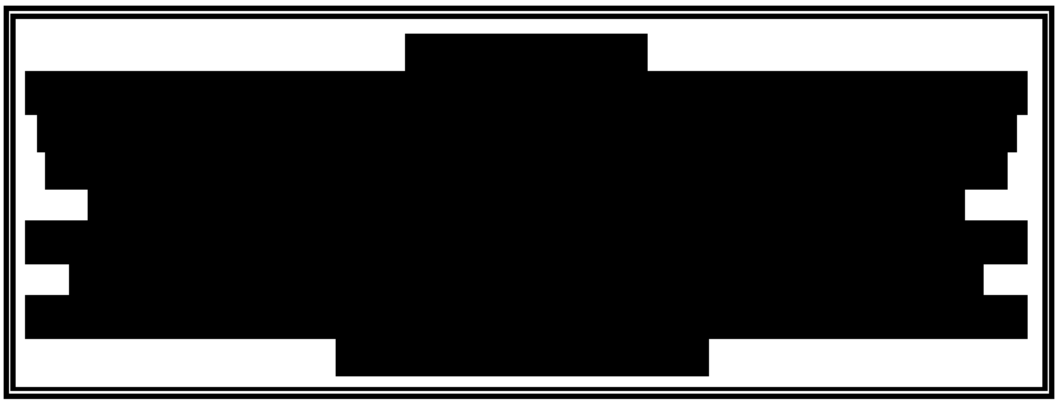
1. CLINICAL TRIAL PROTOCOL

Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis
Protocol Number:	RPC01-3101
Version and Date of Protocol:	7.1 dated 26 Jul 2019
Replaces Version:	6.1 dated 12 December 2018 in Italy
Product:	RPC1063
IND No.:	115,243
EudraCT No.:	2015-000319-41
Trial Phase:	3
Sponsor:	[redacted]
Medical Monitor:	[redacted]
Principal Investigator:	[redacted]



SIGNATURES

PROTOCOL TITLE: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis

PROTOCOL NO: RPC01-3101

[redacted]

{See appended electronic signature page}

Signature Date

[redacted]

[redacted]

[redacted]

Date

Printed Name of Celgene International II Sàrl Representative

2. SYNOPSIS

Sponsor/Company: Celgene International II Sàrl	
Investigational Product: RPC1063	
Name of Active Ingredient: RPC1063	
Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis
Brief Title:	Safety and Efficacy Trial of RPC1063 for Moderate to Severe Ulcerative Colitis
Protocol No:	RPC01-3101
Investigators:	Approximately 325
Regions:	North America, Europe, Asia Pacific, South America, South Africa
Trial Duration: Estimated date of first patient enrolled: May 2015 Estimated date of last patient completed: Q2-2020	**Phase:** 3

Objectives:

Induction Period

Primary:

Demonstrate the efficacy of RPC1063 versus placebo on induction of clinical remission in adults.

Secondary:

- Demonstrate the efficacy of RPC1063 versus placebo on induction of clinical response in adults
- Demonstrate the efficacy of RPC1063 versus placebo on achieving endoscopic improvement in adults
- Demonstrate the efficacy of RPC1063 versus placebo on achieving histologic remission in adults
- Demonstrate the safety and tolerability of RPC1063 induction therapy in all patients

[redacted]

Maintenance Period

Primary:

To demonstrate the efficacy of RPC1063 versus placebo maintenance therapy on clinical remission in adults.

Secondary:

- Demonstrate the efficacy of RPC1063 versus placebo in maintaining clinical response in adults
- Demonstrate the efficacy of RPC1063 versus placebo on achieving endoscopic improvement in adults
- Demonstrate the efficacy of RPC1063 versus placebo on durability of clinical remission in adults
- Demonstrate the efficacy of RPC1063 versus placebo on maintaining clinical remission among patients who achieved remission during induction therapy in adults
- Demonstrate the efficacy of RPC1063 versus placebo in achieving corticosteroid-free remission among patients receiving corticosteroids at entry into the Maintenance Period in adults

[redacted]

[redacted]

Methodology:

The trial is composed of 2 periods: Induction and Maintenance. [redacted]

Induction Period:

The 10-week IP is composed of [redacted]

- Cohort 1: Approximately 600 adult patients will be randomized in a 2:1 ratio to receive either RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) or placebo once daily in a double-blind fashion, stratified by corticosteroid use at Screening (yes or no) and prior anti-TNF use (yes or no)
- Cohort 2: Approximately 300 adult patients will receive open-label RPC1063 1 mg once daily

[redacted]

The trial will include both patients that have received anti-TNF therapy and those who have not. The proportion of patients who have previously received anti-TNF therapy will be limited to approximately 30% in Cohort 1.

Adult patients who have previously received anti-TNF therapy may commence enrollment into Cohort 2 once the randomization limit of approximately 30% anti-TNF therapy adult patients has been reached in Cohort 1. Patient enrollment will be closely monitored to ensure that less than approximately 30% of the total adult patients in this study have had prior exposure to anti-TNF therapy. Those adult patients who are anti-TNF therapy naïve can enroll into Cohort 2 only after Cohort 1 has been closed to enrollment.

The proportion of adult patients who have previously received anti-TNF therapy will be limited to approximately 50% in Cohort 2.

[redacted]

All patients will initiate investigational drug via a 7-day dose escalation regimen starting with RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) or matching placebo (matching placebo for Cohort 1 [redacted] only) on Days 1 to 4, and RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) once daily or matching placebo on Days 5 to 7. Starting on Day 8, patients will receive the final dose level of RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) once daily or matching placebo for 9 weeks.

Patients from Cohort 1, Cohort 2 [redacted] in clinical response at the end of the IP (Week 10) may enter the MP, while patients not in clinical response may enter an optional Open-Label Extension trial.

[redacted]

The final decision to discontinue the patient early for entry into the OLE will be left to the discretion of the Investigator based on the Partial Mayo score and the endoscopy score.

Maintenance Period:

It is anticipated that approximately 400 adult patients treated with RPC1063 during the IP and who complete the IP (both Cohort 1 and Cohort 2) will be in clinical response at Week 10 and will be eligible to enter the randomized, double-blind, placebo-controlled MP. These adult patients in clinical response at Week 10 of the IP will be randomized to receive either RPC1063 1 mg or matching placebo in a 1:1 ratio. Adult patients in clinical response at Week 10 of the IP who were randomized to placebo (Cohort 1) will continue to receive placebo in the MP in a double-blind manner. Adult patients who have disease relapse at any time during the MP will be given the option to enroll in Open-Label Extension trial (RPC01-3102).

[redacted]

All patients will be evaluated for disease activity/efficacy at Week 42 of the MP (52 weeks of treatment).

[redacted]

Planned Number of Patients (approximately):

Induction Period: approximately 900 adult patients[*] [redacted]

Cohort 1: approximately 600 adult patients (400 RPC1063 1 mg, 200 placebo)

Cohort 2: approximately 300 adult patients[*] (all receive RPC1063 1 mg)

[*]The number of patients in Cohort 2 may be increased if necessary to ensure approximately 400 patients who have received RPC1063 will be randomized in the MP.

[redacted]

Maintenance Period: Approximately 400 adult patients from IP Cohorts 1 and 2 who have received RPC1063

Patient Selection Criteria:

Inclusion Criteria:

Patients are eligible if they fulfill all of the following:

1. Must meet one of the following criteria:
   - Male or female adult patients aged 18 to 75 years (at Screening), inclusive for Cohort 1 or Cohort 2, or
   - [redacted]
2. Have had UC diagnosed at least 3 months prior to first investigational drug administration. The diagnosis should be confirmed by clinical and endoscopic evidence and corroborated by a

histopathology report (note: endoscopy and histopathology may be performed at Screening if no prior report is readily available)

3. Evidence of UC extending ≥ 15 cm from the anal verge as determined by Baseline endoscopy (flexible sigmoidoscopy or colonoscopy)
4. Have active UC defined as a complete Mayo score of 6 to 12 inclusive, with endoscopic subscore of ≥ 2, a rectal bleeding score of ≥ 1, and a stool frequency score ≥ 1
5. Must be currently receiving treatment with at least 1 of the following therapies and must continue on these therapies during Induction:
   - Oral aminosalicylates at a therapeutic dose for their disease (eg, mesalamine, sulfasalazine, olsalazine, balsalazide), with the dose stable for at least 3 weeks prior to Screening endoscopy
   - Prednisone (doses ≤ 20 mg per day) or equivalent receiving a stable dose for at least 2 weeks prior to Screening endoscopy
   - Budesonide MMX therapy receiving a stable dose for at least 2 weeks prior to Screening endoscopy
6. Have undergone colonoscopy (or are willing to undergo colonoscopy during Screening):
   - within the past 2 years, to screen for dysplasia (unless otherwise recommended by local and national guidelines) if the patient has had left-sided colitis of > 12 years duration or total/extensive colitis of > 8 years duration
   - within the past 5 years, to screen for polyps if the patient age is > 45 years
   - If oral aminosalicylates or corticosteroids have been recently discontinued, they must have been stopped for at least 2 weeks prior to the endoscopy used for Baseline Mayo score
7. Females of childbearing potential (FCBP):

   Must agree to practice a highly effective method of contraception throughout the trial until completion of the 90-day Safety Follow-up 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 amenorrhoea method are not acceptable methods of contraception.
8. Must provide written informed consent/assent and have the ability to be compliant with the schedule of protocol assessments. The parent/legal guardian of the adolescent must sign an informed consent form. In addition, adolescent patients must also agree to participate in the study by signing an assent.
9. Patients must have documentation of positive *Varicella zoster* virus (VZV) immunoglobulin G (IgG) antibody status or complete VZV vaccination at least 30 days prior to randomization

Exclusion Criteria:

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

Exclusions Related to General Health:

1. Have severe extensive colitis as evidenced by:

- Physician judgment that the patient is likely to require colectomy or ileostomy within 12 weeks of Baseline
- Current or recent (within 3 months) evidence of fulminant colitis, toxic megacolon, or bowel perforation

2. Diagnosis of Crohn's disease or indeterminate colitis or the presence or history of a fistula consistent with Crohn's disease or microscopic colitis or radiation colitis or ischemic colitis
3. Have positive stool examination for pathogens (ova and parasites, bacteria) or positive test for toxin producing *Clostridium difficile* (*C. difficile*) at Screening. PCR (polymerase chain reaction) examination of the stool for *C. difficile* may be used to exclude false positives. If positive, patients may be treated and retested. Documentation of a negative test result for pathogens (ova and parasites, bacteria) is required within 60 days of Day 1.
4. Pregnancy, lactation, or a positive serum β-human chorionic gonadotropin (β-hCG) measured during Screening
5. 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
6. Clinically relevant cardiovascular conditions, including history or presence of:
   - Recent (within the last 6 months) occurrence of 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
   - For Adult patients: Prolonged Fridericia's corrected QT interval (QTcF; QTcF > 450 msec for males, > 470 msec for females), or at additional risk for QT interval prolongation (eg, hypokalemia, hypomagnesemia, congenital long-QT syndrome)

     [redacted]
   - Resting HR < 55 bpm when taking vital signs as part of a physical exam at Screening
7. History of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with glycosylated Hb (HbA1c) > 9%, or diabetic patients with significant comorbid conditions such as retinopathy or nephropathy
8. History of uveitis (within the last year) or macular edema
9. Subject has a known active bacterial, viral, or fungal infection [excluding fungal infection of nail beds, minor upper respiratory tract infections, and minor skin infections], a mycobacterial infection (including tuberculosis[TB] or atypical mycobacterial disease), or any major episode of infection that required hospitalization or treatment with intravenous (IV) antibiotics within 30 days of Screening or oral antibiotics within 14 days of Screening
10. Recurrent or chronic infection (eg, hepatitis A, B, or C, human immunodeficiency virus [HIV]); recurrent urinary tract infections are allowed.
11. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin or uterine cervix that have been excised and resolved) or colonic mucosal dysplasia
12. History of alcohol or drug abuse within 1 year prior to randomization
13. History of or currently active primary or secondary immunodeficiency

Exclusions Related to Medications:

14. History of treatment with a biologic agent within 8 weeks or 5 elimination half-lives (whichever is less) of that agent prior to randomization
15. History of treatment with an investigational agent within 5 elimination half-lives of that agent prior to randomization

16. History of treatment with topical rectal 5-aminosalicylic acid or topical rectal steroids within 2 weeks of Screening endoscopy or anti-motility medications (such as diphenoxylate/atropine) during Screening
17. Receipt of a live vaccine or live attenuated vaccine within 4 weeks prior to randomization
18. Previous treatment with lymphocyte-depleting therapies (eg, Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
19. Have had treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 16 weeks of Screening or tofacitinib within 2 weeks of Screening
20. Previous treatment with D-penicillamine, leflunomide, or thalidomide
21. Previous treatment with natalizumab, fingolimod or etrasimod
22. History of treatment with intravenous immune globulin (IVIg) or plasmapheresis within 3 months prior to randomization
23. Planned concurrent treatment with immunosuppressive agents (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate) after randomization. Patients receiving AZA, 6-MP, or methotrexate at Screening must discontinue treatment with these agents prior to randomization
24. 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)
25. Treatment with Class Ia or Class III anti-arrhythmic drugs or treatment with two or more agents in combination known to prolong PR interval
26. Apheresis (eg, Adacolumn apheresis) within 2 weeks of randomization
27. Patients who were primary non-responders to 2 or more biologic agents approved for the treatment of UC (eg, anti-TNF agents or vedolizumab)
28. Patients receiving treatment with breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine, eltrombopag)
29. Is receiving treatment with any of the following drugs or interventions within the corresponding timeframe:
    - At randomization
      - CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) and inducers (eg, rifampicin)
    - Two weeks prior to randomization
      - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)

