.7)

ITT = intent-to-treat; OLE = Open-label Extension; RBS = rectal bleeding subscore; SFS = stool frequency subscore; TNF = tumor necrosis factor.

[a] Clinical remission (3-component Mayo): RBS = 0 and SFS ≤ 1 (and a decrease of ≥ 1 point from the Baseline SFS), and endoscopy subscore ≤ 1. The 7-day scoring algorithm was used.

[b] Clinical response (3-component Mayo): Reduction from Baseline in the 3-component Mayo score of ≥ 2 points and reduction from Baseline in the 3-component Mayo score ≥ 35%, and reduction from Baseline in the RBS of ≥ 1 point or a RBS of ≤ 1 point. 3-component Mayo score is defined as the sum of RBS, SFS, and the endoscopy subscore. The 7-day scoring algorithm was used.

[c] Endoscopic improvement: Endoscopy subscore of ≤ 1 point.

[d] Clinical remission while off corticosteroids for ≥ 12 weeks.

Note: For efficacy data, Baseline was defined as the last measurement collected on or prior the date of first dose in the parent study.

n1 = number of subjects who met the endpoint criterion; n2 = number of subjects with endpoint assessed at visit and is the denominator for all percentages.

2.4.2. Discussion on clinical efficacy

The applicant has conducted and presented a development program for UC, consisting of one phase 2 trial with dose-finding aspects, and 1 pivotal phase 3 study, which consisted of an induction part with two cohorts, and a maintenance part with re-randomisation of responders. Additionally, long-term, open label follow up data were presented.

Design and conduct of clinical studies

The clinical and endoscopic benefits of ozanimod therapy have been adequately targeted. The parameters studied include clinical endpoints, inclusive of patient-reported outcomes (PROs; rectal bleeding and stool

frequency) as well as endoscopic targets, all of which were achieved in the trial. Using a stringent requirement of being off corticosteroids for at least 12 weeks at Week 52, a statistical benefit of ozanimod in corticosteroid-free remission was demonstrated at the end of the maintenance period.

Superior efficacy for ozanimod 1 mg relative to placebo was shown in the clinical, endoscopic, and histologic measures of UC disease activity in the well-controlled pivotal Phase 3 clinical trial as well as a supportive dose-ranging Phase 2 study in moderate to severe UC. The trials enrolled subjects representative of a broad patient population who were intolerant to or failed conventional therapies, including corticosteroids and/or immunomodulators such as 6-MP, AZA, or MTX, and those who had primary or secondary nonresponse to an anti-TNF or other biologic therapy or were intolerant to either treatment.

Moderate to Severe UC, partial unmet medical need and development rationale for ozanimod

The applicant has chosen to develop ozanimod as a treatment in patients with moderate to severe ulcerative colitis, which have previously had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

The mechanism by which ozanimod exerts therapeutic effects is not fully elucidated, is thought to involve lymphocyte retention in lymphoid tissues and the reduction of lymphocyte migration to sites of inflammation including the central nervous system and intestine. The reduction of peripheral lymphocyte counts has been clearly demonstrated. The product has already been licensed for the treatment of relapsing remitting multiple sclerosis in 2020, and the planning and conduct of the development programme in UC was in parallel with the development in this first indication. The biological rationale, and therapeutic value of the compound have therefore already been demonstrated. Based on this, and on the fact that ulcerative colitis (UC) is an immune-mediated inflammatory disease, for which 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, the rationale for the UC development is sufficiently justified.

Design and conduct of clinical studies

The applicant has presented a comprehensive programme for the development of ozanimod in the UC indication.

The initial study conducted (RPC01-202) was planned based on studies available in healthy volunteers demonstrating a saturation of the peripheral lymphocyte reduction in the dose range between 0.5 mg and 1.0 mg daily. The study was, however, not explicitly planned as a dose-finding trial, but – for the statistical planning – included an induction period of 9 weeks (including 1 week of dose escalation), and a 24-week extension period in a "treat-through" design, during which patients were retained in the originally assigned treatment group in case they had responded to treatment in the induction period. The study was conducted as a double-blind, randomised, multi-centre, multi-national trial.

The included patient population did require the presence of moderate to severe disease, but not necessarily a previous treatment and insufficient response, lost response or intolerance to biologics or conventional immunosuppressants.

The evaluation of efficacy was mainly based on the 4-component Mayo Score and comprised categorical endpoints such as remission, response, and improvement, but also the evaluation of endoscopy, as well as histology. While the study does not fully reflect the requirements for a "pivotal" study as requested by the CHMP UC guideline, it must be acknowledged that it is acceptable overall that not so strict endpoints, and a wider patient population are included into early, non-pivotal studies. Nevertheless, the study by its character of a confirmatory approach and by including a prolonged, blinded treatment period of 6 months is a relevant study, well supporting the pivotal study.

The pivotal study for the programme, study RPC01-3101 comprised two cohorts of patients for induction treatment, one treated open-label with ozanimod 1 mg, and one cohort randomised to placebo or ozanimod 1 mg, for a duration of 10 weeks. Patients from both cohorts experiencing "response" after the initial treatment period, were then re-randomised to active treatment with ozanimod 1 mg daily or placebo for a treatment duration of additional 42 weeks to match a total duration of treatment of 52 weeks.

The trial design is fully compliant with the regulatory requirements, except for the fact that usually, the conduct of 2 randomised induction trials is expected. With the relevant design of the phase 2 trial and the overall supporting nature of this study, the presentation of only one pivotal trial for the short-term treatment can be accepted considering also that criteria related to "one pivotal study are met in term of data quality, robustness.

The study included a patient population with moderate to severe disease as defined by the 4-component Mayo score and required a compulsory ongoing treatment with either 5-aminosalicylates and/or corticosteroids, and with prior treatment with conventional immunosuppressants and/or biologics (anti-TNFs and vedolizumab). Insufficient treatment response, or intolerance was not compulsorily required at entry, but most patients finally complied with the claimed indication (see below). The selection of the patient population is therefore considered adequate and reflects the intended target population. The only drawback was related to the upper age limit set to 75, resulting in a very small proportion of patients in the higher age range.

The evaluation of efficacy was mainly based on the use of the Mayo Score, which is an established tool for the evaluation of disease activity in UC. In this trial, however, the element of subjectivity within this score, the physician's global assessment part was for the most part omitted from the efficacy evaluation, which is compliant with the regulatory recommendations. The main endpoint used was the "3-component Mayo score" which was termed "clinical remission" and includes a normalisation or near normalisation of the symptoms rectal bleeding and stool frequency and of the endoscopic appearance of the large bowel mucosa. While this composite endpoint is the recommended endpoint as per FDA guideline, the CHMP guideline requests the use of the co-primary evaluation of stool frequency and rectal bleeding on one hand, on for healing of the large bowel mucosa on the other hand. Efficacy would be concluded only in cases when both of these criteria have been fulfilled, in order to exclude that the "composite" efficacy would be based on one of these 2 parts only, which could leave either patients not significantly benefitting on their subjective symptoms, or not significantly benefitting from the healing of the mucosa, which has been shown to be predictive of the long-term outcome in the disease. The choice of the primary endpoint, both for the induction, as well as the maintenance part of the trial is therefore not compliant with the current CHMP requirements.

 While the planning of the trial was clearly initiated at the time when the current CHMP recommendations were under revisions, the final recommendations of the guideline could still have been implemented for the final analysis. However, this omission appears to be of minor relevance, due to the results of the trial and also because part of the required analyses were provided post hoc. The trial also included a variety of other endpoints, including clinical response, endoscopic improvement, mucosal healing, histologic remission, or , for the maintenance phase corticosteroid free remission, and "maintenance of remission", which are thought to be of high clinical relevance. The applicant has also post-hoc taken account new requirements related to estimands to demonstrate which estimand strategy has been implicitly followed for the trial (composite strategy), which is appreciated.

Although the trail protocol was amended relatively frequently, the applicant has sufficiently demonstrated adherence to GCP. Therefore, trial planning as well as conduct do not raise relevant concerns.

Efficacy data and additional analyses

- Phase 2 study RPC01-202:

The phase 2 study has demonstrated for the induction period, that a clinical remission can be induced in a statistically significantly different proportion of patients compared to placebo with the higher dose of 1 mg ozanimod (16.4% as compared to 6.2%), while the lower dose of ozanimod was achieving a lower rate of remission, not demonstrating statistical significance. Therefore, statistical significance can only be concluded in confirmatory manner for the chosen primary endpoint for the high dose.

he planned evaluation of the study included a hierarchical testing of the secondary endpoints with control of the type-1 error, but regarded any further testing as exploratory only, once the preceding tests had failed. Therefore, the further demonstration of efficacy with "nominally" significant results of the higher dose for the change in baseline of the Mayo Score, for endoscopic improvement, and 3-component clinical remission, and response have to be regarded to be "exploratory" only. The results of the 24-week extension period showed similar results, but with "nominal" statistical significance demonstrated consistently in both groups. However, this part of the study was not planned to be evaluated in confirmatory manner and was also hampered by the high rates of drop-outs. Nevertheless, both doses indicated the potential for long-term efficacy, with having more than 25% of the patients in (3-component) remission at the end of the 33-week treatment, as compared to only just under 8% for placebo. While the results of the induction period do clearly indicate a higher activity and clinical efficacy of the higher dose, the results of the long-term treatment period are somewhat ambiguous. The modelling exercise conducted by the applicant, however, determined the 1 mg dose as the most appropriate. In conclusion, the choice of the dose, both for the induction as well as the maintenance phase of the pivotal study can be considered acceptable, which is also based on the fact that no relevant differences with regard to safety (see below) do exist for the two doses.

- Pivotal study RPC01-3101:

In the induction period, there was a consistently higher improvement in all parameters tested for measuring clinical efficacy. The rate of "clinical" (a composite of clinical and endoscopic items) 3-component remission was tripled (18.4% vs. 6.0%) after 10 weeks of treatment compared to placebo, and the rate of clinical response almost reached half of the patients (47.8% compared to 25.9%). Similar superiority of the active treatment were seen for the endoscopic and histological evaluations of the mucosa (endoscopic improvement: 27.3% vs. 11.6%; mucosal healing 12.6% vs. 3.7%, and histologic remission 18.2% vs. 7.4%), the latter two of which can be regarded to be highly predictive of the long-term outcome of the disease.

The applicant has also evaluated post-hoc CHMP endpoint of a two-component symptomatic remission ("clinical remission"), which resulted in a rate of 37.5% under active, and 18.5% under placebo treatment. All these results were highly statistically significant, with p-values usually lower than 0.0001, and a minority showing p-values lower than 0.001.

With this post-hoc analysis, the requirements of the CHMP guideline are fulfilled in complete manner, although the 2-component symptom responder evaluation was introduced only post-hoc. However, since there is a high consistency for the statistical evaluation across the full range of endpoints, this can be regarded to be a minor.

Overall, it was considered demonstrated that patients are benefitting from treatment both for the improvement of symptoms as well as for the improvement of their long-term prognosis from this treatment in similar way, and there is no discordance between symptoms and endoscopic appearance of the mucosa. Additional "sensitivity analyses" for imputation of missing data, or using a different estimand, or using a conventional per-protocol analysis showed high consistency. Relevant subgroups analyses similarly showed high consistency across almost all subgroups evaluated. In a similar way,

partly significant advantages of the active treatment group were shown in the evaluation of quality of life and showed consistent effects on work productivity. No relevant differences were seen for health care utilisation. The biomarkers (faecal calprotectin) investigated indicated also relevant advantages for the active treatment against placebo.

For the maintenance phase, the trial demonstrated that the rate of 3-component clinical remission was doubled in the included patient population having responded to induction treatment (37.0 vs. 18.5%). The clinical response achieved reached 60% in total in those actively treated (vs. 41.0% on placebo), while rate of endoscopic improvement, mucosal healing and histologic remission also doubled. The applicant also showed that remission could be maintained in more than half of the patients that initially had achieved remission (51.9%), as compared to only 29.3% on placebo. The rates of relapse was almost 3-times higher in the placebo treated patients (13.5% vs. 35.7%). The CHMP-UC-guideline endpoint "symptomatic remission" also showed clear superiority (51.0% vs. 33.5%).

The applicant evaluated corticosteroid-free remission only for the 3-component Mayo "clinical remission" which also demonstrate superiority (31.7% vs. 16.7%). In fact, the applicant should have evaluated the two-component symptomatic remission, as well as the mucosal healing endpoints with the condition of being corticosteroid free at the final analysis, which would be fully compliant with the European requirements. Overall, all endpoints showed highly statistically significant differences, with p-values in the same range as reported for the induction period. The highest p-value (for the "maintenance of remission" endpoint) showed a p-value of 0.0025. Again, several sensitivity analyses were conducted which yielded consistent results, and again, the conducted subgroup analyses also showed highly concordant results across most of the criteria, with the same exceptions as mentioned for the induction phase. Again, Quality of Life scores improved relevantly, across most subdomains, and work productivity was higher with active treatment. The analysis of health care utilisation did not demonstrate fully consistent results due to the low number of events in total. However, a lower proportion of subjects receiving ozanimod were hospitalised during the observation period as compared to placebo.

The applicant has also presented the long-term extension studies of the phase 2, as well as of the phase 3 study, which do indicate that efficacy can be maintained over longer periods than one year. However, due to the nature of the studies with a selected patient population, and without control group, conclusions regarding efficacy to be drawn are limited.

Overall, the presented studies do indicate a high level of treatment success which appears to be clinically highly relevant. Although the rates of clinical remission appear to be numerically small, these are fully in the range of other compounds that have been licensed during the last years, or even better. The "small" effect sizes are considered to owe to the fact that the success criteria are indeed relatively strict. However, this takes account of the fact that the treatment paradigms in IBD are currently changing from the "induction and maintenance" with improvement of symptoms, to a "treat to target" approach. For this, any new choice of product that addresses the partial unmet need in patients not sufficiently treated with the current armamentarium will be welcomed.

2.4.3. Conclusions on the clinical efficacy

The applicant has convincingly demonstrated superiority of the treatment with ozanimod 1 mg daily in patients with moderate to severe ulcerative colitis that have had an insufficient response to treatments with conventional treatment or with biologics.

2.5. Clinical safety

Introduction

The main safety issues identified in the clinical program of ozanimod in the approved MS indication were small and transient decreases in heart rate (HR), which occurred mainly during titration and were symptomatic in few cases only (bradyarrhythmia), macular oedemas, reversible and mainly asymptomatic increases in liver enzymes and reversible (within three months of treatment cessation) decreases in ALC (lymphopenia), an increased risk of herpes zoster infections with long-term treatment, and a disproportionately higher incidence in malignancies with ozanimod vs. IFN β-1a (i.e. the active comparator in the MS studies).

The long-term risk for serious or opportunistic infections and malignancies could not be sufficiently characterised within the limited duration of clinical MS studies and thus prompted pharmacovigilance activity post-marketing including a Healthcare Professional checklist and Patient/caregiver's guide.

Clinical safety of ozanimod in the newly proposed indication (i.e. treatment of ulcerative colitis; UC) is based on the data obtained from a total of 10 clinical studies of ozanimod across all indications, including 9 Phase 2 and Phase 3 studies and 1 clinical pharmacology study.

In subjects with UC, 2 controlled studies have been completed and 1 open-label extension study is ongoing. (RPC01-3102).

In subjects with CD, 1 Phase 2 open-label study has been completed (RPC01-2201) and 1 Phase 3 open-label extension study is ongoing (RPC01-3204).

● In subjects with MS, 1 Phase 2 study with a core period and an extension period has been completed (RPC01-201 Part A), 2 pivotal Phase 3 controlled studies have been completed (RPC01-201 Part B and RPC01-301), and 1 Phase 3 open-label extension study is ongoing (RPC01-3001). These studies provided the evidence to support the approval/ registration of ozanimod for the treatment of MS in the US and in Europe.

For ongoing studies, the safety cut-off date was 31 Mar 2020.

The MAH presented in the safety overview the pooled placebo-controlled Induction Periods from the Phase 2 study and Phase 3 Cohort 1 and the randomized withdrawal Maintenance Period from the Phase 3 study (3101 MP). Based on the known biology of S1P modulators special attention was directed at assessing cardiac effects, hepatic effects, infections, consequences of lymphopenia, macular oedema, malignancies and pulmonary effects. In the approved indication, the most commonly reported adverse reactions are nasopharyngitis (11%), alanine aminotransferase increased (5%), and gamma-glutamyl transferase increased (5%). The most common adverse reactions leading to discontinuation were related to liver enzyme elevations (1.1%).

Three data pools form the basis of the clinical safety analysis in the ozanimod Phase 2 and Phase 3 studies. The pools are labelled in sequence to the existing pools included in the previous ozanimod MS submission. The UC pool designations are F (UC controlled studies) and G (UC controlled and open-label studies).

The focus of this safety overview is the pooled placebo-controlled Induction Periods from the Phase 2 study and Phase 3 Cohort 1 (Pool F Induction) and the randomized withdrawal Maintenance Period from the Phase 3 study (3101 MP). Pool G includes the placebo-controlled induction studies from Pool F, the Phase 2 Maintenance and Open-label Periods, the 3101 MP, the open-label induction Cohort 2 from RPC01-3101, and the OLE study (RPC01-3102), providing an assessment of the long-term safety of ozanimod 1 mg in UC subjects. Pool D (all completed and ongoing open-label studies in UC, Crohn's

disease [CD], and MS) comprises the largest overall dataset and is used for the exploration of rare events.

Data on subjects with CD in ongoing placebo-controlled trials were not provided in the pooled data since these data are blinded.
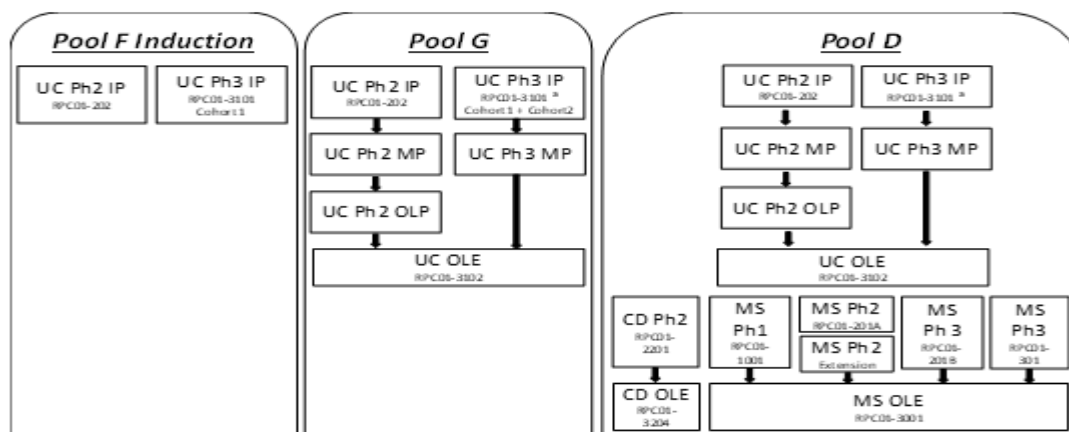
CD = Crohn's disease; IP = Induction Period; MP = Maintenance Period; MS = multiple sclerosis; OLE = Open-label Extension; OLP = Open-label Period; Ph = phase; UC = ulcerative colitis.
[a] Only responders assigned to ozanimod (Cohort 1 and Cohort 2) in the IP were rerandomized to receive ozanimod or placebo in a 1:1 ratio in a double-blinded manner when entering the MP. Adult subjects in clinical response at Week 10 of the IP who were randomized to placebo (Cohort 1) continued to receive placebo in the MP in a double-blinded manner.

Figure 41: Safety analysis pooling strategy (numbers of ozanimod-treated subjects)

Pool F (controlled UC studies) comprises two subsets, i.e.

Pool F-induction (referred to as Fi in this Report) compared the ozanimod 1 mg treatment groups of the induction periods from the UC studies with placebo groups of these periods, i.e. Phase 2 Study 202 (9-week induction period) and Phase 3 Study 3101-Cohort 1 (10-week induction period).

