Official Title of Study:

A Phase 3, Multicenter, Open-Label Extension Trial of Oral RPC1063 as Therapy for Moderate to Severe Ulcerative Colitis

NCT Number: NCT02531126

Document Date (Date in which document was last revised): 10 Aug 2022

1 CLINICAL TRIAL PROTOCOL

Protocol Title:	A Phase 3, Multicenter, Open-Label Extension Trial of Oral RPC1063 as Therapy for Moderate to Severe Ulcerative Colitis
Protocol Number:	RPC01-3102
Version and Date:	10.0 dated 10 August 2022
Replaces Version:	9.0 dated 23 August 2021
Product:	RPC1063 (BMS-986374)
IND No.:	115,243
EudraCT No.:	2015-001600-64
Trial Phase:	3
Sponsor:	Celgene International II Sàrl Route de Perreux 1 2017 Boudry, Switzerland Tel: + 41 32 729 85 00
Medical Monitor:	[redacted] Office: [redacted] Cell: [redacted]

CONFIDENTIAL

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Signatures

PROTOCOL TITLE: A Phase 3, Multicenter, Open-Label Extension Trial of Oral RPC1063 as Therapy for Moderate to Severe Ulcerative Colitis

PROTOCOL NO: RPC01-3102

Receptos Services LLC

[redacted] _____ _____
Date

Signatures

PROTOCOL TITLE: A Phase 3, Multicenter, Open-Label Extension Trial of Oral RPC1063 as Therapy for Moderate to Severe Ulcerative Colitis

PROTOCOL NO: RPC01-3102

Receptos Services LLC

[redacted]

Sponsor: Celgene International II Sàrl

Signature of Celgene International II Sàrl Representative	Date

Printed Name of Celgene International II Sàrl Representative

Sponsor: Celgene International II Sàrl

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 10.0:

The main reason for this amendment is to extend the duration of the study such that all patients complete 5 years (Week 238) of treatment.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 10.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis; Section 8.1: Summary of Trial Design; Table 2: Schedule of Events (footnote d); Section 8.2: Discussion of Trial Design; Section 8.3.4: Safety Follow-Up; Section 8.3.6: Trial Duration; Section 10.1: Treatments Administered	Study duration was extended such that each patient completes 5 years (Week 238) of treatment and follow-up.	Study extended to enable 5 years of efficacy and safety data for all ongoing patients.
[redacted]		
Table 2: Schedule of Events; Section 8.3.4: Safety Follow-Up; Section 9.4: Trial Discontinuation; Section 10.5.2: Concomitant Medications Prohibited Through [redacted] after Investigational Drug Discontinuation; Section 10.5.3: Concomitant Medications Between [redacted] after Investigational Drug Discontinuation and the 90-day Safety Follow-up Visit; Section 10.6: Medical Care of Patients after End of Trial; Section 12.3: Patient-Reported Outcomes; Section 13.1.11: Clinical Laboratory Evaluations	Removed [redacted] Safety Follow-up (SFU) Visit. Language regarding medications prohibited through the [redacted] SFU visit was updated to indicate these medications are prohibited through [redacted] following treatment discontinuation.	The [redacted] SFU Visit removed to streamline assessments for ongoing patients.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 10.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2: Schedule of Events; [redacted]	[redacted]	
Table 2: Schedule of Events	Footnote h was updated to state that endoscopy [redacted] visit will not need to be repeated if an endoscopy has been completed within [redacted].	To avoid unnecessary endoscopies.
Table 2: Schedule of Events	[redacted]	
Table 2: Schedule of Events	Added footnote s to indicate ulcerative colitis disease relapse and related symptoms will be monitored as trial endpoints and thus will not be recorded as adverse events (AEs), unless it qualifies as a serious AE to trigger safety reporting.	Added a reminder to sites so that ulcerative colitis is not recorded as an AE unless serious.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 10.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2: Schedule of Events	Frequency of additional visits for [redacted] and for [redacted] were updated from once a year to [redacted] (as indicated).	To align timing with visit schedule.
Table 2: Schedule of Events; [redacted]	[redacted]	
Table 2: Schedule of Events; Section 13.1.1: Physical Examination	Removed interim physical examination at 90-day SFU.	Complete physical examination should be performed at 90-day SFU.
Table 2: Schedule of Events	[redacted]	
Table 2: Schedule of Events	Updated blood volumes in footnote n past [redacted].	Updated blood volumes to align with frequency and type of blood draws.
Section 8.3.2: Trial Visits	To clarify that patients who have completed 5 years of treatment (Week 238) should come in at the time of their next scheduled visit. At this visit, these patients will complete the [redacted] procedures and then enter the SFU period.	Clarified procedures for patients who have completed 5 years of treatment at the time this amendment is implemented.
Section 8.3.6: Trial Duration	Added information regarding how patients may	Outlined options for treatment post study.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 10.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	continue to receive treatment after the trial.	
Section 10.5.4: Allowed Vaccines	Removed the following text: If non-live vaccinations are to be completed during the study, vaccine titers should be measured 4 to 8 weeks following the last administration of the vaccine.	Measuring titers following vaccination is not necessary for this trial.
Section 13.2.7: [redacted] Pandemic	Language regarding reporting of vaccine administration was updated.	Updated to align with electronic case report forms.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

2 SYNOPSIS

Sponsor/Company: Celgene International II Sàrl	
Investigational Product: RPC1063 (BMS-986374)	
Name of Active Ingredient: RPC1063	
Protocol Title:	A Phase 3, Multicenter, Open-Label Extension Trial of Oral RPC1063 as Therapy for Moderate to Severe Ulcerative Colitis
Protocol No:	RPC01-3102
Trial Sites:	Approximately [redacted] sites
Regions:	North America, Europe, Asia Pacific, South America, South Africa
Trial Duration: Estimated date of first patient enrolled: August 2015 Estimated date of last patient last visit completed: March 2025	**Phase:** 3

Main Objectives:

- Evaluate the long-term safety of RPC1063 for the treatment of all patients with moderate to severe UC.
- Evaluate the long-term efficacy of RPC1063 for the treatment of adult patients with moderate to severe UC.

Methodology:

This is an open-label, multicenter, extension trial to evaluate the long-term safety and efficacy of RPC1063 in patients with moderately to severely active ulcerative colitis (UC). Only those patients who have previously participated in a trial of RPC1063 (eg, RPC01-3101 or completed at least 1 year of the open-label period of RPC01-202) and meet eligibility criteria will be eligible for entry in this trial.

Patients entering the trial from the open-label period of RPC01-202 [redacted] of RPC01-3101 will continue to receive RPC1063/ozanimod HCl at 1 mg (equivalent to ozanimod [redacted] mg) daily. All patients entering the trial from a blinded parent trial or treatment period of RPC1063 [redacted] of RPC01-3101) will initiate RPC1063 treatment in accordance with a 7-day dose escalation regimen starting with RPC1063/ozanimod HCl [redacted] mg (equivalent to ozanimod [redacted] mg) on Days [redacted], followed by RPC1063/ozanimod HCl [redacted] mg (equivalent to ozanimod [redacted] mg) on Days [redacted], and reaching the final dose level, RPC1063/ozanimod HCl 1 mg on Day [redacted]. Each patient will receive RPC1063 at 1 mg/day as part of this clinical trial until they complete 5 years (Week 238) and the Safety Follow-up Visit, unless the Sponsor discontinues the development program. Patients who are not in clinical response or remission at trial entry may be discontinued from investigational drug if they do not show clinical improvement from the Baseline Visit of the RPC01-3102 by [redacted].

Safety Monitoring/Follow-up:

The safety of patients will be monitored by collection of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs leading to discontinuation, and TEAEs of special interest, as well as, physical examination findings, vital signs measures, electrocardiograms (ECGs) findings, [redacted] results, [redacted] results, clinical laboratory test results (blood chemistry including liver transaminases, hematology). White blood cell (WBC) and [redacted] will be centrally monitored.

Patients entering the trial from the open-label period of RPC01-202 or from the open-label [redacted] of RPC01-3101 will continue to receive RPC1063/ozanimod HCl at 1 mg daily and no additional cardiac monitoring is required. All patients who enter this trial from a parent blinded trial or treatment period of RPC1063 [redacted] of RPC01-3101) will undergo [redacted]

Patients who discontinue from treatment for any reason, including lack of response and AE, even if alternative treatment is given, will be followed for 90 days for collection of safety data and for assessment of their disease status.

In the event that commercial ozanimod becomes available prior to end of the study, patients may discontinue and transition to the commercial product after discussion with the Investigator at his/her discretion. Patients who transition to commercial ozanimod prior to completing the study are not required to attend the Safety Follow-up (SFU) Visit after their [redacted] visit as long as commercial ozanimod is started within 14 days of discontinuation of study drug.

Patients who complete 5 years (Week 238) of treatment may transition to commercial RPC1063/ozanimod HCl if approved and available in their country. In countries where commercial ozanimod is not available, patients may be eligible for a country-specific support program where available (see Section 8.3.6 for details).

Endoscopy:

All endoscopies will be recorded and read by a central reader.

Number of patients: Up to [redacted]

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

Patients are eligible if they fulfill all of the following:

1. Previously participated in a trial of RPC1063 (eg, RPC01-3101 or completed at least 1 year of the open-label period of RPC01-202) and meet the criteria for participation in the open-label extension as outlined in the prior trial.
2. Females of childbearing potential (FCBP):

   Must agree to practice a highly effective method of contraception throughout the trial until completion of the 90-day SFU Visit. Highly effective methods of contraception are those that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly. Acceptable methods of birth control in the trial are the following:

   - combined hormonal (oestrogen and progestogen containing) contraception, which may be oral, intravaginal, or transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
   - placement of an intrauterine device (IUD)
   - placement of an intrauterine hormone-releasing system (IUS)
   - bilateral tubal occlusion
   - vasectomized partner
   - complete sexual abstinence
   - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.
3. Must provide written informed consent prior to any trial-related procedures and have the ability to be compliant with the schedule of protocol assessments.

Diagnosis and main criteria for exclusion:

Exclusion Criteria:

Patients are not eligible for this trial if they fulfill any of the following:

Exclusions Related to Medications:

1. Have received any of the following therapies since the first dose of investigational drug in the prior RPC1063 trial:
   - Treatment with a biologic agent
   - Treatment with an investigational agent other than RPC1063
   - Treatment with a live vaccine or live attenuated vaccine within 4 weeks prior to Visit [redacted] of this trial
   - Treatment with D-penicillamine, leflunomide, thalidomide, natalizumab, fingolimod, etrasimod, or tofacitinib

- Treatment with lymphocyte-depleting therapies (eg, Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)

2. Are currently receiving or require initiation of any of the following therapies:
   - Treatment with corticosteroids at a dose that exceeds the prednisone equivalent of 40 mg per day
   - Treatment with immunosuppressive agents (eg, azathioprine, 6-MP, or methotrexate)
   - Chronic non-steroidal anti-inflammatory drug (NSAID) use (Note: occasional use of NSAIDs and acetaminophen [eg, headache, arthritis, myalgias, or menstrual cramps] and aspirin up to 325 mg/day is permitted)
   - Treatment with Class Ia or Class III anti-arrhythmic drugs or treatment with two or more agents in combination known to prolong PR interval

3. Are receiving treatment with any of the following drugs or interventions within the corresponding timeframe:
   - At Day [redacted]
     - CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) or inducers (eg, rifampicin)
   - Two weeks prior to Day [redacted]
     - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
4. Are receiving treatment with breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine, eltrombopag)

Exclusions Related to General Health:

5. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin (hCG)
6. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric or other major systemic disease making implementation of the protocol or interpretation of the trial difficult or that would put the patient at risk by participating in the trial or that would have required a patient to discontinue treatment in the previous RPC1063 trial
7. Clinically relevant cardiovascular conditions, including history or presence of recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea

Exclusions Related to Laboratory Results:

[redacted]

Duration of treatment:

As part of this clinical trial, until the patient completes 5 years (Week 238) and the Safety Follow-up Visit, unless the Sponsor discontinues the development program.

Endpoints:

Definitions:

Complete Mayo score: the sum of the RBS, SFS, PGA subscore, and the MES. Each subscore has a range of 0-3 points and the complete Mayo score has a range of 0-12 points

9-point Mayo score: the sum of the RBS, SFS, and the MES. The 9-point Mayo score has a range of 0-9 points

Partial Mayo score: the sum of the RBS, SFS, and the PGA subscore. The Partial Mayo score has a range of 0-9 points

Clinical Remission

[redacted]

Three-component Mayo: RBS = 0 and SFS ≤ 1 (and a decrease of ≥ 1 point from the Baseline SFS) and MES ≤ 1

Clinical Response

[redacted]

Three-component Mayo: 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

Corticosteroid-free Remission: Clinical remission while off corticosteroids for ≥ 12 weeks

Endoscopic Improvement: MES of ≤ 1 point

Mucosal Healing: MES of ≤ 1 point and a Geboes index score < 2.0

Histologic Remission: Geboes index score < 2.0

For statistical analysis purposes, clinical remission and clinical response will be calculated using the Three-component Mayo definition.

Efficacy Endpoints:

- Proportion of patients in clinical remission
- Proportion of patients with a clinical response
- Proportion of patients with endoscopic improvement
- Proportion of patients with mucosal healing
- Proportion of patients with corticosteroid-free remission
- Change from Baseline in complete Mayo score, partial Mayo score, and 9-point Mayo score
- Proportion of patients with histologic remission
- Proportion of patients with clinical response, clinical remission, or endoscopic improvement in patients who had previously received anti-TNF therapy

Safety Endpoints:

- The incidence, severity, and relationship of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), TEAEs leading to discontinuation of investigational drug, and TEAEs of special interest

[redacted]

Statistical Methods:

All patients who receive at least one dose of investigational drug in this trial will comprise both the Intent-to-Treat population and the Safety population. These populations will be used to summarize all efficacy and safety data.

Each efficacy endpoint will be summarized with the number and percent of patients for proportion-based endpoints, and with the number of patients, mean, standard deviation, median, minimum, and maximum for continuous endpoints. For both types of endpoints, 95% confidence intervals around the estimates may also be presented. Due to the open-label nature of the trial and the lack of a control group, all data will be summarized, and no hypothesis testing will be performed. All efficacy data will be listed.

All safety data will be listed and summarized. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, AEs leading to discontinuation, and AEs of special interest will be summarized and presented in descending order of frequency. Associated clinical laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual patient values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from Baseline will be produced. The change from Baseline for each of the vital signs and ECG parameters will be summarized. Incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

Sample Size Justification: As this is an open-label extension trial for patients who previously participated in a trial of RPC1063 for UC, there is no statistical basis for the sample size. It is anticipated that up to [redacted] patients who participated in prior studies of RPC1063 in UC may be eligible for treatment in this trial.
Version and Date: Version 10.0 dated 10 August 2022

3 TABLE OF CONTENTS

4 LIST OF TABLES

5 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
[redacted]	[redacted]
ALT	Alanine aminotransferase
[redacted]	[redacted]
AST	Aspartate aminotransferase
[redacted]	[redacted]
AZA	Azathioprine
β-hCG	Beta-human chorionic gonadotropin
BCRP	Breast Cancer Resistance Protein
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
[redacted]	[redacted]
CRO	Contract research organization
CYP	Cytochrome P450
DDI	Drug-drug interaction
[redacted]	[redacted]
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
[redacted]	[redacted]
[redacted]	[redacted]
FCBP	Females of Child Bearing Potential
FDA	Food and Drug Administration
[redacted]	[redacted]
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin

Abbreviation	Definition
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
[redacted]	[redacted]
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
IV	Intravenous
IV Ig	Intravenous immunoglobulin
IXRS	Interactive voice / web-based activated response system
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MES	Mayo Endoscopy Score
MMF	Mycophenolate mofetil
MS	Multiple sclerosis
NOAEL	No-Observed-Adverse Effect Level
NSAID	Non-steroidal anti-inflammatory drug
[redacted]	[redacted]
OLE	Open-label extension
PD	Pharmacodynamic(s)
[redacted]	[redacted]
P-gp	P-glycoprotein
PGA	Physician Global Assessment
PK	Pharmacokinetic(s)
[redacted]	[redacted]
[redacted]	[redacted]
RBS	Rectal Bleeding Score
RMS	Relapsing multiple sclerosis
S1P	Sphingosine-1-phosphate
$S1P_1$	Sphingosine-1-phosphate 1 receptor
$S1P_5$	Sphingosine-1-phosphate 5 receptor
SAE	Serious adverse event

Abbreviation	Definition
[redacted]	[redacted]
SD	Standard deviation
SFS	Stool Frequency Score
SFU	Safety Follow-up
SOP	Standard operating procedures
[redacted]	[redacted]
TDAR	T-cell-dependent antibody response
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
UC	Ulcerative colitis
[redacted]	[redacted]
WBC	White blood cell
WHO	World Health Organization

6 INTRODUCTION

6.1 Ulcerative Colitis

Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disorder that involves the surface mucosa, the crypt epithelium, and the submucosa of the colon (Schroeder et al, 1987; Stenson, 2000). 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 (Ordas et al, 2012).