[redacted]

Exclusions Related to Laboratory Results:

31. Serum creatinine > 1.4 mg/dL for females or > 1.6 mg/dL for males
32. Liver function impairment or persisting elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal (ULN), or direct bilirubin > 1.5 times the ULN
33. Platelet count < 100,000/µL
34. Hemoglobin < 8.0 g/dL
35. Neutrophils < 1500 /µL
36. Absolute white blood cell count < 3500/µL
37. Absolute lymphocyte count < 800/µL
38. ECG showing any clinically significant abnormality
39. Forced expiratory volume at 1 second (FEV_1) or forced vital capacity (FVC) < 70% of predicted values at Screening

Test Product, Dose, and Mode of Administration:
Induction Period:

The Induction Period [redacted]

Cohort 1: On Induction Day 1, adult patients will be randomly assigned in a 2:1 ratio to:

RPC1063: Taken by mouth, starting with a 7-day dose escalation regimen of RPC1063/ozanimod HCl daily:

- On Days 1 to 4, one RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) capsule once daily
- On Days 5 to 7, two RPC1063/ozanimod HCl at 0.25 mg capsules (total 0.5 mg [equivalent to ozanimod 0.46 mg]) once daily
- Starting on Day 8 until Week 10 (Visit I 3), one capsule of 1 mg RPC1063/ozanimod HCl (equivalent to ozanimod 0.92 mg) once daily, or

Matching placebo: Taken by mouth once daily x 10 weeks with matching dose escalation Days 1 to 7

Cohort 2: Adult patients take RPC1063 by mouth, starting with a 7-day dose escalation regimen of RPC1063/ozanimod HCl

- On Days 1 to 4, one RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) capsule once daily
- On Days 5 to 7, two RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) capsules (total 0.5 mg [equivalent to 0.46 mg]) once daily
- Starting on Day 8 until Week 10 (Visit I 3), one RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) capsule once daily

[redacted]

Matching placebo: Taken by mouth once daily x 10 weeks with matching dose escalation Days 1 to 7

Maintenance Period:

On Maintenance Day 1, adult patients from Cohort 1 or Cohort 2 with clinical response to RPC1063 during the IP will be randomly assigned in a 1:1 ratio to:

RPC1063 taken by mouth (a single 1 mg capsule) once daily × 42 weeks, or

Matching placebo taken by mouth (a single capsule) once daily × 42 weeks

Adult patients with a clinical response to placebo during the IP (Cohort 1) will continue to receive placebo taken by mouth once daily x 42 weeks.

Adult patients who have disease relapse at any time during the MP will be given the option to enroll in an Open-Label Extension trial.

[redacted]

[redacted]

Reference Therapy, Dose, and Mode of Administration:

Patients who are randomized to receive placebo in either Cohort 1 (adult patients) or Cohort 3 (adolescent patients) of the IP will take a single matching placebo capsule once daily. Adult patients and adolescent patients who continue on placebo in the MP or are randomized to placebo in the MP will also take a single matching placebo capsule once daily.

Duration of treatment:

Induction Period: 10 weeks

Maintenance Period: 42 weeks

Endpoints:

Definitions:

Complete Mayo score: the sum of the Rectal Bleeding subscore, Stool Frequency subscore, Physician Global Assessment subscore, and the Endoscopy subscore. Each subscore has a range of 0-3 points and the complete Mayo score has a range of 0-12 points

[redacted]

Clinical Remission

Four-component Mayo: Complete Mayo score of ≤ 2 points with no individual subscore of > 1 point

Three-component Mayo: Rectal Bleeding subscore = 0 and Stool Frequency subscore ≤ 1 (and a decrease of ≥ 1 point from the Baseline Stool Frequency subscore) and Endoscopy subscore ≤ 1

Clinical Response

Four-component Mayo: A reduction from Baseline in the Complete Mayo score of ≥ 3 points and ≥ 30%, and a reduction from Baseline in the Rectal Bleeding subscore of ≥ 1 point or an absolute Rectal Bleeding subscore of ≤ 1 point

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 Rectal Bleeding subscore of ≥ 1 point or an absolute Rectal Bleeding subscore of ≤ 1 point

Durable Clinical Remission: Clinical remission at Week 10 and at 52 weeks in all patients who entered the MP

Maintenance of Remission: Clinical remission at 52 weeks in the subset of patients who are in remission at Week 10

Corticosteroid-free Remission: Clinical remission at 52 weeks while off corticosteroids for ≥ 12 weeks

Endoscopic Improvement: Endoscopy subscore of ≤ 1 point

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

[redacted]

[redacted]

Induction Period, Cohort 1 in Adult Patients (Efficacy of RPC1063 vs Placebo):

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

Primary Efficacy Endpoint:

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

Key Secondary Efficacy Endpoints:

- The proportion of adult patients with a clinical response at Week 10
- The proportion of adult patients with endoscopic improvement at Week 10
- The proportion of adult patients with mucosal healing at Week 10

[redacted]

Induction Period, Cohort 2 in Adult Patients

- Cohort 2 is open label; therefore, no formal analysis of efficacy endpoints will be conducted on Cohort 2. All efficacy endpoints listed above will be summarized and described without hypothesis testing and reported using descriptive statistics.

[redacted]

Maintenance Period, Adult Patients:

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

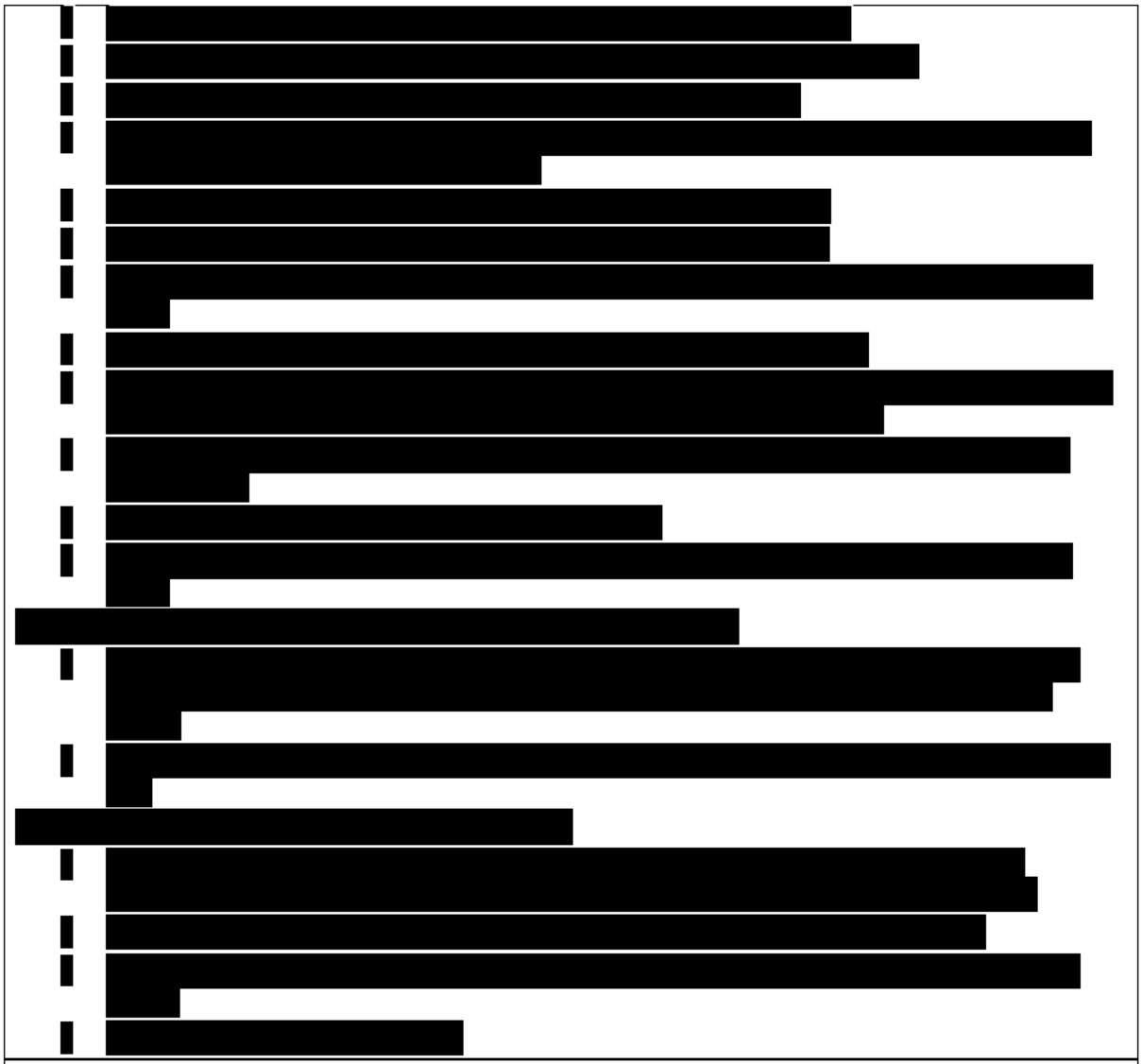
Primary Efficacy Endpoint:

- The proportion of adult patients in clinical remission at 52 weeks

Key Secondary Efficacy Endpoints:

- The proportion of adult patients with a clinical response at 52 weeks
- The proportion of adult patients with endoscopic improvement at 52 weeks
- The proportion of adult patients with durable clinical remission
- The proportion of adult patients in clinical remission at 52 weeks in the subset of patients who were in remission at Week 10
- The proportion of adult patients with corticosteroid-free remission
- The proportion of adult patients with mucosal healing at 52 weeks

[redacted]



Statistical Methods:

Induction Period Efficacy

Cohort 1 (adult patients): The primary analysis of proportion of patients in clinical remission at Week 10 will be carried out using a two-sided Cochran-Mantel-Haenszel (CMH) test at the 5% level of significance, stratified by corticosteroid use at Screening (yes or no) and prior anti-TNF use (yes or no). Results will be expressed as number of patients in remission, remission percentages, weighted difference in remission percentages, odds ratio, and associated 95% confidence intervals (CI) and p-values.

In order to account for multiplicity, the key secondary endpoints will be tested in order in a closed hierarchical testing procedure in order to control the overall Type I error rate for multiple endpoints. If the primary endpoint is statistically significant, the proportion of patients in clinical response at Week 10 will be tested at the 5% level of significance. If that endpoint is significant, then the proportion of patients with endoscopic improvement at Week 10 will be tested at the 5% level of significance. This testing procedure will continue down the key secondary endpoint list until an endpoint fails to reach statistical significance, after which all subsequent key secondary endpoints will be considered exploratory.

Each of the 3 key secondary endpoints will be tested using the same type of CMH test as specified for the primary IP endpoint.

Cohort 2 (adult patients): No hypothesis testing will be conducted on the data collected for Cohort 2. All efficacy endpoints will be analyzed using summary statistics only: number of patients (n), mean, SD, median, minimum, and maximum for continuous variables, and n and percentages for categorical variables.

[redacted]

Maintenance Period Efficacy for Adult Patients

The primary analysis of proportion of adult patients in clinical remission at Week 42 (52 weeks total treatment) will be carried out using a two-sided CMH test at the 5% level of significance, stratified by clinical remission status at Week 10 of the IP (yes or no), and corticosteroid use at Week 10 of the IP (yes or no). Results will be expressed as number of patients in remission, remission percentages, weighted difference in remission percentages, odds ratio, and associated 95% CIs and p-values.

To account for multiplicity, the secondary endpoints will be tested in order, in a closed hierarchical testing procedure to control the overall Type I error rate for multiple endpoints. If the primary endpoint is statistically significant, the proportion of patients in clinical response at Week 42 (52 weeks total treatment) will be tested at the 5% level of significance. If that endpoint is significant, then the proportion of patients with endoscopic improvement at Week 42 (52 weeks total treatment) will be tested at the 5% level of significance. This testing procedure will continue down the key secondary endpoint list until an endpoint fails to reach statistical significance, after which all subsequent key secondary endpoints will be considered exploratory.

Each of the 6 key secondary endpoints will be tested using the same type of CMH test as specified for the primary MP endpoint.

[redacted]

[redacted]

Sample Size Justification

Induction Period

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

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

[redacted]

Maintenance Period for Adult Patients:

The placebo remission rate at Week 42 (52 weeks total treatment) is assumed to be 16% in a randomized withdrawal trial in UC patients who have previously had a clinical response to induction therapy. Based on a 2-sided Fisher's exact test at alpha = 0.05, a sample size of 400 patients (200 patients per treatment group with randomization ratio of 1:1) will provide 90% power to detect a statistically significant improvement in the remission rate of 14 percentage points or larger (ie, an active group remission rate of 30% or higher).