Pool F-maintenance (Fm in this Report) consists of the 42-week randomized withdrawal Maintenance Period from the Phase 3 Study 3101 (comprising Cohort 1 or Cohort 2 subjects, who had a clinical response to ozanimod 1 mg treatment during the Induction Period and were re-randomized to receive either ozanimod 1 mg or placebo as maintenance treatment).

Pool G (controlled and uncontrolled UC studies) includes subjects receiving 1 mg ozanimod or placebo in Phase 2 Study 202 (placebo-controlled induction, maintenance and OLE part), Phase 3 Study 3101 (including placebo-controlled induction (cohort 1), open-label induction (cohort 2), maintenance period) and OLE Study 3102, providing an assessment of the long-term safety of ozanimod 1 mg in UC subjects.

Pool D (all controlled and uncontrolled UC, CD, and MS studies) comprises the largest dataset, useful for evaluation of rare events that are not related to background disease (including UC-Studies 202, 3101, 3102; CD-Studies 2201 and 3204 and MS-Studies 201A, 201B, 301, 3001, and PD Study 1001).

Analyses were based on the treatment group to which a subject was assigned when the event occurred.

Patient exposure

A total of 4057 subjects were exposed to ozanimod 1 mg across all patient studies (Pool D), including 3252 subjects (80.2%) exposed for ≥ 12 months and 2694 subjects (66.4%) exposed for ≥ 24 months. Total cumulative exposure to ozanimod 1 mg was more than 11,600 subject-years (SY).

A total of 1158 subjects with UC have been exposed to ozanimod 1 mg (Pool G), including 868 subjects exposed for ≥ 6 months, 716 subjects exposed for ≥ 12 months, and 322 subjects exposed for ≥ 24 months. In Pool G, the mean exposure to ozanimod 1 mg was approximately 19 months, with a total cumulative exposure of approximately 1842 SY.

The mean duration of exposure in Pool F during the Induction Period was approximately 10 weeks in both the ozanimod 1 mg and placebo treatment groups. In the RPC01 3101 Maintenance Period, the mean duration of exposure was longer for the 230 subjects in the ozanimod 1 mg – ozanimod 1 mg group than for the 227 subjects in the ozanimod 1 mg – placebo group (~38 weeks versus ~31 weeks, respectively).

Table 83: Extent of exposure – Pool G (Safety Population)

Exposure Interval	Placebo (N = 508) n (%)	Ozanimod 1 mg (N = 1158) n (%)
≥ 6 months	220 (43.3)	868 (75.0)
≥ 12 months	37 (7.3)	716 (61.8)
≥ 24 months	0	322 (27.8)

N = number randomized to treatment, n = number receiving treatment for exposure interval.
Note: Patient-years of exposure is calculated as (date of last dose — date of first dose) + 1)/365.25.
Note: A total of 227 subjects who were treated with ozanimod 1 mg in RPC01-3101 Induction Period and were rerandomized to placebo in RPC01-3101 Maintenance Period are included in the total count of the 'Placebo' group.
Note: Pool G includes studies RPC01-202, RPC01-3101, and RPC01-3102.

Demographics and baseline characteristics in Pool Fi were balanced across treatment groups. The median age was approximately 40 years with a minimum age of 18 and a maximum age of 74 years and approx. 60% of subjects were male. The vast majority was White and nearly 30% of the Fi population was from Eastern Europe. Baseline demographics of subjects from Pool Fm and G were generally consistent with Pool Fi.

Subjects were to be excluded from the Phase 2 and Phase 3 UC studies if they had a history of clinically relevant cardiac, hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric, or other major systemic disease making implementation of the protocol problematic, interpretation of the trial difficult, or that would put the subject at risk by participating in the trial.

Similar patterns of concomitant medication use were observed for Pool Fi, Fm and G. In Pool F1 intestinal anti-inflammatory/anti-infective agents were used by 91.5% of subjects (primarily mesalazine [70.8%], sulfasalazine [15.9%], and budesonide [3.8%]), 29.4% subjects used systemic corticosteroids (primarily prednisone [15.9%]).

For disease history and baseline disease characteristics, medical history, prior or concomitant medications refer also to the chapter on "Clinical efficacy" of this Report.

Adverse events

TEAEs and marked laboratory abnormalities were summarized by subject incidence defined as the number of subjects with the specific event divided by the number of subjects included in the analysis. Exposure-adjusted incidence rates: The IR per 1000 subject-years was calculated as the number of subjects / subject years on study x 1000 for the specific system organ class (SOC) category or preferred term (PT) subcategory.

Overview of adverse events:

Placebo-controlled Induction Period (Pool F)

The overall incidence of TEAEs was similar between the ozanimod 1 mg and placebo treatment groups. The incidence of severe TEAEs, serious TEAEs, TEAEs leading to permanent discontinuation of study drug, and TEAEs leading to study withdrawal were low (< 4%) and similar between the 2 treatment groups.

Table 84: Overview of Treatment-emergent Adverse Events – Pool F Induction Period (Safety Population)

Adverse Event Category	Placebo (N = 281) n (%)	Ozanimod 1 mg (N = 496) n (%)
Any TEAE[a]	102 (36.3)	188 (37.9)
Any severe TEAE	6 (2.1)	15 (3.0)
Any serious TEAE	11 (3.9)	19 (3.8)
Any TEAE leading to permanent discontinuation of study drug[b]	8 (2.8)	15 (3.0)
Any TEAE leading to study withdrawal[b]	8 (2.8)	13 (2.6)
Death	0	0

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a]   Coded using MedDRA version 22.1.

[b]   Subjects who permanently discontinued study drug were permitted to remain in the study; data capture allowed for either or both of these outcomes as the result of an AE.

Note: A TEAE is defined as any event with an onset date on or after the first dose date of study drug up through the first dose date of the maintenance period. At each level of subject summarization, a subject is counted only once if the subject reported multiple events.

Note: Pool F Induction Period includes Studies RPC01-202 (Induction Period) and RPC01-3101 (Cohort 1 Induction Period).

Pool Fm Placebo-controlled Maintenance Period (RPC01-3101)

Overall, 49.1% of subjects in the ozanimod 1 mg – ozanimod 1 mg treatment group and 36.6% of subjects in the ozanimod 1 mg - placebo treatment group reported at least 1 TEAE (Table 16). The incidences of severe TEAEs and TEAEs leading to temporary interruption of study drug were generally similar between the treatment groups. Serious TEAEs and TEAEs leading to permanent study drug discontinuation occurred more frequently in subjects treated with ozanimod 1 mg – placebo (7.9% and 2.6%) than subjects treated with ozanimod 1 mg – ozanimod 1 mg (5.2% and 1.3%) due to the TEAE of ulcerative colitis (worsening or exacerbation).

Table 85: Overview of TEAEs –Pool F — RPC01-3101 Maintenance Period (Safety Population)

| | Number (%) of Subjects | | |
| | | Rerandomized Subjects | |
Adverse Event Category	Placebo (N = 69) n (%)	Ozanimod 1 mg - Placebo (N = 227) n (%)	Ozanimod 1 mg - Ozanimod 1 mg (N = 230) n (%)
Any TEAE[a]	27 (39.1)	83 (36.6)	113 (49.1)
Any severe TEAE	1 (1.4)	9 (4.0)	9 (3.9)
Any serious TEAE	4 (5.8)	18 (7.9)	12 (5.2)
Any TEAE leading to interruption of study drug	0	7 (3.1)	8 (3.5)
Any TEAE leading to discontinuation of study drug	0	6 (2.6)	3 (1.3)
Death	0	0	0

AE = adverse event; MedDRA = Medical dictionary for Regulatory Activities; MP = Maintenance Period; TEAE = treatment-emergent adverse event.

[a]   Coded using MedDRA version 22.1.

Note: At each level of subject summarization, a subject is counted only once if the subject reported multiple events. Note: A TEAE is defined as any AE with date of first onset or date of worsening in severity after the date of first MP dose, excluding those with onset after the 90-day safety follow-up visit. Subjects with multiple events reported for the same summary level will be counted only once. Percentages are based upon the number of subjects in the Safety Population.

The most frequently reported TEAEs with ozanimod 1 mg ($\geq$ 2% of subjects) which occurred at a $\geq$ 1% higher incidence compared with placebo were generally consistent with the known safety profile of ozanimod or common in patients with UC and included nasopharyngitis, nausea, pyrexia, arthralgia, and ALT increased (Table 17). Anemia was also reported at a > 2% incidence in the ozanimod 1 mg treatment group (3.6%) but was less frequent than with placebo (5.7%).

Of note, there was a higher incidence of TEAEs of ulcerative colitis (worsening/flare) in the placebo treatment group than in the ozanimod 1 mg treatment group (2.8% versus 1.6%, respectively).

Table below lists the most frequently reported TEAEs with ozanimod 1 mg ($\geq$ 2% of subjects), which occurred at a $\geq$ 1% higher incidence compared with placebo during the induction period.

Table 86: Incidence of Treatment-emergent Adverse Events Reported by ≥ 2% of Subjects in Any Treatment Group — Pool F Induction Period (Safety Population)

Preferred Term[a]	Placebo (N = 281) n (%)	Ozanimod 1 mg (N = 496) n (%)
At least 1 TEAE	**102 (36.3)**	**188 (37.9)**
Anaemia	16 (5.7)	18 (3.6)
Headache	7 (2.5)	15 (3.0)
Nasopharyngitis	3 (1.1)	15 (3.0)
Nausea	5 (1.8)	14 (2.8)
Pyrexia	3 (1.1)	14 (2.8)
Arthralgia	3 (1.1)	12 (2.4)
Alanine aminotransferase increased	0	12 (2.4)
Colitis ulcerative	8 (2.8)	8 (1.6)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.

[a] Coded using MedDRA, version 22.1.

Note: Subjects are counted at most once per system organ class or preferred term for multiple occurrences. TEAEs are sorted by descending percentage in the ozanimod 1 mg column and then alphabetically by preferred term.

Note: Pool F Induction Period includes studies RPC01-202 (Induction Period) and RPC01-3101 (Cohort 1 Induction Period).

Pool Fm Placebo-controlled Maintenance Period (RPC01-3101)

The overall pattern of TEAEs in Pool Fm was generally similar to Pool Fi.

There were 6 subjects with peripheral edema in the ozanimod 1 mg – ozanimod 1 mg treatment group; the majority of peripheral edema TEAEs were mild, did not require intervention, and occurred in subjects with a medical history of peripheral edema.

Of note, the incidence of ulcerative colitis (worsening/flare) was lower in the ozanimod 1 mg – ozanimod 1 mg treatment group (0.4%) than the ozanimod 1 mg – placebo treatment group (4.4%).

Frequent TEAEs by SOC/PT

Pool Fi (Placebo-controlled induction period)

The SOCs with the highest proportions of subjects reporting TEAEs were *Infections and Infestations, Gastrointestinal Disorders, and General Disorders and Administration Site Conditions*. In Pool Fi, the only SOC with ≥ 5% incidence of TEAEs reported by the ozanimod 1 mg treatment group and with a ≥ 2% higher incidence compared to the placebo treatment group was the *Investigations SOC*. This was driven by increases in hepatic transaminases, including ALT, AST, and GGT increased, which were reported more frequently in the ozanimod treatment group compared with the placebo treatment group (2.4% vs. 0%, 1.2% vs. 0%, and 1.2% vs. 0%, respectively).

Table 87: Incidence of TEAEs by System Organ Class Reported for ≥ 2% of Subjects in Any Treatment Group Pool F — RPC01-3101 Maintenance Period (Safety Population)

	Number (%) of Subjects		
		Rerandomized Subjects	
Preferred Term[a]	**Placebo** **N = 69**	**Ozanimod 1 mg – Placebo** **N = 227**	**Ozanimod 1 mg – Ozanimod 1 mg** **N = 230**
At least 1 TEAE	**27 (39.1)**	**83 (36.6)**	**113 (49.1)**
Alanine aminotransferase increased	0	1 (0.4)	11 (4.8)
Headache	0	1 (0.4)	8 (3.5)
Arthralgia	2 (2.9)	6 (2.6)	7 (3.0)
Nasopharyngitis	3 (4.3)	4 (1.8)	7 (3.0)
Gamma-glutamyltransferase increased	0	1 (0.4)	7 (3.0)
Oedema peripheral	0	0	6 (2.6)
Herpes zoster	0	1 (0.4)	5 (2.2)
Upper respiratory tract infection	3 (4.3)	4 (1.8)	2 (0.9)
Vomiting	2 (2.9)	2 (0.9)	2 (0.9)
Colitis ulcerative	1 (1.4)	10 (4.4)	1 (0.4)
Abdominal pain	2 (2.9)	1 (0.4)	1 (0.4)
Constipation	3 (4.3)	1 (0.4)	1 (0.4)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; MP = Maintenance Period; TEAE = treatment emergent adverse event.

[a] Coded using MedDRA, version 22.1.

Note: A TEAE is defined as any AE with date of first onset or date of worsening in severity after the date of first MP dose, excluding those with onset after the 90-day safety follow-up visit. Percentages are based upon the number of subjects in the Safety Population. TEAEs are sorted by descending frequency in the RPC1063 1 mg - RPC1063 1 mg column and then by descending frequency in preferred term and then alphabetically by preferred term in the RPC1063 1 mg - RPC1063 1 mg column.

Note: Subjects are counted at most once per preferred term for multiple occurrences.

Logical grouping of AEs

As part of signal detection to ascertain the true frequency of events that would otherwise be "split" between similar PTs, additional analyses were performed on the Pool F data using logical groupings of PTs. A total of 13 logical groupings of adverse events was performed (abdominal pain, anaemia, dysuria/urinary tract infection, elevated hepatic transaminase, gastroenteritis, headache, herpes simplex infection, hypertension, peripheral oedema, rash, respiratory symptoms, upper respiratory infection and visual impairment).

Relevant findings: in line with the known safety profile, a consistent imbalance across periods was observed in the logical grouping of elevated hepatic transaminase in Pool Fi as well as Fm. Imbalances were observed in one period but not in the other period for the logical groups of hypertension (higher incidence in ozanimod-treated subjects in Pool Fi (1.2% vs. 0%) and the same incidence in Pool Fm (2.2% in both groups)), herpes simplex infection (higher incidence in ozanimod-treated subjects in Pool Fm (1.7% vs. 0%), but not in Pool Fm (0.2% vs. 0%)). Grouping of anaemia resulted in a lower incidence in ozanimod-treated subjects in Pool Fi (4.0% vs 6.4%) and the same incidence in Pool Fm (2.6%)).

According to the Applicant, mild imbalances of unclear significance were observed for logical groupings of the PTs abdominal pain, gastroenteritis, headache, peripheral oedema, and upper respiratory infection. The majority of these cases were nonserious and did not lead to study drug discontinuation and/or study withdrawal. Further, according to the Applicant for the majority of subjects, the grouped TEAEs of headache as well as peripheral oedema were mild in intensity and resolved on treatment in Pool Fi and Fm.

Analysis of the most frequently reported AEs by Severity

In Pool Fi, the incidence of severe TEAEs was low and similar between the ozanimod 1 mg and placebo treatment groups (3.0% versus 2.1%, respectively). Ulcerative colitis (worsening/flare), headache, and anemia were the only severe TEAEs reported in more than 1 subject in any treatment group. Similarly findings resulted from Pool Fm (with 3.9% versus 4.0% severe TEAEs in the ozanimod/ozanimod and ozanimod/placebo group, respectively). There were no severe TEAEs reported in more than 1 subject in the ozanimod 1 mg - ozanimod 1 mg treatment group.

Long term use (Pool G)

The most frequently reported TEAEs with long-term use of ozanimod 1 mg ($\geq$ 5% of subjects) which occurred at a $\geq$ 1% higher incidence compared with placebo were consistent with the known safety profile of ozanimod and included lymphopenia, nasopharyngitis, anemia, ALT increased, lymphocyte count decreased, headache, arthralgia, and upper respiratory tract infection (Table 85). Accounting for the difference in exposure between the ozanimod 1 mg and placebo group (1922.5 versus 249.2 SY, respectively), the incidence rates (IR) of anemia, arthralgia, and upper respiratory tract infection were lower in subjects treated with ozanimod 1 mg compared to placebo.

Overall, there is no evidence of new patterns of TEAEs, increased incidence of TEAEs, or unique TEAEs with longer exposure to ozanimod.

Table 88: Incidence and Incidence Rates of the Most Frequently Reported (≥ 5% of Subjects) Treatment-emergent Adverse Events with Ozanimod and Placebo— Pool G (Safety Population)

Preferred Term[b]	Placebo N = 508 SY = 249.2[a]		Ozanimod 1 mg N = 1158 SY = 1922.5	
	n (%)	IR[c]	n (%)	IR[c]
Any TEAE	207 (40.7)	1120.7	796 (68.7)	949.0
Lymphopenia	0	0.0	103 (8.9)	57.1
Nasopharyngitis	10 (2.0)	40.7	86 (7.4)	47.4
Anemia	21 (4.1)	85.3	85 (7.3)	46.7
Alanine aminotransferase increased	2 (0.4)	8.1	72 (6.2)	39.8
Lymphocyte count decreased	0	0.0	71 (6.1)	38.5
Headache	8 (1.6)	32.5	60 (6.0)	37.6
Arthralgia	12 (2.4)	48.9	62 (5.4)	33.8
Upper respiratory tract infection	11 (2.2)	45.0	59 (5.1)	31.9

IR = incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; SY = subject-years; TEAE = treatment-emergent adverse event.

[a]   Total subject-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. The algorithm for the last date on study is dependent on subject disposition and whether subject enrolled into an extension study.

[b]   Coded using MedDRA, version 22.1.

[c]   IR per 1000 subject-years is calculated as number of subjects / SY x 1000 for specific preferred term subcategory. Subject-years for each category/subcategory: for a subject in a particular subcategory, the time on study is calculated based on the date the subject first has a TEAE within the subcategory (date of first TEAE - first dose date of study drug + 1)/365.25; for subjects who don't have a TEAE in the subcategory, the time on study is the study duration (last date on study - first dose date of study drug +1)/365.25.

Note: Pool G includes subjects in Studies RPC01-202, RPC01-3101, and the open-label extension study, RPC01-3102. Analysis is based on the treatment group to which a subject was assigned when the event occurred, including subjects who were rerandomized to placebo. Treatment-Emergent Adverse Events are sorted by System Organ Class in internationally agreed order, then within preferred term by descending percentage in the ozanimod 1 mg column and then alphabetically by preferred term. Subjects are counted at most once per preferred term for multiple occurrences.

As only the induction part of phase II study 202 is included in the controlled UC Pool (Fi), but the maintenance part was only included in uncontrolled UC Pool G, the safety results derived from controlled **maintenance part of Study 202** are shortly summarized below:

During the Maintenance Period a higher proportion of placebo patients experienced at least one AE (32.0%), a least one moderate or severe AE (16.0%), at least one serious AE (8.0%), and at least one AE leading to withdrawal (12.0%) compared to the combined ozanimod treatment groups (19.2%, 7.7%, 1.3%, and 0%, respectively). There were no serious AEs assessed as related to study drug and no deaths occurred in the Maintenance Period.

Only ulcerative colitis and urinary tract infection occurred in more than one patient in the Maintenance Period and there were no notable differences in incidence of these AEs between treatment groups.

Two related AEs were reported during the Maintenance Period, both in the ozanimod 1 mg group (1 abdominal pain, 1 leukopenia). No AE of special interest occurred during the maintenance period in either treatment group. There were no deaths in the trial. During the Maintenance Period, 3 SAEs in 2 placebo subjects occurred and 1 SAE in the ozanimod 1 mg, reported as colon adenoma and not (at least possibly) related.

The long-term adverse effects seen with ozanimod in subjects with UC was also examined comparing the incidence and study duration-adjusted incidence rate (IR) per 1000 subject years (SY) of TEAEs in subjects treated with ozanimod in the Pools Fi and Fm with data from Pool G with longer term exposure to ozanimod for up to approx. 82 months. No increase in overall rates of TEAEs or specific types of TEAEs were observed. No TEAEs indicative of a long-term cumulative toxicity were observed.