Patients with UC suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever (Schroeder et al, 1987; Stenson, 2000; Hyams, 1994). Ulcerative colitis is characterized by a life-long chronic course of remissions and exacerbations. In severe UC, the bowel wall may become thinned, the mucosa denuded, and the inflammation may extend to the serosa, leading to dilation, toxic megacolon, and perforation (Glickman, 1998). Toxic megacolon commonly requires an urgent colectomy to avoid perforation, peritonitis, and sepsis. Within 10 years of diagnosis, 19.9% of adults with UC had undergone colectomy for their UC (van Limbergen et al, 2008).

In addition, patients with UC have an increased risk of carcinoma when compared with the general population. The estimated risk of colorectal carcinoma increases as the duration and extent of disease increases from 2% of patients with UC for 10 years, to 8% of patients with UC for 20 years, and to 18% of patients with UC for 30 years (Eaden et al, 2001; Bernstein et al, 2001).

The overall goal of treatment for patients with active UC is to induce and maintain remission and to induce and maintain mucosal healing (Ng and Kamm, 2009; Sandhu et al, 2010; Heyman et al, 2005). Treatment of UC consists of anti-inflammatory and immunosuppressive therapies that are chosen to maximize efficacy while minimizing toxicity. The therapy chosen is therefore dependent on the patient's disease severity and their response to therapy (Kornbluth and Sachar, 2010; Ng and Kamm, 2009; Sandhu et al, 2010). While agents used to treat mild to moderate UC are generally well tolerated, as the severity of UC disease increases, so do the potential toxicities of the medications required to manage the disease. Treatment for mild to moderate UC treatment typically starts with topical agents (5-aminosalicylate [5-ASA] or corticosteroids administered via suppository or enema). In patients unresponsive to local therapy or in patients with more severe or more extensive disease, systemic treatment with an oral 5-ASA, such as mesalamine, olsalazine, sulfasalazine, and balsalazide, with or without antibiotics, is commonly required (Rosenberg and Peppercorn, 2010; Ng and Kamm, 2009; Sandhu et al, 2010). Initially, up to 90% of patients with mild to moderate UC can be maintained in remission using once-daily oral administration of 5-ASA, and treatment with 5-ASA is generally safe and well tolerated (Ng and Kamm, 2009).

For those patients who do not respond or lose response to treatment with 5-ASA or those with more severe, extensive disease at presentation, corticosteroids are generally the first-line treatment for inducing disease remission. Although effective in inducing disease remission, treatment with corticosteroids is associated with multiple adverse effects including: weight gain, insomnia, mood swings, osteoporosis, scalp hair loss or facial hair growth, moon face, cataracts, acne, hypertension, diabetes, appearance of stretch marks, and increased susceptibility to infections and bruising.

In pediatric patients with more severe, extensive disease at presentation, corticosteroids are effective for short-term flare-ups, but are not recommended to maintain remission due to undesirable long-term side effects, including stunted growth. Thus, corticosteroids are usually administered for short periods of time and are not recommended for frequent use. Furthermore, it has been shown in pediatric populations that although effective in induction of response, after 1 year, approximately 45% of patients who initially responded to corticosteroids have either become steroid-dependent (Hyams et al, 2006) or have required surgery (Tung et al, 2006).

For those patients who are unresponsive to, or intolerant of corticosteroids, immunomodulators including azathioprine (AZA), 6-mercaptopurine (6-MP), and cyclosporine (Rosenberg and Peppercorn, 2010), or biologics (such as infliximab or vedolizumab), are used to induce and/or maintain remission (Kornbluth and Sachar, 2010; Sandhu et al, 2010). However, these medications have multiple limitations including toxicities. The use of 6-MP and AZA can result in neutropenia, pancytopenia, pancreatitis, nephrotoxicity, hepatotoxicity, and in rare cases, hepatosplenic T-cell lymphoma (Carter et al, 2004; Turner and Griffiths, 2011; Bousvaros, 2010; Chaparro et al, 2009), as well as a delay in onset of action (AZA and 6-MP take as long as 3 months to work). This class of therapy has a similar benefit-risk profile in children as in adults and have been widely prescribed as maintenance therapy for children with UC. However, reluctance to use thiopurines in children, especially males, has increased with the recognition of these potentially severe complications. Infliximab is indicated for pediatric UC, but comes with the potential risk of infusion reactions, [redacted], autoimmunity, and psoriasis known for the tumor necrosis factor (TNF) blocker medication class. A requirement for intravenous medication is disruptive to school and family economics. Adalimumab, also a TNF blocker, is currently indicated for UC in adults only. Therefore, there remains an unmet need for a UC treatment that is highly effective, well-tolerated, and orally active in both the adult and pediatric/adolescent populations.

6.2 RPC1063

RPC1063 (also known as ozanimod or BMS-986374) is a small molecule compound that selectively and potently activates the sphingosine-1-phosphate 1 receptor (S1P1) and the S1P 5 receptor (S1P5), although it is more selective towards S1P1 over S1P5. In vitro, RPC1063 has little activity on the other sphingosine-1-phosphate (S1P) receptors, showing half maximal effective concentration (EC50) greater than 10,000 nM for S1P2, > 5000 nM for S1P3, and > 2000 nM for S1P4. RPC1063 is extensively metabolized in humans with up to 13 metabolites identified in plasma, urine, and feces, including 2 active selective major metabolites and one inactive major metabolite found in human plasma at steady state. The 2 active metabolites (CC112273 and CC1084037) have similar structures to ozanimod and similar selectivity across the S1P receptor family.

Many cell types express $S1P_1$, including vascular endothelial cells, brain cells, and lymphocytes (Rosen et al, 2009). Stimulation (agonism) of this receptor results in biological activities that includes lymphocyte retention in peripheral lymphoid organs (eg, lymph nodes and gastrointestinal Peyer's patches), resulting in reversible systemic reduction in circulating lymphocytes (Mandala et al, 2002). Given the immune dysregulation observed in UC (Ordas et al, 2012), prevention of

trafficking of disease-exacerbating, self-reactive lymphocytes to the gut is likely to have salutary immunomodulatory effects with a consequent dampening of disease processes.

The potential for ozanimod to adversely affect the immune system was evaluated in a rat model for T-cell-dependent antibody response (TDAR) using keyhole limpet hemocyanin (KLH) as the antigenic stimulation (ITR Report No. 72864). The TDAR model is well-characterized and provides a functional evaluation of potential immunotoxic responses as it relies on the coordinated participation of antigen presenting cells, T cells, and B cells. Ozanimod, tested in a dose range of 0.2 to 2 mg/kg/day, resulted in a dose-dependent decrease in circulating T cell and B cell counts and in the primary and recall antibody responses with a no-observed-adverse-effect level (NOAEL) of 0.2 mg/kg/day. The NOAELs for juvenile and adult animals were 0.3 and 0.2 mg/kg/day, respectively, correlating to ≥ 10 times the exposure for ozanimod that was achieved with the clinical administration of [redacted] mg and > 15 times compared to the [redacted] mg dose (RPC01-1001). Therefore, the clinical doses of [redacted] mg and [redacted] mg are unlikely to result in clinically meaningful effects on novel or recall immune responses. Importantly from a safety perspective, there are still a significant number of lymphocytes in the circulation in patients treated with even the highest dose ([redacted] mg) of ozanimod such that serious infection rates are not increased to date, which suggests that the risk for [redacted] should not be significantly increased. [redacted] has been reported in patients treated with S1P receptor modulators and immunomodulatory therapies for multiple sclerosis (MS).

6.2.1 Nonclinical Studies

RPC1063 has been shown to pharmacologically induce rapid and reversible lymphocyte reduction in rodents, rabbits, dogs, nonhuman primates, and humans. Extensive nonclinical in vivo safety studies of up to a 6-month (rat) or 9-month (monkey) duration have shown that RPC1063 is well tolerated in animals at doses that generate robust pharmacodynamic (PD) effects (0.2 mg/kg in rats and 0.1 mg/kg in monkeys). RPC1063 has also been examined in reproductive toxicity studies (rat and rabbit) carcinogenicity studies (Tg.rasH2 mouse and rat), immunotoxicology (rat) and juvenile toxicity studies (rat). RPC1063 is extensively metabolized in humans and animals, with all active moieties having similar selective and potent activity at the $S1P_1$ and $S1P_5$ receptors. Doses examined in the toxicology studies thoroughly examined the on-target pharmacology ($S1P_1$ and $S1P_5$), where effects are similar across species (decreases in absolute lymphocyte counts). Differences in metabolism and clearance of these metabolites, however, results in disproportionate active metabolites in humans (such as CC112273). Coverage of some of these active metabolites (including CC112273) in rodent studies is projected to reach only 1 to 2 fold over efficacious human exposure due to rodent-specific differences in production and clearance. Coverage of CC112273 in nonhuman primate studies is projected to have reached 10 to 20 fold over efficacious human exposure. The data from the entire nonclinical program (including the juvenile rat toxicology study and the juvenile rat immunotoxicology study) with RPC1063 do not suggest that there are any specific sensitivities or new toxicities in pediatric populations that are not present in the adult population.

6.2.2 Clinical Studies

Phase 1 trials completed with RPC1063 in healthy volunteers include, but are not limited to, the first-in-human trial (RPCS 001), a thorough QT trial (RPC01-102), a food-effect trial (RPC01-1901), a drug-drug interaction (DDI) trial with a potent inhibitor and potent inducer of cytochrome P450 3A (RPC01-1902), a DDI trial with a strong inhibitor of P-glycoprotein and Breast Cancer Resistance Protein (RPC01-1903), a trial to evaluate the PK and safety of RPC0163 in Japanese and Caucasian patients (RPC01-1905), a DDI trial with an oral contraceptive (RPC01-1907), and a DDI trial with a calcium channel blocker or a beta blocker (RPC01-1908).

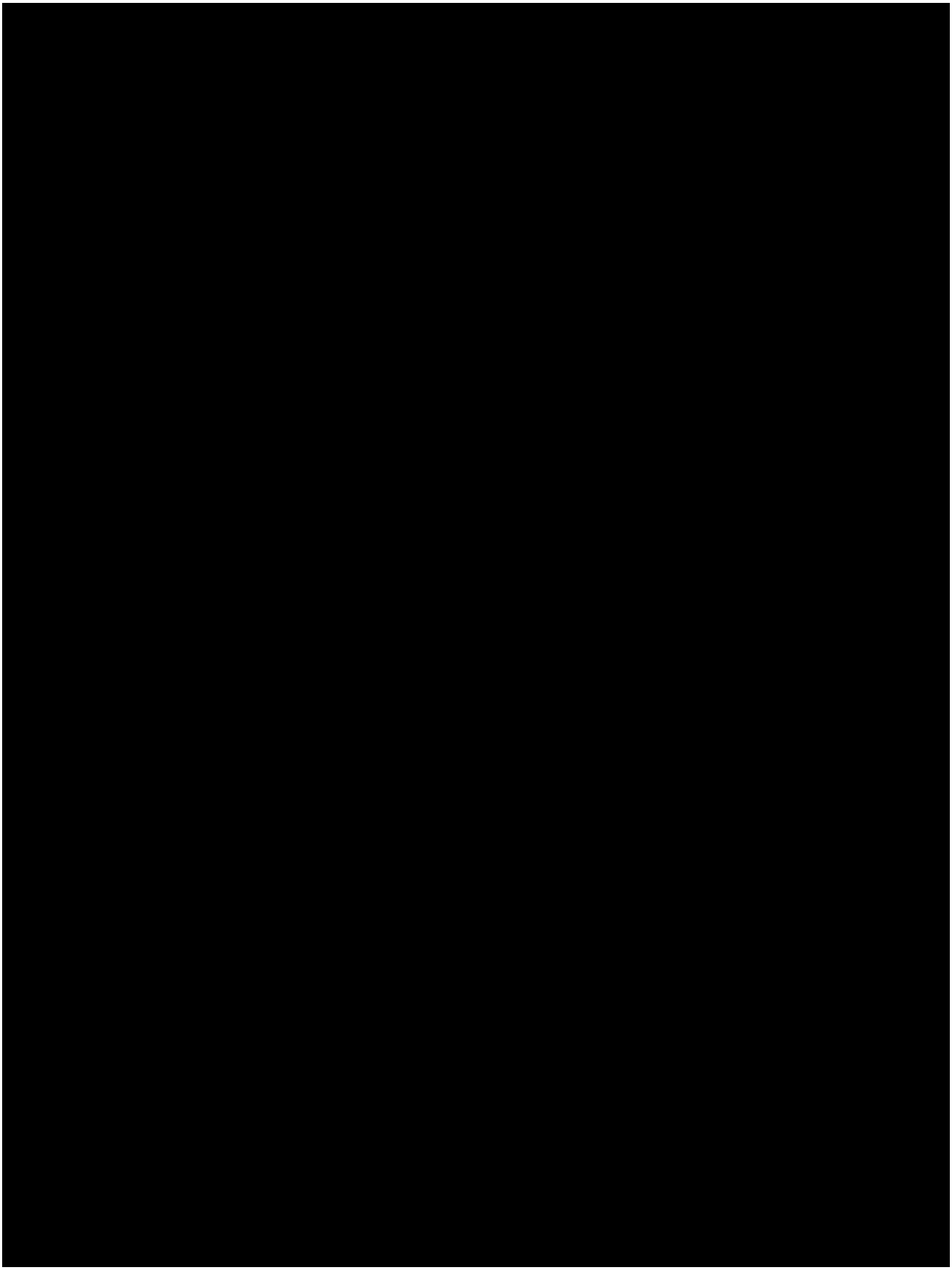
A Phase 2/3 randomized, double-blind, controlled trial (RPC01-201) in patients with relapsing multiple sclerosis (RMS) has been completed. In ulcerative colitis, the induction phase of a Phase 2 trial in adult patients with moderate to severe UC (RPC01-202) was completed in October 2014. At the conclusion of the induction phase, the proportion of patients achieving clinical response and clinical remission with RPC1063 1 mg was greater than placebo and the difference was both clinically meaningful and statistically significant. In addition, all secondary endpoints at the conclusion of the induction phase, including clinical response, change in the Mayo score, and mucosal improvement on endoscopy, were also positive and statistically significant for the RPC1063 1 mg dose. The maintenance phase of this trial ended in March 2015 and the open-label extension period was completed in November 2019, with eligible patients continuing in this study (RPC01-3102). The Phase 3 pivotal study (RPC01-3101) completed in May 2020, and eligible patients entered into this study. In addition, a Phase 2/3 study in UC patients in Japan (RPC01-3103) is ongoing.