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

Date and Version: 26 Jul 2019; Version 7.1

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. 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
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AV	Atrioventricular
AZA	Azathioprine
BCRP	Breast cancer resistance protein
β-hCG	Beta-human chorionic gonadotropin
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CRO	Contract research organization
CYP3A4	Cytochrome P450 3A4
DLCO	Diffusion capacity of the lung for carbon monoxide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
FEV	Forced expiratory volume at 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice

GGT	Gamma glutamyltransferase
HAV	Hepatitis A virus
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin
HBc	Hepatitis B core antigen
HBs	Surface antigen of the HBV
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IP	Induction Period
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine-hormone releasing system
IV	Intravenous
IVIg	Intravenous immunoglobulin
IXRS	Interactive voice / web-based activated response system
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MP	Maintenance Period
NASH	Nonalcoholic steatohepatitis
NOAEL	No-observed-adverse-effect level
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug

OCT	Optical coherence tomography
OLE	Open-Label Extension
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PFT	Pulmonary function tests
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PP	Per protocol
PQC	Product Quality Complaint
[redacted]	[redacted]
QTcF	Fridericia's corrected QT interval
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
SD	Standard deviation
SE	Standard error
SOP	Standard operating procedures
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TFR	Treatment failure rules
TNF	Tumor necrosis factor
UC	Ulcerative colitis
ULN	Upper limit of normal
VZV	Varicella zoster virus
WBC	White blood cell
WHO	World Health Organization

5. INTRODUCTION

5.1. 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 [redacted] 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 [redacted]

Patients with UC suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever [redacted] The pathology of 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 [redacted] 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. [redacted]

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 [redacted]

The overall goal of treatment for patients with active UC is to induce and maintain remission and to induce and maintain mucosal healing [redacted] 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 [redacted] 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 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 [redacted] 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 [redacted]

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 the following: 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 [redacted] or have required surgery [redacted]

For those patients who are unresponsive to, or intolerant of corticosteroids, immunomodulators including azathioprine (AZA), 6-mercaptopurine (6-MP), and cyclosporine [redacted] or biologics (such as infliximab) are used to induce and/or maintain remission [redacted] 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 [redacted] 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, infections, malignancy, 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.

5.2. RPC1063

RPC1063 is a small molecule compound that selectively and potently activates the sphingosine-1-phosphate 1 receptor ($S1P_1$) and the S1P 5 receptor ($S1P_5$), although it is more selective towards $S1P_1$ over $S1P_5$. In vitro, RPC1063 has little activity on the other sphingosine-1-phosphate (S1P) receptors, showing half maximal effective concentration (EC_{50}) greater than 10,000 nM for $S1P_2$, > 5000 nM for $S1P_3$, and > 2000 nM for $S1P_4$. RPC1063 is extensively metabolized in humans with up to 13 metabolites identified in plasma, urine, and feces, including 2 active selective major metabolites and 1 inactive major metabolite found in human plasma at steady state. [redacted]

Many cell types express $S1P_1$, including vascular endothelial cells, brain cells, and lymphocytes [redacted] 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 [redacted] Given the immune dysregulation observed in UC [redacted] 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 using keyhole limpet hemocyanin as the antigenic stimulation. 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. [redacted] Therefore, the clinical doses of 0.46 mg and 0.92 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 subjects treated with even the highest dose (0.92 mg) of ozanimod such that infection rates are not increased to date, which suggests that the risk for progressive multifocal leukoencephalopathy (PML) should not be significantly increased. No cases of PML were identified in the ozanimod clinical program.

There are no known age-related differences in the expression of S1P receptors and their physiological role in the heart which is also supported by clinical PK and pharmacodynamic (PD) data of fingolimod, an S1P receptor modulator approved for the treatment of relapsing MS, showing comparable negative chronotropic effects and decreased lymphocyte count between adolescents (14.1 ± 1.6 years) and adults [redacted] The 7-day dose escalation regimen for ozanimod has minimized the initial heart rate reducing effect in clinical trials in adult subjects and it is believed will serve the same purpose in pediatric subjects.

[redacted]

[redacted]

6. TRIAL OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Induction Therapy

6.1.1.1. Primary Objective

Demonstrate the efficacy of RPC1063 versus placebo on induction of clinical remission in adults.

6.1.1.2. Secondary Objectives

Secondary objectives are to:

- Demonstrate the efficacy of RPC1063 versus placebo on induction of clinical response in adults
- Demonstrate the efficacy of RPC1063 versus placebo on achieving endoscopic improvement in adults
- Demonstrate the efficacy of RPC1063 versus placebo on achieving histologic remission in adults

[redacted]

6.1.2. Maintenance Therapy

6.1.2.1. Primary Objective

To demonstrate the efficacy of RPC1063 versus placebo maintenance therapy on clinical remission in adults.

6.1.2.2. Secondary Objectives

Secondary objectives are to:

- Demonstrate the efficacy of RPC1063 versus placebo in maintaining clinical response in adults
- Demonstrate the efficacy of RPC1063 versus placebo on achieving endoscopic improvement in adults
- Demonstrate the efficacy of RPC1063 versus placebo on durability of clinical remission in adults
- Demonstrate the efficacy of RPC1063 versus placebo on maintaining clinical remission among patients who achieved remission during induction therapy in adults

- Demonstrate the efficacy of RPC1063 versus placebo in achieving corticosteroid-free remission among patients receiving corticosteroids at entry into the Maintenance Period (MP) in adults

[redacted]

6.2. Efficacy Endpoints

The efficacy endpoints will be formally examined with statistical hypothesis tests conducted on the efficacy results obtained from adult patients randomized and dosed in Cohort 1. Cohort 2 is open-label and does not contain a control group, therefore all of the efficacy endpoints will be summarized and described without statistical hypothesis testing.

[redacted]

6.2.1. Definitions:

Complete Mayo score: the sum of the Rectal Bleeding subscore, Stool Frequency subscore, Physician Global Assessment subscore, and the Endoscopy subscore. Each subscore has a range of 0-3 points and the complete Mayo score has a range of 0-12 points

[redacted]

Clinical Remission

Four-component Mayo: Complete Mayo score of ≤ 2 points with no individual subscore of > 1 point

Three-component Mayo: Rectal Bleeding subscore = 0 and Stool Frequency subscore ≤ 1 (and a decrease of ≥ 1 point from the Baseline Stool Frequency subscore) and Endoscopy subscore ≤ 1

Clinical Response

Four-component Mayo: A reduction from Baseline in the Complete Mayo score of ≥ 3 points and ≥ 30%, and a reduction from Baseline in the Rectal Bleeding subscore of ≥ 1 point or an absolute Rectal Bleeding subscore of ≤ 1 point

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 Rectal Bleeding subscore of ≥ 1 point or an absolute Rectal Bleeding subscore of ≤ 1 point

Durable Clinical Remission: Clinical remission at Week 10 and at 52 weeks in all patients who entered the MP

Maintenance of Remission: Clinical remission at 52 weeks in the subset of patients who are in remission at Week 10

Corticosteroid-free Remission: Clinical remission at 52 weeks while off corticosteroids for ≥ 12 weeks

Endoscopic Improvement: Endoscopy subscore of ≤ 1 point

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

6.2.2. Induction Period, Cohort 1 in Adult Patients (Efficacy of RPC1063 vs Placebo):

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

Primary Efficacy Endpoint:

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

Key Secondary Efficacy Endpoints:

- The proportion of adult patients with a clinical response at Week 10
- The proportion of adult patients with endoscopic improvement at Week 10
- The proportion of adult patients with mucosal healing at Week 10

[redacted]

6.2.3. Induction Period, Cohort 2 in Adult Patients

Cohort 2 is open label; therefore no formal analysis of efficacy endpoints will be conducted. All efficacy endpoints listed above will be summarized and described without hypothesis testing and reported using descriptive statistics.

[redacted]

[redacted]

6.2.5. Maintenance Period, Cohort 1 and Cohort 2 in Adult Patients

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

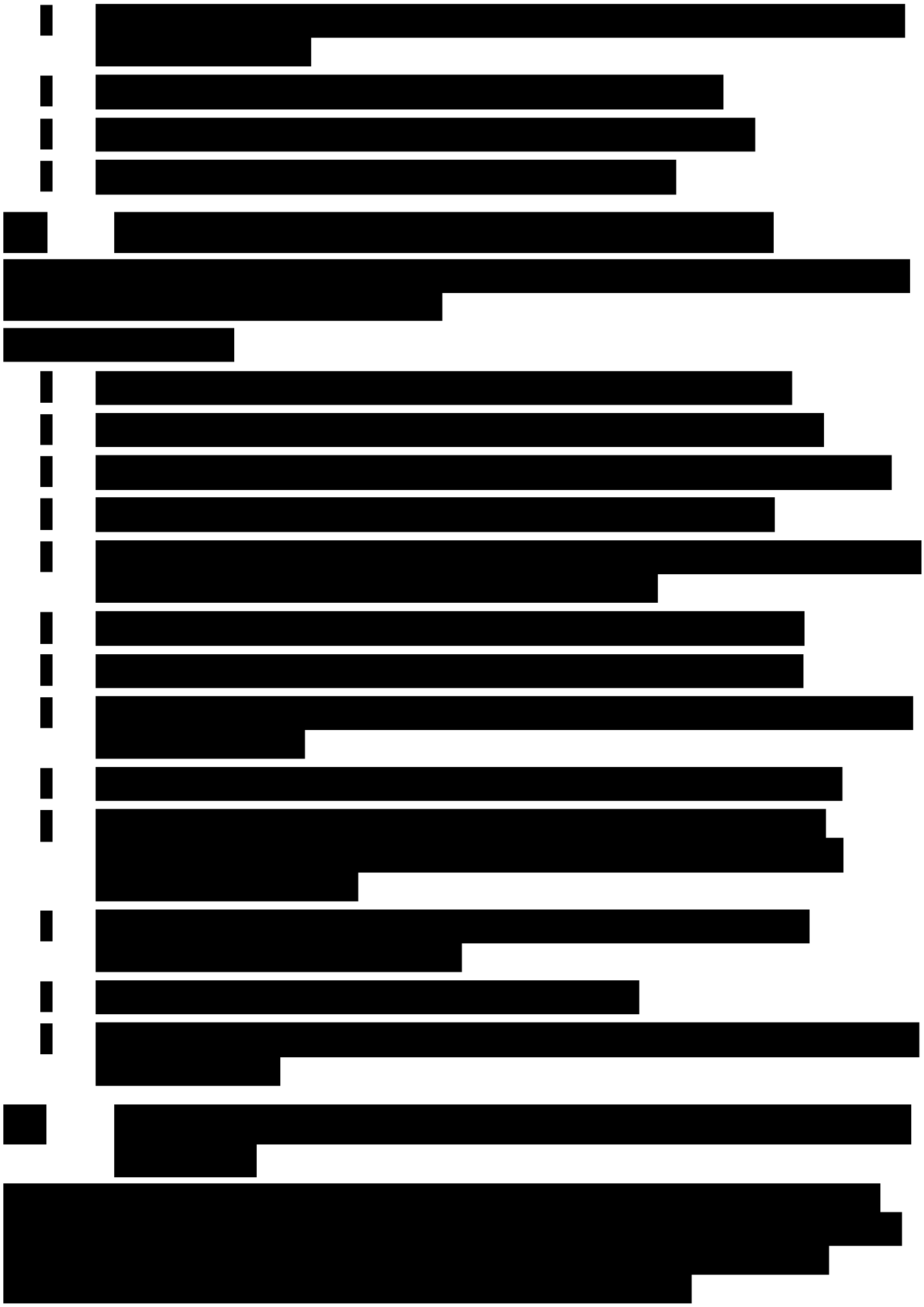
Primary Efficacy Endpoint:

- The proportion of adult patients in clinical remission at 52 weeks

Key Secondary Efficacy Endpoints:

- The proportion of adult patients with a clinical response at 52 weeks
- The proportion of adult patients with endoscopic improvement at 52 weeks
- The proportion of adult patients with durable clinical remission
- The proportion of adult patients in clinical remission at 52 weeks in the subset of adult patients who were in remission at Week 10
- The proportion of adult patients with corticosteroid-free remission
- The proportion of adult patients with mucosal healing at 52 weeks

[redacted]



7. INVESTIGATIONAL PLAN

7.1. Summary of Trial Design

This is a multicenter, randomized, double-blind, placebo-controlled trial of RPC1063 as induction and maintenance therapy for moderate to severe UC. The trial will be conducted at approximately 325 sites in North America, Europe, Asia Pacific, South America, South Africa.

The trial is composed of 2 periods: Induction and Maintenance. Patients will enter into the trial through the Induction Period (IP) [redacted] Adult patients who have previously received anti-TNF therapy may commence enrollment into Cohort 2 once the randomization limit of approximately 30% anti-TNF therapy adult patients has been reached in Cohort 1. Those adult patients who are anti-TNF therapy naïve will continue to enroll into Cohort 1 and can enroll into Cohort 2 only after Cohort 1 has been closed to enrollment. The proportion of adult patients who have previously received anti-TNF therapy will be limited to approximately 50% in Cohort 2. [redacted]

Adult patients from Cohort 1 or Cohort 2 with clinical response at the end of the IP will proceed through to the MP. Patients who participate in this trial may participate in an optional Open-Label Extension trial as described below.