Definition of Adverse Drug Reactions (ADRs) in the product information

Adverse drug reactions (ADRs) were selected based on:

- the incidence of reports ($\geq$ 2% overall and $\geq$ 1% higher than placebo during induction or maintenance in the Phase 3 study, or in the pooled induction period),

- in consideration of AEs reported in the placebo-controlled Phase 1 and 2 studies, and

- medical assessment (including a causality determination by use of the Bradford-Hill criteria and in consideration of the mechanism of action of ozanimod and possible class effects).

Each ADR is categorized by frequency (i.e., very common, common, uncommon, or rare) based on the subject incidence reported in the ozanimod 1 mg group in the MS or UC studies, whichever was higher.

Adverse events of special interest (AESIs)/ Sponsor-designated events of interest (SDEI):

In UC studies 3101 and 202, subjects were closely monitored for AEs relating to cardiac abnormalities, hepatic abnormalities, ophthalmic abnormalities (study 202)/ macular oedema (study 3101), malignancies, pulmonary function, infections, and lymphopenia (study 3101 only).

The Applicant has further provided analyses of SDEI, a retrospective, systematic, and broadly inclusive approach to the review of key safety categories expanding on the concept of AESIs. SDEI are safety event categories that were selected based on potential safety concerns related to the biological effects of S1P1 modulation.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

In **Pool Fi** the incidence of SAEs was low and similar between the ozanimod 1 mg and placebo treatment groups (3.8% versus 3.9%, respectively). An imbalance was observed in the incidence of SAEs of anaemia, which occurred in 4 subjects (0.8%) in the ozanimod 1 mg treatment group and none on placebo. All 4 subjects had evidence of anaemia at baseline laboratory testing. In all cases, the investigator and the sponsor deemed the event not related to study drug. Overall, laboratory data have not revealed any evidence of a drug effect of ozanimod on haemoglobin and haematocrit, as shifts in these parameters from normal to low were more frequent with placebo.

Serious ulcerative colitis (worsening/ flare) was the only other SAE that occurred in more than 2 subjects in either treatment group and had a similar incidence between ozanimod 1 mg (8 subjects, 1.6%) and placebo (6 subjects, 2.1%).

In **Pool Fm** the incidence of SAEs was slightly lower in the ozanimod 1 mg – ozanimod 1 mg treatment group than in the ozanimod 1 mg – placebo treatment group (5.2% versus 7.9%). SAEs of ulcerative colitis (worsening/ flare) occurred predominantly in subjects who were re-randomized to placebo (4.0% versus 0.4% for ozanimod 1 mg – ozanimod 1 mg), and complicated appendicitis (0.9% versus 0), also occurred in subjects re-randomized to placebo. No other SAEs were reported in more than two subjects.

Long-term Use in UC (**Pool G**): Overall, serious TEAEs were infrequent across the UC program (151/1158 [13.0%] with ozanimod 1 mg versus 35/508 [6.9%] with placebo). Most SAEs were reported in only 1 subject. The most frequently reported serious TEAE in the ozanimod 1 mg and placebo treatment groups was ulcerative colitis (worsening/ flare), which occurred in 44 (3.8%) and 17 (3.3%) of subjects in the ozanimod 1 mg and placebo treatment groups, respectively. Other most common SAEs included anaemia, appendicitis, ischemic stroke, pneumonia, haemolytic anaemia, and abdominal pain.

Accounting for the difference in exposure between the ozanimod 1 mg and placebo group (1922.5 versus 249.2 SY, respectively), the IR of ulcerative colitis (worsening/ flare) was lower with ozanimod 1 mg than placebo (23.2 versus 68.8).

Deaths

There were 14 subject deaths in the entire ozanimod clinical development program as of 31 Mar 2020, including 10 deaths in the MS program, 3 deaths in the UC program, and 1 death in the CD program. Seven deaths were previously described in the MS SCS including 5 subjects with MS), 1 subject with UC, and 1 subject with CD. The remaining 7 deaths are described below including 2 deaths in the UC program and 5 deaths in the MS program. In addition, the UC subject included in the MS SCS is described below.

Death During the Phase 3 UC Study (RPC01-3101 Open-label Induction Cohort 2)

•   Subject XX was a 64-year-old male subject with UC and a medical history of ischemic cardiomyopathy, right bundle branch block, chronic obstructive pulmonary disease, prolonged tobacco use (over 40 years), and Type 2 diabetes mellitus, and received prior treatment with mesalamine. The subject was administered ozanimod 1 mg for approximately 6 weeks in Study RPC01-3101 and terminated the study early on Study Day 43 (Early Termination Visit) due to severe fatigue and overall poor health. On Study Day 45, the subject was hospitalized for acute respiratory distress syndrome and pneumonia influenzal and subsequently died on Study Day 59. Both events were fatal and were considered to be unrelated to study drug by the investigator. The Sponsor considered the events not suspected to be related to study drug. The death occurred during a regional outbreak of influenza.

Death During the UC OLE (RPC01-3102 OLE)

•   Subject XY (RPC01-3101 ozanimod 1 mg/ozanimod 1 mg group) was a 57-year-old male with a past history of myocarditis and hypertension who had an unwitnessed sudden death event on Day 184 of the OLE study. Concomitant medications during the OLE included lisinopril, carvedilol, mesalazine, and pregabalin. The subject's last recorded BP on Day 145 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 1 of the OLE showed sinus rhythm, atrial premature complexes, and intraventricular conduction delay (nonspecific); normal T wave morphology was noted. On Day 173 of the OLE, an echocardiogram revealed a mildly dilated left ventricle, mildly reduced global systolic function, ejection fraction 49%, normal wall thickness, impaired relaxation, normal right ventricular size and function, mildly dilated left atrium, borderline enlarged right atrium, mitral valve prolapse with mild mitral regurgitation, trace tricuspid regurgitation, normal pulmonary artery pressure, no aortic valve abnormality, normal aorta, and normal pericardium. On Day 184 of the OLE, it was reported that the subject had been found lying in the street, unresponsive, and was pronounced deceased upon arrival at the medical facility. The cause of the death event was unknown. No autopsy was performed. The subject had been treated with ozanimod for a total of approximately 19 months in the

parent study and extension study. The investigator considered the relationship of the event to the study drug unlikely. The Sponsor considered the relationship of the event to study drug unrelated.

Deaths During the RMS OLE (RPC01-3001)

• Subject XZ was a 22-year-old female subject with RMS who received ozanimod 0.5 mg per day for 729 days and placebo IM injection weekly for 723 days in Study RPC01-201B. The subject entered Study RPC01-3001 OLE and received 837 days of treatment with ozanimod 1 mg. The subject died due to road traffic accident on Study Day 838; the subject was hit by a car with an intoxicated driver while driving a motorbike. The last dose of ozanimod was administered on Study Day 837. The investigator considered the event unrelated to study drug. The Sponsor considered the event not related to study drug.

Death During the Phase 2 UC OLP (RPC01-202) already described during authorisation procedure of ozanimod:

• Subject XXX was a 43-year-old female subject 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. On study ALC levels were < 0.5 x 109/L on Study Day 830. The subject died in the hospital from mucinous adenocarcinoma (of gastric, pancreatic, bilial, or endometrial [intestinal type] origin) on open-label extension Study Day 911. The event was considered to be possibly related to study drug by the investigator. The Sponsor considered the event to be unrelated to study drug.

Deaths during the RMS OLE (RPC01-3001)

• Subject XXY (22-year-old, female subject with RMS, received ozanimod 0.5 mg per day) was hit by a car with an intoxicated driver while driving a motorbike. The investigator considered the event unrelated to study drug. The Sponsor considered the event not related to study drug.

• Subject XXZ was a 48-year-old female subject with RMS who received 729 days of treatment with placebo and 722 days with interferon (IFN) β-1a 30 µg weekly in Study RPC01-201B. The subject entered the RPC01-3001 OLE and received 512 days of treatment with ozanimod 1 mg per day. On Study Day 506, the subject was hospitalized with neoplasm malignant (unknown primary focus). C reactive protein was increased. An MRI of the head performed on Day 510 showed a metastatic tumor in the area of the cerebellum. A computed tomography (CT) scan done on Study Day 512 showed numerous tumors in the lung, liver, adrenal gland, and peritoneum. The subject subsequently experienced severe events of pneumonia and epilepsy and died on Study Day 531 due to the neoplasm malignant. The investigator considered the event possibly related to study medication. The Sponsor considered the event unrelated to study medication.

• Subject XXXX was a 46-year old female subject with RMS who received 171 days with ozanimod 1 mg per day in Study RPC01-201A and continued in the RPC01-201A Blinded Extension and received 753 days with ozanimod 1 mg per day. The subject subsequently enrolled in Study RPC01-3001 and received 977 days of ozanimod 1 mg in this study. The total treatment duration was 1901 days. The subject was hospitalized on Study Day 977 due to severe pneumonia and died on Study Day 988. The investigator considered the event possibly related to study medication. The Sponsor considered the event unrelated to study medication.

• Subject XXXY was a 54-year-old female subject with RMS and a medical history of hemangioma, received 732 days of treatment with ozanimod 1 mg per day and 729 days of treatment with placebo IM injection weekly in Study RPC01-201B. The subject entered RPC01-3001 OLE and received 151 days of ozanimod 1 mg. On Study Day 126, the subject was hospitalized with glioblastoma and underwent surgical removal of the tumor located in the left temporal lobe. Chemotherapy and radiotherapy were subsequently administered. Study medication was discontinued on Study Day 151 due to the glioblastoma. The subject

died due to glioblastoma multiforme on Study Day 1508. The investigator considered the event unrelated to study medication. The Sponsor considered the event not related to study medication.

• Subject XXXZ was a 42-year-old female subject with RMS who received 728 days with placebo oral capsule and 722 days with IFN β-1a 30 µg weekly. The subject entered RPC01-3001 OLE and received 1199 days of treatment with ozanimod 1 mg. On Study Day 1200, the subject was hospitalized with cerebral hemorrhage after being found unconscious on a sidewalk. The event was fatal despite attempts of resuscitation. Comorbidities included stage 2 arterial hypertension, MS progression, impaired glycemia, cytolysis syndrome, and acute renal impairment. The subject died on Study Day 1205. The investigator considered the event unrelated to study medication. The Sponsor considered the event not related to study medication.

Cardiac Effects

The S1P1 receptor is highly expressed in atrial, septal, and ventricular cardiomyocytes, 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. After initial agonism, continuous dosing results in functional antagonism and down-regulation of S1P activity due to S1P1 internalization. Activation of S1P receptors on cardiac cells provides an explanation for the transient effects on heart rate (bradycardia) and atrioventricular conduction, while modulation of the receptor on vascular smooth muscle cells could lead to vasoconstriction causing a mild increase in blood pressure.

The UC clinical studies excluded subjects who in the last 6 months experienced myocardial infarction, or who had unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea. Subjects with prolonged QTcF (> 450 msec for males, > 470 msec for females) or who were at additional risk for QT interval prolongation, as well as subjects with a resting heart rate < 55 bpm, were also excluded.

Effects on heart rate (HR) during treatment initiation:

Initiation of ozanimod may cause a transient reduction in heart rate. Based on Phase 1 data and in line with the MS clinical studies, a dose-escalation approach was implemented in the ozanimod UC Phase 2 and 3 clinical development programs to mitigate potential first dose cardiac effects.

In the **placebo-controlled UC Phase 2 study 202**, a complete 24 hours of Holter monitoring has been performed on Day 1 (and up to amendment of the study protocol in a subset of subjects also on Day 5 and 8, respectively). No symptomatic bradycardia occurred. On Day 1, minimum hourly HRs between 40 and 44 bpm were recorded for 5 (4.0%) ozanimod-treated subjects (versus no placebo subjects) during the normal diurnal reduction in HR observed during sleep.

In addition, as described in RPC01-202 CSR Erratum 2, 3 ozanimod-treated subjects had minimal HR values of < 45 bpm on Day 1, all of which occurred overnight and none of which were associated with an adverse event or required treatment. In one of these latter subjects (503-2001), a minimal heart rate of 38 bpm occurred at 2 AM; the subject's heart rate during the first 6 hours after dosing was ≥ 64 bpm.

HR in the other 2 subjects were above 40 bpm. According to the Summary of clinical safety, no other minimum HR < 40 bpm were recorded in this study (also not within the first 6 hours after treatment).

With Holter monitoring on Days 5 and 8, there were no subjects in any treatment group with a minimum HR < 45 bpm. In general, the daily minimum hourly HRs were recorded at night (while most subjects were asleep) in all treatment groups.

In the 496 subjects treated with ozanimod in **Pool Fi**, initiation of ozanimod 0.25 mg resulted in a modest and clinically uneventful reduction in HR on Day 1 (mean HR reduction from baseline of 0.7 bpm with a nadir at Hour 5, with return towards baseline by Hour 6 with a mean HR reduction of 0.4 bpm),

which is consistent with the corresponding reduction from baseline in HR of 1.2 bpm in the active-controlled Phase 3 MS studies.

In the **Phase 3 UC study**, there were 2 subjects who experienced TEAE of bradycardia on Day 1 of dosing. One subject of the blinded cohort 1 with onset of bradycardia within 6 hours of fist dose and lowest documented HR of 45 bpm at Hour 8 and one subject of open-label cohort 2 with lowest HR at Hour 2 of 43 bpm. This latter case was symptomatic (headache, nausea, and lightheadedness), however, for both subjects, no treatment for bradycardia was required and no action was taken for study drug for the adverse events

There was 1 subject with HR < 45 bpm on Day 1 (asymptomatic HR 42 bpm at Hour 3, which increased to 47 bpm at Hours 5 and 6 and was not reported as a TEAE). Importantly, **within all the UC studies**, there were no occurrences of second-degree type 2 or third-degree atrioventricular (AV) block. Ozanimod did not significantly affect cardiac repolarization or HR. The applicant concludes that totality of cardiac monitoring data supports the approved MS prescribing information, including monitoring restricted to patients with specific pre-existing cardiac conditions.

Subjects with Extended Monitoring (Pool Fi)

There were no clinically meaningful changes in HR and no reports of second-degree type 2 or third-degree AV block during chronic treatment with ozanimod 1 mg. Furthermore, there were no TEAEs of bradycardia in the RPC01-3101 Maintenance Period.

4.2% of subjects in the ozanimod treatment group and 2.1% of subjects in the placebo treatment group underwent protocol-mandated extended monitoring. The most common reason for extended monitoring was the lowest post-dose HR occurring at Hour 6. None of the subjects who received extended monitoring had symptomatic bradycardia.

HR during chronic therapy: In Pool Fi, by week 5, the next vital sign assessment after the Day 1 assessments, the mean sitting/supine HR returned towards and exceeded the baseline values in both treatment groups and generally remained stable up to Week 10.

Cardiac conduction effects/ECG results:

Study 202: Seven subjects were identified with cardiac findings of second-degree AV block type 1 or sinus pause occurring during 24-hour Holter monitoring on Day 1 (RPC01-202 CSR Erratum 2). Of these 7 subjects, 4 had received ozanimod 0.25 mg and 3 had received placebo. Of the 4 ozanimod-treated subjects, 3 subjects had minimal HR values of < 45 bpm on Day 1, all of which occurred overnight, described in the context of HR reduction, directly above. None of these Holter findings were associated with an TEAE or required treatment.

In addition, 3 ozanimod treated subjects had second-degree AV block type 1 (n = 2) or sinus pause (n = 1) occurring during 24-hour Holter monitoring on Day 1 of the OL period. All of these subjects had received placebo during the core period. For these 3 subjects, no TEAEs were reported on the day of the events and no action was taken with study drug. The follow-up ECG at Week 10 of the OL period demonstrated that the events of second-degree AV block type 1 have resolved.

During chronic therapy, 1 subject in **Pool F1** had a second-degree AV block type 1 at week 10. Prior to treatment the subject had first-degree AV block; an ECG four months later showed normal sinus rhythm without AV block with continued treatment.

Shift analyses of day 1 ECG findings from **Pool F1** did not reveal any new safety findings.

Blood Pressure during chronic therapy:

In Pool Fi, mean systolic blood pressure increased by 3.7 mm Hg with ozanimod and by 2.3 mm Hg with placebo at week 10 compared to baseline and mean diastolic blood pressure increased by 2.3 mm HG with ozanimod and 0.6 mm Hg with placebo. In Pool Fm, mean increase in systolic blood pressure was 5.1 mm Hg in the ozanimod-ozanimod group and 2.3 mm Hg in the placebo-ozanimod group at week 52 compared to baseline and mean increase in diastolic blood pressure was 2.2 mm Hg in the ozanimod-ozanimod group and 0.8 mm Hg in the placebo-ozanimod group at week 52. In Pool G, increases in systolic blood pressure remained rather stable from week 20 to 48. These results are consistent with BP changes observed at Month 24 for the ozanimod 1 mg treatment group in the MS Phase 3 studies, where there was a mean increase from baseline of 5.2 mm Hg in SBP and of 2.3 mm Hg in DBP.

The incidence of hypertension TEAEs (as per logical grouping) was low and slightly higher in the ozanimod 1 mg treatment group compared with the placebo treatment group during the Pool F Induction Period (1.2% versus 0%) and similar during the RPC01-3101 Maintenance Period (2.2% and 2.2%). In Pool G, hypertensive crisis was reported by 2 subjects on ozanimod and 1 subject on placebo; all subjects had a history of hypertension, recovered without clinical sequelae, and continued with study drug after the event. These data from the ozanimod UC development program are consistent with those described in the MS program, where hypertension TEAEs in the 2 active-controlled Phase 3 MS studies occurred in 3.4% of subjects treated with ozanimod 1 mg.

Collectively, as it was for MS, the cardiac experience at initiation in the UC studies indicates that dose escalation of ozanimod over 1 week mitigates the S1P1 receptor-mediated HR reduction (chronotropic) and conduction (dromotropic) effects, supporting monitoring restricted to patients with specific pre-existing cardiac conditions. These results in UC are generally consistent with findings in MS..

Cardiac related TEAEs:

Cardiac TEAEs during treatment initiation

In **Pool Fi** on Day 1, there was 1 TEAE from the Cardiac Disorders SOC in each treatment group (1 subject [0.2%] in the Cohort 1 ozanimod treatment group experienced bradycardia and 1 subject [0.4%] in the placebo treatment group experienced ventricular extrasystoles) and 1 TEAE from the Vascular Disorders SOC in the ozanimod 1 mg treatment group (hypertensive crisis, non-serious, in a subject with ongoing hypertension and no documented treatment with antihypertensives, considered not related).

Cardiac TEAEs during Days 1 to 30

In **Pool Fi** during Days 1 to 30, the incidence of TEAEs in the Cardiac Disorders SOC was low and similar between the ozanimod 1 mg (0.8%) and placebo treatment groups (1.1%). Four subjects (0.8%) in the ozanimod 1 mg treatment group and no subject in the placebo treatment group reported TEAEs in the Vascular Disorders SOC during Days 1 to 30; the only TEAE reported by more than 1 subject was hot flush (reported by 2 subjects [0.4%]).

In **Pool Fi**, two subjects (0.4%) in the ozanimod 1 mg treatment group reported **bradycardia**, 1 occurred on Day 1 during treatment initiation, also reported above) and 1 occurred on Day 2. In this latter case, the subject reported bradycardia, however no HR value was available and not treatment was given. No further TEAEs of bradycardia occurred in Pool Fi.

In addition, one subject of open-label Cohort 2 of study 3101 experienced a TEAE of bradycardia at Day 1 (described above) and 2 subjects of this Cohort reported bradycardia during the Induction Period beyond Day 1: In one subject, bradycardia (with HR ≥ 50 bpm) occurred on Day 10 on which the subject was started on bisopropol. In the second subject, bradycardia (HR of 45 bpm reported by subject as lowest value; subject further noted lightheadedness and headaches) was reported after 7 weeks of treatment. 4 Days after ozanimod discontinuation at week 9 the bradycardia resolved without treatment.