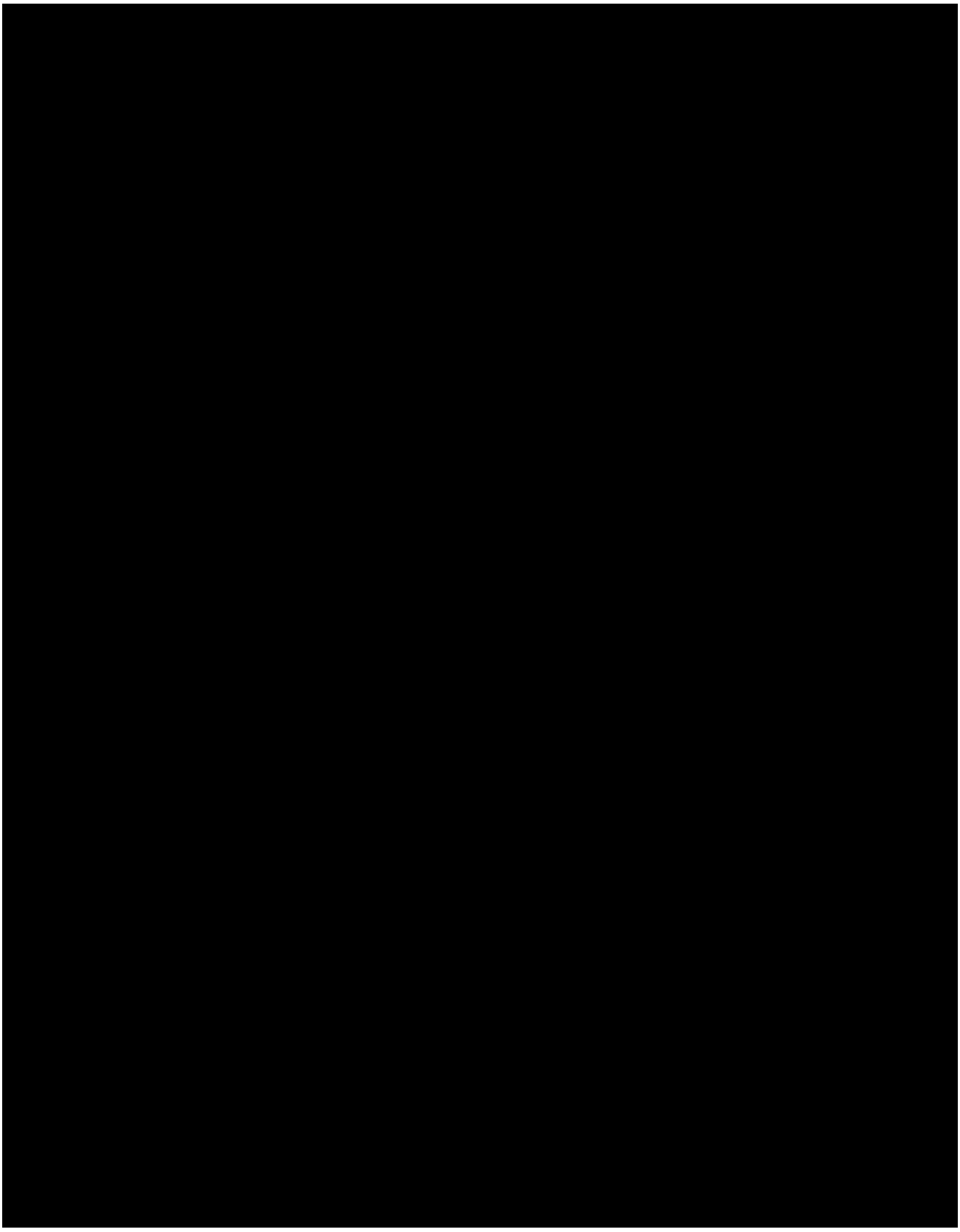
Additional information regarding company-sponsored trials in the RPC1063 clinical development program is provided in the Investigator's Brochure (IB).

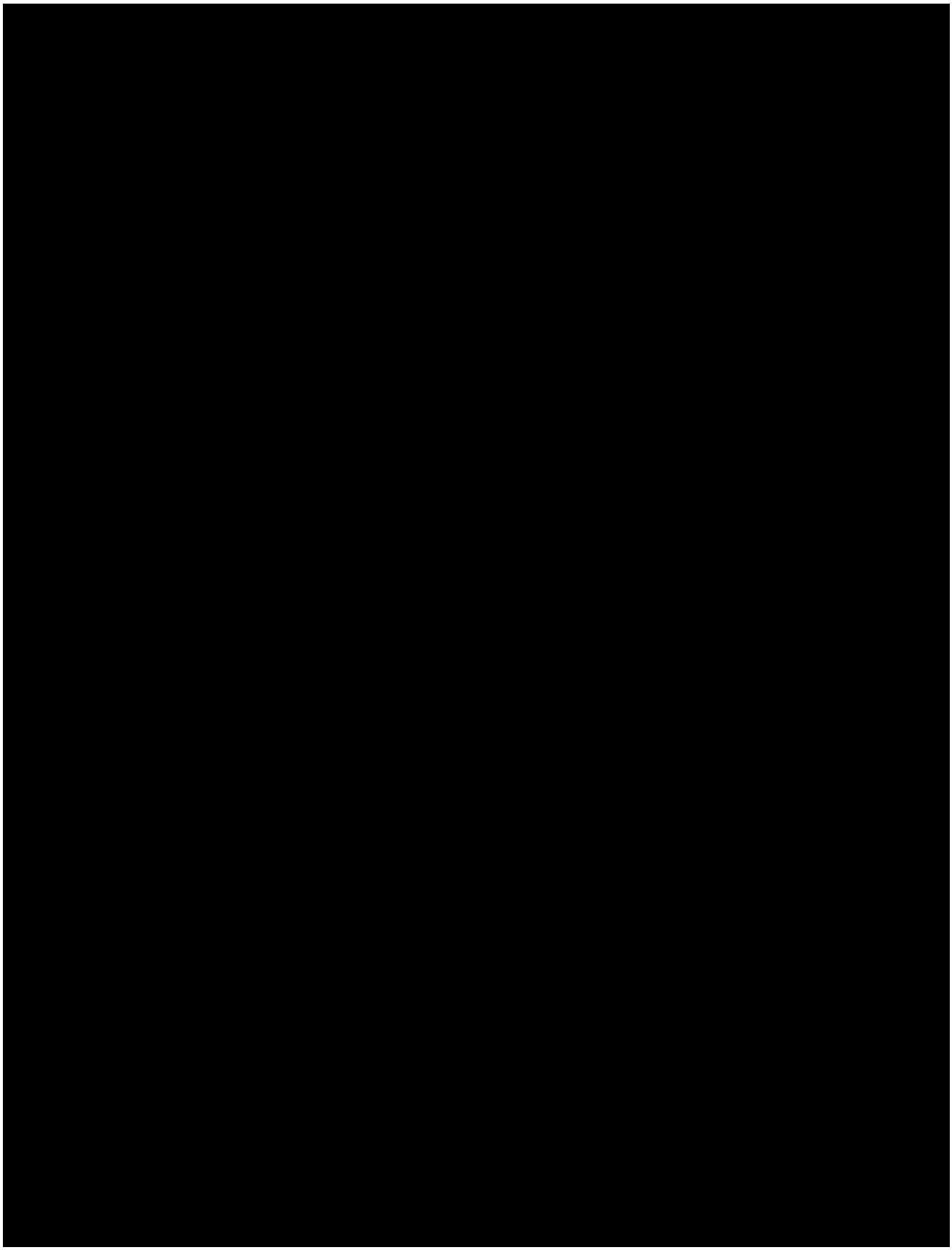
6.3 Rationale for the Current Trial

The objective of the RPC1063 clinical development program in UC is to demonstrate that RPC1063 administered orally is safe and effective for treating patients with moderate to severe UC. The positive results obtained in the Phase 2 (RPC01-202) and the Phase 3 pivotal trial (RPC01-3101) for the primary and all secondary endpoints led to the approval of the marketing application in the United States on 27 May 2021. Continued treatment with ozanimod 1 mg daily will provide greater long-term safety and durability data.

The objective of the current trial is to evaluate the long-term safety and efficacy of RPC1063 for the treatment of patients with moderate to severe UC.







7 TRIAL OBJECTIVES AND ENDPOINTS

7.1 Objectives

- Evaluate the long-term safety of RPC1063 for the treatment of all patients with moderate to severe UC.
- Evaluate the long-term efficacy of RPC1063 for the treatment of adult patients with moderate to severe UC.
- [redacted]

7.2 Efficacy Endpoints

7.2.1 Definitions

Complete Mayo score: the sum of the RBS, SFS, PGA subscore, and the MES. Each subscore has a range of 0-3 points and the complete Mayo score has a range of 0-12 points

9-point Mayo score: the sum of the RBS, SFS, and the MES. The 9-point Mayo score has a range of 0-9 points

Partial Mayo score: the sum of the RBS, SFS, and the PGA subscore. The Partial Mayo score has a range of 0-9 points

Clinical Remission

[redacted]

Three-component Mayo: RBS = 0 and SFS ≤ 1 (and a decrease of ≥ 1 point from the baseline SFS) and MES ≤ 1

Clinical Response

[redacted]

Three-component Mayo: 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

Corticosteroid-free Remission: Clinical remission while off corticosteroids for ≥12 weeks

Endoscopic Improvement: MES of ≤ 1 point

Mucosal Healing: MES of ≤ 1 point and a Geboes index score < 2.0

Histologic Remission: Geboes index score < 2.0

For statistical analysis purposes, clinical remission and clinical response will be calculated using the Three-component Mayo definition.

7.2.2 Efficacy Endpoints

- Proportion of patients in clinical remission
- Proportion of patients with a clinical response

- Proportion of patients with endoscopic improvement
- Proportion of patients with mucosal healing
- Proportion of patients with corticosteroid-free remission
- Change from Baseline in complete Mayo score, partial Mayo score, and 9-point Mayo score
- Proportion of patients with histologic remission
- Proportion of patients with clinical response, clinical remission, or endoscopic improvement in patients who had previously received anti-TNF therapy

For statistical analysis purposes, clinical remission and clinical response will be calculated using the Three-component Mayo definition.

7.3 Safety Endpoints

- The incidence, severity, and relationship of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), TEAEs leading to discontinuation of investigational drug, AEs of special interest (AESIs), and TEAEs of special interest will be summarized.

8 INVESTIGATIONAL PLAN

8.1 Summary of Trial Design

The Schedule of Events is provided in Table 2 [redacted]

This is an open-label, multicenter, extension trial to evaluate the long-term efficacy and safety of RPC1063 in patients with moderately to severely active UC. Patients who have previously participated in a trial of RPC1063 (eg, RPC01-3101 or completed at least 1 year of the open-label period of RPC01-202) for UC and meet the eligibility criteria will be eligible for entry in this trial.

Patients entering the trial from the open-label period of RPC01-202 [redacted] of RPC01-3101 will continue to receive RPC1063/ozanimod HCl at 1 mg/day. All patients entering the trial from a blinded parent trial or treatment period [redacted] of RPC01-3101) will initiate RPC1063 treatment in accordance with a 7-day dose escalation regimen starting with RPC1063/ozanimod HCl [redacted] mg on Days [redacted], followed by RPC1063/ozanimod HCl [redacted] mg on Days [redacted], and reaching the final dose level, 1 mg, on Day [redacted]. Patients will then receive RPC1063 at 1 mg/day as part of this clinical trial until the patient completes 5 years (Week 238) and the Safety Follow-up Visit, unless the Sponsor discontinues the development program (see Section 8.3.6 for details on treatment options post study). Adult patients who are not in clinical response or remission at trial entry may be discontinued from investigational drug if they do not show clinical improvement from the Baseline Visit of the RPC01-3102 by [redacted].

Table 2: Schedule of Events

	Trial Procedures	[redacted]
	Informed consent	
	Inclusion/exclusion criteria	
	Dispense investigational drug	
	Administer investigational drug at clinic	
	Review drug compliance	
	Prior and concomitant medications	
Safety Assessments	Adverse events[s]	
	12-Lead ECG	
	Vital signs	
	Hematology	
	Blood chemistry[n,p]	
	Urine pregnancy test[e]	
	Contraception education	
	Urinalysis	
	[redacted]	

Table 2: Schedule of Events

	Trial Procedures	[redacted]
	Complete Physical Exam[f]	
	Interim Physical Exam[f]	
	Height and Weight	
	[redacted]	
PD and PK Assessments	[redacted]	
	[redacted]	
	PK blood draw[redacted]	
	[redacted]	
Efficacy Assessments	Endoscopy and colonic biopsy[g]	
	Mayo patient diary	
	Complete Mayo score	
	Partial Mayo score	

Abbreviations: AE = adverse event; [redacted] ECG = electrocardiogram; [redacted] PD = pharmacodynamics; [redacted]; PK = pharmacokinetic; [redacted]; SFU = Safety Follow up; UC = ulcerative colitis.

[a] Patients will be entering the trial from a parent RPC1063 trial (eg, RPC01-3101 or completed at least 1 year of the open-label period of RPC01-202). In general, the last visit of the prior trial will serve as Visit [redacted] of this trial. Patients entering the trial from the open-label period of RPC01-202 [redacted] of RPC01-3101 will continue to receive RPC1063/ozanimod HCl at 1 mg/day and will not require dose escalation and [redacted]. All patients entering the trial from a blinded parent trial or treatment period [redacted] of RPC01-3101) will undergo dose escalation and [redacted].

[b] Visit [redacted] should be scheduled in the morning, when possible, and patients should be instructed not to take the investigational drug from the prior trial until Visit [redacted] during which they will receive RPC01-3102 investigational drug.

[c] Patients should enter the trial within [redacted] of the last visit of the prior trial. Procedures completed at the last visit of the prior trial do not need to be repeated if Visit [redacted] occurs within 14 days of the last visit of the prior trial. All Visit [redacted] procedures, including the endoscopy, must be completed prior to first dose except for [redacted] and [redacted]. If indicated, patients must complete the [redacted] and [redacted] no later than 14 days after Visit [redacted].

[d] Patients who continue past Visit [redacted] will have additional visit assessments performed at [redacted]. Patients entering from the open-label period of RPC01-202 will begin visits at [redacted]. The trial will continue until the patient completes 5 years (Week 238) and the Safety Follow-up Visit, unless the Sponsor discontinues the development program.

[e] In addition to the scheduled pregnancy tests in the clinic, monthly urine pregnancy tests should be performed by the patient between scheduled visits up until the 90-day SFU Visit. If a urine pregnancy test is positive, the Investigator will instruct the patient to suspend further RPC1063 dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test has to be performed for confirmation, even if the test is done after the 90-day SFU Visit.

[f] For all patients, a complete physical examination (which includes height and weight) will be performed at Visit [redacted], 90-day SFU, and [redacted]. The complete physical examination at [redacted] Visit also includes height and weight (See section 13.1.2). The complete physical examination consists of a full examination of the skin for lesions as well as a check for visual symptoms (ie, blurred vision or decreased visual acuity). A check for visual symptoms and a full examination of the skin should be repeated [redacted]. At all other visits, an interim physical examination may be performed. The interim physical examination will include body systems with previously noted abnormalities and/or those body systems associated with any new complaints from the patient.

[g] Endoscopy at Day [redacted] does not need to be repeated if an endoscopy has been completed within [redacted] of Visit [redacted]. All subsequent endoscopies should be performed either on day of visit or within [redacted] of the visit date.

[h] After the endoscopy at the [redacted] visit, an endoscopy will be performed at [redacted] and a Complete Mayo score will be calculated for those visits. Endoscopy at the [redacted] visit will not need to be repeated if an endoscopy has been completed within [redacted] of the [redacted] visit.

[redacted]

[j] The SFU Visit should occur 90 days (± 10 days) after the last dose of investigational drug in the RPC01-3102 trial. Patients who transition to commercial ozanimod within 14 days of the last dose of investigational drug will not require an SFU Visit.

[redacted]

[redacted]

[n] The following amounts of blood will be taken per visit: At [redacted], approximately 18.5 mL; at [redacted], approximately 6.5 mL; at every [redacted] visit after [redacted], approximately 5.5 mL; at [redacted] visit after [redacted], approximately 21 mL; at [redacted], approximately 26 mL, and at the 90-day SFU Visit, up to approximately 11.5 mL.

[redacted]

[p] HbA1c will be assessed at Baseline, [redacted].

[redacted]

[s] Ulcerative colitis disease relapse and related symptoms will be monitored as trial endpoints and thus will not be recorded as AEs, unless it qualifies as a serious AE to trigger safety reporting as described in Section 13.2.5.

8.2 Discussion of Trial Design

This trial is designed to evaluate the long-term safety and efficacy of RPC1063 for the treatment of patients with moderate to severe UC. All patients will receive RPC1063 at 1 mg/day as part of this clinical trial until the patient completes 5 years (Week 238) and the Safety Follow-up Visit, unless the Sponsor discontinues the development program (see Section 8.3.6 for treatment options post study).

Patients entering the trial from the open-label period of RPC01-202 [redacted] of RPC01-3101 will continue to receive RPC1063/ozanimod HCl at 1 mg daily. All patients entering this trial from a blinded parent trial or treatment period ([redacted] of RPC01-3101) of RPC1063 will initiate RPC1063 treatment in accordance with a 7-day dose escalation regimen (in order to maintain the blind of the parent trial) starting with RPC1063/ozanimod HCl [redacted] mg on Days [redacted], followed by RPC1063/ozanimod HCl [redacted] mg on Days [redacted], and reaching the final dose level, 1 mg, on Day [redacted].

Patients entering this trial from an open-label trial of RPC01-202 will not undergo dose escalation.

The dosing regimen for RPC1063 is based on previous clinical studies with RPC1063 (see Section 10.3).

8.3 Trial Periods

It is recommended that the trial visits are scheduled in the morning.

Whenever possible, the sequence of when assessments are done should remain constant and at approximately the same time of day throughout the trial.

It is recommended that procedures are performed in the following order (note that not all procedures are performed at every visit):

- Spontaneous or solicited AE reporting
- ECG
- Vital signs
- Clinical laboratory tests
- Physical examination
- Efficacy assessments
- Investigational drug administration (Visit [redacted])

8.3.1 Visit [redacted]

Patients must start this trial within [redacted] of their final visit in the prior RPC1063 trial in which they participated.