Approximately 900 adult patients will be entered into the trial in 2 separate cohorts through the IP and may proceed through to the MP and/or the Open-Label Extension trial.

[redacted]

Induction Period:

The IP of the trial [redacted] will be treated for 10 weeks and evaluated for clinical response/remission:

- Cohort 1: Approximately 600 adult patients will be randomized in a 2:1 ratio to receive either RPC1063 1 mg (400 patients) or placebo (200 patients) once daily in a double-blind fashion, stratified by corticosteroid use at Screening (yes or no), and anti-TNF use (yes or no)
- Cohort 2: Approximately 300 adult patients* will receive open-label RPC1063 1 mg once daily

*The number of adult patients in Cohort 2 may be increased if necessary to ensure approximately 400 adult patients who have received RPC1063 will be randomized in the MP.

[redacted]

[redacted]

Patient eligibility for the IP will be determined during a 5-week Screening Period prior to entry into either Cohort 1, Cohort 2, [redacted]

The trial will include both patients that have received anti-TNF therapy and those who have not. The proportion of adult patients who have previously received anti-TNF therapy will be limited to approximately 30% in Cohort 1. The proportion of adult patients who have previously received anti-TNF therapy will be limited to approximately 50% in Cohort 2.

[redacted]

All patients will initiate investigational drug in accordance with a 7-day dose escalation regimen starting with RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) or matching placebo (matching placebo for Cohort 1 [redacted] on Days 1 to 4 and RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) once daily or matching placebo on Days 5 to 7. On Day 8, patients will receive the final dose RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) once daily or matching placebo for 9 weeks.

The total duration of the IP is 10 weeks.

[redacted]

Maintenance Period:

It is anticipated that approximately 400 adult patients treated with RPC1063 during the IP and who complete the IP (both Cohort 1 and Cohort 2) will be in clinical response (by either definition in Section 6.2.1) at Week 10 and will be eligible to enter the randomized, double-blind, placebo-controlled MP. These adult patients in clinical response at Week 10 of the IP will be randomized to receive either RPC1063 1 mg or matching placebo in a 1:1 ratio. Adult patients in clinical response at Week 10 of the IP who were randomized to placebo (Cohort 1) will continue to receive placebo in the MP in a double-blind manner. Adult patients from Cohort 1 or Cohort 2 who do not show a clinical response at Week 10 or who lose response at any time during the MP may enter the optional Open-Label Extension trial, if appropriate.

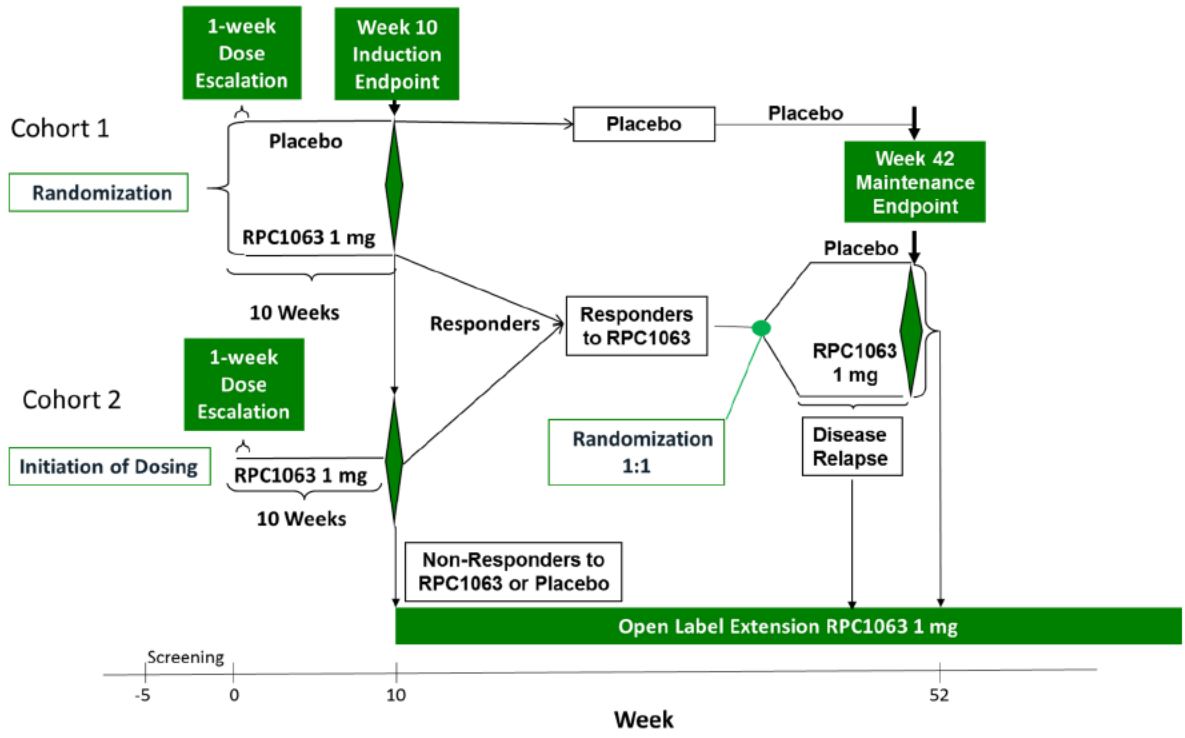
Adult patients randomized in the MP will be stratified by clinical remission status (by either definition in Section 6.2.1) at Week 10 (yes or no) and corticosteroids use at Week 10 (yes or

no). Adult patients will be evaluated for disease activity/efficacy at Week 42 of the MP (52 weeks total treatment).

[redacted]

Trial schematics for Cohort 1 and Cohort 2 are presented in Figure 1 [redacted]

Figure 1: Trial Schematic for Cohort 1 and Cohort 2



Note: Adult patients in Cohort 1 will be randomized to receive RPC1063 or placebo in a 2:1 ratio in a double-blinded manner. Adult patients in Cohort 2 will receive RPC1063 in an open-label manner. Adult patients in clinical response at Week 10 of the IP who were randomized to placebo (Cohort 1) will continue to receive placebo in the MP in a double-blind manner. Only responders assigned to RPC1063 (Cohort 1 and 2) in the IP will be randomized to receive RPC1063 or placebo in a 1:1 ratio in a double-blinded manner when entering the MP.

Table 1: Schedule of Events

	Trial Procedures		Induction			Maintenance						Early Term[q]	Safety Follow-up[s]	
			Dose Escalation	Assigned Dose		Treatment								
	(Visit Label)	Screening	Visit I 1[a,b] (Week 0)	Visit I 2[w] (Week 5)	(EoT) Visit Visit I 3[b] (Week 10)	Visit M 1[b,c] (Week 0)	Visit M 2 (Week 8)	Visit M 3 (Week 18)	Visit M 4 (Week 30)	Relapse Visit (When Indicated)	(EoT) Visit M 5[b] (Week 42)			
	(Visit Day and Window)	Day -35 to 0	Day 1	Day 35±5	Day 70±10	Day 1	Day 56±10	Day 126±10	Day 210±10		Day 294±10	Day of Early Term	Last dose + 30 to 60 days	Last dose + 90 days ± 10 days[t]
	(Overall Duration)		0 weeks	5 weeks	10 weeks	10 weeks	18 weeks	28 weeks	40 weeks		52 weeks			
	Informed consent/assent	X												
	Inclusion/exclusion criteria	X	X			X								
	Demographics	X												
	Medical history[d,e]	X	X											
	Viral serology[f]	X												
	Stool culture[g]	X												
	Randomization		X			X								
	Dispense investigational drug		X	X	X[h]	X	X	X	X	X	X[r]			
	Administer investigational drug at clinic		X		X	X					X			
	Review drug compliance			X	X	X	X	X	X	X	X	X		
	Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
	Medical procedures (non-trial)		X	X	X	X	X	X	X		X	X	X	

	Trial Procedures		Induction			Maintenance						Early Term[q]	Safety Follow-up[s]	
			Dose Escalation	Assigned Dose		Treatment								
	(Visit Label)	Screening	Visit I 1[a,b] (Week 0)	Visit I 2[w] (Week 5)	(EoT) Visit Visit I 3[b] (Week 10)	Visit M 1[b,c] (Week 0)	Visit M 2 (Week 8)	Visit M 3 (Week 18)	Visit M 4 (Week 30)	Relapse Visit (When Indicated)	(EoT) Visit M 5[b] (Week 42)			
	(Visit Day and Window)	Day -35 to 0	Day 1	Day 35±5	Day 70±10	Day 1	Day 56±10	Day 126±10	Day 210±10		Day 294±10	Day of Early Term	Last dose + 30 to 60 days	Last dose + 90 days ± 10 days[t]
	(Overall Duration)		0 weeks	5 weeks	10 weeks	10 weeks	18 weeks	28 weeks	40 weeks		52 weeks			
Safety Assessments	Adverse events[z]		X	X	X	X	X	X	X	X	X	X	X	X
	12-Lead ECG	X	X		X						X	X		X[y]
	Vital signs	X	X	X	X	X	X	X	X		X	X	X	X[y]
	Hematology[v]	X	X	X	X	X	X	X	X		X	X	X	X
	Blood chemistry[x]	X	X	X	X	X	X	X	X		X	X	X	X[y]
	Pregnancy test[i]	X	X	X	X	X	X	X	X		X	X	X	X
	Contraception education	X	X	X	X	X	X	X	X	X	X	X	X	
	Urinalysis	X			X						X	X	X	X[y]
	Pulmonary function tests[p]	X			X			X			X	X		X[y]
	Complete Physical examination[j]	X									X	X		X[y]
	Interim Physical examination[j]		X	X	X	X	X	X	X				X	X[y]
	Height and Weight (adults)	X												X[y]
	Height (adolescents)	X									X	X		X[y]
	Weight (adolescents)	X	X	X	X			X			X	X		X[y]
	Optical coherence tomography	X			X						X	X		X[y]

	Trial Procedures		Induction			Maintenance						Early Term[q]	Safety Follow-up[s]	
			Dose Escalation	Assigned Dose		Treatment								
	(Visit Label)	Screening	Visit I 1[a,b] (Week 0)	Visit I 2[w] (Week 5)	(EoT) Visit Visit I 3[b] (Week 10)	Visit M 1[b,c] (Week 0)	Visit M 2 (Week 8)	Visit M 3 (Week 18)	Visit M 4 (Week 30)	Relapse Visit (When Indicated)	(EoT) Visit M 5[b] (Week 42)			
	(Visit Day and Window)	Day -35 to 0	Day 1	Day 35±5	Day 70±10	Day 1	Day 56±10	Day 126±10	Day 210±10		Day 294±10	Day of Early Term	Last dose + 30 to 60 days	Last dose + 90 days ± 10 days[t]
	(Overall Duration)		0 weeks	5 weeks	10 weeks	10 weeks	18 weeks	28 weeks	40 weeks		52 weeks			
[redacted]														
[redacted]														
[redacted]														
Efficacy assessments	Endoscopy[l,w] and colonic biopsy	X		X[w]	X[m]	X[m]				X	X[m]	X		
	Mayo patient diary	X[n]	X	X	X	X	X	X	X	X	X	X	X	
	Mayo full clinical score	X			X	X				X	X	X		
	[redacted]													
[redacted]														
	[redacted]													
	[redacted]												X	

(See footnotes and abbreviations on next page.)

[a] The duration of Visit I 1 will be approximately 7 hours. Prior to dosing a 12-lead ECG will be performed and following dosing patients will have hourly vital signs recorded at 1, 2, 3, 4, 5, and 6 hours postdose. A second 12-lead ECG will be performed at the end of the observation period.

[b] Visit I 1, Visit I 3, Visit M 1, and Visit M 5 should be scheduled in the morning, where possible. On Visits I 1, I 3, M 1, and M 5, since trough PK samples are to be drawn, patients should be instructed to withhold the dose until the trial visit and the dose should be administered during the visit.

[c] In general, for patients completing the IP and entering the MP, Visit 3 of the IP (Visit I 3) will serve as Visit 1 of the MP (Visit M 1). Patients should enter the MP within 21 days of the Visit I 3 endoscopy. Procedures completed during Visit I 3 do not need to be repeated if Visit M 1 occurs within 14 days of I 3 visit. Patients may complete the M 1 visit prior to completing the OCT and PFT scheduled for the I 3 visit. OCT and PFT must be completed within 14 days of the I 3 visit.

[d] Medical history will include smoking history. The Visit I 1 medical history can be abbreviated, noting events that occurred between Screening and Visit I 1.

[e] TB must be ruled out according to local medical practices, such as a TB skin test, QuantiFERON Gold test, or other interferon gamma release assay (eg, T-SPOT). Subjects with a positive test result using a TB skin test or QuantiFERON Gold test must have documentation of completed TB treatment by local standard of care.