<u>Cardiac TEAEs in Pool Fi (Up to Week 10)</u>

In Pool Fi, no imbalance was found with regard to TEAEs in the Cardiac Disorders SOC (1.2% and 1.4% in ozanimod and placebo subjects, respectively). Apart from 2 TEAEs of bradycardia, which occurred at Day 1 and 2, no further cases of bradycardia occurred in Pool Fi. TEAEs in the Vascular Disorders SOC were more frequently reported in the ozanimod 1 mg treatment group compared with the placebo treatment group (2.0% vs. 0.4%, respectively); the difference was primarily driven by events of hypertension and hot flush both of which were observed in the ozanimod 1 mg treatment group only (6 subjects [1.2%] and 2 subjects [0.4%], respectively).

<u>Cardiac TEAEs in Pool Fm (i.e. during Weeks 10 through 52 of 3101-Maintenance Period)</u>

In Pool Fm, there were 3 subjects in the ozanimod 1 mg – ozanimod 1 mg treatment group and no subject in the ozanimod 1 mg - placebo treatment group with TEAEs in the Cardiac Disorders SOC. The 3 subjects in the ozanimod 1 mg - ozanimod 1 mg treatment group reported 4 TEAEs in the Cardiac Disorders SOC (arrhythmia, cardiac failure chronic, coronary artery disease, and pericarditis), all of which occurred > 60 days after the first dose. Of these TEAEs, cardiac failure chronic and coronary artery disease occurred concurrently in the same subject, and pericarditis was considered serious. There were no TEAEs of bradycardia in Pool Fm.

There were 6 subjects in the ozanimod 1 mg – ozanimod 1 mg treatment group and 4 subjects in the ozanimod 1 mg - placebo treatment group who reported TEAEs in the Vascular Disorders SOC. The TEAEs of hypertension, which were reported by 4 and 3 subjects in the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg - placebo treatment groups, respectively, were generally reported at a consistent rate during the different exposure intervals. TEAEs of hypertensive crisis (1 in each treatment group) occurred > 60 days after the first dose in the RPC01-3101 Maintenance Period.

<u>Cardiac TEAEs in Pool G (analysis during long-term treatment by 3 months intervals)</u>

No Cardiac Disorders or Vascular Disorders TEAEs indicative of a long-term cumulative toxicity were observed. TEAEs of hypertension were generally reported at a consistent rate during the different exposure intervals.

<u>TEAEs of Hypertension</u>

The incidence of hypertension TEAEs (as per logical grouping) was low and somewhat higher in the ozanimod 1 mg treatment group compared with the placebo treatment group in Pool Fi (1.2% vs. 0%) and similar in Pool Fm (2.2% and 2.2%). In Pool G, hypertensive crisis was reported by 2 subjects on ozanimod and 1 subject on placebo; all subjects had a history of hypertension, recovered without clinical sequelae, and continued with study drug after the event. The data from the ozanimod UC development program are consistent with the MS program, where hypertension TEAEs in the 2 active-controlled Phase 3 MS studies occurred in 3.4% of subjects treated with ozanimod 1 mg.

Hepatic Effects

Consistent with what has been observed with ozanimod and other S1P receptor modulators in MS, hepatic enzyme elevations, including ALT, AST, and GGT, were seen with ozanimod 1 mg treatment. Small increases in mean total bilirubin also occurred with ozanimod. When elevations in liver function tests occurred, they were generally asymptomatic and resolved with continued treatment and did not lead to severe drug-induced liver injury.

The incidences of hepatic-related TEAEs were evaluated in the SOCs of Hepatobiliary Disorders and Investigations. The incidence of hepatic laboratory-related TEAEs (Investigations SOC) was higher with ozanimod 1 mg than placebo during the Pool F Induction Period (5.4% versus 2.8%) and the RPC01-3101 Maintenance Period (11.3% versus 4.0%). However, the incidence of Hepatobiliary Disorders TEAEs (eg,

hyperbilirubinemia, non-alcoholic steatohepatitis) was low and similar between the ozanimod 1 mg and placebo treatment groups (0.2% versus 0.7% during the Pool F Induction Period and 0.9% versus 1.3% during the RPC01-3101 Maintenance Period). Discontinuations due to hepatic-related TEAEs were only seen with ozanimod and were infrequent (2 subjects [0.4%] during the Pool F Induction Period and 1 subject [0.4%] during the RPC01-3101 Maintenance Period).

Hepatic laboratory analyses:

The incidences of hepatic-related laboratory TEAEs during induction period and maintenance period are presented in the following tables.

Table 89: Incidence of hepatic-related laboratory TEAEs Pool Fi (Safety Population)

Investigations[c] (includes non-hepatic TEAEs)	8 (2.8)	27 (5.4)
Alanine aminotransferase increased	0	12 (2.4)
Aspartate aminotransferase increased	0	6 (1.2)
Gamma-glutamyltransferase increased	0	6 (1.2)
Hepatic enzyme increased	0	3 (0.6)
Liver function test increased	0	2 (0.4)
Transaminases increased	0	2 (0.4)

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class;

TEAE = treatment-emergent adverse event.

a Coded using MedDRA, version 22.1.

b Subjects were counted at most once per SOC or PT for multiple occurrences.

c Only PTs under the Investigations SOC that were reported in ≥ 2 subjects in any treatment group are included in this table.

Note: Pool F Induction Period includes Studies RPC01-202 (Induction Period) and RPC01-3101 (Cohort 1 Induction Period).

Table 90: Incidence of hepatic-related laboratory TEAEs Pool Fm (Safety Population)

Investigations[b] (includes non-hepatic TEAEs)	4 (5.8)	9 (4.0)	26 (11.3)
Alanine aminotransferase increased	0	1 (0.4)	11 (4.8)
Gamma-glutamyltransferase increased	0	1 (0.4)	7 (3.0)
Hepatic enzyme increased	1 (1.4)	0	2 (0.9)
Liver function test increased	0	0	3 (1.3)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; MP = Maintenance Period;
PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
a Coded using MedDRA, version 22.1. A subject is counted only once for multiple events within PT/SOC.

Elevations in ALT ≥ 3x ULN, ≥ 5x ULN, and ≥ 10x ULN were observed in 2.6%, 0.9%, and 0.5% of subjects treated with ozanimod 1 mg in the RPC01-3101 Induction Period (versus 0.5%, 0.5%, and 0% of subjects on placebo), and in 2.3%, 0.9%, and 0% of subjects treated with ozanimod 1 mg in the RPC01-3101 Maintenance Period (versus none on placebo). Data from the ozanimod UC development program are consistent with the MS program, where elevations in ALT ≥ 3x ULN, ≥ 5x ULN, and ≥ 10x ULN occurred in 5.5%, 1.6%, and 0.5% of subjects treated with ozanimod 1 mg in the 2 active-controlled Phase 3 MS

studies for up to 2 years. The majority of subjects with a post-baseline ALT > 3x ULN (approx. 96% of subjects in the controlled and uncontrolled UC studies and 79% of subjects in the 2 active-controlled Phase 3 MS studies) continued treatment with ozanimod 1 mg with most values returning to ≤ 3x ULN within approx. 2 to 4 weeks. In the UC and MS clinical trials, ozanimod was discontinued for a confirmed elevation of ALT or AST > 5x ULN. Overall, the discontinuation rate due to elevations in hepatic enzymes was low (0.8% of subjects treated with ozanimod 1 mg in the controlled and uncontrolled UC studies) and similar to the 2 active-controlled Phase 3 MS studies (1.1%).

In the UC development program, there was 1 subject who had AST ≥ 3x ULN and bilirubin > 2x ULN. The subject had a specific concurrent disease/ alternative diagnosis (autoimmune haemolytic anaemia) that was responsible for the elevation in bilirubin and AST. The case therefore did not meet the criteria for Hy's Law and was previously described for the MS indication.

Subjects with elevations of ALT > 10x ULN **(Pool G)**

A total of 5 subjects (0.4%) in the ozanimod 1 mg treatment group had elevations of ALT > 10x ULN. Of these 5 subjects with ALT > 10x ULN, 1 subject had evidence of liver disease (compensated cirrhosis) at study entry, 1 subject had a history of and ongoing pancreatitis during the study with ALT above normal prior to study entry (ALT elevations resolved after discontinuation of study drug), 2 subjects had a history of elevation in hepatic enzymes prior to study entry (1 was associated with prior biologic therapy and the other was receiving ursodeoxycholic acid due to elevated liver enzymes of unknown origin), and 1 subject had an elevation in ALT following discontinuation of treatment with ozanimod and after taking oral nimesulide for the treatment of oligomenorrhea. None of the subjects progressed to severe liver injury.

Hepatic events of potential clinical significance:

An examination of the overall program hepatic safety, including laboratory changes and adverse events, was conducted to identify specific cases of potential clinical significance (including potential Hy's law cases).

Subjects with concurrent elevations of aminotransferase and bilirubin

In the MS clinical development program, a total of 10 subjects had concurrent elevations of ALT or AST ≥ 3x ULN and total bilirubin > 2x ULN. Of these 10 subjects, 1 was a UC subject, 1 was a CD subject, and 8 were MS subjects. A review of unblinded cases by an external panel of hepatologist experts concluded that no case met Hy's law due to alternate explanations and the pattern of abnormalities. As of the 31 Mar 2020 safety cut-off date, no new cases of concurrent elevations of ALT or AST ≥ 3x ULN and total bilirubin > 2x ULN were reported.

Drug-induced liver injury TEAEs

In Pool G, there were 2 subjects in the ozanimod 1 mg treatment group who reported a TEAE of drug-induced liver injury:

• One Subjec, a 60-year-old male, who received ozanimod 1 mg for 10 weeks in Study RPC01-3101 (Induction Period) and was then re-randomized to placebo in the maintenance period, experienced an abnormal ALT of 98 U/L (reference ≤ 41 U/L) on Day 325 of Study RPC01-3102, followed by 43 U/L on Day 331. The elevation was considered mild but persistent. The Investigator deemed the event as drug-induced liver injury, study drug was not stopped, and no treatment was given. The subject was discontinued from the study on Day 457 due to persistent mild elevation of ALT. The ALT value at the time of discontinuation was just above the ULN (44 U/L). The subject had no previous history of liver function abnormality at screening or during study. The subject neither had a relevant medical history nor did he receive concomitant medication.

• Subject XX, a 52-year-old female, who received ozanimod 1 mg for 10 weeks in the Study RPC01-3101 Induction Period and was re-randomized to placebo in maintenance, experienced an abnormal ALT of 71 U/L (reference ≤ 33 U/L) on Day 33 of Study RPC01-3102. The investigator deemed the event as drug-induced liver injury. The elevation was considered mild but persistent; the highest ALT value recorded was 96 U/L on Day 111. The subject was prescribed ademetionine and no change was made to study drug. The subject stopped ademetionine after 60 days and subsequent ALT was 41 U/L on Day 154. The subject continued onto the open-label extension. The subject had no history of liver function abnormality at screening or during study. The subject had no relevant past medical history and was not on any contributing medication.

Infections

Reduction in circulating lymphocytes is a result of the mechanism of action of S1P receptor modulators but can potentially lead to increased susceptibility to infections, including serious and opportunistic infections. Subjects enrolled in the UC studies had to have documented positive varicella zoster virus (VZV) antibody status or complete VZV vaccination at least 30 days prior to randomization.

Controlled UC studies: Duringinduction Period (Pool Fi), the incidence of infections was similar between the ozanimod 1 mg and the placebo treatment groups, with the most common infection being nasopharyngitis. In the RPC01-3101 Maintenance Period, the incidence of nasopharyngitis (3.0% versus 1.8%), herpes zoster (2.2% versus 0.4%), gastroenteritis (1.3% versus 0), and oral herpes (1.3% versus 0) was slightly higher in the ozanimod 1 mg - ozanimod 1 mg treatment group than in the ozanimod 1 mg - placebo treatment group. No TEAE of infections led to discontinuation of study drug during either treatment period.

Serious infections (infection-related SDEI)

Controlled UC studies: The incidence of serious infections in **Pool Fi** was low in both treatment groups and numerically higher in the ozanimod 1 mg treatment group compared with the placebo treatment group (0.8% versus 0.4%, respectively) with no specific pattern. All serious infections were reported in single subjects. The incidence of serious infections **Pool Fm** was low in all treatment groups and lower in the ozanimod 1 mg - ozanimod 1 mg treatment group compared with the ozanimod 1 mg - placebo treatment group (0.9% versus 1.8%, respectively). In the ozanimod-ozanimod group, all serious infections were reported in single subjects only.

In both controlled UC Pools (Fi and Fm), all serious infections resolved, mostly with no change in the study drug.

Opportunistic infections (infection-related SDEI)

In the **Pool Fi**, 3 (0.6%) subjects in the ozanimod 1 mg treatment group and no subjects in the placebo treatment group had opportunistic infections SDEIs. These were campylobacter gastroenteritis in one and herpes zoster in two subjects, respectively. No opportunistic infections SDEIs were serious.

In **Pool Fm**, there were 5 (2.2%) subjects in the ozanimod 1 mg treatment group and 1 (0.4%) subject in the placebo treatment group who had opportunistic infections SDEIs, all of whom had herpes zoster. No events of herpes zoster were serious, severe, or led to study drug withdrawal or study discontinuation.

Pool G (all UC studies)

Incidence and incidence rates (IR) of the most frequent (≥ 5%) infection TEAEs, serious and opportunistic infections, and infections leading to study drug withdrawal during long-term treatment in UC are given in the following table.

Table 91: **Comparison of the Incidence and Incidence Rate of Infections and Infestations TEAEs, Serious Infections or Opportunistic Infections SDEIs, and Discontinuation of Study Drug Due to Infections and Infestations TEAEs in All UC Studies (Pool G) (Safety Population)**

System Organ Class or SDEI Preferred Term	Pool G			
	Placebo N = 508 SY = 249.2[a]		Ozanimod 1 mg N = 1158 SY = 1922.5[a]	
	n (%)	IR[b]	n (%)	IR[b]
TEAEs (≥ 5% of subjects in either treatment group)				
Infections and Infestations	71 (14.0)	314.3	337 (29.1)	228.1
Nasopharyngitis	10 (2.0)	40.7	86 (7.4)	47.4
Upper respiratory tract infection	11 (2.2)	45.0	59 (5.1)	31.9
SDEIs (≥ 2 subjects in either treatment group)				
Any Serious Infection	7 (1.4)	28.4	25 (2.2)	13.2
Appendicitis	1 (0.2)	4.0	6 (0.5)	3.1
Pneumonia	0	0	4 (0.3)	2.1
Clostridium difficile infection	0	0	2 (0.2)	1.0
Gastroenteritis	0	0	2 (0.2)	1.0
Urinary tract infection	0	0	2 (0.2)	1.0
Complicated appendicitis	2 (0.4)	8.0	0	0
Any Opportunistic Infection	2 (0.4)	8.1	28 (2.4)	14.8
Herpes zoster	2 (0.4)	8.1	25 (2.2)	13.2
TEAEs leading to study drug discontinuation (> 1 subject in either treatment group)				
Infections and Infestations	0	0	7 (0.6)	3.6
Herpes zoster[c]	0	0	3 (0.3)	1.6

IR = incidence rate; PT = preferred term; SDEI = Sponsor-designated event of interest; SOC = system organ class; SY = subject-years; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

[a] Total subject-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. The algorithm for the last date on study is dependent on subject disposition and whether subject enrolled into an extension study. If there is a duration gap between parent and extension study, the duration gap is counted.

[b] Incidence rate per 1000 subject-years is calculated as number of subjects / SY x 1000 for specific SOC category or PT subcategory. Subject-years for each category/subcategory: for a subject in a particular category/subcategory, the time on study is calculated based on the date the subject first has a TEAE within the category/subcategory (date of first TEAE - first dose date of study drug + 1)/365.25; for subjects who do not have a TEAE in the category/subcategory, the time on study is the study duration (last date on study - first dose date of study drug + 1)/365.25.

Most cases of Herpes zoster with ozanimod in Pool G were mild to moderate (96%) and most subjects (88%) remained on study drug. Thirteen of the 25 (52.0%) subjects were > 50 years of age and at risk for herpes zoster reactivation. None of the subjects with herpes zoster had an ALC < 2x 10^9/L.

Overall, there was no clear association between ALC < 0.2× 10^9/L and serious or opportunistic infections.

With regard to <u>Corticosteroid use and infections</u> see safety in special populations, extrinsic factors, below.

<u>Pool D (all UC, CD and MS studies)</u>

As of data-cut off, there were no cases of PML or cryptococcal meningitis SDEIs in the ozanimod development program (Pool D).

Macular Edema

Macular edema was examined closely because of the effect of S1P receptor modulation on vascular endothelial cells. In the ozanimod UC program, optical coherence tomography (OCT) was used as a standard screening tool to identify subjects for further ophthalmologic examination. The OCT was

evaluated in the placebo-controlled study, RPC01-3101, at baseline and at the end of the Induction (Week 10) and Maintenance Periods (Week 52), and in the open-label extension study RPC01-3102, at baseline, Week 10, Week 46, and annually thereafter. An OCT was also conducted at the end of Study RPC01-202 OLP. If an OCT abnormality was identified, or if visual signs or symptoms of ME observed, an ophthalmological examination was performed by an ophthalmologist (preferably a retina specialist), including eye history, visual acuity, and dilated ophthalmoscopy, to confirm the diagnosis of ME and/or to identify other ophthalmic abnormalities. No trend in macular thickness changes were noted over time with repeat OCTs with mild increases balanced across groups in Pool G.

An assessment of ME was conducted by an expert panel (Macular Edema Review Panel [MERP]) who reviewed AEs of macular edema and AE preferred terms that could be associated with ME, as well as OCT findings potentially suggestive of ME (regardless of whether an ME-related AE was reported), and ophthalmic examinations. The MERP was comprised of 3 neuro-ophthalmologists and a retina specialist who were blinded to study treatment throughout all panel reviews (MERP Charter).

Macular oedema was closely examined because of the effect of S1P receptor modulation on vascular endothelial cells. In the ozanimod UC program, optical coherence tomography (OCT) was used as a standard screening tool to identify subjects for further ophthalmologic examination. If an OCT abnormality was identified, or if visual signs or symptoms of ME observed, an ophthalmological examination was performed by an ophthalmologist. An assessment of potential cases of ME was conducted by an expert panel (Macular Edema Review Panel [MERP]).

In Pool G, the incidence of ME TEAEs (preferred terms of macular oedema or cystoid macular oedema) in the UC studies was low. Five (0.4%) of the 1158 subjects had TEAEs of ME, all of whom were in the ozanimod 1 mg treatment group: 4 (0.3%) subjects had a TEAE of ME and 1 (< 0.1%) subject had a TEAE of cystoid macular oedema. All cases were reversible, and 3 cases resulted in discontinuation of study drug. There were 4 MERP-confirmed ME events in the ozanimod UC program, for an incidence of 0.3% in the ozanimod 1 mg treatment group. All confirmed cases were associated with pre-existing risk factors and/ or comorbid conditions that are known to be associated with ME.

No trend in macular thickness changes were noted over time with repeat OCTs with mild increases balanced across groups in Pool G.

Malignancies

Malignancies were examined due to the potential effects of ozanimod as an immunomodulatory agent. Subjects with a history of malignancies (other than treated basal cell carcinoma and in situ squamous cell carcinomas of the skin or [in Phase 3 only] uterine cervix) were excluded from the Phase 2 and Phase 3 UC studies.

Controlled UC study parts: During the induction Period (Pool Fi), there was a single case of malignancy (cutaneous squamous cell carcinoma) in 1 subject (0.2%) in the ozanimod 1 mg treatment group. Total time on study at time of diagnosis was 12 days.

During the RPC01-3101 Maintenance Period (Pool Fm), the incidence of any malignancy was low and similar between the ozanimod 1 mg – ozanimod 1 mg and the ozanimod 1 mg – placebo groups (2 subjects [0.9%] in each treatment group). One subject (0.4%) in the ozanimod 1 mg – ozanimod 1 mg treatment group had basal cell carcinoma.