In general, procedures completed at the final visit of the prior trial will not need to be repeated if Visit [redacted] occurs on the same day as the final visit of the prior trial. All patients undergoing dose escalation will follow the [redacted] procedures as outlined in Section 13.1.10 and in [redacted]

[redacted]

8.3.2 Trial Visits

Visits, assessments, and procedures will be performed according to the Schedule of Events (Table 2).

Adult patients who are not in clinical response or remission at trial entry may be discontinued from investigational drug if they do not show clinical improvement from the Baseline Visit of the RPC01-3102 by [redacted]

At the time this amendment is approved, patients who have completed 5 years of treatment (Week 238) should come in at the time of their next scheduled visit. At this visit, these patients will complete the [redacted] procedures and then enter the SFU period.

[redacted]

8.3.4 Safety Follow-Up

For patients who discontinue the trial for any reason, every attempt should be made to complete the assessments detailed at the 90-day SFU Visit in the Schedule of Events (Table 2). In the event that commercial ozanimod or an access program becomes available prior to end of the study, patients may transition to the commercial product after discussion with the Investigator at his/her discretion. Patients who transition to commercial ozanimod are not required to attend a 90-day SFU Visit after their [redacted] as long as commercial ozanimod is started within 14 days of discontinuation of study drug. A 90-day (±10 days) SFU Visit was added to ensure adequate collection of adverse events that could be associated with investigational drug.

[redacted] Additional safety assessments may be required for patients who have an ongoing AE or safety issue at the 90-day SFU Visit, at the Investigator's discretion. Patients may be followed as necessary for an additional

period of time after the 90-day SFU Visit to review the results of any assessments which were conducted at the 90-day SFU Visit.

8.3.5 Study Stopping Rules

The Sponsor has the right to terminate the trial for safety reasons. In addition, the Sponsor may terminate the trial for administrative reasons. In all cases, all necessary measures must be taken to guarantee appropriate SFU of all patients already included in the trial.

The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and the Regulatory Authorities will be informed in writing about any termination of the trial.

8.3.6 Trial Duration

Patients will receive open-label treatment as part of this clinical trial until the patient completes 5 years (Week 238) and the Safety Follow-up Visit, unless the Sponsor discontinues the development program.

In countries where ozanimod is approved, the treating physician may elect to transfer the patient to commercially available ozanimod.

In countries were ozanimod is not commercially available, patients who continue to demonstrate clinical benefit may be eligible to receive ozanimod through a country-specific patient support program where available.

9 SELECTION AND WITHDRAWAL OF PATIENTS

9.1 Inclusion Criteria

Patients are eligible if they fulfill all of the following:

1) Previously participated in a trial of RPC1063 (eg, RPC01-3101 or completed at least 1 year of the open-label period of RPC01-202) and meet the criteria for participation in the open-label extension as outlined in the prior trial
2) Females of childbearing potential (FCBP) [Y]:

   Must agree to practice a highly effective method of contraception£ throughout the trial until completion of the 90-day SFU Visit. Highly effective methods of contraception are those that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly. Acceptable methods of birth control in the trial are the following:

   - combined hormonal (oestrogen and progestogen containing) contraception, which may be oral, intravaginal, or transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
   - placement of an intrauterine device (IUD)
   - placement of an intrauterine hormone-releasing system (IUS)
   - bilateral tubal occlusion
   - vasectomized partner
   - complete sexual abstinence
   - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.
3) Must provide written informed consent prior to any trial-related procedures and have the ability to be compliant with the schedule of protocol assessments.

[Y] For the purposes of this study, a female patient is considered to be of childbearing potential if she has reached menarche, and 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

[£] Contraception Education: Counselling about pregnancy precautions and the potential risks of fetal exposure must be conducted for FCBP. The Investigator will educate all FCBP about the different options of contraceptive methods or abstinence, as appropriate, at the Screening and Baseline Visits. The patient will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female patient's chosen form of contraception must be effective by the time the female patient is randomized into the study (for example, hormonal contraception should be initiated at least [redacted] before baseline).

9.2 Exclusion Criteria

Patients are not eligible for this trial if they fulfill any of the following:

Exclusions Related to Medications:

1) Have received any of the following therapies since the first dose of investigational drug in the prior RPC1063 trial:
   - Treatment with a biologic agent
   - Treatment with an investigational agent other than RPC1063
   - Treatment with D-penicillamine, leflunomide, thalidomide, natalizumab, fingolimod, etrasimod, or tofacitinib
   - Treatment with lymphocyte-depleting therapies (eg, Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
   - Treatment with a live vaccine or live attenuated vaccine within 4 weeks prior to Visit [redacted] of this trial
2) Are currently receiving or require initiation of any of the following therapies:
   - Treatment with corticosteroids at a dose that exceeds the prednisone equivalent of 40 mg
   - Treatment with immunosuppressive agents (eg, azathioprine, 6-MP, or methotrexate)
   - Chronic non-steroidal anti-inflammatory drug (NSAID) use (Note: occasional use of NSAIDs and acetaminophen [eg, headache, arthritis, myalgias, or menstrual cramps] and aspirin up to 325 mg/day is permitted)
   - Treatment with Class Ia or Class III anti-arrhythmic drugs or treatment with two or more agents in combination known to prolong PR interval
3) Are receiving treatment with any of the following drugs or interventions within the corresponding timeframe:
   - At Day [redacted]
     - CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) or inducers (eg, rifampicin)
   - Two weeks prior to Day [redacted]
     - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
4) Are receiving treatment with breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine, eltrombopag)

Exclusions Related to General Health:

5) Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin (hCG)
6) Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric or other major systemic disease making implementation of the protocol or interpretation of the trial difficult or that would put the patient at risk by participating in the trial or that would have required a patient to discontinue treatment in previous RPC1063 trial
7) Clinically relevant cardiovascular conditions, including history or presence of recent myocardial infarction, unstable angina, stroke, transient ischemic attack,

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

Exclusions Related to Laboratory Results:

[redacted]

9.3 Considerations for Patients with Comorbid Conditions

9.3.1 Patients with Type 2 Diabetes Mellitus

Patients with type 2 diabetes mellitus were permitted in parent induction/maintenance studies if their glycosylated hemoglobin A1c (HbA1c) was ≤ 9% at Screening. Such patients should receive appropriate diabetes management and treatment during this trial.

Gestational diabetes and steroid-induced diabetes occurring in the past and resolved prior to Screening are not exclusionary.

The treating Investigator should ensure that diabetic patients who are included in the trial are closely monitored for signs or symptoms of [redacted] (see Section 13.2.6). Patients with diabetic uveitis or diabetic patients with significant comorbid conditions such as retinopathy or nephropathy are excluded.

Duration of disease and medication history throughout the trial will be recorded in source documents and in the electronic case report form (eCRF).

9.3.2 Patients with History of Cardiac Disease

Patients with some pre-existing cardiac conditions, who have stable disease and would not be placed at significant safety risk by participating in a trial of RPC1063, were considered for participation in parent induction/maintenance studies and are eligible for enrollment in this trial.

Patients entering this trial should continue to be monitored in the manner in which they were monitored during the parent trial. The treating Investigator should ensure these patients included in the trial are closely monitored for signs of any [redacted] after the first dose of RPC1063, as these patients may be at higher risk for [redacted]

All patients will follow the detailed [redacted] procedures as outlined in Sections 10.5.2 and 13.1.10.

9.4 Trial Discontinuation

Patients may voluntarily withdraw from the trial at any time. The Investigator will provide a written explanation in the source documentation to be entered on the appropriate eCRF page describing the reason for discontinuation.

The criteria for enrollment are to be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, the Medical Monitor must be contacted, and that patient will be withdrawn from the trial if continuation is determined to be a safety risk.

Reasons for discontinuation include, but are not limited, to the following:

- Physician decision: The Investigator must discontinue investigational drug if it is determined that it is not safe or in the patient's best interest to receive further treatment. The Medical Monitor should be promptly notified of the decision
- Non-compliance with investigational drug: After consultation between the Investigator, the Medical Monitor, or and the Sponsor when appropriate, a patient may be discontinued from the trial for failure to comply with dosing regimen as specified by the protocol
- Non-compliance with protocol/protocol deviation: A patient fails to follow protocol procedures, or other event or decision that stands in contrast to the guidelines set in the protocol.
- Adverse event: A patient must be discontinued from investigational drug if, in the judgment of the Investigator or if specified in the protocol, the patient develops an AE such as an intercurrent illness or complication that justifies discontinuation of investigational drug.
- Lack of efficacy: Decision by the patient and/or the Investigator to discontinue treatment due to a lack of expected or desired effect related to a therapy.
- Withdrawal by Patient: The patient may choose to discontinue investigational drug at any time. Patients who discontinue investigational drug will be withdrawn from the trial. Every effort should be made within the bounds of safety and patient choice to have each patient complete the [redacted] Visit and 90-day SFU Visit. If a patient withdraws consent, the only additional trial data to be collected will be the follow up of SAEs as mandated by the protocol.
- Pregnancy: If the patient becomes pregnant investigational drug must be discontinued (see Section 13.2.10)
- Trial termination by Sponsor
- Other (including discontinuation criteria described as part of AESIs in Section 13.2.6)

All patients who discontinue investigational drug should complete an [redacted] Alternative treatment for UC can be started, if needed, [redacted] after discontinuing investigational drug. With the exception of patients who withdraw consent or are lost to follow-up, patients should complete the 90-day SFU Visit for the collection of safety data and to assess their disease status.

The reason for discontinuation of investigational drug will be recorded in the clinical records and the patient's eCRF. For those patients whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw, the Investigator should show due diligence by

documenting in the source documents steps taken to contact the patient (eg, dates of telephone calls, registered letters) prior to withdrawing the patient from the trial.

Patients who withdraw from the trial will not be replaced.

10 INVESTIGATIONAL DRUGS

10.1 Treatments Administered

The Investigator must ensure that the investigational drug will be used only in accordance with the protocol.

Patients should be instructed to take investigational drug orally at approximately the same time each day with or without food.

Patients entering the trial from the open-label period of RPC01-202 will continue to receive RPC1063/ozanimod HCl 1 mg daily. All patients entering the trial from a blinded parent trial or treatment period ([redacted] of RPC01-3101) of RPC1063 will initiate RPC1063 treatment in accordance with a 7-day dose escalation regimen of RPC1063/ozanimod HCl at [redacted] mg [redacted] on Days [redacted] (one RPC1063/ozanimod HCl at [redacted] mg/day [redacted] capsule), RPC1063/ozanimod HCl at [redacted] mg [redacted] on Days [redacted] (two RPC1063/ozanimod HCl [redacted] mg capsules), and reaching RPC1063/ozanimod HCl 1 mg one RPC1063/ozanimod 1 mg capsule) on Day [redacted]. Patients will continue to take open-label RPC1063/ozanimod HCl 1 mg once daily (one RPC1063/ozanimod 1 mg capsule) as part of this clinical trial until the patient completes 5 years (Week 238) and the Safety Follow-up Visit, unless the Sponsor discontinues the development program. See Section 8.3.6 for details on treatment options post study. Patients entering this trial from a prior open-label trial of RPC1063 will not undergo dose escalation.

10.1.1 Instructions for Missed Dose(s)

Patients should be instructed that if they forget to take a dose, they can take the dose within 4 hours of the normal dosing time; otherwise, they should take their next dose at the regular time on the following day. If the patient vomits the capsule, they should be instructed not to take another capsule on the same day, but to take the next dose at the regular time on the following day. Patients will record whether they took the daily dose of medication in a diary that will be reviewed periodically by site staff and the site monitor.

If a dose is missed during the first 2 weeks of treatment, or for more than 7 consecutive days during Days [redacted], reinitiate treatment using the 7-day titration regimen. If a patient misses a dose during dose escalation, the Medical Monitor should be contacted to discuss completing the dose escalation schedule.

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

If the patient misses more than 14 consecutive doses for any reason including AE/SAE, the Medical Monitor must be contacted to discuss procedures for resuming therapy, which may include dose escalation and Day [redacted] procedures on the first day that the patient resumes dosing.

10.2 Method of Assigning Patients to Treatment

Patients must provide proper informed consent before any trial procedures are performed. Refer to Section 17.3 for further details regarding obtaining patients informed consent.

Consented patients meeting all eligibility criteria will be enrolled using the Interactive voice/web-based activated response system (IXRS) which will also be used to log distribution of investigational drug. Further instructions on the use of the system will be provided in a separate IXRS manual.

10.3 Selection of Dose in the Trial

The dose of RPC1063 1 mg once each day was based on the completed Phase 1 (RPCS-001 and RPC01-102) and Phase 2 (RPC01-202) and Phase 2/3 (RPC01-201) trials (see Section 6.2.2 and subsections). The 1 mg/day dose demonstrated better efficacy than the [redacted] mg/day dose across various clinical and endoscopic endpoints in these clinical trials. Furthermore, the expected magnitude of the pharmacodynamic effect on peripheral lymphocyte reduction was observed and this dose demonstrated an acceptable safety profile.

A dose escalation over the first 7 days ([redacted] mg/day on Days [redacted] and [redacted] mg/day on Days [redacted]) will be implemented, as results from the Phase 1 study (RPCS 001) and preliminary results from the Phase 2 study (RPC01-202) indicate that use of a dose escalation regimen appears to mitigate the magnitude of reduction in heart rate (HR). Preliminary evidence from these studies suggested that patients who increase their dose progressively over the first week are less likely to have a profound decrease in HR or blood pressure; therefore, a dose escalation starting with [redacted] mg RPC1063 for the first 4 days of dosing followed by [redacted] mg on Days [redacted] before progressing to the 1 mg/day dose will be used.

10.4 Selection and Timing of Dose for Each Patient

Patients will self-administer RPC1063 orally once daily. Investigational drug should be taken at approximately the same time each day with or without food. See Section 10.1.1 for instructions regarding missed doses.

10.5 Prior and Concomitant Treatments

All treatments, other than RPC1063, being taken by the patients on entry to the trial or at any time during the trial including through the 90-day SFU Visit are regarded as concomitant medications and must be documented on the appropriate section of the eCRF. All ongoing medications indicated at the completion of RPC01-3101 and RPC01-202 must be recorded in the RPC01-3102 concomitant treatment eCRF.

Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dosage information, dates of administration, and reasons for use. For medications with a single active ingredient, generic names for concomitant medication should be used, if possible. For combination products, brand names should be used. The total daily dose should be filled in whenever possible.

10.5.1 Allowed Medications

All prior medications (including over-the-counter medications) administered [redacted] prior to the date of informed consent and any concomitant therapy administered to the patient during the course of the trial (including any ongoing medications at the end of the parent study and new medication started after the completion of the parent study or medications that were initiated in

the prior study) until [redacted] after the final dose of investigational drug will be recorded. Any medication that is considered necessary for the patient's health and that is not expected to interfere with the evaluation of or interact with investigational drug may be continued during the trial.

10.5.2 Concomitant Medications Prohibited Through [redacted] After Investigational Drug Discontinuation

The following medications cannot be used during the trial through [redacted] after investigational drug discontinuation:

- Treatment with Class Ia or Class III anti-arrhythmic drugs [redacted] or treatment with 2 or more agents in combination known to prolong PR interval (eg, combination of a beta blocker and calcium channel blocker such as verapamil) are prohibited during the study unless approved by the Sponsor's representative.
- Marketed biologic therapies such as abatacept, infliximab, etanercept, adalimumab, golimumab, certolizumab, anakinra, rituximab, vedolizumab, and ustekinumab
- Immunomodulatory agents (eg, etrasimod, natalizumab, fingolimod, or tofacitinib)
- Immunosuppressive agents (eg, AZA, 6-MP, cyclosporine, methotrexate, oral cyclosporine, tacrolimus, sirolimus or MMF) or other antineoplastic therapies or immune-modulating therapies
- Any investigational treatment other than the investigational drug specified in this trial
- Live vaccines or live attenuated vaccines
- Intravenous immunoglobulin (IV-Ig) or plasmapheresis
- D-penicillamine, leflunomide, or thalidomide
- Breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine, eltrombopag)
- Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
- CYP2C8 inducers (eg, rifampicin). For patients who are currently enrolled and are receiving monoamine oxidase inhibitors or CYP2C8 inducers, an individual safety assessment will be conducted and, if indicated, either the concomitant medication will be discontinued and the patient will continue in the study or investigational drug will be discontinued and the patient will be withdrawn from the study.