[f] Serology testing will be performed at Screening to determine the patient's immune status with respect to the following viruses (see Section 12.1.11): Human immunodeficiency virus antibodies, anti-hepatitis A virus IgM, hepatitis B surface antigen, anti-hepatitis B core antigen, hepatitis B DNA, anti-hepatitis C virus IgG or IgM. In addition, patients must have documentation of positive Varicella Zoster Virus IgG antibody status or complete Varicella Zoster Virus vaccination at least 30 days prior to first dose of investigational drug.

[g] At Screening, the stool sample should be used to rule out serious infection and should include evaluation for C. difficile toxin as well as ova and parasitic examination.

[h] Investigational drug will only be dispensed for patients that could not complete the M1 Visit on the same day as the I 3 Visit.

[i] For females of childbearing potential only, a serum β-hCG pregnancy test at Screening is required and a urine β-hCG pregnancy test is required at each visit. Between scheduled visits up until the 90-day Safety Follow-up Visit, monthly home urine pregnancy tests should be performed by the patient. If a urine pregnancy test result is positive, the investigator will instruct the patient to suspend further study dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including after the 90-day Safety Follow-up Visit, if needed.

[j] For all patients, a complete physical examination (which includes height and weight) will be performed at Screening. For adult patients, the complete physical examination at M 5/EoT/Early Term visit does not include height and weight. Patients who enter the trial as adolescents should continue to be assessed as adolescents throughout the trial, regardless of an age change. The complete physical examination consists of a full examination of the skin for lesions as well as a check for visual symptoms (ie, blurred vision or decreased visual acuity). A check for visual symptoms and a full examination of the skin should be repeated every 6 months. At all other visits following Screening (except M 5/EoT/Early Term), an interim physical examination will be performed. The interim physical examination will include body systems with previously noted abnormalities and/or those body systems associated with any new complaints from the patient.

[k] At Visit I 1, blood samples for PK evaluation are to be taken prior to the administration of investigational drug (predose) and just prior to discharge from the clinic (6 to 8 hours postdose). At Visit I 2, blood samples should be taken 2 to 6 hours after dosing; therefore, patients should be instructed to take investigational drug at home prior to arriving for this visit. At Visits I 1, I 3, M 1, and M 5, blood samples will be used to determine trough level, therefore patients should be instructed to withhold the dose until the trial visit, where the dose will be administered after the PK blood draw is done. The actual time of investigational drug administration for all visits with PK evaluation will be recorded on the dosing log. The blood sample at the 30-day and 90-day Safety Follow-up Visits can be collected at any point during the visit. An additional PK sample will be obtained for patients with any adverse event resulting in unblinding, discontinuation, or serious adverse event.

[l] At Screening, a flexible sigmoidoscopy may be used if a colonoscopy is not required. A colonoscopy will be required if the patient has had left-sided colitis of > 12 years duration or total/extensive colitis of > 8 years duration and has not had a colonoscopy within 2 years (unless otherwise recommended by local and national guidelines) of the screening date to rule out dysplasia, or if the patient's age is > 45 years and the patient has not had a colonoscopy within 5 years to screen for polyps. The screening endoscopy must be completed no more than 21 days prior to randomization. A flexible rectosigmoidoscopy will be performed at Week 5 or later for adolescent patients who meet clinical symptom criteria for early discontinuation, with the understanding that the procedure may occur within approximately 7 days from the last visit prior to entering the OLE, to allow for preparation. The final decision to discontinue the patient early for entry into the OLE will be left to the discretion of the Investigator based on the Partial Mayo score and the endoscopy score.

[m] Sigmoidoscopy should be performed no more than 10 days prior to the I 3 visit date in Induction and no more than 10 days prior to the M 5 visit date in Maintenance.

[n] At Screening, patients will be issued with a Mayo diary and will be trained in the completion of the diary.

[o] The Mayo partial clinical score on Visit I 1 should be combined with the central endoscopic read in order to assess the patient for "Mayo Score" entrance criteria.

[p] DLCO, if locally available, will be done at Screening, Visit I 3, Visit M 3, and M 5/Early Term visit.

[q] Early Term procedures performed at the Relapse Visit do not need to be repeated for patients who are early terminating due to relapse.

[r] In cases when a patient's End of Treatment (Week 42 of Maintenance) visit and the first visit of the open-label extension study do not occur on the same day, an extra bottle of investigational drug may be dispensed to cover the period of time prior to entering the open-label extension.

[s] The Safety follow-up visit should occur between 30 days to 60 days and at 90 days (±10 days) after the last dose of investigational drug in the RPC01-3101 trial. However, if the patient continues treatment in the open-label extension, the safety follow-up visits are not required for the RPC01-3101 trial.

[t] Every effort should be made to conduct the 90-day Safety Follow-up Visit as a clinic visit in order to allow PK and hematology blood samples to be drawn. In addition, additional safety assessments may be required for patients who have an ongoing AE or safety issue at the 90-day Safety Follow-up Visit, at the Investigator's discretion. Patients may be followed as necessary for an additional of period of time after the 90-day Safety Follow-up Visit to review the results of any assessments which were conducted at the 90-day Safety Follow-up Visit (eg, ALC < 200 cells/μL).

[u] [redacted]

[v] If the ALC is confirmed below the 200 cells/μL limit, the Investigator will temporarily discontinue investigational drug. Laboratory testing will be repeated weekly during the treatment period until ALC > 500 cells/μL. For patients who have a confirmed ALC below the 200 cells/μL limit at the Early Termination visit, or at the 30-day or 90-day Safety follow-up visit, central laboratory testing will continue every 14 days (± 3 days) after the Early Termination Visit until the ALC is above the lower limit of normal.

[w] Starting at Week 5 or later, adolescent patients (Cohort 3) may request early discontinuation from the Induction Period if they meet either of the following criteria: 1) Partial Mayo score is ≥ 7 and is the same or worse than baseline or, 2) Partial Mayo score is 6 and worse than baseline. A flexible rectosigmoidoscopy must be performed before entering the OLE. The final decision to discontinue the patient early for entry into the OLE will be left to the discretion of the Investigator based on the Partial Mayo score and the endoscopy score.

[x] The following amounts of blood will be taken per visit: At the Screening Visit, up to 26 mL (about 5 teaspoons); at Visit I1, 20 mL (about 4 teaspoons); at Visits I3, M5 or the Early Termination Visit, 18.5 mL (less than 4 teaspoons); Safety Follow-Up Visits, up to 18.5 mL (less than 4 teaspoons); at Visits I2 and M1, 12.5 mL (less than 3 teaspoons); at Visit M2, M3 and M4 6.5 mL (less than 2 teaspoons). In total, about 164.5 mL maximum (about 33 teaspoons) of blood will be collected during the whole study for patients who complete the study.

[y] Additional safety assessments may be requested at the PI's discretion in case of an ongoing safety event at the 90-day Safety Follow-up Visit.

[z] The reporting of AEs will begin at Induction Day 1 post first dose for all randomized patients. The reporting of SAEs for any patient will begin from the time written informed consent/assent is signed through the last visit. Any SAE that is ongoing when the patient completes the trial or discontinues from the trial will be followed by the Investigator until the event has resolved, stabilized, or returned to Baseline status.

Abbreviations: β-hCG = beta human chorionic gonadotrophin; DLCO = diffusion capacity of the lung for carbon monoxide; Early Term = Early Termination; ECG = electrocardiogram; EoT = End of Treatment; I = Induction Period; Igs = immunoglobulins; M = Maintenance Period; PD = pharmacodynamic; PK = pharmacokinetic; [redacted]; TB = tuberculosis

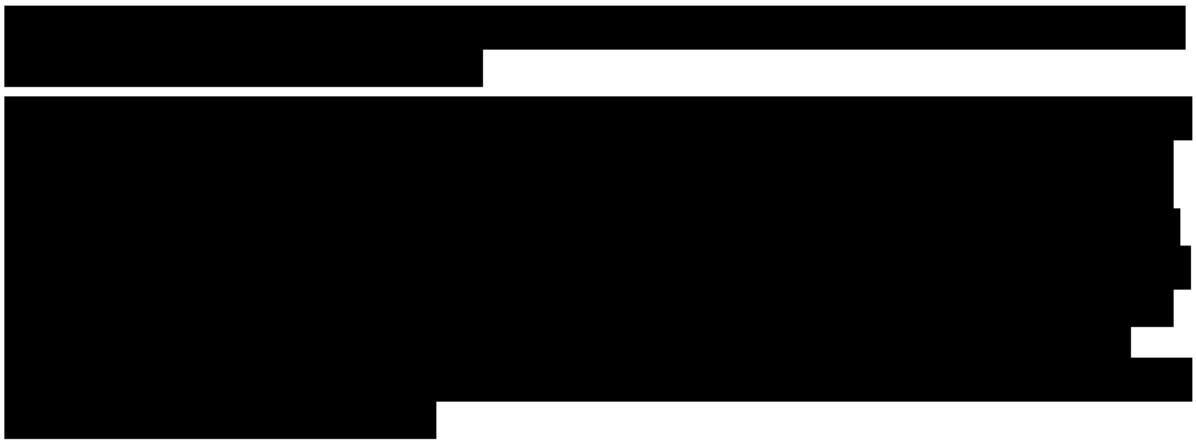
Table 2: Cardiac Monitoring During Dose Escalation

	Induction Day 1		
Procedure [a]	**Predose**	**Hours 1, 2, 3, 4, 5**	**Hour 6**
Vital signs[b]	X	X	X
12-lead ECG	X[c]		X
Assess Discharge Criteria[d]			X

[a] These assessments should also be conducted as on Induction Day 1 at the indicated times on Days 5 and 8 if issues are identified on the day prior to dose escalation.
[b] Resting pulse and blood pressure in the sitting position at each time point.
[c] Baseline or predose ECG should be provided by the site and be available for comparison to the postdose ECG in order to determine if discharge criteria are met.
[d] See Section 12.1.10 for discharge criteria and monitoring guidelines. Additional observation should be instituted until the finding has resolved in the following situations: pulse (per hourly vital signs measurement) 6 hours postdose is < 45 bpm; pulse (per hourly vital signs measurement) 6 hours postdose is at the lowest value postdose and lower than any other timepoint (unless this value is greater than or equal to baseline); ECG 6 hours postdose shows new onset second degree or higher AV block; for adult patients, the ECG 6 hours postdose shows a prolonged QTcF interval (> 450 msec males, > 470 msec females); for adolescent patients (> 450 msec for both males and females)

Abbreviations: AV = atrioventricular; ECG = electrocardiogram; QTcF = Fridericia's corrected QT interval.

[redacted]



7.3. Trial Periods

It is recommended that the trial visits are scheduled in the morning. On days of trial visits when trough PK samples are to be drawn, patients should be instructed to withhold the dose until the office visit, and the dose will be administered during the visit. At the Induction 2 (Week 5) visit, PK evaluations will be 2 to 6 hours after dosing. Therefore, patients should be instructed to take investigational drug at home prior to arriving for this visit.

Whenever possible, the sequence of assessments 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, including predose PK sampling
- Physical examination
- Efficacy assessments
- Investigational drug administration (on visits when trough PK blood draws are collected)

7.3.1. Screening Period

Written, signed, and dated informed consent/assent from the patient or patient's parent/legal guardian prior to the performance of any trial-related procedures must be obtained by the Investigator or designee (refer to Section 16.3 for further details regarding obtaining patients informed consent/assent). A copy of the signed informed consent form (ICF)/assent must be given to the patient for his/her records.

Screening procedures must be completed within 35 days prior to receiving the first dose of investigational drug. All Screening assessments and procedures as per Table 1 (IP and MP) are to be performed by the Investigator or a qualified designee.

A screen failure is defined as a patient or patient's parent/legal guardian who has given informed consent/assent, and failed to meet the inclusion and/or exclusion criteria. Patients who fail to meet the inclusion/exclusion criteria can be rescreened per Investigator discretion. Additional screening attempts beyond the first should be approved by the Medical Monitor prior to rescreening. Each patient or patient's parent/legal guardian must be re-consented/re-assented prior to each screening attempt.

During Screening the patient's prior use of medications to treat UC and whether they responded to adequate treatment with each medication will be assessed and documented. When considering response, an adequate treatment regimen for each of the following medications will be defined as:

- Oral aminosalicylates ≥ 2.4 g/day for at least 8 weeks
- Corticosteroids: oral prednisone ≥ 30 mg or budesonide MMX ≥ 9 mg for at least 2 weeks or intravenous corticosteroids for 1 week
- Immunomodulators: oral azathioprine ≥ 1.5 mg/kg or 6-mercaptopurine ≥0.75 mg/kg or methotrexate ≥ 12.5 mg/week for at least 8 weeks
- TNF-α antagonist (approved for marketing at an approved labeled dose) used for induction therapy for at least 4 weeks or recurrence of disease activity despite scheduled maintenance therapy

It will also be documented when the patient has been intolerant to one of these therapies (eg, unable to achieve doses, dose levels, or treatment durations because of treatment-related side effects and/or laboratory abnormalities).

The endoscopy at Screening must confirm disease extent, defined as 1) left-sided colitis (up to the splenic flexure), or 2) extensive colitis (beyond the splenic flexure).