The **long-term incidence** of malignancies was evaluated using Pool G, which comprises all UC studies and therefore provides a broader base of safety information in the UC population. Approximately 35% of subjects in Pool G had been previously treated with corticosteroids and approximately 13% of subjects had received prior immunosuppressants, including anti-TNFs.

There were 14 malignancies reported in the UC program (Pool G), including 12 that occurred during ozanimod treatment and 2 that occurred after completing ozanimod induction and being rerandomized to the placebo group (Table 21). Malignancies were varied with no predominant type of malignancy and no malignancies suggestive of immunosuppression (ie, lymphoma).

Table 92: Incidence of Malignancies – Pool G (Safety Population)

Malignancy Preferred Term	Placebo (N = 508) (SY = 249.6)[a]		Ozanimod 1 mg (N = 1158) (SY = 1923.6)[a]	
	n (%)	IR[b]	n (%)	IR[b]
Any malignancy	2 (0.4)	8.1	12 (1.0)	6.3
Noncutaneous Malignancy[c]	2 (0.4)	N.C.	6 (0.5)	N.C.
Adenocarcinoma	0	0.0	1 (< 0.1)	0.5
Adenocarcinoma of colon	1 (0.2)	4.0	0	0.0
Breast cancer	1 (0.2)	4.0	1 (< 0.1)	0.5
Lung neoplasm malignant	0	0.0	1 (< 0.1)	0.5
Prostate cancer	0	0.0	1 (< 0.1)	0.5
Rectal adenocarcinoma	0	0.0	1 (< 0.1)	0.5
Rectal cancer stage II	0	0.0	1 (< 0.1)	0.5
Cutaneous Malignancy[d]	0	N.C.	6 (0.5)	N.C.
Basal cell carcinoma	0	0	5 (0.4)	2.6
Squamous cell carcinoma	0	0.0	1 (< 0.1)	0.5

IR = incidence rate; N.C. = not calculated; PT = preferred term; SDEI = sponsor-designated event of interest; SY = person-years.

[a] Total subject-years equals the sum of the number of years on study contributed by each subject from time of first dose per treatment group in the pool to last date on study per treatment group in the pool. The algorithm for the last date on study is dependent on subject disposition and whether subject enrolled into an extension study. If there is a duration gap between parent and extension study, the duration gap is counted.

[b] IR per 1000 SY is calculated as number of subjects / SY × 1000 for specific SDEI category or subcategory. For a subject in a particular category/subcategory, the time on study is calculated based on the date the subject first meets an SDEI criterion within the category/subcategory per treatment group in the pool (date first criterion is met - first dose date of study drug per treatment group in the pool + 1)/365.25; for subjects who don't meet an SDEI criterion in the category/subcategory per treatment group in the pool, the time on study is the study duration per treatment group in the pool (last date on study per treatment group in the pool - first dose date of study drug per treatment group in the pool +1)/365.25.

[c] Excluding basal cell and squamous cell skin cancers (non-melanoma skin cancer).

[d] Nonmelanoma skin cancer.

Notes: Pool G includes studies RPC01-202, RPC01-3101, and RPC01-3102. A total of 227 subjects who were treated with ozanimod 1 mg in RPC01-3101 Induction Period and were rerandomized to placebo in RPC01-3101 Maintenance Period, were included in the total count of the "Placebo" group. Coded using MedDRA, version 22.1.

<u>Summary of background information and discussion provided by the Applicant</u> (in the CO and SCS, respectively):

The IR for all malignancies in Pool G (6.3 per 1000 SY) was similar to the background IR per 1000 PY of any malignancies in patients with IBD, estimated at 7.856 (95% CI: 7.54, 8.185) in the province of Quebec in the period 1998 to 2015 (Loo, 2019).

The literature is generally in agreement that the risk for the development of colorectal cancer (CRC) in patients with IBD exceeds that of the general population by at least 3- to 5-fold, increasing with duration and extent of disease (Eaden, 2004). The cumulative incidence of colorectal cancer in patients with UC has been estimated as 2% at 10 years, 8% at 20 years, and 18% at 30 years (Eaden, 2001). In the HealthCore Integrated Research Database (HIRDSM), the annual time adjusted IR per 1000 PY for colon cancer is 2.07 among patients with moderate to severe IBD (McAuliffe, 2015). There were 3 cases of CRC across the UC program involving 1666 subjects (0.2%); given an observation patient-time of 2000 PY, the incidence of CRC in the UC program is consistent with published data and contemporaneous rates in a US population of IBD patients. All 3 subjects had a relatively long duration of disease (10 to 18 years since diagnosis at screening), and 2 had extensive disease and prior use of azathioprine. Duration and extent of disease, as well as immunomodulator use, have been identified as risk factors for CRC among UC patients (Garg, 2016; Manninen, 2013). Given the increased risk, these subjects were closely followed by the Sponsor and rereviewed with the central reader and an external gastroenterologist consultant. In all 3 cases, the baseline endoscopy was found in retrospect to have evidence to suggest that the malignancy may have been present at baseline.

The incidence and IR per 1000 SY of <u>non-melanoma skin cancer</u> (NMSC) for ozanimod were also in the expected range of the general population. In Pool G, the incidence of NMSC was 0.5%; the IR per 1000 SY for basal cell carcinoma was 2.6 and for squamous cell carcinoma was 0.5. In Minnesota, the age and sex-adjusted (US 2010 population) IR per 1000 PY of NMSC was 4.84 over the period 2000 to 2010 (Muzic, 2017). In Germany, the crude IR per 1000 PY of NMSC in 2012 was 2.78 and 2.41 in men and women, respectively, in the federal state of Schleswig-Holstein and 1.86 and 1.63 in men and women,

The malignancies reported do not demonstrate any particular pattern and are not typical of those observed in an immunosuppressed population (e.g., no cases of lymphoma were reported). The IRs do not appear to indicate a significantly increased overall risk of malignancies or an incidence rate that increases with greater exposure duration. Longer follow-up with larger numbers of exposed patients are required to make a robust assessment regarding risk of malignancy associated with ozanimod treatment.

In **Pool D** (UC, CD and MS studies), SDEIs of malignancy were reported in 47 (1.2%) out of 4057 subjects in the ozanimod 1 mg treatment group and 2 (0.3%) out of 596 subjects in the placebo treatment group, which corresponds to an IR per 1000 SY of 4.0 and 6.9, respectively.

Non-cutaneous malignancies (excluding NMSC) were reported in 29 (0.7%) subjects in the ozanimod 1 mg treatment group and 2 (0.3%) subjects in the placebo treatment group.

Non-melanoma skin cancers (cutaneous malignancies) were reported 18 (0.4%) subjects and 0 placebo subjects, respectively. Of note, phase 2 and 3 MS studies were active controlled. Breast cancers (preferred terms breast cancer, breast neoplasm, invasive breast carcinoma, and invasive ductal breast carcinoma) were reported in 9 (0.2%) out of 4057 subjects in the ozanimod 1 mg treatment group and 1 (0.2%) out of 596 subjects in the placebo treatment group.

Pulmonary Effects

Pulmonary function is known to be affected by S1P modulators. In nonclinical studies, ozanimod did not induce smooth muscle hypertrophy, increased collagen or fibrin deposition in the lung as has been

reported with fingolimod. No effect on respiratory function was observed with ozanimod administration in rodents.

Pulmonary safety for ozanimod was examined in the clinical development program using spirometry, diffusing capacity (DLCO) and AEs related to pulmonary function designated as AESIs in Phase 2 and Phase 3 UC studies.

Small changes were observed with the spirometry assessments specifically the FEV_1 and FVC (less than 100 ml, 1.3%) parameters for the ozanimod 1 mg treatment group and were primarily driven by changes during the first 3 months. At week 10, median change from baseline in FEV1 (FVC) was -0.05 (-0.03) in the ozanimod and -0.02 (± 0) in the placebo group (Pool Fi).

These small changes were not progressive with longer observation. In addition, there is evidence for reversibility based on the data from the RPC01-3101 MP where subjects re-randomized to placebo had a return towards baseline of their spirometry assessments (FEV1 and FVC).

Change from baseline in FEV1 during controlled maintenance phase (Pool Fm) is presented in the following table. Respective course in FVC was generally comparable.

Table 93: Change from baseline in FEV1 (L) by Visit – Pool Fm (Safety Population)

		Rerandomized Subjects	
Time Point	Placebo (N = 69)	Ozanimod 1 mg - Placebo (N = 227)	Ozanimod 1 mg - Ozanimod 1 mg (N = 230)
Week 28			
n	55	160	192
Mean (SD)	-0.063 (0.406)	-0.092 (0.407)	-0.088 (0.358)
Median	-0.040	-0.050	-0.085
Week 52			
n	45	118	180
Mean (SD)	-0.076 (0.529)	-0.036 (0.423)	-0.075 (0.389)
Median	-0.060	-0.010	-0.085

FEV_1 = forced expiratory volume in 1 second; SD = standard deviation.
Note: Baseline is defined as the last nonmissing value prior to the first dose of study drug.
Source: RPC01-3101 CSR Table 14.3.7.1B.

Small but highly variable changes were noted in DLCO with only a fraction of subjects (≤ 26%) assessed.

To account for visit-to-visit variability in FEV_1 and FVC, an outlier analysis of PFTs was conducted examining subjects with < 70% of predicted and < 70% of baseline values at two consecutive visits, or at the last postbaseline visit. Using this approach, the incidence was lower with ozanimod 1 mg (0.2% for FEV_1 and < 0.1% for FVC) than placebo (0.7% and 0.7%, respectively). These subjects did not have accompanying respiratory AEs.

Respiratory SOC TEAEs in the controlled studies were similar across treatment groups (2.2% in ozanimod and 1.4% in placebo subjects in Pool Fi and 3.0% in the ozanimod-ozanimod and 3.1% in the ozanimod-placebo group in Pool Fm, respectively) with no serious TEAEs and 1 TEAE that led to treatment discontinuation (shortness of breath, mild, considered not related in a subject with a history of chronic bronchitis).

Examination of subjects who are at greater risk for lung disease (i.e., smokers) demonstrated no clinically meaningful changes FEV_1, FVC, and FEV_1/FVC ratio in subjects treated with ozanimod.

The totality of the pulmonary data indicates that mild reductions in FEV_1 and DLCO occurred early in treatment with ozanimod 1 mg, but were not clinically meaningful and these changes were not progressive over time. Furthermore, the data do not demonstrate an increased incidence of respiratory-related AEs in

comparison to placebo. The limited effect on pulmonary function in patients with UC treated with ozanimod is similar to that observed in MS.

Posterior Reversible Encephalopathy Syndrome (PRES)

One case of PRES has been reported in Pool D, has occurred in the MS program and has been evaluated during authorisation procedure of ozanimod. No further case of PRES has occurred in the UC studies.

Laboratory findings

Clinical laboratory evaluations were performed in the Phase 2 and Phase 3 UC studies at baseline, regular intervals ranging between 4 to 12 weeks throughout the treatment periods, and approximately 1 month following discontinuation of study drug.

Absolute Lymphocyte Count

In **Pool Fi**, as expected decreases in absolute lymphocyte count (ALC), were evident at the first assessment at Week 5 in subjects treated with ozanimod 1 mg. The mean percent decreases from baseline in ALC were 47.2% (to approx. 53% baseline value) at Week 5 and 52.8% (to approx. 47% baseline value) at Week 10 in the ozanimod 1 mg group. Subjects who received ozanimod 1 mg during Study 3101 Induction and Maintenance Periods showed a sustained reduction of ALC that was generally maintained below the baseline value. Steady state simulations indicated that UC patients receiving ozanimod 1 mg are predicted to have a mean steady state reduction in ALC of 57.2% (please refer to assessment of PK/PD modelling, in Section 5.3.4 of this Report, above).

In **Pool Fi**, there was a low incidence of ALC values < 0.2 x 109/L in the ozanimod 1 mg treatment group (1/475 [0.2%] at Week 5 and 5/460 [1.1%] at Week 10 (vs. no cases in the placebo group each). In **Pool Fm**, among subjects in the ozanimod 1 mg – ozanimod 1 mg treatment group, the overall incidence of ALC values < 0.2 x 109/L at any time throughout the treatment period was 3.0% and at the last available assessment was 1.4%. Following withdrawal of ozanimod 1 mg among subjects who were re-randomized to placebo there were no subjects who had an ALC < 0.2 x 109/L from the first assessment at Week 18 through the last assessment at Week 52.

Lymphocyte recovery:

According to the UC study protocols, if ALC was confirmed < 0.2×10^9/L then the investigator was to temporarily discontinue investigational drug and repeat laboratory testing weekly until ALC > 0.5 x 109/L, at which point reinitiation of study drug was permitted.

Based on the minimum values across all assessments in **Pool G**, an ALC < 0.2 x 109/L occurred in 60 (5.3%) subjects treated with ozanimod 1 mg. Of these, 52 subjects had an available subsequent laboratory assessment on study drug and were evaluable for on-treatment ALC recovery. Of these 52 subjects, 25 subjects had laboratory assessments available for analysis at 2 weeks following the first abnormality in ALC of < 0.2×10^9/L. Nineteen of these 25 subjects had an increase in ALC to $\geq 0.2 \times 10^9$/L and 4 had an increase in ALC $\geq 0.5 \times 10^9$/L. All 52 subjects who had an ALC < 0.2×10^9/L while on treatment with ozanimod 1 mg recovered to an ALC $\geq 0.2 \times 10^9$/L.

Off-treatment recovery: Based on the Kaplan-Meier estimates conducted on 325 subjects in **Pool G**, the median time to recovery of ALC to the normal range ($\geq 1 \times 10^9$/L) was 35 days (95% CI 33, 37). Approximately 68% of subjects recovered to the normal range 2 months after discontinuation of ozanimod 1 mg, and approximately 82% subjects recovered to the normal range 3 months after discontinuation of ozanimod 1 mg.

These observations are generally consistent with the PK/PD simulations for ALC recovery to $\geq 1 \times 10^9$/L, which predicted a mean time to recovery of 32.8 days with 90% of subjects recovering in ~3 months.

In Pool Fi, mean percent decreases from baseline in leukocyte [WBC] count were approximately 17% at the first assessment (Week 5) and 23% at the end of the Induction Period (Week 10) in the ozanimod 1 mg treatment group. These changes were expected and related to the reduction in ALC. There were no subjects with a WBC value < 2 x 10^9/L in **Pool Fi**.

Reductions in absolute neutrophil count (ANC) < 1 x 10^9/L occurred in <1% in both treatment groups of **Pool Fi** and occurred in one subject in each treatment group during 3101 maintenance period.

For liver enzyme parameters, please see section on AESI. There were no other notable changes from baseline or trends over time in chemistry in subjects receiving ozanimod.

Urinalysis

In Pool Fi, Pool Fm and Pool G, respectively, there were no clinically meaningful changes from baseline in mean urinalysis parameters in the ozanimod treatment group relative to placebo.

Safety in special populations

Age (Evaluation of Pool G):

Population PK analysis showed that CC112273 steady-state exposure in elderly subjects with UC was increased compared to younger adults with UC, with a 22% increase in adults 55 to 65 years of age and 27% increase in those > 65 years of age compared to adults < 45 years of age.

The effect of age on TEAE and serious TEAE incidence in Pool G was evaluated on subjects < 65 years and $\geq$ 65 years. Approximately 95% of the subjects in the Safety Population of Pool G were < 65 years; thus, comparisons between subgroups should be interpreted with caution. The subgroup < 65 years included 481 subjects in the placebo treatment group and 1103 subjects in the ozanimod 1 mg treatment group, while the subgroup $\geq$ 65 years was limited to 27 subjects in the placebo treatment group and 55 subjects in the ozanimod 1 mg treatment group. Of the 55 subjects $\geq$ 65 years who were treated with ozanimod 1 mg, 28 of these subjects (50.9%) were exposed for at least 12 months.

The overall incidence of TEAEs in the placebo treatment group was higher in the subgroup $\geq$ 65 years compared to those < 65 years (55.6% versus 39.9%, respectively), but the overall incidence of TEAEs among subjects treated with ozanimod 1 mg was similar in the subgroup $\geq$ 65 years compared with the subgroup < 65 years (69.1% versus 68.7%, respectively). A greater percentage of serious TEAEs were reported for subjects $\geq$ 65 years than < 65 years in both placebo and ozanimod 1 mg treatment groups (11.1% versus 6.7% and 20.0% versus 12.7%, respectively). However, most serious TEAEs were isolated events with no apparent relationship to age with the exception of a slightly higher percentages of subjects $\geq$ 65 years reporting infections compared with those < 65 years in both ozanimod 1 mg (5.5% versus 2.0%, respectively) and placebo (3.7% versus 1.2%, respectively) treatment groups.

Based on a median age of 40 years, the effect of age on TEAEs has also been evaluated on subjects $\leq$ 40 years and > 40 years. There was no clinically meaningful difference in the overall incidence of TEAEs or SAE between subjects $\leq$ 40 years of age and > 40 years of age in the ozanimod or placebo groups, respectively.

Gender:

The overall incidence of TEAEs was greater among female than male subjects in the both, the placebo and ozanimod 1 mg treatment groups of Pool G, which is partially attributable to higher incidences of TEAEs in the Blood and Lymphatic Disorders (24.9% vs. 14.8%) and Nervous System Disorders (14.0% vs. 9.0%)

SOCs among female versus male subjects, respectively. Among subjects treated with ozanimod 1 mg, higher incidences of lymphopenia and lymphocyte count decreased were reported for female subjects compared to male subjects (12.6% vs. 6.4%, respectively, and 9.1% vs. 4.1%, respectively). This imbalance and associated risk of lymphopenia are consistent with an ~34% increase in the PK exposure of CC112273, the major active metabolite, in female patients compared to males.

Additionally, while the overall incidence of Investigations was similar between female and male subjects who were treated with ozanimod 1 mg, greater proportions of male subjects experienced TEAEs related to elevated liver function tests than female subjects.

Within the subgroups of female and male subjects, the pattern of TEAEs was generally consistent with the overall population. The predominant SOCs ($\geq$ 15% among ozanimod-treated subjects in either subgroup) were Infections and Infestations, Gastrointestinal Disorders, and Investigations.

There were no clinically meaningful effects of sex on serious TEAE incidence among subjects who were treated with ozanimod 1 mg in Pool G.

Extrinsic factors

Baseline Corticosteroid Use

Pool G comprised approximately twice as many subjects who reported not using corticosteroids than using corticosteroids at screening. The predominant SOCs were Infections and Infestations, Gastrointestinal Disorders, and Investigations (> 15 % among ozanimod-treated subjects in either subgroup). Among subjects who were treated with ozanimod 1 mg, the incidence of TEAEs was higher in the subgroup using corticosteroids at screening than the subgroup not using corticosteroids at screening (74.7% versus 65.3%, respectively). The incidence of infections in the ozanimod 1 mg treatment group was higher in subjects using corticosteroids at screening than in those not using corticosteroids at screening (35.7% versus 25.3%) and higher compared with placebo in both subgroups (16.0% versus 13.0%, respectively). The most frequently reported infections among ozanimod-treated subjects using corticosteroids at baseline were nasopharyngitis, upper respiratory tract infection, and bronchitis; and nasopharyngitis, urinary tract infection, and herpes zoster among subjects not using corticosteroids at baseline. The incidence of serious infections in the ozanimod 1 mg treatment group was low and similar between subjects using and not using corticosteroids at screening (2.4% versus 2.0%, respectively), with no predominant type of serious infection in either subgroup. Overall, similar patterns of TEAEs and SAEs by corticosteroid use at screening were observed for Pool Fm.