[redacted]

10.5.3 Concomitant Medications Between [redacted] After Investigational Drug Discontinuation and the 90-day Safety Follow-up Visit

The following medications should not be used between [redacted] after investigational drug discontinuation and the 90-day SFU Visit:

- Treatment with Class Ia or Class III anti-arrhythmic drugs or treatment with 2 or more agents in combination known to prolong PR interval (eg, combination of a beta blocker and calcium channel blocker such as verapamil) are prohibited during the study unless approved by the Sponsor's representative.
- Natalizumab, fingolimod, or etrasimod
- Immunosuppressive agents that deplete lymphocytes
- Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
- Live vaccines or live attenuated vaccines

10.5.4 Allowed Vaccinations

- The vaccinations administered during the trial will be recorded in EDC (Electronic Data Capture).

10.6 Medical Care of Patients after End of Trial

Patients who leave the trial and complete their end of trial assessments, including the 90-day SFU Visit, do not require any additional care provided by the sponsor; they will return to the care of their personal physician(s).

10.7 Treatment Compliance

It is the Investigator's responsibility to ensure that patients are correctly instructed on how to take their investigational drug and that each patient is fully compliant with their assigned dosage regimen. Records of investigational drug used and intervals between visits will be kept during the trial. Drug accountability will be noted by the monitor during site visits and at the completion of the trial. Patients will be asked to return any remaining unused investigational drug at the end of the trial. The investigational drug should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained as described below in Section 11.3.

Patients who take less than 80% or more than 120% of investigational drug during the entire treatment period are considered non-compliant.

At each visit, previously dispensed investigational drug capsules will be collected by the Investigator and compliance assessed. Patients will record whether they took the daily dose of investigational drug in a diary that will be reviewed periodically by site staff and the Clinical Monitor. Patients exhibiting poor compliance as assessed by investigational drug counts (ie, 2 or more missed investigational drug days in 1 week) should be counseled on the importance of good compliance to the trial dosing regimen. Patients who are persistently non-compliant (< 80% or >

120%) should be discussed with the Medical Monitor to determine whether they should be withdrawn from the trial.

10.8 Blinding

This is an open-label extension trial. However, to maintain the blind from the parent trial from which a patient may be entering, certain procedures such as dose escalation and cardiac monitoring and certain laboratory values such as leukocytes for all patients entering from a blinded parent trial (eg, end of the Induction Period [redacted] or end of the Maintenance Period of RPC01-3101) will be conducted as outlined in this protocol.

11 INVESTIGATIONAL DRUG MATERIALS AND MANAGEMENT

11.1 Investigational Drug

RPC1063 capsules will be manufactured, quality control tested, and released in accordance with Good Manufacturing Practices (GMP). A clinical distribution vendor will supply the investigational drug (RPC1063 capsules).

RPC1063 will be provided as powder-filled capsules. RPC1063 drug substance is blended with microcrystalline cellulose, silicon dioxide, croscarmellose sodium, and magnesium stearate in Swedish orange opaque hard-gelatin capsules. Two RPC1063 dosage strengths have been prepared for the clinical investigations; [redacted] mg [redacted] and [redacted] mg [redacted]

All investigational drug must be stored in a secure location.

11.2 Packaging and Labelling

RPC1063 capsules will be packaged in [redacted], apart from the dose escalation kits), closed with a [redacted]. The [redacted] on the treatment [redacted] will be [redacted], and [redacted]

The labelling will be in accordance with GMP and Good Clinical Practice (GCP) and any other local regulatory requirements. The label(s) for Investigational Product (IP) will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

11.3 Investigational Drug Accountability

Investigational drug should not be used for purposes other than as defined in this protocol.

All supplies of investigational drug will be accounted for in accordance with GCP. There will be an individual investigational drug accountability record for each patient and the Investigator should maintain accurate records of the disposition of all investigational drug supplies received during the trial. These records should include the amounts and dates clinical drug supplies were received, dispensed to the patient, returned by the patient, and returned to the Sponsor. If errors or damages in the clinical drug supply shipments occur, the Investigator should contact the clinical supply distribution vendor and the Site Monitor immediately. The Site Monitor will periodically check the supplies of investigational drug held by the Investigator or pharmacist to verify accountability of all medication used.

The Investigator will provide the investigational drug only to the identified patients of this trial, according to the procedures described in this trial protocol. After the end of the trial, the Site Monitor will perform final accountability, package, seal, and prepare for shipment. Investigational drug and all investigational drug containers will be returned to the clinical supply distribution vendor and documentation will be returned to the contract research organization (CRO). The CRO

will verify that a final report of drug accountability is prepared and maintained in the Investigator's Trial Master File.

12 ASSESSMENT OF EFFICACY

12.1 Complete Mayo Score, Partial Mayo Score, 9-Point Mayo Score, and Mayo Subscores

The Complete Mayo Score is a composite of four assessments, each rated from 0 to 3: SFS, RBS, MES, and PGA (Schroeder et al, 1987). The MES of the complete Mayo score is derived from an evaluation of findings on endoscopy based on central reading by a qualified central laboratory. The 9-Point Mayo score eliminates the PGA, resulting in a composite of the RBS, SFS, and MES. The Partial Mayo Score eliminates the MES, resulting in a composite of the RBS, SFS, and PGA subscores. The complete Mayo score has a range of 0 to 12 and the 9-Point Mayo score and Partial Mayo Score each have a range of 0 to 9.

The complete Mayo score consists of four subscores, each ranging from (0-3) for a total score that ranges from 0 to 12:

1) Stool frequency[a]
   a) 0 = Normal number of stools for this patient
   b) 1 = 1 to 2 stools more than normal
   c) 2 = 3 to 4 stools more than normal
   d) 3 = 5 or more stools more than normal
2) Rectal bleeding[b]
   a) 0 = No blood seen
   b) 1 = Streaks of blood with stool less than half the time
   c) 2 = Obvious blood with stool most of the time
   d) 3 = Blood alone passes
3) Findings on endoscopy
   a) 0 = Normal or inactive disease
   b) 1 = Mild disease (erythema, decreased vascular pattern, does not include friability)
   c) 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
   d) 3 = Severe disease (spontaneous bleeding, ulceration)
4) Physician's Global Assessment[c]
   a) 0 = Normal
   b) 1 = Mild disease
   c) 2 = Moderate disease
   d) 3 = Severe disease

[a] Each patient serves as his or her own control to establish the degree of abnormality of the SFS.

[b] The daily RBS represents the most severe bleeding of the day.

[c] The PGA acknowledges the 3 other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

See Section 6.2.1 for definitions of clinical remission, clinical response, corticosteroid-free remission, endoscopic improvement, mucosal healing, and histologic remission.

Partial Mayo Scores are calculated using data from Items 1, 2, and 4 only and are calculated using the SFS and RBS data from the most recent consecutive 3-day period prior to the visit, excluding the following:

- The day(s) of a procedure or preparation for a procedure (eg, enemas, other laxative, clear liquid diet) that would affect bowel frequency or blood content of the stool

12.2 Flexible Sigmoidoscopy/Colonoscopy

To ensure quality data and standardization, the same endoscopist should be used throughout the trial wherever possible. Endoscopy images will be obtained during each endoscopy and will be sent for central reading and determination of the Mayo MES. A detailed image review charter from the central reading laboratory will outline the endoscopic procedures, video recordings and equipment. For each patient, video recording of the entire endoscopic procedure will be performed using an acceptable storage medium. The endoscopic recordings will be read centrally in a blinded manner for mucosal lesions and endoscopic severity by a qualified gastroenterologist according to the image review charter. The MES will be determined both at the Investigator site and centrally as described above. The complete and 9-point Mayo score used for clinical endpoints in the trial will utilize the MES derived from the central reader.

Biopsy

Each patient entered into the trial will have colonic biopsies obtained during flexible sigmoidoscopy/full colonoscopy as follows (see Table 2):

- One biopsy pair will be taken from the most inflamed area of the left colon. Biopsies will be placed in formalin. These biopsies will be analyzed centrally.
- ONLY if there is suspicion for clinically significant cytomegalovirus (CMV) colitis, one biopsy should be taken from the base of an ulcer to evaluate for histological presence of CMV, but otherwise is not necessary for inclusion in the trial. Analysis will be performed locally.
- Only if there is suspicion for dysplasia or malignancy, appropriate biopsies should be taken to exclude malignancy or assess dysplasia. Analysis should be performed locally.

Necrotic areas of ulcerated mucosa should be avoided during biopsy. The original location (colonic segment and endoscopic depth) of biopsy specimens should be clearly indicated.

In all cases, the video recordings are to be taken prior to biopsy and sent to central reading center of the study.

12.3 Patient-Reported Outcomes

Patient-reported outcomes (SFS and RBS components of the complete, 9-point, and partial Mayo score), and the clinician-reported PGA will be collected in an electronic diary. Patients will complete the SFS and RBS components of the Mayo subscore daily from the Baseline Visit until the [redacted] Visit.

Patients will be instructed on the use and completion of questions on the electronic diary. The patients' baseline SFS is to be recorded in RPC01-3102 using data collected on the first day of Screening from the RPC01-3101 or RPC01-202 trial. This is defined as the number of stools the patient passed in a 24-hour period prior to having UC or when the patient is in remission.

The diary entries will be reviewed by site personnel during screening (prior to dosing, if applicable) and during all trial visits, through the [redacted] Visit. The SFS and RBS diary entries 2 weeks prior to each trial visit will be used to calculate the complete, 9-point, and partial Mayo score.

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

13 ASSESSMENTS OF SAFETY

13.1 Safety Parameters

13.1.1 Physical Examination

A complete physical examination will include evaluation of the heart, lungs, head and neck, abdomen, skin, and extremities, as well as a check for visual symptoms. All significant findings that are present at the Baseline Visit must be reported on the relevant medical history/current medical conditions eCRF. A check for visual symptoms and a full examination of the skin should be repeated [redacted]. Significant findings made after Baseline that meet the definition of an AE must be recorded on the AEs eCRF.

At all other visits following the Baseline Visit (except [redacted] and 90-day SFU), an interim physical examination will be performed (Table 2). The interim physical examination will include body systems with previously noted abnormalities and/or those body systems associated with any new complaints from the patient.

13.1.2 Height and Weight

For all patients, height and weight will be measured at Visit [redacted] and at the [redacted] visit. Height and weight can also be measured at the SFU Visit at the discretion of the Investigator (eg, in the case of ongoing AEs that need to be further evaluated).

13.1.3 Vital Signs

Systolic and diastolic blood pressure and pulse will be assessed in a sitting position. An automated validated device may be used, if available. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

[redacted]

13.1.4 Electrocardiogram

The 12-lead digital ECG devices will be provided to each clinical site by the central ECG laboratory for the duration of the trial. Detailed instructions describing the process for recording and transmission of the digital ECGs will be outlined in the trial-specific manual and provided to the site before the start of the trial. Paper versions of ECG tracings recorded at the times specified in the Schedule of Events (Table 2) will be printed and photocopied to preserve the ink if necessary, and kept at the site as source documentation.

An ECG will be performed while resting. Electrocardiograms will be performed [redacted] will be evaluated by the treating physician, with input if needed from a local cardiologist or a central reader to confirm if extended monitoring is required. Additional ECG monitoring will be performed on Days [redacted] if cardiac issues are identified on the prior day of dose escalation, as described in Section 13.1.10.

Only clinically significant abnormalities should be reported in the medical history/current medical conditions or the AE eCRF. Clinically significant findings must be discussed with the Medical Monitor before enrolling the patient in the trial.

13.1.5 Ophthalmological Examination

[redacted] will be performed in patients with a history of uveitis or diabetes mellitus or underlying/coexisting retinal disease or in all patients if deemed necessary by local or national requirements, as scheduled in Table 2. All original [redacted] images (colored printouts) are considered source documents that should be made available to the site upon request, or otherwise at the end of the study. [redacted] The [redacted] images may be reviewed by an independent panel of ophthalmologists assigned to this trial.

13.1.6 Dermatological Examination

Dermatological evaluations will be performed by the treating Investigator or designee as part of the physical exam, as scheduled in Table 2. Patients with any suspicious finding noted during the examination will be referred to an appropriately qualified dermatologist for evaluation and treatment, if warranted.

[redacted]

[redacted]

13.1.8 Monitoring of Adverse Events and Serious Adverse Events

Throughout the course of the trial, every effort must be made to remain alert to possible AEs or SAEs. Refer to Section 13.2 for definitions of AEs/SAEs, monitoring, and reporting. Refer to Section 13.2.6 for AEs of special interest.

13.1.9 Monitoring of Concomitant Therapy

The use of concomitant medication and procedures will be monitored throughout the trial. Refer to Section 10.5.2 for prohibited concomitant therapies.

13.1.10 Guidelines for Cardiac Monitoring

Patients entering the trial from the open-label period of RPC01-202 will continue to receive RPC1063 and no additional cardiac monitoring is required.

[redacted]

[redacted]

[redacted]

13.1.11 Clinical Laboratory Evaluations

The central laboratory will analyze the samples. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a laboratory manual.

Additional and repeat laboratory safety testing may be performed at the discretion of the Investigator and analyzed by the local laboratory. Approval from the Medical Monitor must be obtained if any lab test is required to be repeated > 2 times.

- Hematology: Red blood cell count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin (Hb), hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Total WBC count and all differential WBC counts will not be disclosed for Visit [redacted] only and will be monitored centrally throughout the trial.

[redacted]

[redacted]

- Chemistry:
  - Full chemistry panel at Baseline: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, HbA1c, albumin, alkaline phosphatase, creatinine, ALT, AST, gamma glutamyl transferase (GGT), total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and [redacted].
    - HbA1c will be repeated annually
  - All other visits – blood urea nitrogen, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, total bilirubin, conjugated bilirubin, [redacted]. Of note, [redacted] will not be disclosed for Visit [redacted] to maintain the blind from the parent trial from which a patient may be entering.
- Urinalysis: Leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen

[redacted]

- The central laboratory will analyze routine [redacted]. Details regarding collection of samples, shipment of samples, reporting of results, laboratory reference ranges, and alerting abnormal values will be supplied to the site before site initiation in a trial laboratory manual. The results of the analysis will be made available to each site by the central laboratory.
- Investigators will be asked to comment on those abnormalities on the respective laboratory result page, including a notation of the clinical significance of each abnormal finding in the patient's source documents. The laboratory sheets will be filed with the patient's source documents.
- Pregnancy test: Serum β-hCG must be performed in females of childbearing potential at Baseline if more than 1 month has elapsed from the last pregnancy test in the parent trial. Urine

β-hCG will be performed in females of childbearing potential at each scheduled visit. Between scheduled visits up until the 90-day SFU Visit, monthly home urine pregnancy tests should be performed by the patient. If a urine pregnancy test result is positive, the Investigator will instruct the patient to suspend further RPC1063 dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including after the 90-day SFU Visit, if needed.

13.2 Adverse Events and Serious Adverse Events

13.2.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A, II.A.1).

Ulcerative colitis disease relapse and related symptoms will be monitored as trial endpoints and thus will not be recorded as AEs, unless it qualifies as a serious AE to trigger safety reporting as described in Section 13.2.5.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

An Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product causally related to any dose (ICH E2A, II.A.2).

An Unexpected ADR is defined as an adverse reaction, the nature of which is not consistent with the applicable product information (ICH E2A, II.A.3).

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

13.2.2 Definition of Serious Adverse Events

Definition of Serious Adverse Event (SAE): An SAE (experience) or reaction is any untoward medical occurrence that at any dose (ICH E2A, II.B):

- Results in death
- Is life-threatening

NOTE: The term life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital abnormality/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but jeopardize the patient or may require

intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*

Examples of such events may be related to CNS (Central Nervous System), cardiovascular, pulmonary, ophthalmic, gastrointestinal, genitourinary or other body systems and include events such as intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

In case of a fatality, the cause of death is considered as the SAE, and the death is considered as its OUTCOME.

13.2.3 Assessment of Adverse Event Severity

The severity of the AE will be characterized as "mild, moderate, or severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events are incapacitating and interrupt the patient's usual daily activity.

13.2.4 Assessment of Adverse Event Relationship to Investigational Drug

The causal relationship between the investigational drug and the AE has to be characterized as unrelated, unlikely, possible, probable, or related. This medical assessment should be made as soon as feasible when reporting an SAE.