If a colonoscopy is required at Screening, it should include removal of any adenomatous polyps prior to trial entry and documented evidence of surveillance for dysplasia for all patients with left-sided colitis of > 12 years duration and total or extensive colitis of > 8 years duration.

7.3.2. Induction and Maintenance Periods

Eligible patients will be randomized to treatment on Day 1 of both the Induction and Maintenance Periods. Visits, assessments, and procedures will be performed as per the Schedule of Events in Table 1. Guidelines for dose escalation are in Section 7.1.

7.3.3. Early Termination

For patients who discontinue the trial for any reason, every attempt should be made to complete the assessments detailed in the End of Treatment/Early Termination visit and the 30-day and 90-day Safety Follow-up Visits in the Schedule of Events (Table 1).

[redacted]

7.3.5. Relapse Assessment Visit

If during the MP the Investigator becomes aware of a potential relapse outside the normal visit schedule, patients should be evaluated for relapse as outlined in the Schedule of Events (Table 1).

7.3.6. Safety Follow-Up

For patients who discontinue the trial for any reason, every attempt should be made to return to the study site in order to complete the assessments detailed in the 30-day and 90-day Safety Follow-up Visits in the Schedule of Events (Table 1). [redacted] PK and hematology samples will be collected in all patients at the 30-day and 90-day visit. For patients with a confirmed ALC below the 200 cells/µL limit at the 30-day or 90-day Safety Follow Up Visit, central laboratory testing will continue every 14 days (± 3 days) after these visits until the ALC is above the lower limit of normal. In addition, additional safety assessments may be required for patients who have an ongoing AE or safety issue at the 90-day Safety Follow-up Visit, at the Investigator's discretion. Patients may be followed as necessary for an additional period of time after the 90-day Safety Follow-up Visit to review the results of any assessments which were conducted at the 90-day Safety Follow-up Visit.

7.3.7. 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 have to be taken to guarantee appropriate safety follow-up 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.

7.4. Trial Duration

The trial duration from first patient enrolled to the last patient's last visit is estimated to be approximately 58 months. Patients who complete the MP are anticipated to receive 52 weeks of treatment (10 week IP + 42 week MP).

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

For inclusion in the trial, all of the following inclusion criteria must be fulfilled:

1. Must meet one of the following criteria:
   - Male or female adult patients aged 18 to 75 years (at Screening), inclusive for Cohort 1 or Cohort 2, or
   - [redacted]
2. Have had UC diagnosed at least 3 months prior to first investigational drug administration. The diagnosis should be confirmed by clinical and endoscopic evidence and corroborated by a histopathology report (note: endoscopy and histopathology may be performed at Screening if no prior report is readily available)
3. Evidence of UC extending ≥ 15 cm from the anal verge as determined by Baseline endoscopy (flexible sigmoidoscopy or colonoscopy)
4. Have active UC defined as a complete Mayo score of 6 to 12 inclusive, with endoscopic subscore of ≥ 2, a rectal bleeding score of ≥ 1, and a stool frequency score ≥ 1
5. Must be currently receiving treatment with at least 1 of the following therapies and must continue on these therapies during Induction:
   - Oral aminosalicylates at a therapeutic dose for their disease (eg, mesalamine, sulfasalazine, olsalazine, balsalazide), with the dose stable for at least 3 weeks prior to Screening endoscopy
   - Prednisone (doses ≤ 20 mg per day) or equivalent receiving a stable dose for at least 2 weeks prior to Screening endoscopy
   - Budesonide MMX therapy receiving a stable dose for at least 2 weeks prior to Screening endoscopy
6. Have undergone colonoscopy (or are willing to undergo colonoscopy during Screening):
   - within the past 2 years, to screen for dysplasia (unless otherwise recommended by local and national guidelines) if the patient has had left-sided colitis of > 12 years duration or total/extensive colitis of > 8 years duration
   - within the past 5 years, to screen for polyps if the patient age is > 45 years

- If oral aminosalicylates or corticosteroids have been recently discontinued, they must have been stopped for at least 2 weeks prior to the endoscopy used for Baseline Mayo score

7. Females of childbearing potential (FCBP)[Ψ]:

Must agree to practice a highly effective method of contraception[£] throughout the trial until completion of the 90-day Safety Follow-up 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 amenorrhoea method are not acceptable methods of contraception.

8. Must provide written informed consent/assent and have the ability to be compliant with the schedule of protocol assessments. The parent/legal guardian of the adolescent must sign an informed consent form. In addition, adolescent patients must also agree to participate in the study by signing an assent.
9. Patients must have documentation of positive Varicella zoster virus (VZV) immunoglobulin G (IgG) antibody status or complete VZV vaccination at least 30 days prior to randomization

[Ψ] For the purposes of this study, a female patient is considered to be of childbearing potential if she is ≥ 12 years of age or has reached menarche, whichever occurred first, 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 at the Screening and Baseline visits, as appropriate. 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 28 days before baseline).

8.2. Patient Exclusion Criteria

Patients will not be entered in the trial for any of the following reasons:

Exclusions Related to General Health:

1. Have severe extensive colitis as evidenced by:
   - Physician judgment that the patient is likely to require colectomy or ileostomy within 12 weeks of Baseline
   - Current or recent (within 3 months) evidence of fulminant colitis, toxic megacolon, or bowel perforation
2. Diagnosis of Crohn's disease or indeterminate colitis or the presence or history of a fistula consistent with Crohn's disease or microscopic colitis or radiation colitis or ischemic colitis
3. Have positive stool examination for pathogens (ova and parasites, bacteria) or positive test for toxin producing *Clostridium difficile* (*C. difficile*) at Screening. PCR (polymerase chain reaction) examination of the stool for *C. difficile* may be used to exclude false positives. If positive, patients may be treated and retested. Documentation of a negative test result for pathogens (ova and parasites, bacteria) is required within 60 days of Day 1.
4. Pregnancy, lactation, or a positive serum beta-human chorionic gonadotropin (β-hCG) measured during Screening
5. 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
6. Clinically relevant cardiovascular conditions, including history or presence of:
   - Recent (within the last 6 months) occurrence of 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
   - For Adult patients: Prolonged Fridericia's corrected QT interval (QTcF; QTcF > 450 msec for males, > 470 msec for females), or at additional risk for QT interval prolongation (eg, hypokalemia, hypomagnesemia, congenital long-QT syndrome)
   - [redacted]
   - Resting HR < 55 bpm when taking vital signs as part of a physical exam at Screening

7. History of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with glycosylated Hb (HbA1c) > 9%, or diabetic patients with significant comorbid conditions such as retinopathy or nephropathy
8. History of uveitis (within the last year) or macular edema
9. Subject has a known active bacterial, viral, or fungal infection [excluding fungal infection of nail beds, minor upper respiratory tract infections, and minor skin infections], a mycobacterial infection (including tuberculosis [TB] or atypical mycobacterial disease), or any major episode of infection that required hospitalization or treatment with intravenous (IV) antibiotics within 30 days of Screening or oral antibiotics within 14 days of Screening
10. Recurrent or chronic infection (eg, hepatitis A, B, or C, human immunodeficiency virus [HIV]); recurrent urinary tract infections are allowed.
11. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin or uterine cervix that have been excised and resolved) or colonic mucosal dysplasia
12. History of alcohol or drug abuse within 1 year prior to randomization
13. History of or currently active primary or secondary immunodeficiency

Exclusions Related to Medications:

14. History of treatment with a biologic agent within 8 weeks or 5 elimination half-lives (whichever is less) of that agent prior to randomization
15. History of treatment with an investigational agent within 5 elimination half-lives of that agent prior to randomization
16. History of treatment with topical rectal 5-aminosalicylic acid or topical rectal steroids within 2 weeks of Screening endoscopy or anti-motility medications (such as diphenoxylate/atropine) during Screening
17. Receipt of a live vaccine or live attenuated vaccine within 4 weeks prior to randomization
18. Previous treatment with lymphocyte-depleting therapies (eg, Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
19. Have had treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 16 weeks of Screening or tofacitinib within 2 weeks of Screening
20. Previous treatment with D-penicillamine, leflunomide, or thalidomide
21. Previous treatment with natalizumab, fingolimod or etrasimod
22. History of treatment with intravenous immunoglobulin (IVIg) or plasmapheresis within 3 months prior to randomization

23. Planned concurrent treatment with immunosuppressive agents (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate) after randomization. Patients receiving AZA, 6-MP, or methotrexate at Screening must discontinue treatment with these agents prior to randomization
24. 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)
25. Treatment with Class Ia or Class III anti-arrhythmic drugs or treatment with two or more agents in combination known to prolong PR interval
26. Apheresis (eg, Adacolumn apheresis) within 2 weeks of randomization
27. Patients who were primary non-responders to 2 or more biologic agents, approved for the treatment of UC (eg, anti-TNF agents or vedolizumab)
28. Patient receiving treatment with breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine, eltrombopag)
29. Is receiving treatment with any of the following drugs or interventions within the corresponding timeframe:
    - At randomization
      - CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) and inducers (eg, rifampicin)
    - Two weeks prior to randomization
      - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)

[redacted]

Exclusions Related to Laboratory Results:

31. Serum creatinine > 1.4 mg/dL for females or > 1.6 mg/dL for males
32. Liver function impairment or persisting elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal (ULN), or direct bilirubin > 1.5 times the ULN
33. Platelet count < 100,000/μL
34. Hemoglobin < 8.0 g/dL
35. Neutrophils < 1500 /μL
36. Absolute white blood cell count < 3500/μL
37. Absolute lymphocyte count < 800/μL
38. ECG showing any clinically significant abnormality
39. Forced expiratory volume at 1 second (FEV_1) or forced vital capacity (FVC) < 70% of predicted values at Screening

8.3. Considerations for Patients with Comorbid Conditions

8.3.1. Patients with Type 2 Diabetes Mellitus

Patients with type 2 diabetes mellitus are permitted in the trial if their HbA1c is ≤ 9% at Screening. Such patients should receive appropriate diabetes management and treatment during the trial.

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

The Investigator should ensure that diabetic patients who are included in the trial are closely monitored for signs or symptoms of macular edema (See Section 12.2.6). Patients with diabetic uveitis or diabetic patients with significant comorbid conditions such as retinopathy or nephropathy are excluded.

Duration of disease and medication history for 3 months prior to randomization and throughout the trial will be recorded in source documents and in the electronic case report form (eCRF).

8.3.2. 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 the trial, may be considered for participation in the trial. Please refer to Section 8.2 for a list of cardiac exclusion criteria. These patients should have a cardiology consultation to determine whether it is appropriate for them to participate in the trial and whether they need additional cardiac monitoring. The results and recommendations of this consultation should be discussed with the medical monitor before patient enrollment.

If more intensive monitoring is not deemed necessary by the consulting cardiologist, these patients will follow the detailed first dose monitoring procedures as outlined in Section 12.1.10. The Investigator should ensure these patients included in the trial are closely monitored for signs of any bradycardia or other rhythm disturbances after the first dose of RPC1063, as these patients may be at higher risk for cardiac AEs.

8.4. 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, 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 investigational drug due to a lack of expected or desired effect related to a therapy.
- Withdrawal by Patient (or Patient's Parent/ Legal Guardian): The patient (or patient's parent/legal guardian) may choose to discontinue investigational drug at any time. Patients who discontinue investigational drug will be withdrawn from the study. Every effort should be made within the bounds of safety and patient (or patient's parent/legal guardian) choice to have each patient complete the Early Termination Visit and 30-day and 90-day Safety Follow-up Visits. If a patient (or patient's parent/legal guardian) withdraws consent/assent, the only additional investigational 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 12.2.9).
- Trial termination by Sponsor
- Other

All patients who discontinue the trial should complete an End of Treatment/Early Termination Visit (see Table 1). For patients who have a confirmed ALC below the 200 cells/µL limit and permanently discontinue from participation in the study, central laboratory testing will continue every 14 days (± 3 days) after the Early Termination Visit until the ALC is above the lower limit of normal. With the exception of patients who withdraw consent/assent or are lost to follow-up, patients should complete the 30-day and 90-day Safety Follow-up Visits for the collection of safety data and to assess their disease status. For patients who have a confirmed ALC below the 200 cells/µL limit at the 30-day or 90-day Safety Follow-up Visit, central laboratory testing will continue every 14 days (± 3 days) after these visits until the ALC is above the lower limit of normal. Alternative treatment for UC can be started, if needed, after the 30-day Safety Follow-up visit.

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 discontinue trial participation, the Investigator should document in the source documents the steps taken to contact the patient or patient's

parent/legal guardian (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.

[redacted]

9. TRIAL TREATMENTS

9.1. Treatments Administered

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

Patients should be instructed to take investigational drug (either RPC1063 or placebo) at approximately the same time each day with or without food.