Prior anti-TNF use

Pool G comprised approximately twice as many subjects who reported no prior anti-TNF use (364 placebo and 782 ozanimod 1 mg subjects) compared with prior anti-TNF use (144 placebo and 376 ozanimod 1 mg subjects), and exposure to ozanimod 1 mg was longer in the subgroup with no prior anti-TNF exposure relative to the subgroup with prior anti-TNF exposure (approximately 21 months versus 15.5 months, respectively). Within subgroups, the pattern of TEAEs was generally consistent with that of the overall Pool G population. However, the overall incidence of TEAEs was greater among subjects who had prior anti TNF exposure relative to those without prior anti-TNF exposure for both ozanimod 1 mg (75.5% versus 65.5%, respectively) and placebo group (45.1% versus 39.0%, respectively) due to greater incidences of commonly reported TEAEs across multiple SOCs, including Infections and Infestations, Gastrointestinal Disorders, Musculoskeletal and Connective Tissue Disorders, General Disorders and Administration Site Conditions, and Skin and Subcutaneous Tissue Disorders (35.4%, 27.1%, 16.8%, 16.0% , and 14.4% versus 26.1%, 18.3%, 9.0%, and 7.4%, 7.2%, respectively).

The incidence of serious infections was slightly higher among subjects with prior anti-TNF exposure than those without prior anti-TNF exposure in both the ozanimod 1 mg treatment group (3.2% versus 1.7%) and the placebo group (2.1% versus 1.1%); no pattern of infections was seen.

Use in pregnancy and lactation

In reproductive toxicity studies presented in the MS submission, embryofoetal development was adversely affected by maternal treatment with ozanimod, with low (rats) or no (rabbits) safety margins based on comparison of systemic exposures to total active drug, resulting in embryolethality and teratogenicity (generalised oedema/anasarca and malpositioned testes in rats, malpositioned caudal vertebrae and malformations of the great vessels in rabbits). The vascular findings in rats and rabbits are consistent with the expected S1P1 pharmacology.

Pre- and post-natal development was not affected by ozanimod administration up to the 5.6-fold the systemic exposure to total active drug at the maximum human dose of 0.92 mg ozanimod. Ozanimod and metabolites were present in rat milk.

Throughout the ozanimod clinical development program, pregnant and lactating women were excluded from study participation. Female subjects of reproductive potential were required to use protocol-approved, effective means of contraception for the duration of their participation in ozanimod studies.

As of 31 Mar 2020, a total of 75 pregnancies have been reported in the safety database in subjects treated with ozanimod (n = 55) or their partners (n = 20) across all indications (UC, CD, and MS) and including 1 healthy volunteer. All pregnancy exposures for study subjects occurred during the first trimester and subjects discontinued study medication promptly, with the exception of subjects who elected termination and did not discontinue study medication. No teratogenicity was observed. Of the 55 subject pregnancies, 24 resulted in live birth of a healthy infant, 2 resulted in live birth with congenital abnormality, 3 resulted in premature delivery, 8 resulted in spontaneous early loss, 12 subjects underwent elective abortion, and 6 subjects had not yet delivered. Among 20 partner pregnancies, 7 resulted in live birth of a healthy infant, 2 resulted in live birth with congenital abnormality not considered to be teratogenic effects, 5 resulted in premature delivery, 1 resulted in spontaneous early loss, and 1 was ongoing.

Overdose

Unintentional overdose of ozanimod 1 mg, defined as any dose given to, or taken by, a subject that exceeded the dose described in the protocol, was reported in approximately 60 subjects in RPC01 3101 and RPC01-3102. Of these, there were 3 subjects who experienced TEAEs (all nonserious) associated with the overdose of ozanimod 1 mg in RPC01 3101: one Subject experienced LFT increased, which led to discontinuation; another Subject experienced abdominal distention, which did not lead to any action taken with study drug (the subject withdrew from the study); and one Subject experienced ECG QTcF prolongation with dizziness, which resolved on treatment.

Withdrawal and rebound

The long half-life of the drug's active metabolites leads to a very slow decline in drug activity. Thus, discontinuation of therapy does not result in an abrupt decline in S1P agonist activity.

To evaluate disease rebound or relapse effects following discontinuation of ozanimod 1 mg treatment in the UC clinical program, an assessment of TEAEs with onset after the last dose of ozanimod 1 mg was performed on Pool G and Pool D.

In **Pool G**, 78 of 488 subjects (16.0%) in the ozanimod 1 mg treatment group and 5 of 48 subjects (10.4%) in the placebo treatment group had an TEAE with an onset after the last dose of study drug. The

higher frequency of subjects having TEAEs between treatment groups can be attributed to the disparate observation periods (amounting to 6.6 and 80.7 patient years for the placebo and ozanimod 1 mg treatment groups after the last dose of study drug). In Pool G, TEAEs that occurred in ≥ 0.5% of subjects in the ozanimod 1 mg treatment group after the last dose of study drug were ulcerative colitis (2.9%), anaemia (1.6%), headache (0.8%), hypertension (0.8%), nausea (0.8%), vomiting (0.6%), ALT increased (0.6%), blood alkaline phosphatase increased (0.6%), and nasopharyngitis (0.6%). Similar findings were observed in **Pool D**, albeit at a lower overall frequency.

According to the Applicant, there was no evidence of severely increased disease activity in subjects who were re-randomized to placebo in the Phase 3 UC study.

Safety related to drug-drug interactions and other interactions

It is noted that the patients in the main studies were not allowed to have any concomitant immunosuppressant (e.g. thiopurines). Since thiopurines are a cornerstone in the treatment of moderate/severe UC, this information is important for the prescriber and updated information on the concomitant use of immunosuppressive therapies that should be avoided and the limited long term data are introduced (section 4.4).

Discontinuation due to adverse events

The incidence of TEAEs leading to study drug discontinuation and/or study withdrawal was low and similar between the ozanimod 1 mg and placebo treatment groups during the **Pool Fi** (3.0% versus 2.8%, respectively) and between the ozanimod 1 mg – ozanimod 1 mg and ozanimod 1 mg – placebo treatment groups during the RPC01-3101 Maintenance Period **Pool Fm** (1.3% versus 2.6%, respectively). In both periods, ulcerative colitis (worsening/flare) was the only TEAE leading to discontinuation of more than 1 subject, at a lower incidence with ozanimod 1 mg than placebo in both **Pool FI** and **Pool Fm.**

Post marketing experience

Not applicable; ozanimod was not commercially available at the time of the safety cut-off (31 Mar 2020).

2.5.1. Discussion on clinical safety

The safety database available for the proposed UC indication is generally considered acceptable. Overall exposure with the intended maintenance dose of 1 mg ozanimod comprises a total of 1158 UC subjects and 4057 subjects across all indications. 868 UC subjects have been exposed for ≥ 6 months, 716 subjects for ≥12 months and 322 subjects for ≥ 24 months. In order to mitigate fist dose cardiac effects, a one-week dose escalation was applied in the UC studies in line with the titration proposed and approved for the MS indication.

However, available efficacy and safety data in the MS indication in subjects > 55 years is still limited. From the hitherto provided analyses of safety data in UC subjects ≥ 65 years, which are mainly based on a cut-off age of 40 years, only a small group of patients >65 is included.

Evaluation of safety is focused to the controlled experience with ozanimod 1 mg compared to placebo during the induction period (Pool Fi) as well as the placebo-controlled randomised withdrawal period of study 3101 (Pool Fm). In addition, long-term safety in UC was assessed based on overall UC Pool G, Pool D comprising all indications was used for the evaluation of rare events.

Safety data derived from Pool Fi are generally adequate in order to evaluate adverse effects of ozanimod associated with treatment initiation. However, the duration of the induction period, i.e. total treatment including titration of 9 weeks (study 202) and 10 weeks (study 3101), respectively, is too short, in order to evaluate any long-term effects. Of note, the nadir of mean ALC reduction is expected to have been reached only towards the end of the induction period. Evaluation of the frequency of TEAEs during the 42-week maintenance Pool Fm is limited due to prior ozanimod treatment of subjects, who have been re-randomised to placebo, inclusion of subjects with prior open-label ozanimod treatment in the blinded ozanimod-ozanimod group, as well as different exposure rates across treatment groups (approx. 166 SY in the ozanimod-ozanimod and 134 in the ozanimod-placebo group, respectively). The small placebo group of study 3101 (n=69) with a short exposure was not included in Pool Fm.

In study 202, randomised subjects were continuously treated with the assigned treatment (ozanimod 1mg, 05 mg or placebo, respectively). However, overall treatment duration comprised 33 weeks only (9 weeks during induction and 24 weeks maintenance treatment, respectively). While the induction period of this study was included in Pool Fi, the maintenance period of this study was only included in the uncontrolled UC Pool G due to differences in design and duration of studies 202 and 3103, respectively. Nevertheless, evaluated on its own, no new safety signals derived from the controlled maintenance part of this study.

Comparability of frequencies of TEAEs across MS and UC studies is limited due to differences in study duration and design. However, taking the above limitations into account, the safety profile of ozanimod appears largely similar in the MS and UC indication.

The main safety issues identified in the MS clinical program were small and transient decreases in heart rate, mainly during the first 8 days of dose titration and symptomatic in few cases only (brady-arrhythmias), macular oedemas, overall reversible increases in liver enzymes and reversible decreases in ALC, as well as an increased risk of herpes zoster infections with long-term treatment and a disproportionate higher incidence in malignancies with ozanimod vs. IFN ß-1a. The long-term risk for serious or opportunistic infections and malignancies could not sufficiently be characterised within the limited period of clinical MS studies and thus prompted pharmacovigilance activity post-approval.

Apart from a higher incidence of Herpes zoster ("common" instead of "uncommon") and addition of Herpes simplex as an ("common") event, no relevant changes to the safety profile of ozanimod are proposed to be added by the Applicant within this variation procedure. These changes are based on the findings from controlled maintenance Pool Fm with Herpes zoster being reported in 2.2% of ozanimod vs. 04% placebo subjects, which is also consistent with the reporting rate of Herpes zoster in (long-term) Pool G in ozanimod treated subjects of 2.2%. Herpes simplex was reported (per logical grouping with PT oral herpes or herpes simplex) in 1.7% of ozanimod subjects (vs. 0 placebo subjects) in the maintenance period of study 3101 (Pool Fm).

In the UC studies, the most frequently reported TEAEs, which occurred at a ($\geq$ 1%) higher frequency compared with placebo during the induction period (Pool Fi) are in line with the findings in the MS indication, apart from nausea, pyrexia and arthralgia. These are common complaints in patients with UC and differences in ozanimod vs. placebo subjects were still small (< 2% each). Further, nausea, pyrexia and arthralgia were not among the most frequent TEAEs, which occurred at a ($\geq$ 1%) higher frequency in Pool Fm.

However, during the controlled maintenance period (Pool Fm), the TEAEs which occurred at a ($\geq$ 1%) higher frequency in the ozanimod (ozanimod-ozanimod) compared to the placebo (ozanimod-placebo) group and are not yet included in 4.8 of the SmPC were headache (3.5% vs. 0.4%) and peripheral oedema (2.6% vs. 0%). Only 9 of 19 cases of headache in the ozanimod group of Pool Fi were mild, and headache occurred also with higher frequency (6.0% vs. 1.6%), but also with higher incidence rate (IR, 37.6 vs. 32.5) in ozanimod-ozanimod vs. ozanimod-placebo subjects in Pool G.

In addition, hot flush occurred on Day 1 in 2 ozanimod but in no placebo subjects in the UC studies (Pool Fi). Of note, hot flush also occurred in the active controlled phase 3 RMS studies (Pool A1) likewise on Day 1 with higher frequency in ozanimod (0.2%) vs. placebo subjects (0.1%).

No new safety signal arose from analyses of SAEs in Pool Fi and Pool Fm. Nevertheless, there appeared some imbalance with regard to SAEs of ischaemic stroke derived from Pool G with an incidence of 4 (0.3%) in ozanimod vs. 0 placebo subjects and corresponding IRs per 1000 SY of 2.1 vs. 0, respectively. Subjects with clinically relevant cardiac conditions were excluded from the UC studies. No increased risk of thromboembolic events was derived from the MS development program of ozanimod and ulcerative colitis itself is associated with a higher risk of venous and arterial thromboembolism.

The incidence of TEAEs leading to study drug discontinuation and/or study withdrawal was low and similar between the ozanimod 1 mg and placebo treatment groups in Pool Fi (3.0% versus 2.8%, respectively) and between the ozanimod 1 mg – ozanimod 1 mg and ozanimod 1 mg – placebo treatment groups in Pool Fm (1.3% vs. 2.6%, respectively).

As of data cut-off (31 Mar 2020), 14 deaths occurred in the overall ozanimod program across all indications, 7 of which have already been assessed during the marketing authorisation procedure for MS. While a numerical imbalance of death cases was found in the MS study program (2 death cases in Pool A1 occurring on ozanimod vs. none on placebo), death cases the UC indication occurred only during open-label treatment with ozanimod (N=3). In line with the findings from the death cases reviewed during the marketing authorisation of ozanimod for MS, no common pattern could be derived from the additional death cases provided with this variation. Two cases might involve immunosuppressant properties and two cases were reported in the context of malignancies.

Frequency and type of cardiac TEAEs (mainly bradycardia during treatment initiation and blood pressure effects with continued treatment) reported in the UC studies appear in line with the known safety profile of ozanimod. Patients with severe cardiac pre-morbid conditions were excluded from clinical studies in both, the MS and UC indication, and are likewise to be excluded from treatment with ozanimod (contraindication in section 4.3). In other less severe instances of cardiovascular impairment, cardiologist advice should be obtained prior to initiation of treatment. The proposed SmPC was amended in order to correctly inform about an increase in diastolic blood pressure observed in UC subjects in section 4.8, which is in line with the increase in DBP described for the MS indication.

The hepatic effects of ozanimod established for the MS indication, i.e. increase in liver function tests, typically ALT ≥3x ULN and GGT>2.5x ULN, occurred likewise in the UC population. No severe cases of DILI or confirmed cases of Hy's law occurred in the UC studies. Patients with severe hepatic impairment (Child-Pugh class C) were not studied and treatment with ozanimod is thus contraindicated in such patients. Severe liver injury is a potential risk in the RMP. However, increased AST, which occurred almost congruently with ALT elevations but generally at a smaller magnitude and has also been reported as TEAE in the UC studies (e.g. 1.2% in ozanimod vs. 0% in placebo subjects in Pool Fi) and was added to section 4.8 of the SmPC under selected adverse drug reactions.

Consistent with the MS program, TEAEs of infections in the UC program were mainly characterised by non-serious infections of the upper respiratory tract (nasopharyngitis, pharyngitis, viral respiratory tract infection). During long-term treatment (Pool G), the incidence of serious infections was 2.2% with ozanimod and 1.4% with placebo. Opportunistic infections were more frequently reported with ozanimod compared with placebo with an incidence of 2.4% vs. 0.4% (and an IR of 14.8 vs. 8.1, respectively), and were predominantly cases of Herpes zoster. As of the data-cut off, there were no cases of PML or cryptococcal meningitis SDEIs in the entire ozanimod development program.

Overall, based on the UC studies, herpes zoster, headache and peripheral oedema ADRs in section 4.8 of the SmPC are introduced with a frequency of common.

From the UC program, no new safety signals arose with regard to macular oedema, which concerned exclusively subjects with pre-existing risk factors, Posterior Reversible Encephalopathy Syndrome (PRES, no new cases) and pulmonary effects, respectively.

There is a potential risk of malignancies with ozanimod. From the controlled UC program as well as from the incidence rates (IR) provided for the overall UC studies no imbalance was found with regard to all malignancies and non-cutaneous malignancies, respectively. However, interpretability of controlled maintenance (Pool Fm) data with regard to malignancies is limited by the fact, that subjects re-randomised to placebo were treated with ozanimod for approx. 10 weeks prior to the maintenance study phase. Few patients (n=69) in the maintenance part of study 3101 were exclusively treated with placebo and no malignancy was observed within this group. However, the extent of safety follow up in this subgroup was comparably low and these subjects were not included in Pool Fm.

The overall incidence of any malignancy as well as colorectal cancer (CRC) malignancies (3 cases in approx. 2000 SY) in the UC study program was in the range of epidemiological UC data. Furthermore, no cluster of non-cutaneous malignancies or lymphoma was found and there was no apparent increase in IR with greater exposure duration. Half of the neoplasms reported with ozanimod in UC studies were non-melanoma skin malignancies with basal cell carcinoma presenting as the most common skin neoplasm congruent with the findings in the MS population. Of note, cutaneous malignancies, i.e. 5 cases (0.4%) of basal cell carcinoma and 1 case (< 0.1%) of squamous cell carcinoma solely occurred in ozanimod but not in placebo subjects in Pool G.). While there is considerable variability across countries, the IRs of NMSC in the UC study program (2.6 for basal cell carcinoma and 0.5 for squamous cell carcinoma, respectively) were also generally within the range reported in literature. However, a warning has been introduced in section 4.4 as follows:

In patients treated with ozanimod in UC controlled clinical studies one patient (0.2%) had squamous cell carcinoma of the skin, in the induction period, and one patient (0.4%) had basal cell carcinoma, in the maintenance period. There were no cases in patients who received placebo.

UC associated CRC is considered a serious complication of the disease and colorectal cancer (UC indication)" is now included as an important potential risk in the RMP upon request from PRAC.

The RMP version 2.1 submitted by the MAH on 30th September is considered approvable and represents a consolidated version between the last approved version with the recent PML variation and the versions assessed across this procedure.

The ongoing long-term studies are deemed essential to further address the potential risk of malignancies.

The findings derived from the UC studies with regard to mean reduction in ALC from baseline, the incidence of CTCAE Grade 4 ALC reductions < 0.2 x 109/L, as well as ALC recovery were in largely in line with those seen in the MS studies. However, as the nadir of mean decrease in ALC is expected to have been reached only towards the end of the induction period, the incidence of Grade 4 ALC decrease to <0.2 x 10^9/L in SmPC section 4.8 was corrected from '< 3%' to '3%' (as derived from analyses of Pool Fm).

2.5.2. Conclusions on clinical safety

The safety database available for the proposed UC indication is considered acceptable and the posology including titration proposed for UC is in line with the one established for MS. Available data in the MS indication in subjects > 55 years is still limited. From the provided analyses of limited safety data in UC subjects ≥ 65 years, no indication of a worse safety profile in the elderly is evident but data is very limited.

The clinical safety profile of ozanimod in UC based on the available short- and long-term study data are considered to be manageable by applying the proposed risk minimisation measures in the product information together with continued long-term safety data collection post-marketing.

Although, comparability of the frequencies of adverse events across indications is limited due to differences in design and duration of studies, the safety profile derived from the UC study program appears largely in line with that of the MS clinical program. A higher incidence of Herpes zoster (frequency "common" instead of "uncommon"), addition of Herpes simplex, headache and peripheral oedema as "common" event are introduced.

The case of a squamous cell carcinoma is also introduced in section 4.4 as well as recommendation to avoid concomitant use of antineoplastic, non-corticosteroid immunosuppressive (e.g. azathioprine and 6-mercaptopurine in UC), or immune-modulating therapies with ozanimod

The RMP (version 2.1) is also updated to reflect the safety profile in patients with UC, in particular CRC as an important potential risk and acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Ozanimod is being approved for UC patient, which represent a different patient population than the current indication (RRMS). indication. Therefore, the PRAC/CHMP considered that an increase in PSUR frequency is warranted to monitor adequately the safety profile of mepolizumab in the new patient population. The PSUR frequency is therefore increased to 6 monthly-basis. The MAH should plan at least a further 6-month DLP period after the next December 2021 submission.