The Investigator is requested to assess the relationship of any AEs to treatment using the following definitions:

- Unrelated: Those AEs which are clearly and incontrovertibly due to extraneous causes (concurrent drugs, environment, etc.) and do not meet the criteria for drug relationship listed under Unlikely, Possible, Probable, or Related.
- Unlikely: An AE may be considered unlikely if it includes at least the first two features:
  - It does not follow a reasonable temporal sequence from administration of the drug
  - It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
  - It does not follow a known pattern to the suspected drug
  - It does not reappear or worsen when the drug is re-administered
- Possible: an AE may be considered possible if it includes at least the first two features:
  - It follows a reasonable temporal sequence from administration of the drug
  - It could readily have been produced by the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient
  - It follows a known response pattern to the suspected drug

- Probable: an AE may be considered probable if it includes at least the first three features:
  - It follows a reasonable temporal sequence from administration of the drug
  - It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient
  - It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug (eg, bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.)
  - It follows a known pattern of response to the suspected drug
- Related: an AE may be considered related if it includes all of the following features:
  - It follows a reasonable temporal sequence from administration of the drug
  - It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient
  - It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug (eg, bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc)
  - It follows a known pattern of response to the suspected drug
  - It reappears or worsens if the drug is re-administered

All efforts should be made to classify the AE according to the above categories.

After initiation of investigational drug, all AEs, regardless of relationship to investigational drug, will be recorded until the patient completes his or her last trial visit.

13.2.5 Reporting of Serious Adverse Events

Reporting requirements for SAEs will be managed on behalf of the Sponsor by the CRO. Full details of the procedures to be adopted will be documented in a safety management plan approved by responsible parties, in brief:

The Investigator will report any SAE that occurs to any patient from the time written informed consent is signed through the last visit. If an SAE occurs after informed consent and is resolved before the first dose of investigational drug in RPC01-3102, the event will be captured in the parent trial only (eg, RPC01-3101 or RPC01-202). If the SAE is ongoing at the time of the first dose in RPC01-3102, it will be transcribed into the eCRF for RPC01-3102. If an SAE occurs after the first dose of investigational drug in RPC01-3102, it will be captured in the eCRF for RPC01-3102. All SAEs that occur within 90 days of the last dose of treatment with the investigational drug, whether or not considered related to the investigational drug, must also be reported. Any SAE that is ongoing when the patient completes the trial or discontinues from the trial will be followed by the Investigator until the event has resolved, stabilized, or returned to Baseline status.

Any AE considered serious by the Investigator or Sub-investigator or that meets serious criteria should be reported to the CRO's Pharmacovigilance group using the designated SAE reporting forms as well as eCRF forms and procedures. Data entry must be completed within 24 hours from the time the trial site personnel first learned of the event.

The SAE hotline contacts are as follows:

Phone Number: +1 866-599-1341

Fax Number: +1 866-599-1342

Email: QPV_Receptos@iqvia.com

The initial report should be promptly followed by detailed, written reports, which will include copies of hospital case records, discharge summaries, autopsy reports, and other documents when requested and applicable. For unrelated cases, a full detailed case description may negate the need for additional hospital case records, discharge summaries, etc.

13.2.5.1 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

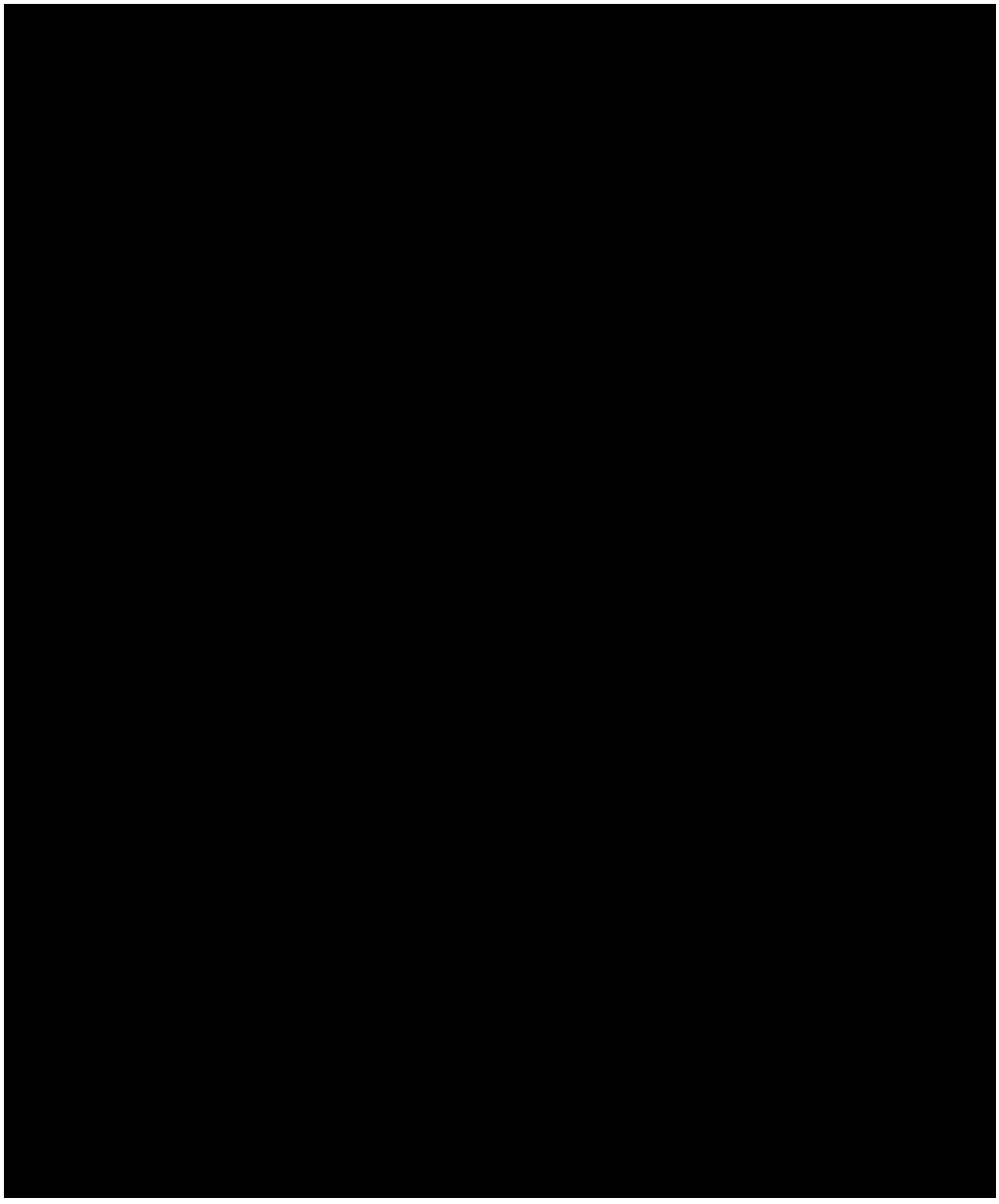
Investigators will be notified by the CRO of all SAEs that require prompt submission to their IRB or IEC. Investigators should provide written documentation of IRB/IEC notification for each report to the CRO. The CRO will ensure that all SAEs are reported to the appropriate Regulatory Authorities as required. Reporting of SAEs must comply with ICH E6, 4.11.1.

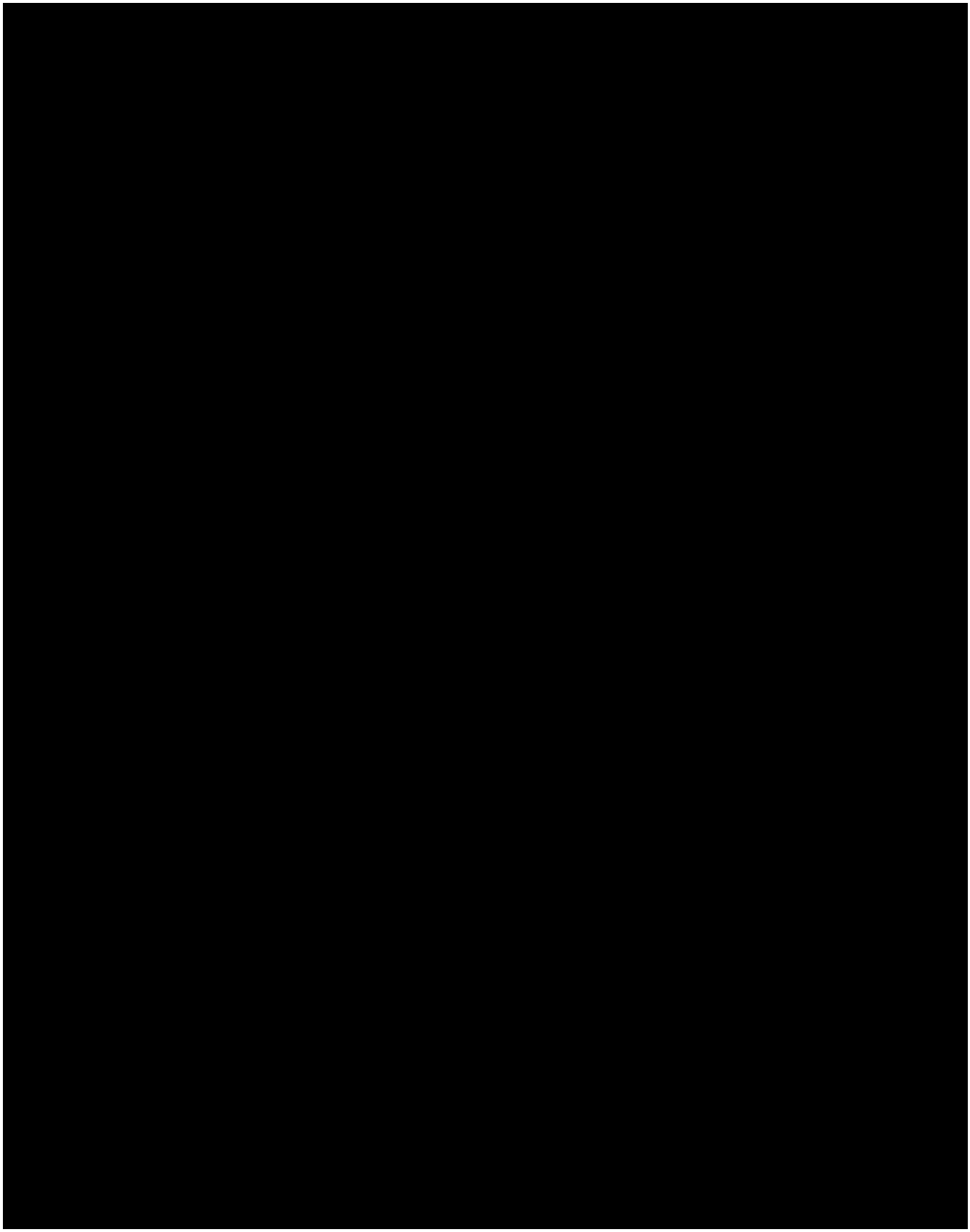
13.2.6 Adverse Events of Special Interest

Potential AEs that may be a consequence of $S1P_1$ modulation will be closely monitored during the trial. [redacted] The study team will perform routine safety reviews starting after the first patient is dosed with investigational product.

Special considerations regarding monitoring for these events are as follows:

[redacted]





13.2.7 [redacted] Pandemic

[redacted] pandemic has been identified as a potential risk to clinical trial patients in general and may particularly affect individuals with underlying chronic diseases on immunomodulatory therapies. It is not known whether taking ozanimod increases the risk of [redacted] infection, or the duration or severity [redacted].

Evaluation and management of [redacted] infections arising during the course of the trial are left to the discretion and expertise of the investigator. For patients who exhibit symptoms consistent with [redacted], testing for [redacted] to inform decisions and clinical care during the study should follow local standard practice. The Sponsor advises the Investigator to consult the Medical Monitor.

Each study visit will include an assessment for AEs including [redacted] and other infections. In order to facilitate reporting of [redacted] events that occur during the study, all AEs and SAEs related to [redacted] should be reported from the time of consent until the final study visit.

Procedures related [redacted] and treatment (eg, intubation, dialysis) must be reported in the appropriate eCRF.

[redacted]

Administration of vaccinations must be reported along with dates of administration, vaccine name/trade name, location, and laterality in the appropriate eCRF. A separate logline should be entered for each vaccine administered.

13.2.8 Monitoring of Patients with Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

- Investigators must carefully monitor each patient for AEs. This includes clinical laboratory variables. Assessments must be made of the seriousness, severity, and relationship to the administration of the investigational drug. After the initial AE/SAE report, the Investigator is required to follow up proactively with each patient and provide further information to the CRO on the patient's condition. During the trial, all AE/SAEs should be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow-up. Safety reporting must comply with ICH E6, 4.11.

13.2.9 Overdose of Investigational Drug

An overdose is any dose of investigational drug given to a patient or taken by a patient that exceeds the dose described in the protocol. There is no information available regarding overdose with

RPC1063. Any overdose, with or without associated AEs, must be promptly reported to the CRO's Medical Monitor or other designated Drug Safety Center. Overdoses need to be recorded in the drug log in the eCRF; but only in the case of any AEs associated with the overdose should these be reported on relevant AE/SAE sections in the eCRF.

13.2.10 Procedures in Case of Pregnancy

If a urine pregnancy test is positive, the Investigator will instruct the patient to suspend further RPC1063 dosing. If the test was performed by the patient between scheduled visits, a follow-up appointment will be scheduled as soon as possible. A serum pregnancy test will be performed for confirmation.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational drug may have interfered with the effectiveness of a contraceptive medication; however, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the patient was discontinued from the trial. In cases of live birth, the infant will be followed for up to a year.

Male patients should also be instructed to notify the Investigator in the event that their female partner becomes pregnant. Attempts should be made to follow female partners of trial patients, if they should become pregnant. The Investigator must obtain informed consent from the pregnant partner of a trial patient prior to collecting data on her pregnancy and its outcome.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the Sponsor and/or its designee. In cases of live birth, the infant will be followed for up to a year.

13.2.11 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) was charged with monitoring data from the trial as part of the ozanimod UC Phase 3 program, as well as general aspects of trial conduct. The DSMB scope, conduct, processes, and accountabilities are specified in a separate charter.

The committee met periodically during the trial (approximately 4 times each year) to review aggregate analyses by treatment group including but not limited to enrollment, treatment compliance, adherence to follow-up schedule, and safety data from the trial. The DSMB recommended to continue the study without modification and did not recommend modifying or stopping the trial early due to safety concerns based on data reviews.

As the maintenance period has been completed for the RPC01-3101 study, the DSMB will no longer meet to review data from the UC Phase 3 program. The internal team will continue to monitor the data from this open-label extension study.

[redacted]

[redacted]

13.4 Appropriateness of Measurements

The efficacy and safety assessments are standard assessments and deemed to be reliable, accurate, and relevant for this indication and patient population.

14 PLANNED STATISTICAL METHODS

14.1 Determination of Sample Size

As this is an open-label extension trial for patients who previously participated in a trial of RPC1063 in UC, there is no statistical basis for the sample size. It is anticipated that up to [redacted] patients who participated in prior studies of RPC1063 in UC may be eligible for treatment in this trial.

14.2 Statistical Methods

14.2.1 General Considerations

All efficacy and safety data will be listed by patient. Baseline is defined as the last observed measurement prior to the Day [redacted] receipt of investigational drug.

In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using number of patients (n), mean, standard deviation (SD), minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.

14.2.2 Analysis Populations

All patients who receive at least one dose of investigational drug will comprise both the Intent-to-Treat (ITT) population and the Safety population. These populations will be used to summarize all efficacy and safety data, respectively.

14.3 Disposition, Demographics, and Baseline Characteristics

The number and percentage of patients in each population will be summarized. Patient disposition, including the number of patients screened, dosed, and not completing trial by reason for dropout will be summarized. Patient demographics will be summarized and will include age, sex, race, ethnicity, height, weight, and body mass index.

Baseline characteristics for each patient from their previous trial will be summarized and will include age at UC symptom onset, age at UC diagnosis, years since UC symptom onset, years since UC diagnosis, prior anti-tumor necrosis factor use, prior corticosteroid use, each component of the Mayo score, the complete Mayo score, the partial Mayo score, and the 9-Point Mayo score.

Compliance with investigational drug will be summarized and will include the number of patients estimated to be < 80% compliant, 80 to 100% compliant, > 100%, and > 120% compliant.

14.4 Efficacy

Due to the open-label nature of the trial and the lack of a control group, all data will be summarized, and no hypothesis testing will be performed. Each efficacy endpoint will be summarized and 95% confidence intervals around the estimates may also be presented. All efficacy data will be listed.

14.4.1 Handling Missing Data

For all proportion-based efficacy endpoints, patients with missing efficacy data will be considered non-responders.

For continuous efficacy endpoints, patients with missing data will have their last post-baseline value carried forward.

Observed-cases analyses will also be presented for all efficacy endpoints.

14.5 Safety Analyses

Adverse events will be monitored during the trial and the data analyzed with respect to incidence within each parent trial treatment group as well as severity and potential relationship of the AEs to investigational drug.