9.1.1. Induction Period

Cohort 1 (adults) [redacted] On Induction Day 1, patients will be randomly assigned in a 2:1 ratio to initiate investigational drug in accordance with a 7-day dose escalation regimen starting with:

- On Days 1 to 4, RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) or matching placebo once daily (one 0.25 mg capsule)
- On Days 5 to 7, RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) or matching placebo once daily (two 0.25 mg capsules)
- On Day 8, patients will receive the final dose RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) or matching placebo once daily for 9 weeks (one 1 mg capsule)

Cohort 2 (adults): On Induction Day 1, all patients will initiate investigational drug in accordance with a 7-day dose escalation regimen starting with:

- On Days 1 to 4, RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) once daily (one 0.25 mg capsule)
- On Days 5 to 7, RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) once daily (two 0.25 mg capsules)
- On Day 8, patients will receive the final dose RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) once daily for 9 weeks (one 1 mg capsule)

9.1.2. Maintenance Period

On Maintenance Day 1, patients from Cohort 1, Cohort 2 [redacted] with clinical response to RPC1063 during the IP will be randomly assigned 1:1 to:

- RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) once daily for 42 weeks (one 1 mg capsule), or
- Matching placebo; a single capsule once daily for 42 weeks

Patients from Cohort 1 [redacted] who had been randomized to receive placebo and showed a clinical response at Week 10 will continue to receive placebo in the MP in a double-blind manner.

9.1.3. 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, he/she 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 patient misses a dose during dose escalation, the Medical Monitor should be contacted to discuss completing the dose escalation schedule.

If the patient misses more than 14 consecutive doses for any reason, the Medical Monitor must be contacted to discuss procedures for resuming therapy, which will include Day 1 cardiac monitoring procedures on the first day that the patient resumes dosing.

9.2. Method of Assigning Patients to Treatment Group

Patients must provide proper informed consent/assent before any trial procedures are performed. [redacted]

Consented/assented patients meeting all eligibility criteria will be assigned to treatment/randomized using the Interactive voice /web-based activated response system (IXRS). Further instructions on the use of the system will be provided in a separate IXRS manual.

9.2.1. Induction Period

Cohort 1 (adults): After all Screening and baseline (Week 0) assessments have been completed and the Investigator has verified that the patient is eligible per the inclusion (Section 8.1) and exclusion criteria (Section 8.2), patients will be randomized in a double-blind manner to either RPC1063 or placebo (2:1 ratio). Patients will be stratified according to corticosteroid use at Screening (yes or no) and prior anti-TNF use (yes or no). This stratified randomization will be centrally allocated across all centers via the IXRS.

Cohort 2 (adults): After all Screening and baseline (Week 0) assessments have been completed and the Investigator has verified that the patient is eligible per the inclusion and exclusion criteria, patients will be entered into treatment with RPC1063 1 mg in an open-label manner.

[redacted]

9.2.2. Maintenance Period

Patients from Cohort 1, Cohort 2 [redacted] who complete the IP and are in clinical response at Week 10 will be eligible to enter the randomized, double-blind, placebo-controlled MP. Patients who received RPC1063 and showed a clinical response during the IP (Cohort 1, Cohort 2 [redacted] will be randomized to receive either RPC1063 1 mg or placebo in a 1:1 ratio. Patients randomized to placebo in Cohort 1(adults) [redacted] who demonstrate a clinical response during the IP will continue to receive placebo in the MP in a double-blind manner. [redacted]

In general, for patients completing the IP and entering the MP, Visit I3 of the IP will serve as Visit M 1 of the MP. Procedures completed during IP Visit I 3 (Week 10) do not need to be repeated if the MP Visit M 1 occurs within 14 days of the I 3 visit. Patients should enter the MP within 21 days of the Visit I 3 endoscopy.

Patients randomized into the MP will be stratified by clinical remission status at Week 10 (yes or no) and corticosteroids use at Week 10 (yes or no).

9.3. 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), ongoing Phase 2 (RPC01-202), and Phase 2/3 (RPC01-201) trials (see Section 5.2.2 and subsections). The 1 mg/day dose demonstrated better efficacy than the 0.5 mg/day dose across various clinical and endoscopic endpoints. 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 (0.25 mg/day on Days 1 to 4 and 0.5 mg/day on Days 5 to 7) 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 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 0.25 mg RPC1063 for the first 4 days of dosing followed by 0.5 mg on Days 5 through 7 before progressing to the 1 mg/day dose will be used.

[redacted]

9.4. Selection and Timing of Dose for Each Patient

Patients will self-administer either RPC1063 or placebo by mouth once per day. Investigational drug should be taken at approximately the same time each day with or without food. See Section 9.1.3 for instructions regarding missed doses.

9.5.1. Steroid Taper

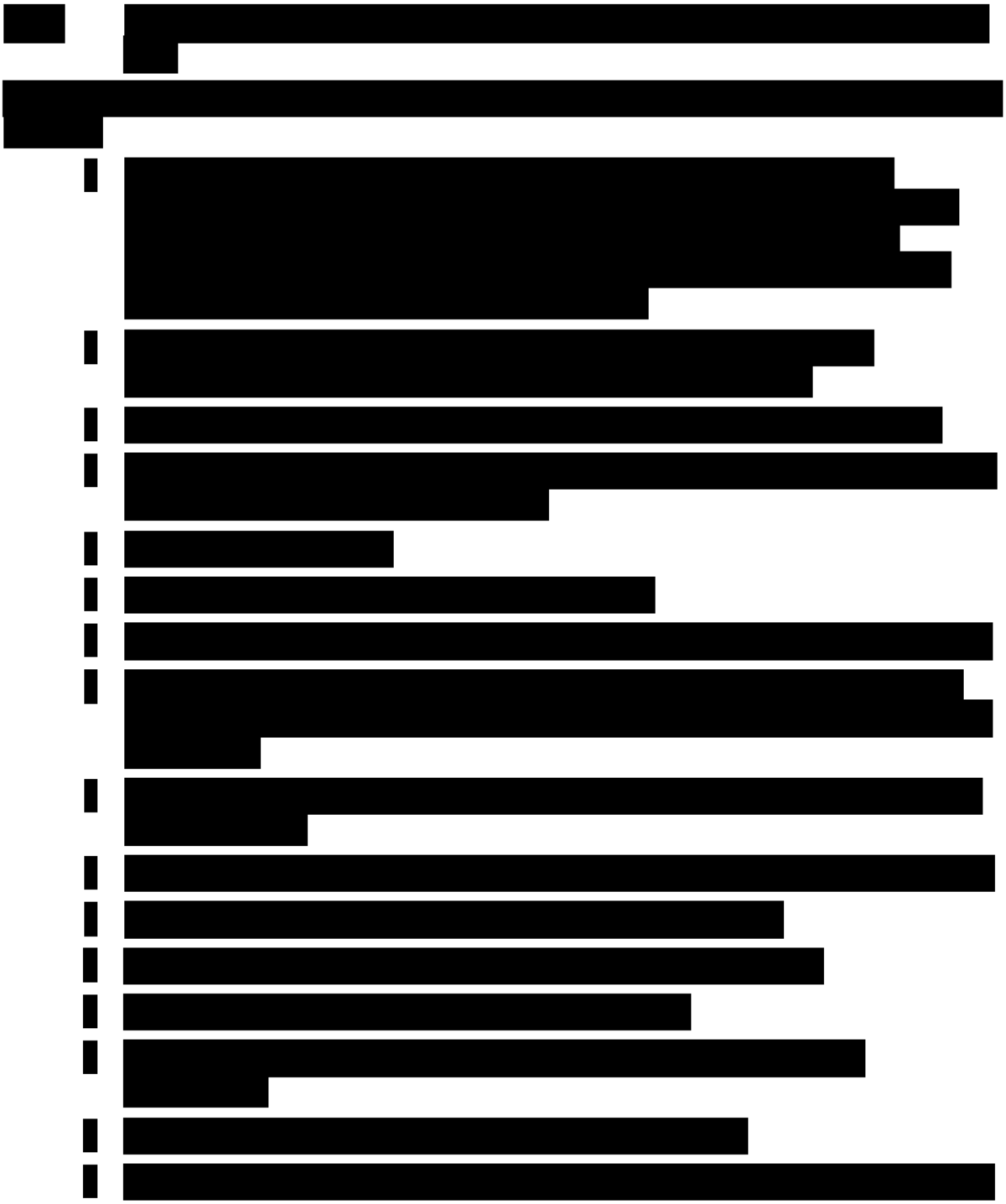
During the Induction Phase, patients are to maintain their stable baseline corticosteroid dose.

Corticosteroids should be tapered upon entering the MP (Week 10). Patients receiving prednisone at a dose of > 10 mg/day (or equivalent) should have their dose reduced at a rate of 5 mg per week until a 10 mg/day dose is achieved. Patients receiving prednisone at doses of 10 mg/day (or equivalent), or once a 10 mg/day dose (or equivalent) is achieved by tapering, are to have their dose reduced at a rate of 2.5 mg/week until discontinuation. Beginning at Week 10, patients receiving budesonide MMX should taper their dose of 9 mg every day to 9 mg every other day for 2 weeks and then discontinue budesonide MMX treatment. For patients who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms of either UC or steroid withdrawal, the corticosteroid dose may be increased (up to the dose at trial entry if required), but tapering should begin again within 2 weeks.

9.5.2. Allowed Medications

All prior medications (including over-the-counter medications) administered 30 days prior to the date of informed consent/assent and any concomitant therapy administered to the patient during the course of the trial until 90 days after the final dose of investigational drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to UC should 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.

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.



[redacted]

Table 3: Examples of Prohibited Cardiac Medications (Systemic Use)

Pharmaceutical Class	Example Medications
Anti-arrhythmic drugs	amiodarone, bepridil hydrochloride, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, sotalol, lidocaine, procainamide, propafenone, quinidine, tocainide

[redacted]

9.6. Medical Care of Patients after End of Trial

Patients who leave the trial and complete their end of trial assessments, including the 30-day and 90-day Safety Follow-up Visits, do not require any additional care provided by the sponsor; they will return to the care of their personal physician(s).

9.7. 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 10.1.

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 medication in a diary that will be reviewed periodically by site staff and the site monitor. Patients exhibiting poor compliance as assessed by investigational drug counts (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.

9.8. Blinding

This is a randomized, double-blind, placebo-controlled trial with limited access to the randomization code (note: Cohort 2 of the IP is open-label with all patients receiving RPC1063, see Section 9.2.1). RPC1063 and placebo capsules will be identical in physical appearance. The treatment each patient will receive will not be disclosed to the Investigator, site staff, patient, Sponsor, or the clinical staff at the Contract Research Organization (CRO) involved with trial conduct or data collection/analysis. Access to treatment assignments will be strictly limited to groups directly involved with drug distribution, preparation of unblinded output for the DSMB, safety personnel unblinded to treatment for SAE cases, and personnel involved in the conduct of PK assays.

For Cohort 1, the adult patient's treatment group assignment blind will not be broken until after the last patient in Cohort 1 has had their last Cohort 1 visit, unless medical treatment of that patient depends upon knowledge of the assigned treatment. For the randomized component of the MP, the adult patient's treatment group assignment blind will not be broken until after the last patient has had their last Maintenance visit, unless medical treatment of that patient depends upon knowledge of the assigned treatment.

[redacted]

In the event that the blind needs to be broken because of a medical emergency, the Investigator may unblind an individual patient's treatment allocation through the IXRS. The Investigator should attempt to contact the Medical Monitor as soon as practicable to discuss the medical emergency and detail the reasons that the patient was unblinded. Reasons for treatment unblinding must also be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

A PK sample will be obtained whenever possible for patients with any AE resulting in unblinding, discontinuation, or SAE.

10. INVESTIGATIONAL DRUG MATERIALS AND MANAGEMENT

10.1. Investigational Drug

RPC1063 and matching placebo 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 and matching placebo).

RPC1063 and placebo 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 investigation: 0.25 mg (size 4 capsule) and 1 mg (size 4 capsule).

For placebo, the same size 4 Swedish orange opaque hard-gelatin capsules will contain the same blended excipients described above without the active pharmaceutical ingredient. All three doses of RPC1063 and placebo capsules are identical in appearance.

All investigational drug must be stored in a secure location.

[redacted]

10.3. Investigational Drug Accountability

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

All supplies of RPC1063 and placebo 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 investigational drug 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 CRO. The CRO will verify that a final report of drug accountability is prepared and maintained in the Investigator's Trial Master File.

11. ASSESSMENT OF EFFICACY

Unless stated otherwise, all efficacy assessments will be performed for all patients (adults and adolescents).

11.1. Efficacy Assessments

11.1.1. Key Efficacy Measure: The Mayo Score

The Complete Mayo score is a composite of four assessments, each rated from 0 to 3: stool frequency, rectal bleeding, endoscopy, and Physicians Global Assessment (Schroeder et al. 1987). The endoscopy subscore 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 Physicians Global Assessment subscore, resulting in a composite of the rectal bleeding, stool frequency, and endoscopy subscores. The partial Mayo score eliminates the endoscopy subscore, resulting in a composite of the rectal bleeding, stool frequency, and Physicians Global Assessment subscores. The complete Mayo score has a range of 0 to 12 and the 9-point Mayo score and partial Mayo score each has a range of 0 to 9.