Based on the above considerations, the CHMP is of the opinion that the already existing entry in the EURD list for mepolizumab needs to be amended as follows: the PSUR cycle for the medicinal product should follow a half-yearly cycle. The next data lock point will be 19 Nov 2021.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application. The CHMP received the following PRAC Advice on the submitted Risk Management Plan: The PRAC considered that the risk management plan version 2.1 is acceptable. The CHMP endorsed this advice without changes.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Serious opportunistic infections including PML	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, and 4.8. PL Sections 2 and 4. Ozanimod is contraindicated in patients with severe active infections, active chronic infections such as hepatitis and tuberculosis (SmPC Section 4.3, PL Section 2). Recommendation to discontinue ozanimod if PML is confirmed is included in SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** ADR follow-up form for PML (see Annex 4). External expert review of potential PML cases. **Additional pharmacovigilance activities:**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Recommendation that discontinuation of ozanimod be considered in case of opportunistic infection is included in SmPC Section 4.4. Recommendations to measure blood cell counts prior to and during treatment with ozanimod, advice to monitor patients at risk of infection, clinical symptoms or MRI findings that physicians should be vigilant for signs suggestive of PML, treatment instructions in cases suggestive of PML and treatment discontinuation if PML is confirmed are provided in SmPC Section 4.4 and PL Section 2. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.	UC PASS ORION study (MS patients)
Important Potential Risks		
Symptomatic bradycardia	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1. PL Sections 2, 3 and 4. Ozanimod is contraindicated in patients at risk of symptomatic bradycardia (SmPC Section 4.3, PL Section 2). Initial dose escalation regimen for ozanimod and advice regarding re-initiation of therapy following treatment interruption is described in SmPC Section 4.2 and PL Section 3. Recommendation that an ECG in all patients should be obtained prior to treatment initiation with ozanimod to determine whether any pre-existing cardiac abnormalities are present is included in SmPC Section 4.4 and PL Section 2. Warning that ozanimod may result in transient reductions in HR is included in SmPC Sections 4.4 and 5.1. Initiation pack covering dosing for the first 7 days, or in the case of resuming treatment following treatment interruption. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** UC PASS ORION study (MS patients)
Severe liver injury	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2. PL Sections 2 and 4. Ozanimod is contraindicated in patients with severe hepatic impairment (SmPC Section 4.3, PL Section 2). Recommendations to measure transaminase and bilirubin levels before treatment initiation, for liver function monitoring and treatment discontinuation if significant liver injury is confirmed, are included in SmPC Section 4.4. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) UC PASS ORION study (MS patients) Long-term follow-up of Study RPC01-3001 (MS patients)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Macular oedema	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8. PL Sections 2 and 4. Recommendations for treatment of patients with risk factors for macular oedema (SmPC Section 4.4) and treatment discontinuation if significant macular oedema is confirmed are described in SmPC Section 4.4. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) UC PASS ORION study (MS patients) Long-term follow-up of Study RPC01-3001 (MS patients)
Malignancy	**Routine risk minimisation measures:** SmPC Sections 4.3 and 4.4. PL Section 2 Ozanimod is contraindicated in patients with active malignancies (SmPC Section 4.3, PL Section 2). Advice regarding monitoring of patients with concurrent conditions or known factors, such as previous antineoplastic non-corticosteroid immunosuppressive therapy, is included in SmPC Section 4.4. Recommendation that patients treated with ozanimod should be cautioned against exposure to sunlight without protection. Warning that patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy (SmPC Section 4.4). **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Reports of NMSC will be discussed in the PSUR **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) UC PASS ORION study (MS patients) Long-term follow-up of Study RPC01-3001 (MS patients)
PRES	**Routine risk minimisation measures:** SmPC Section 4.4. PL Section 2 Recommendation to discontinue ozanimod if PRES is suspected is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) UC PASS ORION study (MS patients) Long-term follow-up of Study RPC01-3001 (MS patients)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Embryofoetal toxicity in exposed pregnant females	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, 4.6 and 5.3. PL Section 2 Advice for women of childbearing potential to use effective contraception during treatment, and for at least 3 months after ozanimod treatment discontinuation is included in SmPC Sections 4.4 and 4.6, and PL Section 2. Ozanimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception, a negative pregnancy test must be available in women of childbearing potential before starting treatment, and counselling information regarding the serious risk to the foetus (SmPC Sections 4.4 and 4.6, and PL Section 2) and ultrasonography examinations should be provided (SmPC Section 4.6 and PL Section 2). Instruction not to use ozanimod during pregnancy, or in women of childbearing potential not using effective contraception, and advice for women of childbearing potential, are provided in PL Section 2. If a woman becomes pregnant during treatment, treatment should be discontinued, and the woman should receive pre-natal monitoring (SmPC Section 4.6 and PL Section 2). **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide – Pregnancy specific patient reminder card.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** ADR follow-up form for pregnancy (see Annex 4). **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) ORION study (MS patients) Long-term follow-up of Study RPC01-3001 (MS patients)
Thrombo-embolic events	**Routine risk minimisation measures:** Use of ozanimod is contraindicated in patients who in the previous 6 months had a MI, unstable angina pectoris, stroke/TIA, decompensated heart failure (requiring inpatient treatment), or NYHA Class III/IV heart failure (SmPC Section 4.3). Blood pressure should be regularly monitored during treatment with ozanimod (SmPC Section 4.4). PL Section 2 **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Thromboembolic events will be presented in each PSUR **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) UC PASS ORION study (MS patients) Long-term follow-up of Study RPC01-3001 (MS patients)
Risk of colorectal cancer (UC indication)	**Routine risk minimisation measures:** SmPC Sections 4.3 and 4.4. PL Section 2 Ozanimod is contraindicated in patients with active malignancies (SmPC Section 4.3, PL Section 2). Advice regarding monitoring of patients with concurrent conditions or known factors, such as previous antineoplastic non-corticosteroid immunosuppressive therapy, is included in SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) UC PASS

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None proposed.	
Missing Information		
Long-term cardiovascular effects	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) UC PASS ORION study (MS patients) Long-term follow-up of Study RPC01-3001 (MS patients)
Effects following withdrawal of drug	**Routine risk minimisation measures:** SmPC Section 4.4 PL Sections 2 and 3 Warning regarding the potential for severe exacerbation of disease after ozanimod discontinuation and advice on monitoring and treatment is included in SmPC Section 4.4 and PL Sections 2 and 3. Advice to monitor patients for infections after ozanimod discontinuation is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Cases of rebound effects will be presented in each PSUR (by indication) **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) UC PASS ORION study (MS patients) Follow-up after discontinuation in study RPC01-3001 (MS patients)
Use in patients over 55 years	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) UC PASS ORION study (MS patients). Long-term follow-up of Study RPC01-3001 (MS patients).

2.7. Update of the Product information

As a consequence of this new indication sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and Annex IID are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes throughout the product information.

In addition, an update of sections 4.4 and 4.5 of the SmPC in order to update the current SmPC description about PK interaction with BCRP inhibitors based on the study report from a drug interaction study with cyclosporine (RPC-1063-CP-001).

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: limited changes introduced.

2.8. Therapeutic Context

2.8.1. Disease or condition

The indication applied for is for the induction and maintenance of remission of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response with, loss of response to, or were intolerant to either conventional therapy or a biologic agent. The treatment is by the oral route.

UC is a chronic, relapsing, inflammatory disease of the colon characterized by alternating episodes of remission and spontaneous relapse. The primary treatment goal is to induce remission and then to maintain this state. As mentioned earlier in this report, this treatment paradigm is currently proposed to be changed to a "treat-to-target" approach, which requires continuous monitoring and therapeutic adjustments with an aim to achieve the targets of full resolution of symptoms and mucosal and histological normalisation of the mucosa in order to protect patients from complications and the need for surgery. The "therapeutic adjustment" therefore requires a potential high variety of treatment options which can address the partial unmet medical need based on the fact that available treatments have relevant rates of missing or minor clinical and endoscopic response and remission rates only.

Ozanimod is approved for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features.

The mechanism by which ozanimod exerts therapeutic effects in MS and UC is unknown but may involve the reduction of lymphocyte migration into the central nervous system (CNS) and intestine. The ozanimod-induced reduction of lymphocytes in the peripheral circulation has differential effects on leucocyte subpopulations, with greater decreases in cells involved in the adaptive immune response. Ozanimod has minimal impact on cells involved in innate immune response, which are key components of immunosurveillance.

2.8.2. Available therapies and unmet medical need

The treatment paradigm for UC has historically comprised an initial treatment for acute disease, with the goal of inducing a state of clinical remission, followed by a therapeutic intervention to maintain remission. Generally, patients presenting with mild to moderate disease activity are initially administered an anti-

inflammatory agent such as a 5-aminosalicylate (5-ASA) derivative, with or without concurrent corticosteroids. Patients who fail to respond to initial therapy or who present with moderate to severe disease activity require treatment with agents indicated for moderate to severe disease such as immunomodulators/-suppressives and biologic therapy. For nearly 2 decades, biological therapies were dominated by anti-tumor necrosis factor (TNF)-α agents but have recently included anti-integrin and anti–interleukin (IL)-12/IL-23 antibodies, as well as JAK inhibitors (tofacitinib).

Although biological therapies have led to substantial improvements in the care of patients with UC and have become an integral part of standard therapy, not all treated patients benefit from these therapies. Depending on the duration of therapy and the clinical endpoints chosen, approximately one-third of patients do not respond after initiation of biological therapy (primary nonresponse). Among patients who initially respond to treatment with biologics, 30% to 50% eventually stop responding (secondary nonresponse), resulting in exposure to potential side effects and toxicities without durable clinical benefit. These findings highlight the partial unmet medical need still present in these patients. In recent years there appears to be a paradigm shift in the treatment of IBD (including UC) from the "induction and maintenance" to a "treat to target approach" where the final aim of treatment is the prevention of abdominal surgery/colectomy. The risk of surgery is still considered substantial with about 11-12% of the patients receiving surgery within 5, and 15-16% within 10 years of disease duration. The paradigm shift is expressed as moving from the aim to induce and maintain clinical remission, to a full resolution of the inflammatory signs within the mucosa, expressed as endoscopic healing or histological normalisation, which both have been identified to be predictive factors of the avoidance of surgery.

Despite the advances in therapies for patients, there remains a significant need for UC treatments with novel mechanisms and an acceptable safety profile that can be administered orally to patients who do not respond to, or have an inadequate response to conventional therapy or who had primary or secondary nonresponse to anti-TNF or other biologic therapy or were intolerant to either treatment.

2.8.3. Main clinical studies

The main evidence for the demonstration of efficacy comes from the pivotal phase 3 study RPC01-3101, which was a multi-centre, multi-national, randomised, double-blind, placebo-controlled efficacy and safety study in patients with moderate to severe ulcerative colitis. The study was divided into two parts with an induction phase of 10 weeks, and a maintenance phase of additional 42 weeks. The induction phase included two different cohorts of patients, one of which was randomised 2:1 to receive ozanimod 1 mg or placebo (n=429 and 216), and the other of which received open-label treatment for 10 weeks (n=367). This latter cohort (as well as the 2:1 randomisation) was obviously implemented in order to achieve a sufficient number of patients reaching clinical response at the end of the 10-week treatment period.

Patients were included into this trial based on the presence of moderate to severe disease for at least 3 months, and based on a 6-12 4-component Mayo score with additional requirements for endoscopic score (at least 2) and the two symptoms rectal bleeding and stool frequency abnormality (at least 1). Patients were requested to receive either 5-aminosalicylate and/or corticosteroid treatment at inclusion, the additional option of having received previously either biological or immunosuppressant treatment with an at least 8-week duration and having not or only insufficiently responded (or experienced tolerability problems) with these treatments. Patients with acute severe colitis were not admitted to the study.

Patients to be included into the maintenance phase of the study had to achieve "clinical response" which was defined both on the total (4-component) Mayo Score as well as the 3-point Mayo score (excluding physician's global assessment). Response usually comprised a relevant reduction of the respective score with requirements for all components included.

For the maintenance phase, patients were randomised 1:1 to be treated with either placebo or ozanimod 1 mg daily (n=227 and 230). The treatment continued for 42 weeks in order to make up a total treatment duration of 52 weeks.

Patients not reaching response during the induction period (both cohorts), patients experiencing relapse during the maintenance period, and patients reaching the end of the 52-weeks treatment period could enter an open-label long-term extension study.

2.9. Favourable effects

At the end of the induction period, the percentage of patients achieving the primary endpoint "clinical response" (defined as Rectal Bleeding subscore = 0 and Stool Frequency subscore ≤ 1 (and a decrease of ≥ 1 point from the Baseline Stool Frequency subscore) and Endoscopy subscore ≤ 1; hence being a composite of two symptoms and mucosal improvement) was 18.4% in the active treatment group and 6.0% in the placebo group. This difference was highly statistically different (p<0.0001).

The key secondary endpoints (tested hierarchically with full type I error control showed rates of clinical response of 47.8% and 25.9%, endoscopic improvement of 27.3% and 11.6%, mucosal healing of 12.6% and 3.7, respectively. Other secondary endpoints such as histologic remission and symptomatic remission (defined post-hoc) showed rates of 18.2% and 7.4%, and 37.5% and 18.5% for the active and placebo groups, respectively. All results were consistently highly statistically significant. The results for the open-label induction cohort were very much concordant with the results achieved in the randomised active treatment group of cohort 1. Favourable effects were also seen for part of the domains of quality of life, for work productivity, as well as for the biomarker calprotectin.

For the maintenance period, the results for the primary endpoint "clinical remission" (similar definition as above) showed a rate of 37.0% for active treatment and 18.5% for placebo.

A range of "key secondary endpoints" were included with full type I error control which were clinical response, endoscopic improvement, maintenance of remission (in those in remission when entering the maintenance period), corticosteroid free remission, mucosal healing, and durable remission (proportion of subjects with durable clinical remission defined as clinical remission at Week 10 and at 52 weeks in all patients who entered the maintenance phase), which all demonstrated superiority of the active treatment, similar to the "other" secondary endpoints histologic remission and symptomatic remission (defined post-hoc).

The rate of relapse was higher in the placebo group as compared to the active treatment group (35.7% vs. 13.5%). All results were highly statistically significant with the majority of p-values being <0.0001 and the "highest" p-value of 0.0025. Statistically significant effects were shown for part of the QoL domains, and work productivity, and also for part of the health care utilisation evaluation. Superiority was also demonstrated for the biomarker calprotectin.

Both parts of the study were evaluated with relevant subgroup analyses, of which the most important were those used as stratification factors at inclusion (corticosteroid use and prior use of biologics/anti-TNFs). For these subgroups, as well as relevant other subgroups (e.g. age, severity of baseline disease, years since diagnosis) highly consistent and statistically significant differences between active treatment and placebo could be demonstrated. The magnitude of effects, however, was slightly smaller in anti-TNF experienced subjects, compared to those not having received such treatments.

Consistency of results was also demonstrated across a couple of other factors (e.g. region of the world, race, etc) but due to smaller sizes of the subgroups, statistical significance was not achieved in all of them.

Analysis of the main results with a couple of so-called sensitivity analyses (e.g. using the PP population or using different imputation methods) also showed highly consistent results.

Additionally PK interaction with BCRP inhibitors based on a drug interaction study with cyclosporin (RPC-1063-CP-001) have been submitted and an update of sections 4.4 and 4.5 of the SmPC is agreed to inform prescribers on the absence of interaction in case of co-administration of ozanimod with ciclosporin.

2.10. Uncertainties and limitations about favourable effects

The applicant has conducted only one pivotal study for the induction of remission, whereas regulatory expectations usually request the presentation of two such studies. However, the applicant also presented a relatively robust phase 2 study (demonstrating statistically significant superiority of the dose of 1 mg daily in the primary endpoint) which would fulfil the requirements of two pivotal studies. Furthermore, the results achieved may be considered to fulfil the increased requirements on data quality, validity and statistical robustness for applications based on one single pivotal study. In addition, the open-label data provided (cohort 2 in the pivotal study and the open-label extension studies) also partly address this concern.

The applicant has also included the wide variety of heterogeneous patients failing on previous treatments, which encompassed the huge variety of conventional immunosuppressants as well as biologics, when usually a separate trial in these "second line" and "third line" populations would be recommended. However, the level of consistency demonstrated with the trials could be considered sufficient to alleviate this concern. There is however some caveat related to the subgroups analysed, which did not display full consistency, but this may due to the limited number of included patients. Consistency has also been demonstrated in patients who failed other therapies historically, or a time of inclusion current both for biologics and conventional immunosuppressants.

The study has also included patients up to the age of 75 only (as per inclusion criteria). The number of patients older than 65 is rather limited, introducing some uncertainty with regard to efficacy in this population. Although UC is a disease occurring at younger age, it is increasingly relevant also for an elderly patient population above 65 years of age. Respective warnings on the paucity of data in the elderly have been included in the product information.

2.11. Unfavourable effects

The safety database available for the proposed UC indication is generally considered acceptable. Overall exposure with the intended maintenance dose of 1 mg ozanimod comprises a total of 1158 UC subjects and 4057 subjects across all indications. 868 UC subjects have been exposed for $\geq$ 6 months, 716 subjects for $\geq$12 months and 322 subjects for $\geq$ 24 months. In order to mitigate fist dose cardiac effects, a one-week dose escalation was applied in the UC studies in line with the titration proposed and approved for the MS indication. Initiation of ozanimod treatment using dose titration over 7 days is mechanistically based on the successive desensitization of G-protein-coupled inwardly rectifying potassium channels via down-modulation of S1P1 receptors and was associated with a transient reduction in HR.

In line with MS studies, treatment with ozanimod in UC resulted in a small average increase in systolic (SBP) and diastolic (DBP) blood pressure over placebo (mean increase in SBP was 5.1 mm Hg in the ozanimod-ozanimod group and 2.3 mm Hg in the placebo-ozanimod group and mean increase in DBP was 2.2 mm Hg in the ozanimod-ozanimod group and 0.8 mm Hg in the placebo-ozanimod group at week 52 compared to baseline); similar findings resulted from Pool Fi after 10 weeks of treatment.

The main safety issues identified in the MS clinical program were small and transient decreases in heart rate, mainly during the first 8 days of dose titration and symptomatic in few cases only

(bradyarrhythmias), macular oedemas, overall reversible increases in liver enzymes and reversible decreases in ALC, as well as an increased risk of herpes zoster infections with long-term treatment and a disproportionate higher incidence in malignancies with ozanimod vs. IFN ß-1a. The long-term risk for serious or opportunistic infections and malignancies could not sufficiently be characterised within the limited period of clinical MS studies and thus prompted pharmacovigilance activity post-approval.

The hepatic effects of ozanimod established for the MS indication, i.e. increase in liver function tests, typically ALT $\geq$3x ULN and GGT>2.5x ULN, occurred likewise in the UC population. No severe cases of DILI or confirmed cases of Hy's law occurred in the UC studies. Patients with severe hepatic impairment (Child-Pugh class C) were not studied and treatment with ozanimod is thus contraindicated in such patients. Severe liver injury is a potential risk in the RMP. However, increased AST, which occurred almost congruently with ALT elevations but generally at a smaller magnitude and has also been reported as TEAE in the UC studies (e.g. 1.2% in ozanimod vs. 0% in placebo subjects in Pool Fi) and was added to section 4.8 of the SmPC under selected adverse drug reactions. Patients with severe hepatic impairment (Child-Pugh class C) were not studied and treatment with ozanimod is thus contraindicated in such patients. Severe liver injury is a potential risk in the RMP.

Reductions in lymphocyte counts have, based on the mode of action of ozanimod, expectedly been reported in nearly all patients in the ozanimod 1 mg group. In the UC clinical studies, the incidence of CTCAE Grade 4 ALC reductions < 0.2 x 109/L was 1.1% with ozanimod at the end of Pool Fi period, 3.0% at any time throughout maintenance in the ozanimod-ozanimod group (Pool Fm), and 5.3% in Pool G among subjects who were treated with ozanimod 1 mg. In Pool G, the majority of ozanimod subjects evaluable for on-treatment recovery subsequently recovered to $\geq$ 0.2 x 109/L within 2 weeks. In Pool G, the median time to off-treatment recovery of ALC to the normal range ($\geq$ 1 x 109/L) was 35 days (95% CI 33, 37).