All AEs with a start date before the first dose date in RPC01-3102, which are ongoing from a previous trial to RPC01-3102, will be listed in the AE data listing and labeled as "Prior Adverse Event."

Adverse events with an onset date on or after the first open-label dose date in RPC01-3102, or with onset prior to the first open-label dose date in RPC01-3102 that increase in severity on or after the first dose of investigational drug will be considered treatment emergent. Treatment-emergent AEs will be summarized for the Safety population by System Organ Class and Preferred Term and presented in descending order of frequency within each System Organ Class. Serious AEs and AEs leading to discontinuation will be summarized similarly.

Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together. For each laboratory test, individual patient values outside the standard reference range will be flagged and listed. Shift tables will be produced showing the frequency of shifts from Baseline to the highest and to the lowest on-trial value in and out of the normal range as well as by visit. Changes from Baseline to each visit for each numeric laboratory parameter will also be summarized.

The change from Baseline to each visit for each of the vital sign variables will be summarized. Abnormal vital sign values will be flagged and listed.

The change from Baseline to each visit for each of the ECG parameters will be summarized. An outlier analysis of ECG results will be conducted.

14.6 Interim Analyses

Interim analyses were performed to support regulatory submission activities for the MS and UC indications.

15 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1 Monitoring

The Sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical trial. The CRO monitors will work in accordance with CRO standard operating procedures (SOPs) and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact with the Investigator.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each site while patients are enrolled in the trial.

15.2 Data Management/Coding

Electronic Data Capture (EDC) will be used for this trial, meaning that all eCRF data will be entered in electronic forms at the site. All EDC systems used in the trial will have access-controlled security and an audit history available to document any changes made to the data throughout the course of the trial. Data collection recorded in site source documents will be entered into the eCRF by authorized site staff designated by the Investigator. Patients will record whether they took the daily dose of investigational drug directly into an electronic diary, and this will be considered a source document. Appropriate training and security measures will be completed with the Investigator, all authorized site staff, and patients prior to the trial being initiated and any data being entered into the system for and/or by any trial patients.

All data entered by the site staff must be entered in English. The eCRFs should be completed contemporaneous to the patient's visit. The Investigator may delegate data entry, but is responsible for verifying that all data entries in the eCRFs are accurate and correct at the conclusion of the trial.

Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the trial. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

Source documents will be made available for inspection by the trial monitor at each monitoring visit. The Investigator must complete eCRFs for each patient who receives investigational drug. Any copy of source document(s) that are provided to the Sponsor or its representatives for any purpose (eg, in support of an SAE report) must be redacted such that all patient-identifying information is removed, and clearly labeled with the trial and patient number.

All AEs and medical histories recorded in the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary. Versions of dictionaries to be used will be specified in the data management plan for the trial.

15.3 Quality Assurance and Inspections

Sites, the trial database, and trial documentation may be subject to Quality Assurance audit during the course of the trial by the Sponsor or CRO on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

16 QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Study Monitoring and Source Data Verification

According to the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs. Study Monitoring including, risk-based monitoring, risk management and mitigation strategies as well as analytical risk-based monitoring, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) will be followed as per the monitoring plan.

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Central laboratories for clinical laboratory parameters and ECGs
- Site initiation visit
- Early site visits post-enrollment
- Routine site monitoring
- Ongoing site communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report

In addition, Sponsor and/or CRO Clinical Quality Assurance Department may conduct periodic audits of the trial processes, including, but not limited to site facilities, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all trial-related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

16.2 Investigational Medicinal Product Quality Issues

Investigational Medicinal Product Quality Issues such as IP safety, purity, potency, quality and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to the study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report any issue or concern of all sponsor-supplied IP (eg, manufacturing, packaging and labelling, storage, and/or distribution), if suspected to have occurred before the product was received, becomes the responsibility of the investigational site. This includes suspected quality issues of components co-packaged with the drug, labelling, and IP device/drug combination products, and medical devices.

- In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps).

- When reporting, provide as much product information as possible. Suspected IP quality issues will be investigated, and a response will be provided back to the investigational site.

17 ETHICS

17.1 Institutional Review Board or Independent Ethics Committee

An IEC should approve the final protocol, including the final version of the Informed Consent Form (ICF), and any other written information and/or materials to be provided to the patients. The Investigator will provide the Sponsor or CRO with documentation of IRB/IEC approval of the protocol and ICF before the trial may begin at the site(s). The Investigator should submit the written approval to the Sponsor or representative before enrollment of any patient into the trial.

The Sponsor or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor or CRO of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the ICF document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of patients or the conduct of the trial. Similarly, the Investigator will submit written summaries of the trial status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the trial, the Investigator will provide the Ethics Committee with a brief report of the outcome of the trial, if required.

17.2 Ethical Conduct of the Trial

This trial will be conducted and the informed consent will be obtained according to the ethical principles stated in the applicable version of the Declaration of Helsinki, the applicable guidelines for Good Clinical Practice (GCP; CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the trial will be conducted.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human patients. The trial will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety and well-being of the participating trial patients are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

17.3 Patient Information and Informed Consent

The Investigator will explain the benefits and risks of participation in the trial to each patient and/or the impartial witness and obtain written informed consent. Written informed consent must be obtained prior to the patient entering the trial and before initiation of any trial-related procedure. The final, version dated form must be agreed to by the IRB/IEC and must be provided in language readily understood by the patient. In case the patient is unable to read or write, an impartial witness should be present during the entire informed consent discussion. After the patient has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee will retain an original consent form for each patient, signed and dated by the patient, or witness, and by the person who conducted the informed consent discussion. The Investigator will

supply all enrolled patients with either a copy of their signed informed consent or, depending upon local requirements, a second original informed consent, signed by both parties.

The consent form may need to be revised during the trial due to a protocol amendment or should important new information become available that may be relevant to the safety of the patient. In this instance, approval should always be given by the IRB/IEC and existing patients informed of the changes and re-consented, as directed by the IRB/IEC and in accordance with its policies and procedures; however, in some instances where an immediate change is necessary to eliminate an apparent hazard to patients, then it would not be necessary for a protocol amendment to receive IRB/IEC review and approval before being implemented. Those patients who are presently enrolled and actively participating in the trial should be informed of the change if it might relate to the patients' willingness to continue their participation in the trial.

With the consent of the patient, the Investigator should inform the patient's primary physician about participation in the clinical trial.

17.4 Patient Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

17.5 Investigator Obligations

This trial will be conducted in accordance with the International Council on Harmonization (ICH) Harmonized Tripartite Guideline for GCP (GCP, 1997); the US Code of Federal Regulations (CFR) Title 21 parts 50, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

A summary of Investigator Obligations is provided in (Appendix 2).

The Investigator agrees to conduct the clinical trial in compliance with this protocol after the approval of the protocol by the IRB/IEC in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

17.6 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 1). By signing the protocol, the Investigator confirms in writing that they have read, understand, and will strictly adhere to the trial protocol and will conduct the trial in accordance with ICH Tripartite Guidelines for Good Clinical Practice and applicable regulatory requirements. The trial will not be able to start at any site where the Investigator has not signed the protocol.

18 DATA HANDLING AND RECORD KEEPING

18.1 Inspection of Records

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient enrolled in the trial.

The Investigator will allow the Sponsor, CRO, and authorized regulatory authorities to have direct access to all documents pertaining to the trial, including individual patient medical records, as appropriate.

18.2 Retention of Records

It is the Investigator's responsibility to maintain essential trial documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The trial site should plan on retaining such documents for approximately 15 years after trial completion. The trial site should retain such documents until at least 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the trial is being conducted. Patient identification codes (patient names and corresponding trial numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any trial records.

No records should be disposed of without the written approval of the Sponsor.

19 PUBLICATION POLICY, FINANCING, AND INSURANCE

The data generated by this trial are confidential information of the Sponsor. The Sponsor will make the results of the trial publicly available. The publication policy, financing, and insurance information with respect to the Investigator and the site will be set forth in the Clinical Trial Agreement.

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21 APPENDICES

APPENDIX 1 INVESTIGATOR SIGNATURE

PROTOCOL TITLE: A Phase 3, Multicenter, Open-Label Extension Trial of Oral RPC1063 as Therapy for Moderate to Severe Ulcerative Colitis

PROTOCOL NO: RPC01-3102

This protocol is a confidential communication of Celgene International II Sàrl. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Celgene International II Sàrl.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

APPENDIX 2 INVESTIGATOR RESPONSIBILITIES

Per Good Clinical Practices 21CFR312.53

The Investigator:

- Will conduct the study in accordance with the relevant, current protocol and will only make changes in the protocol after notifying the Sponsor, except when necessary to protect the safety, the rights, or welfare of patients;
- Will comply with all requirements regarding the obligations of clinical Investigators and all other pertinent requirements;
- Will personally conduct or supervise the described investigation;
- Will inform any potential patients that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and IEC review and approval are met;
- Will report to the Sponsor adverse experiences that occur in the course of the investigation in accordance with Section 312.64;
- Has read and understands the information in the Investigator's Brochure, including the potential risks and side effects of the drug; and
- Will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

Per Good Clinical Practices 21CFR312.60

General Responsibilities of Investigators:

An Investigator is responsible for ensuring that an investigation is conducted according to the signed Investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of drugs under investigation. An Investigator shall, in accordance with the provisions of part 50, obtain the informed consent of each human patient to whom the drug is administered, **except as provided in 21CFR50.23.**

This document summarizes the changes to Protocol RPC01-3102 from Version 8.0 (12 June 2020) to Version 9.0 (dated 23 August 2021).

1. OVERVIEW OF KEY CHANGES (JUSTIFICATION FOR AMENDMENT)

Main reason/purpose for amendment: Significant changes and rationale for the changes included in the amendment are briefly summarized below in Section 1 with detailed description in Section 2.

1. **Extension of the duration of trial to evaluate the long-term safety and durable efficacy in UC patients treated with ozanimod.**

   To ensure that a patient's preference for commercially available Zeposia (in the country of approval) is respected and a smooth transition is provided in the event that commercial ozanimod or an access program becomes available prior to March 2023, patients may transition to the commercial product after discussion with the Investigator. Patients who transition to commercial ozanimod are not required to attend safety follow-up visits after their [redacted] as long as commercial ozanimod is started within 14 days of discontinuation of study drug.

   Revised Sections: Protocol Synopsis and Section 8.3.4 Safety Follow-Up

2. **Safety evaluation criteria to justify less frequent visit schedule, decreasing the burden on the patient.**

   Given the well-established safety profile and to simplify the visit schedule in this long-term extension, frequency of visits after [redacted] was reduced from [redacted] intervals, with the exception for patients with specific safety concerns who require more frequent visits.

   Revised Sections: Protocol Synopsis, Section 8.3.4 Safety Follow-Up and Schedule of Events (Table 1) footnote (j),

[redacted]

5. **Cardiac Monitoring requirement revision.**

[redacted]

Revised Section: Section 13.1.10 Guidelines for Cardiac Monitoring was updated

6. [redacted].

Updated [redacted] to align with risk-based monitoring and current ozanimod prescribing information.

Revised Sections: Section 13.1.5 Ophthalmological Examination and Schedule of Events

Table 1-[redacted]

7. **Guidance on [redacted] (following pandemic).**

Provided additional guidance on [redacted] infection, risk, and vaccinations in accordance with Sponsor-wide and ozanimod specific recommendations.

Revised Section: New Objective 7.1 and Section 13.2.7 [redacted] Pandemic were added

8. **Prohibited Medication Revisions (to ease restrictions and simplify):**
   a. Removed prohibition of antimotility medications (minimal impact on disease activity)
   b. Removed prohibition of chronic NSAID (Non-steroidal anti-inflammatory drugs) use, as these medications are rarely used in UC
   c. Removed CYP2C8 inhibitors as a prohibited medication during the study given that there is no meaningful impact on ozanimod metabolism; CYP2C8 inducers are prohibited through [redacted] SFU (Safety Follow-up) only (no longer through 90 Day SFU)
   d. Consolidated medications of the same type/class

Revised Sections: Section 10.5.2 Concomitant Medications Prohibited Through the [redacted] Safety Follow-up Visit, Section 10.5.3 Concomitant Medications Between the [redacted] Safety Follow-up Visit and the 90-day Safety Follow-up Visit, and Section 12.1 Complete Mayo Score, Partial Mayo Score, 9-Point Mayo Score, and Mayo Subscores

9. **Packaging and Labelling**

Details were updated as appropriate to reflect the information shown on the package and labelling for IP.

Revised Section: 11.2 Packaging and Labelling

10. [redacted]

Revised Section: Section 13.2.6 Adverse Events of Special Interest

11. **Study Monitoring.**

    Updated new language for Study Monitoring, which also allows for a risk-based approach and remote monitoring where possible.

    Revised Section: Section 16.1 Study Monitoring and Source Data Verification

This document summarizes the changes to Protocol RPC01-3102 from Version 7.0 (dated 22 May 2019) to Version 8.0 (dated 12 June 2020).

1. OVERVIEW OF KEY CHANGES

The following bulleted list identifies the key changes to the protocol and provides the rationale for each change:

- [redacted]
- Section 10.5.2 and 10.5.3: Concomitant medications has been updated to specify that calcium channel blockers, when combined with beta blockers, increase the risk of prolonged QT interval. This was previously implied by giving the example of verapamil.
- [redacted]
- [redacted]
- [redacted]
- References to Cohort 3 ([redacted]) have been removed throughout the protocol, as no adolescents were enrolled in parent study RPC01-3101.
- Drug dependence and withdrawal assessments have been removed from the protocol. These assessments were originally included to complement the abuse liability data being collected in the Ozanimod multiple sclerosis (MS) program.

- An additional notation was added to Section 13.2.10 to indicate that the Data Safety Monitoring Board (DSMB) no longer needs to review the data from this open-label extension study. As RPC01-3101 (blinded parent study) is now complete, the internal study team will continue to monitor the data for the duration of the study.
- Additional instructions for missed doses were added to Section 10.1.1, in accordance with the prescribing information for ozanimod.
- Section 6.2.2 now includes updated information on the status of ozanimod clinical studies under the ulcerative colitis indication.
- Section 10.5.2 Concomitant Medications Prohibited: Antineoplastic therapies and immune-modulating therapies were added to be consistent with the Investigator's Brochure, in order to avoid additive immunosuppressive effects.
- Section 10.5.1 on allowed medications section was updated per a previous protocol clarification letter. This clarification now specifies to include any ongoing medications at the end of the parent study and new medication started after the completion of the parent study or medications that were initiated in the prior study.
- The text in Section 14.6 was updated to indicate that interim analyses were performed to support regulatory submission activities for the MS and ulcerative colitis (UC) indications.
- [redacted].

This document summarizes the changes to Protocol RPC01-3102 from Version 6.0 (dated 18 Dec 2018) to Version 7.0 (dated 22 May 2019).

1. OVERVIEW OF KEY CHANGES

The following bulleted list identifies the key changes to the protocol and provides the rationale for each change:

- The 75-day (±10 days) Safety Follow-up Visit was extended to a 90-day (±10 days) Safety Follow-up Visit. [redacted]
- Extended the requirements for contraception in females after treatment discontinuation from the 75-day Safety Follow-up Visit to the 90-day Safety Follow-up Visit.
- Extended the requirements for reporting of adverse events (AEs) after treatment discontinuation from the 75-day Safety Follow-up Visit to the 90-day Safety Follow-up Visit.
- The requirement for male contraception was removed. Using safety factor assumptions of tenfold higher concentration in the semen than plasma, a twofold higher dose of ozanimod, and semen levels at the maximum concentration (C_{max}), exposure ratio estimates were negligible for female partners of male patients and do not represent a meaningful risk.
- Added the following Safety Follow-up Visits for up to approximately 80 adult patients: Last dose +1, 4 (±1 day), 7 (±2 days), 14 (±3 days), 21 (±3 days), and 90 (±10 days) days. Relevant assessments at these visits include AEs, vital signs, concomitant medications, and the following newly added assessments: Physician's Withdrawal Checklist (PWC-20), Hospital Anxiety and Depression Scale (HADS), and Epworth Sleepiness Scale (ESS). These assessments will also be performed at the [redacted] and in all adult patients at the first scheduled visit on study treatment after approval of Protocol Amendment Version 7, in order to provide a baseline assessment while on study drug.
- As described in the "Assessment of Abuse Potential of Drugs" FDA guidance document, an evaluation of abuse potential is most relevant for New Molecular Entities with Central Nervous System activity that have not previously been assessed by the Food and Drug Administration (FDA) for abuse potential. Considering this general guidance, the dependence and withdrawal questionnaires are being included in this protocol to complement the abuse liability data being collected and generated in the Ozanimod Multiple Sclerosis program.
- Updated the section for safety assessments to include newly added dependence and withdrawal assessments.

- Updated safety endpoints section(s) to include newly added assessments for withdrawal/dependence.
- Updated statistics section(s) to include planned summaries for newly added assessments.
- Updated the Table of Events for additional visits such that the reference point is Day [redacted] (versus the last visit). Also clarified that HbA1c assessments will be performed at Baseline, [redacted].
- [redacted], as the Safety Follow-up Period follows this visit before the [redacted] will be declared.
- Removed language regarding consultation with the Medical Monitor for medications prohibited between [redacted] and 90 days for the Safety Follow-up Period.
- Removed tofacitinib as a prohibited medication between [redacted] and 90 days for the Safety Follow-up Period.
- Clarified that patients who enter as adolescents should continue with assessments for adolescents for continuity purposes, and that they do not need to complete assessments specific only for adults.
- Removed [redacted] from discontinuation criteria, [redacted]
- Removed reference to adult partner pregnancies, as partner pregnancies should be followed for all male patients.
- Clarified language around scope and duration of the Data Safety Monitoring Board (DSMB).
- Clarified that WBC counts and WBC differentials, as well as [redacted], will not be disclosed for Visit [redacted] only (to maintain the blind from the parent trial from which the patient is entering). In addition, [redacted] and [redacted] values of interest were updated to include SI units.
- Added references, abbreviations, and other minor edits as appropriate.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- [redacted] this protocol is being amended to include adolescent patients in Study RPC01-3102. Eligible adolescent patients will enter the trial from parent study PRC01-3101.
- Throughout the protocol, [redacted], and Definition 2 is now referred to as the Three-component Mayo to better describe the constituents of the definition.
- For statistical analysis purposes, clinical remission and clinical response will be calculated using the Three-component Mayo definition for all regions. This is in accordance with the recent FDA and European Medicines Agency (EMA) guidelines, and removes the subjectivity of the Physician's Global Assessment (PGA) from the calculation.

  Newly added language or revised text appears in the following sections of the protocol:

  - Synopsis; Throughout the Synopsis
  - Section 7.1; Objectives
  - Section 7.2; Efficacy Endpoints
  - Section 8.1.; Summary of Trial Design
  - Section 8.2.; Discussion of Trial Design
  - Section 8.3.2.; Trial Visits
  - Section 10.1.; Treatments Administered
  - Section 10.3.1.; Selection of Dose in the Trial for Adolescent Patients
  - Section 10.8.; Blinding
  - Section 12.1; Assessment of Efficacy; Mayo Score, Partial Mayo Score, and 9-Point Mayo Score, Pediatric Ulcerative Colitis Activity Index
  - Section 13.1.2.; Assessments of Safety; Height and Weight
  - Section 13.1.10.; Assessments of Safety; Guidelines for Monitoring Patients at Baseline Visit (Day [redacted])
  - Section 14.3; Planned Statistical Methods; Disposition, Demographics, and Baseline Characteristics
- Other updates and additions related to the adolescent cohort include:
  - Section 4. List of Tables
  - Section 6.1. Ulcerative Colitis
  - Section 6.2. RPC1063

- Section 6.2.1. Nonclinical Studies
- Updated footnote d in Table 2 (Section 8.1 Summary of Trial Design).
- Added Table 4 (Section 12.1) to include Pediatric Ulcerative Colitis Activity Index (PUCAI) and included PUCAI in Schedule of Events (Section 8.1 Summary of Trial Design/Table 1 Schedule of Events).
- Updated Table 1, Schedule of Events, to include specific adolescent patient assessments. (Section 8.1 Summary of Trial Design).
- Guidelines on informed consent/assent, early discontinuation guidelines, and withdrawal were included for the adolescents in Cohort 3. (Section 9.1 Inclusion Criteria, Section 9.4 Trial Discontinuation, Section 10.2; Method of Assigning Patients to Treatment, and Section 17.3 Patient Information and Informed Consent/Assent)

- Other important updates and their rationale include:
  - The volume of blood taken at each visit, added [redacted] (Section 8.1 Summary of Trial Design/Table 1 Schedule of Events, footnote n).
  - Updated language in Section 9.4. (Trial Discontinuation) to clarify when alternative treatments for UC can begin.
  - Section 10.5.2; Cholestyramine was removed as a prohibited medication because bile acid malabsorption is not known to have an effect on ulcerative colitis disease status.
  - Updated language in Section 12.3 (Patient Reported Outcomes) to clarify when the questionnaires are to be completed, and updated Table 1, Schedule of Events, Mayo patient diary line to be consistent with Section 12.3.
  - Updated language in Section 13.1.1. (Physical Examination) to clarify the difference between the complete physical examination and interim physical examination, and at which visits each is conducted. Footnote f in Table 1, and Schedule of Events were also updated to be consistent with Section 13.1.1.
  - A separate line was added in Table 1, Schedule of Events, for interim physical examination to clarify the visits when the interim physical examinations would be conducted, consistent with Section 13.1.1.
  - [redacted]
  - [redacted]
  - Added footnote e in Table 2 and updated Section 10.1 (Treatments Administered) to specify which subjects would undergo first dose escalation and cardiac monitoring.

- Additional height and weight assessments for adolescent patients added [redacted] (Section 8.1 Summary of Trial Design/Table 1 Schedule of Events and Section 13.1.2 Height and Weight).
- Added hematology blood draw and optional safety assessments at the 75-day Safety Follow-up Visit to monitor safety (Section 8.1 Summary of Trial Design/Table 1 Schedule of Events and Section 8.3.4 Safety Follow-Up).
- [redacted]
- Updated Section 6.2 with additional information regarding metabolites of ozanimod.
- [redacted]
- HbA1c was added at the Baseline Visit and annually thereafter (Section 8.1/Table 1 Schedule of Events, Section 13.1.11 Clinical Laboratory Evaluations) in order for subjects to receive appropriate diabetes management and treatment during this trial.
- Etrasimod and tofacitinib were added to the list of excluded and prohibited UC medications during the study (Section 2 Synopsis, Section 9.2 Exclusion Criteria, Section 10.5.2 Concomitant Medications Prohibited Through the [redacted] Safety Follow-up Visit, and Section 10.5.3 Concomitant Medications Between the [redacted] Safety Follow-up Visit and the 75-Day Safety Follow-up Visit).
- Section 13.1.5 (Ophthalmological Examination) was updated with details regarding source documentation and review of [redacted].
- [redacted]

- Minor updates include the following:
  - Updated Section 6.2.1 to include nonclinical study information, which was previously referenced to the IB.
  - [redacted]
  - Updated language in Section 13.2.9. (Procedures in Case of Pregnancy) to specify that only adult patients are required to follow pregnancy partner procedures.
  - Added "/assent" to the word "consent" throughout the protocol.
  - Updated signature page.
  - Updated List of Abbreviations and Definitions of Terms.

- Corrected date for last patient completed in Synopsis.
- Added definition for females of childbearing potential (FCBP) including contraception educational language (Section 9.1 Patient Inclusion Criteria). Contraception education was also added to Table 1, Schedule of Events.
- [redacted]
- Added notation to Section 10.8 Blinding and Section 13.1.11 Clinical Laboratory Evaluations such that certain laboratory results will not be disclosed to maintain the blind from the parent trial from which a patient may be entering.
- Removed requirement for collection of nontrial diagnostic, therapeutic, or surgical procedures relating to UC (Section 10.5.1 Allowed Medications).
- Separated Table of Contents and List of Tables into 2 separate sections (Section 3 and Section 4, respectively).
- Specified throughout that patients will receive treatment as part of this trial until the end of 2021, or until marketing approval of RPC1063 for UC is obtained in their country, or until the Sponsor discontinues the development program, whichever comes first.
- Updated acronym for ICH to International Council on Harmonisation (Section 5, Section 17.5)
- References (Section 20. REFERENCES) were updated.

This document summarizes the changes that were made between Protocol RPC01-3102 Version 5.0 (dated 07 Jun 2017) and Version 5.0 (dated 29 May 2018).

1. OVERVIEW OF KEY CHANGES

The following bulleted list identifies the key changes to the protocol and provides the rationale for each change:

- Updated description of RPC1063 to include metabolite CC112273.
- A 75-day (±10 days) Safety Follow-up Visit was added to ensure adequate collection of adverse events that could be associated with investigational drug. [redacted]
- [redacted]
- [redacted]
- [redacted].
- Added details regarding previous RPC1063 trial participation requirement to inclusion criterion #1.
- Added dosing instructions and timing of visits for patients entering the study from the open-label period of Study RPC01-202.
- Added breast cancer resistance protein (BCRP) inhibitors to the list of medications that are prohibited during the trial until the [redacted] Safety Follow-up Visit. In a Phase 1 drug-drug interaction study, a strong inhibitor of BCRP, cyclosporine, had no effect on ozanimod exposure, while it approximately doubled the exposure of its active metabolites, RP101988 and RP101075. While the major active metabolite CC112273 is not a substrate of drug transporters, it is unknown if the increase in RP101075 (via RP101988) may also lead to a similar increase in CC112273, which is formed directly from RP101075.
- Added monoamine oxidase inhibitors to the list of excluded medications and the list of medications that are prohibited during the trial and safety follow-up period because in vitro data show that the major active metabolite CC112273 is formed by and inhibits MAO-B. The potential for clinical interaction with MAO inhibitors has not been studied.
- Added CYP2C8 inducers or inhibitors to the list of excluded medications and the list of medications that are prohibited during the trial and safety follow-up period because in vitro data show that the major active metabolite CC112273 is further metabolized by CYP2C8 (and by carbonyl reductase). The potential for clinical interactions with

CYP2C8 inhibitors or inducers has not been studied and therefore co-administration is not recommended.

- Changed “titration” to “dose escalation” throughout the protocol for consistency with other ongoing RPC1063 protocols.
- Added nomenclature and dose equivalency between RPC1063/ozanimod HCl ([redacted] mg, [redacted] mg, and 1 mg) and ozanimod ([redacted] mg, [redacted] mg, and [redacted] mg) for consistency across RPC1063 protocols.
- Removed hemoglobin A1c from the chemistry panel because it is not needed for routine evaluation of patient safety.
- Updated protocol to add new protocol template language regarding handling of product quality complaints for any drug product manufactured by or on behalf of Celgene.
- Updated Sponsor’s address.
- Made minor editorial changes and changes for clarification.

This document summarizes the changes that were made between Protocol RPC01-3102 Version 3.0 (dated 7 June 2016) and Version 4.0 (dated 7 June 2017).

1. OVERVIEW OF KEY CHANGES

The following bulleted list identifies the key changes to the protocol and provides the rationale for each change:

- Contraception methods and the frequency of pregnancy testing were aligned with the "Recommendations related to contraception and pregnancy testing in clinical trials" (15 Sep 2014) by the Clinical Trial Facilitation Group. Additionally, the requirement for male contraception was maintained from Inclusion Criterion #2 from the previous version of the protocol.
- The prohibition on concomitant use of CYP3A4 inhibitors and inducers was removed based on the results of the clinical pharmacology study RPC01-1902.
- The prohibition on concomitant [redacted] was removed based on the results of the clinical pharmacology study RPC01-1908.
- Timing windows were extended for select visits. These changes were made to provide operational flexibility to the study sites.
- A number of changes were made to clarify previously existing instructions and improve readability.

This document summarizes the changes that were made between Protocol RPC01-3102 Version 2.0 (dated 08 May 2015) and Version 3.0 (dated 7 June 2016).

Receptos, Inc. was acquired by Celgene Corporation, and, effective 29 Jan 2016, Celgene International II Sàrl ("CIS II"), a subsidiary of Celgene Corporation, has assumed responsibility as the sponsor of record for all RPC1063 clinical studies for which Receptos, Inc. was previously named sponsor. Receptos Services LLC ("Receptos"), a wholly owned subsidiary of Celgene Corporation, is and will serve as an authorized representative for CIS II, supporting RPC1063 clinical studies.

Overview of Changes:

- Corrections were made to remove reference to a "maintenance trial" and in some instances replaced with "extension trial"
- The Introduction was updated to include the relevant trial, RPC01-1901 (to support removal of the fasting restriction prior to dosing with RPC1063), to include a third metabolite of RPC1063 due to the addition of RPC01-1901 results, to update the status of completed trials, and to reference the Investigator's Brochure as the most up-to date source of information about studies within the RPC1063 clinical development program.
- The definition of mucosal healing and histologic remission was updated.
- For the purposes of clarity, complete Mayo score, partial Mayo score, and 9-point Mayo score were listed in the description of other efficacy endpoints.
- Physical examinations and [redacted] were removed from the list of safety endpoints as they will not be summarized as change from Baseline.
- The section "Pharmacodynamic Endpoints" was added to include the description of [redacted] and [redacted]. Text regarding markers of inflammation have been revised throughout the protocol to include examples.
- The required window to complete vital signs was removed.
- Instruction to take RPC1063 in a fasted state was removed based on results of the food effect study (Study RPC01-1901).
- The requirement that patients should enter the trial [redacted].
- Instruction for patients not to take study medication from the prior trial until Visit [redacted] during which they will receive RPC01-3102 study medication was added.
- The timepoint after which patients will begin to have additional visit assessments at [redacted].
- A full examination of the skin for lesions was added as a procedure required for the interim physical examination.
- The window to complete endoscopies was changed from [redacted] to within [redacted] of the visit date to allow adequate time for completion of procedures. The Day [redacted] endoscopy does not need to be repeated if an endoscopy has been completed within [redacted].

- [redacted]
- Table 2 - footnote d describing pulse monitoring guidelines was updated.
- Inclusion criterion #4 removed "Are capable of providing" to emphasize that the subject must provide informed consent.
- Added a time window for which treatment with a live vaccine should be exclusionary for exclusion criteria #1.
- For clarification purposes and to maintain consistency with protocol RPC01-3101, additional detail (P450 3A4) was added to the CYP3A4 description.
- "Calcium channel blockers" was replaced with examples of calcium channel blockers in exclusion criteria #2. QT interval prolonging drugs with a known risk of torsades de pointes were removed from the exclusion.
- [redacted].
- For clarification purposes, the statement patients will be encouraged to complete the trial was revised to only note that the patient may voluntarily withdraw from the trial at any time.
- The definition of "withdrawal by patient" was clarified to note that patients who discontinue study medication will be withdrawn from the study.
- Additional clarity was added to describe dosing (added [redacted] to be taken).
- Correction was made to ensure that prior medication history is captured starting at the date of informed consent. The phrase "date of informed consent" was removed from the description of concomitant medications.
- QT prolonging drugs were removed from the list of excluded medications [redacted]
- Methotrexate was added as an example of an immunosuppressive agents.
- Tofacitinib was added as an excluded medication.
- Proprietary names for components (eg, chemical excipients or capsules) and packaging of investigational and commercial drug products have been removed in favor of using generic terms. This has been done to simplify the text and limit the use of trademarked or registered names.
- Instructions to the Investigator regarding investigational drug accountability along with record transfer and on site destruction were deleted.
- For clarification purposes, [redacted] was changed [redacted] for documentation of history of prior medications.
- Details regarding colonic biopsies have been revised.

- For the purpose of clarity, the time period in which stool frequency and rectal bleeding diary entries will be used to calculate Mayo Score was further defined. Additional details regarding calculation of Mayo Score was deleted since this will be outlined in the Statistical Analysis Plan.
- The details of the condition in which ECGs will be performed were revised.
- [redacted]
- Criteria #2 for additional extended monitoring of first dose heart rate was revised.
- An additional directive for the requirement of Medical Monitor approval if retest is required to be repeated > 2 times was added. Additional text was added to clarify that repeat laboratory safety testing would be analyzed by the local laboratory.
- Criteria for repeating hematology laboratory results were added.
- A correction was made to section titled "Handling Missing Data" to delete instructions if no post-baseline values are available since all patients in this study will have post-baseline values available from the parent study (RPC01-3101).
- Details on the version of Declaration of Helsinki were removed since the version varies based on region.

Global Changes:

- The Sponsor name and address were changed.
- Confidentiality language was modified.
- The Medical Monitor's company was updated.
- A Celgene International II Sàrl signatory was added.
- The list of abbreviations was updated, as appropriate.
- References to "Receptos, Inc." and "Receptos" were modified.
- Minor typographical corrections

[redacted]

This document summarizes the changes that were made between Protocol RPC01-3102 Version 1.0 (dated 20 April 2015) and Version 2.0 (dated 08 May 2015).

Overview of Changes:

- Vitals signs assessment was added to Safety Follow-up visit
- Erroneous text relating to questionnaires was removed.
- Minor corrections

[redacted]