The decrease in ALC due to ozanimod may increase susceptibility to infections. Consistent with the MS program, TEAEs of infections in the UC program were mostly characterized by non-serious infections of the upper respiratory tract. In the controlled UC studies, the incidence of serious infections was low in both treatment groups and numerically higher in the ozanimod 1 mg compared with the placebo group in Pool Fi (0.8% versus 0.4%, respectively) but lower in the ozanimod 1 mg - ozanimod 1 mg treatment group compared with the ozanimod 1 mg - placebo group in Pool Fm (0.9% versus 1.8%, respectively). Opportunistic infections were more frequent with ozanimod compared with placebo with an incidence of 2.4% vs. 0.4% (and an IR of 14.8 vs. 8.1, respectively), and were predominantly cases of Herpes zoster. Most cases of Herpes zoster with ozanimod in Pool G were mild to moderate (96%) and most subjects (88%) continued treatment with ozanimod. Based on the findings from controlled maintenance Pool Fm with Herpes zoster being reported in 2.2% of ozanimod vs. 04% placebo subjects, which is also consistent with the reporting rate of Herpes zoster in (long-term) Pool G in ozanimod treated subjects of 2.2%, the Applicant proposes to increase the frequency of Herpes zoster to common in SmPC section 4.8. None of the subjects with herpes zoster had an ALC < 2 x 109/L.

There is a potential risk of malignancies with ozanimod. From the controlled UC program as well as from the incidence rates (IR) provided for the overall UC studies no imbalance was found with regard to all malignancies and non-cutaneous malignancies, respectively. However, interpretability of controlled maintenance (Pool Fm) data with regard to malignancies is limited by the fact, that subjects re-randomised to placebo were treated with ozanimod for approx. 10 weeks prior to the maintenance study phase. Few patients (n=69) in the maintenance part of study 3101 were exclusively treated with placebo and no malignancy was observed within this group. However, the extent of safety follow up in this subgroup was comparably low and these subjects were not included in Pool Fm. The overall incidence of any malignancy as well as colorectal cancer (CRC) malignancies (3 cases in approx. 2000 SY) in the UC study program was in the range of epidemiological UC data. Furthermore, no cluster of non-cutaneous malignancies or lymphoma was found and there was no apparent increase in IR with greater exposure

duration. Half of the neoplasms reported with ozanimod in UC studies were non-melanoma skin malignancies with basal cell carcinoma presenting as the most common skin neoplasm congruent with the findings in the MS population. Of note, cutaneous malignancies, i.e. 5 cases (0.4%) of basal cell carcinoma and 1 case (< 0.1%) of squamous cell carcinoma solely occurred in ozanimod but not in placebo subjects in Pool G.). While there is considerable variability across countries, the IRs of NMSC in the UC study program (2.6 for basal cell carcinoma and 0.5 for squamous cell carcinoma, respectively) were also generally within the range reported in literature. However, a warning has been introduced in section 4.4.

Overall based on the UC studies, herpes zoster, headache and peripheral oedema ADRs in section 4.8 of the SmPC are introduced with a frequency of common.

As of data-cut off, there were no confirmed cases of PML or cryptococcal meningitis SDEIs in the entire ozanimod development program. PML is included as important potential risk in the RMP.

Similar to what has been found in the MS program, ozanimod led to small reductions in pulmonary function tests (mainly FEV1, FVC, and DLCO) in the UC studies. The median change from baseline for FEV and FVC was approx. 100 mL in the controlled MS studies and below 100 mL in the controlled UC studies.

Ozanimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (COPD) as currently stated in section 4.4 of SmPC.

One case of Posterior Reversible Encephalopathy Syndrome (PRES) was reported in the MS study program. PRES was also found related with S1P receptor modulators. No new case occurred in the UC program.

The receptor affected by ozanimod (Sphingosin-1 Phosphate) is known to be involved in vascular formation during embryogenesis and preclinical studies indicate a clear evidence for teratogenicity in rodents and non-rodents. Due to the risk to the foetus, ozanimod is contraindicated during pregnancy and in women of child-bearing potential not using effective contraception.

2.12. Uncertainties and limitations about unfavourable effects

The following important potential risks have been derived from the development MS program of ozanimod: Symptomatic bradycardia, Severe liver injury, Serious opportunistic infections including progressive multifocal leukoencephalopathy (PML), Macular oedema, Malignancy, Posterior reversible encephalopathy syndrome, Embryofetal toxicity in exposed pregnant females. The safety profile of ozanimod resulting from the UC development program appears to be largely similar to that resulting from the MS clinical program, however comparability of frequencies of TEAEs across MS and UC studies is limited due to differences in study duration and design, which is mainly due to the randomised withdrawal design of UC phase 3 study 3101 and the overall shorter controlled observation period in the clinical UC studies of a maximum of 52 weeks.

Available efficacy and safety data in the MS indication in subjects > 55 years is still limited. From the provided analyses of safety data in UC subjects by age based on a cut-off age of 40 years and 65 years, respectively, no clear indication of a worse safety profile in older patients arises, however, the amount of available data is limited. Therefore, caution is advised in UC patients over 65 years and in MS patients over 55 years of age.

There is a potential risk of malignancies with ozanimod. From the controlled UC program as well as from the incidence rates (IR) provided for the overall UC studies no clear imbalance was found with regard to all malignancies and non-cutaneous malignancies, respectively. However, some imbalance appears to be present for cutaneous malignancies which might be considered relevant despite the longer exposure for

patients treated with ozanimod as compared to those treated with placebo. Malignancies typically observed with broader immunosuppressive therapies, such as lymphomas, have not been reported with ozanimod. Overall, a causal relationship of the malignancies with ozanimod can neither be established nor ruled out at present. UC has a disease specific increased risk of colorectal malignancy. Malignancy is included as potential risk in the RMP. Active malignancies are a contraindication in section 4.3 of SmPC. An increased risk of skin malignancies is labelled for S1P receptor modulators. As such, a dedicated section for Cutaneous neoplasms is included in section 4.4 of the SmPC. The ongoing long-term studies are deemed essential to further address the potential risk of malignancies.

There appeared some imbalance with regards to SAEs of ischaemic stroke derived from Pool G with an incidence of 4 (0.3%) in ozanimod vs. 0 placebo subjects and corresponding IRs per 1000 SY of 2.1 vs. 0, respectively which required further clarification. It can be seen that in UC subjects, apart from thrombophlebitis, which occurred more frequently in the placebo compared to the ozanimod group, all other thromboembolic related events by PT occurred only in the ozanimod 1 mg group but not in the placebo group (Pool G). These events comprised ischaemic stroke (IR of 2.1), but also retinal vein thrombosis in two cases (IR of 1.0), as well as one case each of deep vein thrombosis, pulmonary embolism, pulmonary microembolism. Overall, the TE cases observed in Pool G could reflect the generally higher incidence of TE in UC patients and do not indicate a clear causal relationship with ozanimod. It is thus agreed, that TE is currently not classified as adverse drug reaction. As requested by PRAC, TE has been added as an important potential risk in the RMP. To further explore this risk, the Applicant has proposed to add the following secondary endpoints to the planned UC post-approval safety study (PASS): (1) the subcomponents of major adverse cardiovascular events (MACE), (specifically, nonfatal myocardial infarction, nonfatal stroke and cardiac death) and (2) venous thromboembolism (including pulmonary embolism). This 10-year study is intended to accumulate long-term data to describe the risk of cardiovascular events in the UC ozanimod population.

Because of the established risk of S1P receptor modulators regarding bradycardia and hypertension, respectively, ozanimod is already contraindicated in patients with relevant cardiac conditions including unstable angina/MI, stroke/TIA and decompensated heart failure within the previous 6 months, which additionally increase the TE risk (beyond UC). No further changes to the SmPC are therefore proposed by the Applicant at the present state, which is agreed. However, the Applicant was requested to provide review of TE and discuss respective labelling consequences with upcoming PSURs.

As of safety data cut-off (31 Mar 2020), 14 deaths occurred in the overall ozanimod program across all indications, 7 of which have already been assessed during the marketing authorisation procedure for MS. While a numerical imbalance of death cases was found in the MS study program (2 death cases in Pool A1 occurring on ozanimod vs. none on placebo), death cases in the UC indication occurred only during open-label treatment with ozanimod (N=3). In line with the findings from the death cases reviewed during the marketing authorisation of ozanimod for MS, no common pattern could be derived from the additional death cases provided with this variation across all indications. Two of the additional cases might involve immunosuppressant properties and two cases were reported in the context of malignancies.

During the controlled maintenance period (Pool Fm), the TEAEs which occurred at a ($\geq$ 1%) higher frequency in the ozanimod (ozanimod-ozanimod) compared to the placebo (ozanimod-placebo) group and are not yet included in 4.8 of the SmPC were headache (3.5% vs. 0.4%) and oedema peripheral (2.6% vs. 0%). In addition, hot flush occurred on Day 1 in 2 ozanimod but no placebo subjects in the UC studies (Pool Fi) and occurred in the active controlled phase 3 RMS studies (Pool A1) likewise on Day 1 with higher frequency in ozanimod (0.2%) vs. placebo subjects (0.1%).

Herpes zoster, Headache and peripheral oedema are included as ADRs in section 4.8 of the SmPC as appropriate, with a frequency of "common" ($\geq$ 1/100 to < 1/10).

2.13. Effects Table

Effects Table for Ozanimod 1 mg in Ulcerative colitis

Effect	Short description	Unit	Treatment Ozanimod 1 mg	Control Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Clinical remission Induction	Based on 3-component Mayo score[b] at Week 10	%	18.4%	6.0%	p < 0.0001	Efficacy endpoints are reported from Study RPC01-3101 Induction and Maintenance Periods
Clinical remission maintenance	Based on 3-component Mayo score[c] at week 52	%	37%	18.5%	p < 0.0001	
Clinical response Induction	Based on 3-component Mayo score at Week 10	%	47.8%	25.9%	p < 0.0001	
Clinical response maintenance	Based on 3-component Mayo score At week 52	%	60.0%	41.0%	p < 0.0001	
Corticosteroid-free remission (Maintenance)	Clinical remission[b] at Week 52 while off CS for ≥ 12 weeks	%	31.7%	16.7%	p < 0.001	
Maintenance of remission (Maintenance)	Clinical remission[b] at Week 52 among subjects in remission at Week 10	%	51.9%	29.3%	p = 0.0025	
Durable clinical remission	Complete remission[b] at both Week 10 and 52	%	17.8%	9.7%	p = 0.0030	
Disease relapse	Proportion of subjects who relapsed during the MP[i]	%	13.5%	35.7%	Post hoc *p < 0.001*	
Early onset of action (Induction)	Change from baseline in RBS at Week 2	Mean / LS mean	-0.59 / -0.56	-0.43 / -0.40	Post hoc LS mean diff. -0.16 (95% CI: -0.298, -0.023)	
	Change from baseline in SFS at Week 5	Mean / LS mean	-0.71 / -0.65	-0.55 / -0.46	LS mean diff. -0.19 (95%: CI: -0.336, -0.047)	
Endoscopic normalization Induction	Mayo endoscopy score = 0 … at Week 10	%	6.1%	2.8%	Post hoc *p = 0.0685*	
Maintenance	… at Week 52	%	24.3%	11.9%	*p = 0.0004*	
Unfavourable Effects						
Elevated	Proportion of	%			Most	Safety

Effect	Short description	Unit	Treatment Ozanimod 1 mg	Control Placebo	Uncertainties / Strength of evidence	References
hepatic enzymes Induction	subjects with ALT ≥ 3x ULN[b] during induction …during maintenance		2.6% 2.3%	0.5% 0	elevations ≥ 3 x ULN resolved on treatment	endpoints are reported from the Pool F Induction Period (3101+202) and the RPC01-3101 Maintenance Period, unless otherwise footnoted
	Proportion of subjects with ALT ≥ 5x ULN[b] during induction …during maintenance	%	 0.9% 0.9%	 0.5% 0	Subjects with confirmed ALT ≥ 5 x ULN were to be discontinued per protocol[c]	
Discontinuation due to hepatic events	Proportion of subjects who discontinued due to hepatic enzyme elevation	%	0.4%	0		
Heart rate reduction Bradycardia	Mean change from baseline in supine/ sitting heart rate at nadir during Hours 1 to 6 on Day 1	bpm	-0.7	N/A (no decrease in heart rate)	No clinically significant bradycardia or conduction effects (second-degree type 2 or third-degree AV block)	
Blood pressure increases/	Mean increase in systolic blood pressure Induction	mmHg	3.7	2.3		
	Maintenance		5.1	1.5		
Hypertension	Proportion of subjects with hypertension logical grouping TEAE Indution Maintenance	%	 1.2% 2.2%	 0 2.2%		
Macular edema	… during induction	%	0.2%	0	Predisposing risk factors or co-morbid conditions present.	
	…during maintenance	%	0.4%	0		
Infections	… during induction	%	9.9%	10.7%		
	…during maintenance	%	23.0%	11.9%		
Serious or opportunistic	Proportion of subjects with	%				

Effect	Short description	Unit	Treatment Ozanimod 1 mg	Control Placebo	Uncertainties / Strength of evidence	References
infection	serious infection AE …during induction		0.8%	0.4%		
	…during maintenance		0.9%	1.8%		
	Herpes Zoster Induction&maintenance	%	2.6%	0.4%	No disseminated or serious herpes zoster infections	
	Herpes simplex Induction&maintenance	%	1.9%	0		
Pulmonary effects	Mean change in FEV$_1$ from baseline …during induction	L	-0.064	-0.049	Reversible changes, not clinically meaningful.	
	…during maintenance	L	-0.085	-0.050		
	Mean change in FVC from baseline …during induction	L	-0.049	-0.025		
	…during maintenance	L	-0.058	-0.033		
ALC < 0.2 x 10^9/L	Proportion of subjects with ALC < 0.2 x 10^9/L …during induction	%	2.1%	0	Median time to recovery to normal range (all subjects) 35 days; no concurrent serious or opportunistic infection	
	…during maintenance	%	3.0%	0		

AE = adverse event; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; AV = atrioventricular; CI = confidence interval; CR = clinical response; CS = corticosteorids; EQ-5D VAS = EuroQol quality of life visual analog scale; LS = least squares; MCID = minimum clinically important difference; MP = Maintenance Period; N/A = not applicable; PCS = Physical Component Summary; RBS = rectal bleeding subscore; SF-36 = 36-item Short Form Health Survey; SFS = stool frequency subscore; ULN = upper limit of normal.

[a] Efficacy endpoints are reported from Study RPC01-3101 Induction and Maintenance Periods. Safety endpoints are reported from the Pool F Induction Period (3101+202) and the RPC01-3101 Maintenance Period, unless otherwise footnoted.

[b] Clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the Baseline SFS) and endoscopy subscore ≤ 1 point.

[c] 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 RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.

[d] Endoscopic improvement is defined as a Mayo endoscopic score ≤ 1.

2.14. Benefit-risk assessment and discussion

2.14.1. Importance of favourable and unfavourable effects

The induction study demonstrated superiority of ozanimod 1 mg daily compared to placebo in inducing remission, improvement of clinical symptoms, and endoscopic improvement, remission, as well as histologic remission across a variety of second and third line patients. Consistent results were shown for patients with and without corticosteroid treatment and with and without previous anti-TNF treatment. A high consistency of results was shown both across endpoints as well as patient subgroups, and analysis methods.

The maintenance study demonstrated a similar superiority of ozanimod 1 mg once daily compared to placebo in maintaining remission up until week 52. Similar to the induction phase, all results were consistent across subgroups, different endpoints, and types of analysis.

Overall, the data presented in the application support the proposed indication and dosing recommendations in the SmPC. The oral formulation may also be an advantage, since, besides tofacitinib, all currently available antibody-based biologics for the treatment of UC are administered parenterally.

The safety database for ozanimod in the UC indication is considered comprehensive with more than 4057 subjects exposed across all indications and 1158 exposed UC subjects. 716 UC subjects have been treated for at least 12 months and 322 for at least 24 months. The currently available safety profile in UC subjects is qualitatively largely in line with that established for the MS indication. Although comparability of incidences of AEs across MS and UC studies is limited due to differences in study durations and designs, the most relevant safety findings with ozanimod in the UC indication occurred with general similar frequency, i.e. heart rate decreases, blood pressure changes, liver enzyme increases, macular oedema, pulmonary function decrease, CTCAE Grade 4 ALC reductions, infections, and malignancies.

There is a potential risk of malignancies with ozanimod. From the controlled UC program as well as from the incidence rates (IR) provided for the overall UC studies no clear imbalance was found with regard to all malignancies and non-cutaneous malignancies, respectively. However, some imbalance could be detected for cutaneous malignancies. Malignancies typically observed with broader immunosuppressive therapies, such as lymphomas, have not been reported with ozanimod. Nevertheless, a causal relationship can neither be established nor ruled out based on available clinical data. Therefore, the ongoing long-term studies are deemed essential to address the potential risk of malignancies.

In the controlled UC studies, the incidence of serious infections was low in both treatment groups and while numerically slightly higher with ozanimod compared to placebo group during the pooled induction period, the risk was somewhat lower in subjects with continued ozanimod treatment vs. subjects re-randomised to placebo during the maintenance phase. Opportunistic infections were more frequent with ozanimod compared to placebo and were predominantly cases of Herpes zoster. Most cases of Herpes zoster in the UC studies were mild to moderate (96%) and most subjects (88%) continued treatment with ozanimod. None of the subjects with herpes zoster had an ALC reduction < 2 x 109/L. As of the current safety data cut-off for the current submission (31 Mar 2020), there were no confirmed cases of PML or cryptococcal meningitis SDEIs in the entire ozanimod development program. However, the diagnosis of a definitive PML case has meanwhile been reported in a patient with RRMS under treatment with ozanimod, which will be addressed in a dedicated type II variation to update the PI and RMP (if needed) on the risk of PML.

Overall, based on the UC studies, herpes zoster, headache and peripheral oedema ADRs in section 4.8 of the SmPC are introduced with a frequency of common.

Long-term safety data are still limited, as open-label extension studies RPC01-3001 in MS as well as RPC01-3102 in UC are still ongoing.

Overall, the safety profile of ozanimod in UC patients is considered manageable with appropriate risk minimisation measures. The Applicant has agreed and committed to further evaluations of the newly added important potential risk of thromboembolic events.

2.15. Balance of benefits and risks

The applicant has provided a clear and convincing evidence of efficacy for the treatment of ulcerative colitis, both in the short-term, as well as in long-term treatment. The benefits of treatment have been demonstrated both at the level of improvement of symptoms (mainly diarrhoea and blood in stools), and well as on the signs relevant for the long-term prognosis, such as endoscopic improvement, mucosal healing, and histological remission. Therefore, benefits have been convincingly shown for the subjective well-being of patients, as well as for the inflammatory process in the colonic mucosa. While in the short term, the rate of full remission of patients remains modest (but is still relevantly higher than under treatment with placebo) a relevant rate of remission can be achieved with long-term treatment once an initial response has been achieved and the rate of patients remaining in remission, once this has been achieved is considered similarly relevant.

The safety profile of ozanimod in the UC population is overall in line with the safety profile established in the MS indication. Ozanimod belongs to the class of S1P receptor modulators, the first of which (fingolimod) was approved approx. 10 years ago in the European Union and for which risk minimisation measures proved efficacious. The safety issues concerning ozanimod are considered manageable. Current uncertainties mainly pertain to the safety profile with long-term concomitant corticosteroids, the limited safety data in older subjects as well as a potential rebound phenomenon. The determination of the long-term safety risk is still outstanding and will be further addressed in ongoing long-term open-label studies 3102 (UC indication) and 3001 (MS indication).

2.16. Conclusions

The overall B/R of Zeposia for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent is positive.

3. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of	Type II	I, II and IIIB

	a new therapeutic indication or modification of an approved one		

C.I.6.a (Extension of indication)
Extension of indication to include the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent for Zeposia; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and Annex IID are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes throughout the product information. Version 2.1 of the RMP has been approved.

C.I.4
Update of sections 4.4 and 4.5 of the SmPC in order to update the current SmPC description about PK interaction with BCRP inhibitors based on the study report from a drug interaction study with cyclosporine (RPC-1063-CP-001).

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

4. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion on Zeposia EMEA/H/C/004835/II/0002/G.