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

1. Stool frequency[a]

   0 = Normal number of stools for this patient, prior to the onset of UC disease, or while in remission

   1 = 1 to 2 stools more than normal

   2 = 3 to 4 stools more than normal

   3 = 5 or more stools more than normal

2. Rectal bleeding[b]

   0 = No blood seen

   1 = Streaks of blood with stool less than half the time

   2 = Obvious blood with stool most of the time

   3 = Blood alone passes

3. Findings on endoscopy

   0 = Normal or inactive disease

   1 = Mild disease (erythema, decreased vascular pattern, does not include friability)

   2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)

   3 = Severe disease (spontaneous bleeding, ulceration)

4. Physician's Global Assessment[c]

   0 = Normal

1 = Mild disease

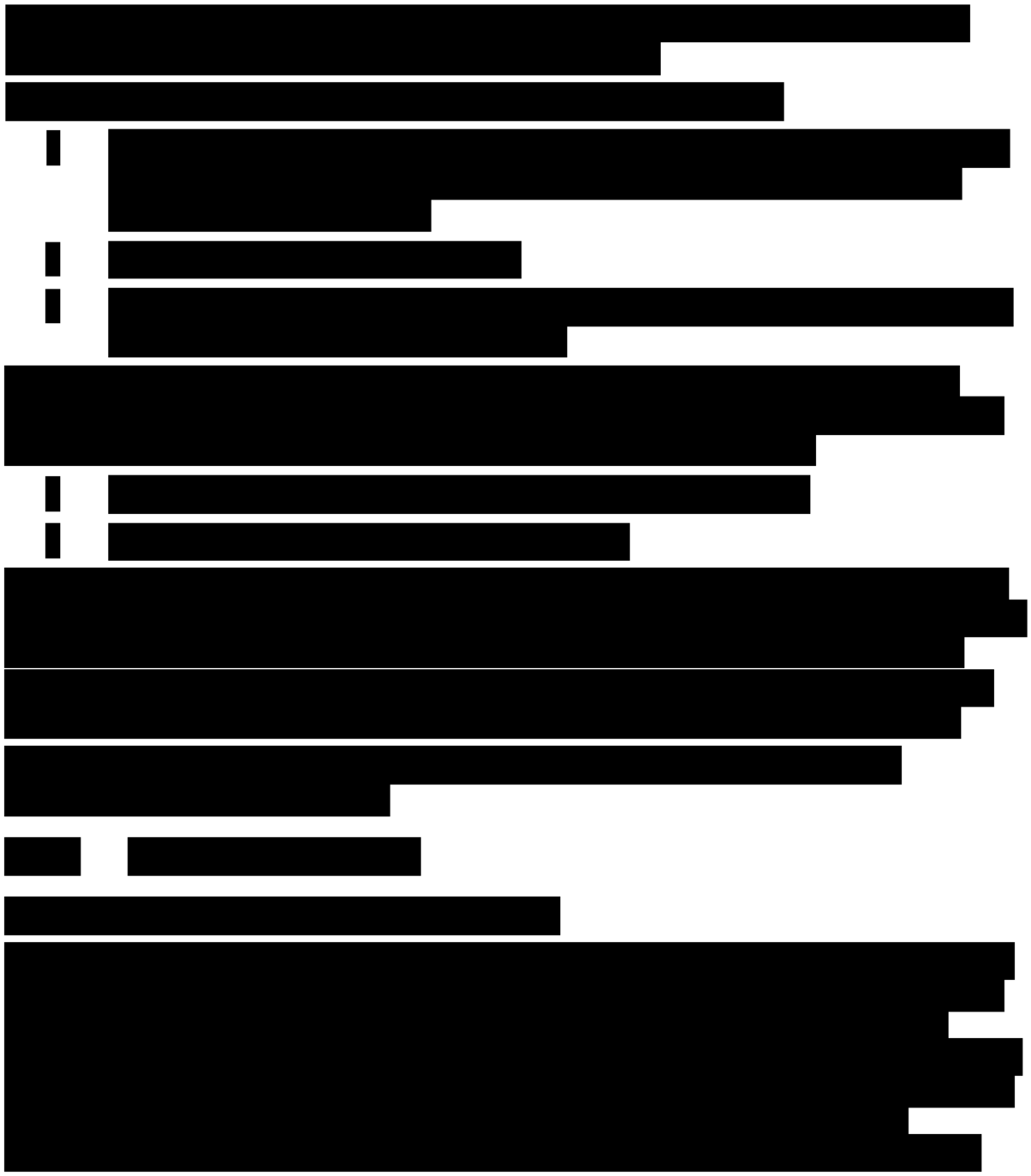
2 = Moderate disease

3 = Severe disease

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

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

[c] The physician's global assessment acknowledges the three 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.



[redacted]

[redacted]

11.1.2.3. Biopsy

Each patient entered into the trial will have colonic biopsies obtained during flexible sigmoidoscopy/full colonoscopy as follows (see Table 1):

- 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 histopathologic confirmation of UC is needed to meet trial eligibility, an additional biopsy can be used for histopathologic confirmation of UC (analysis should be performed locally, if possible).
- 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.

[redacted]

[redacted]

12. ASSESSMENTS OF SAFETY

This section describes the procedures for the recording of safety parameters, specific monitoring requirements, and the reporting of adverse events, including adverse events of special interest. A description of the risk-benefit profile of RPC1063 is summarized in Appendix 3 of this protocol

12.1. Safety Parameters

12.1.1. Physical Examination

A complete physical examination will be performed at Screening, M 5, and at the EoT or ET visit, and will include evaluation of heart, lungs, head and neck, abdomen, skin, and extremities, as well as a check for visual symptoms. All significant findings that are present at Screening 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 every 6 months. Significant findings made after randomization that meet the definition of an AE must be recorded on the AEs eCRF.

At all other visits following Screening (except M 5/EoT/ET), an interim physical examination will be performed. The interim physical examination will include body systems with previously noted abnormalities and/or those body systems associated with any new complaints from the patient.

12.1.2. Height and Weight

For all patients, height and weight will be measured at Screening.

[redacted]

Height measurements should be made using stadiometry if possible and recorded to the nearest 0.1 cm or ¼ inch. Ideally, the same person should conduct the height measure at each visit in order to minimize variability.

12.1.3. 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.

Patients will be carefully monitored after the first dose of investigational drug with a 6 hour postdose monitoring period of hourly recording of pulse and blood pressure as described in Section 12.1.10.

12.1.4. 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 (Section 7.1) 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. The screening ECG report from the central reader must be available to confirm patient eligibility before randomization. Electrocardiograms will be performed before and 6 hours after the first dose of investigational drug administration for all patients on Induction Day 1 while the patient is in the clinic. The 6 hour postdose ECG 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 5 and 8 if cardiac issues are identified on the prior day of dose escalation, as described in Section 12.1.10.

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.

12.1.5. Ophthalmological Examination

Optical coherence tomography (OCT) will be performed as scheduled in Table 1. All original OCT images are considered source documents that should be made available to the site upon request, or otherwise at the end of the study. If there is a suspicion of new onset macular edema, then general retinal exams, including eye history, visual acuity, and dilated ophthalmoscopy will be obtained. A general ophthalmologist can do the examination, although a retinal specialist would be preferred to do the exams wherever possible. OCT images may be reviewed by an independent panel of ophthalmologists assigned to this trial.

12.1.6. Pulmonary Function Tests

Pulmonary function tests including FEV_1 and FVC measurements will be performed as scheduled in Table 1. In addition, DLCO measurements will be performed at Screening, Visit I 3, Visit M 3, and at the End of Trial or Early Termination visit (see Table 1, footnote p) where locally available. DLCO will not be required at sites where there is no local testing facility. Pulmonary function tests may be performed at a qualified pulmonary function laboratory, respiratory department, or at the clinical trial site. If being performed at the clinical trial site, the Principal Investigator may delegate the performance of this test to any staff member that is qualified to perform the pulmonary function test. If the pulmonary function test results are not within normal range, the results must be verified by a pulmonologist, and potential confounding factors identified. If the patient has a decline in PFT values, the patient should have adequate evaluation as clinically indicated by a pulmonologist as described in Section 12.2.6. Please refer to the American Thoracic Society/European Respiratory Society guidelines for standardization of spirometry and single breath determination of carbon monoxide uptake in the lung (MacIntyre 2005; Miller 2005a; Miller 2005b).

12.1.7. Dermatological Examination

Dermatological evaluations will be performed by the treating Investigator or designee as part of the physical exam, as scheduled in Table 1. Patients with any suspicious finding noted during the examination will be referred to an appropriately qualified dermatologist for evaluation and treatment, if warranted.

12.1.8. 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 12.2 for definitions of AEs/SAEs, monitoring and reporting. Refer to Section 12.2.6 for AEs of special interest.

12.1.9. Monitoring of Concomitant Therapy

The use of concomitant medication and procedures will be monitored throughout the trial. Refer to Section 9.5.3 for prohibited concomitant therapies.

12.1.10. Guidelines for Monitoring Patients Taking Their First Dose of RPC1063

On Day 1 of treatment for the IP, careful cardiac monitoring of the patients is required. The Investigator is responsible for monitoring the patient following the first intake of the investigational drug, as well as managing bradycardia symptoms should they occur. The Investigator must review the Baseline predose ECG, pulse, and blood pressure during the 6-hour monitoring period, postdose ECG, and assess discharge status at 6 hours after dosing. Baseline predose ECG should be provided by the site and be available for comparison to the postdose ECG in order to determine if criteria requiring extended monitoring are met.

Resting pulse and blood pressure in the sitting position will be measured before the first dose of investigational drug and every hour for at least 6 hours thereafter (by the Investigator, an assisting nurse, or other medically qualified staff member). When obtaining the pulse and blood pressure before the first dose, the patient should be allowed to rest in a seated position at least 10 minutes before taking measurements. The HR and sitting blood pressure measurements should be repeated 2 additional times (only before the first dose of investigational drug) and the lowest HR and blood pressure will be recorded in the eCRF. The repeat measurements will be made at approximately 2-minute intervals. For the hourly measurements after investigational drug administration, HR and sitting blood pressure will be measured once and recorded in the eCRF. The lowest predose value of sitting heart rate and blood pressure (based on systolic blood pressure) will be recorded in the case report form and serve as baseline for comparison to postdose values.

If possible, patients should receive the first dose of investigational drug before 12:00 pm (noon) in the clinic with or without food. The first dose of investigational drug must be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. A member of the Investigator team should be available to monitor the patient for the 6-hour monitoring period and will need to report any abnormalities to the Investigator. Atropine and epinephrine or isoproterenol need to be readily available to the site personnel.

If any of the following criteria are met, additional extended monitoring should be instituted until the finding has resolved. Baseline and hourly vital signs measurements (Hours 1 through 6) should be used to assess pulse (criteria 1 and 2 below) and ECG device results should only be used to assess for AV block and QTcF interval (criteria 3 and 4 below).

1. The pulse 6 hours postdose is < 45 bpm
2. The pulse 6 hours postdose is at the lowest value postdose and lower than any other timepoint (suggesting that the maximum PD effect on the heart may not yet have occurred), unless this value is greater than or equal to baseline
3. The ECG 6 hours postdose shows new onset second degree or higher AV block
4. For Adult patients, the ECG 6 hours postdose shows a prolonged QTcF interval (> 450 msec for males, > 470 msec for females)

[redacted]

Should postdose symptomatic bradycardia occur, the treating physician should be notified and he or she should initiate appropriate management, begin continuous ECG monitoring, and continue observation until the symptoms have resolved.

Should a patient require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated the following day (Day 2). The first dose monitoring strategy should also be repeated at Day 5 or at Day 8 if any cardiac safety issues were observed on the previous Day of dose escalation (see Table 2).

Patients should have written instruction on when to return to the clinic and a 24-hour contact phone number to call in the event of any new or warranted symptoms (eg, chest pain, dizziness, palpitations, syncope, nausea, vomiting). Patients should be instructed not to drive on the same day after the first dose of investigational drug administration.

12.1.11. 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.

Repeat testing for protocol required laboratory tests are to be analyzed by the central laboratory. Additional 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 retest 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, Hb, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Total WBC count and all differential WBC counts will be blinded information for the treating Investigator after initiation of investigational drug. Of note, WBC, basophil, eosinophil, lymphocyte, monocyte, and neutrophil counts will not be disclosed to preserve the blind.

During the treatment period, WBC differential results will be available to an unblinded medical reviewer not directly participating in study conduct. Reductions in ALC levels is a known pharmacodynamic effect of RPC1063. If any of the following results are observed, the Investigator will be notified and asked to repeat the laboratory tests within approximately 7 days:

- Absolute neutrophil count (ANC) < 1000 cells/µL
- Absolute lymphocyte count (ALC) < 200 cells/µL

If the ANC is confirmed below the 1000 cells/µL limit, the Investigator will be requested to closely monitor for risk of serious infection and institute appropriate follow-up, at the discretion of the Investigator.

If the ALC is confirmed below the 200 cells/µL limit, the Investigator will temporarily discontinue investigational drug and then consult with the Medical Monitor. Laboratory testing will be repeated weekly during the treatment period until the ALC > 500 cells/µL. When ALC has returned to > 500 cells/µL, the treatment may be reinitiated at the Investigator's discretion (see Section 9.1.3 for instructions on resuming treatment after missing doses).

For patients who have a confirmed ALC below the 200 cells/µL limit and permanently discontinue from participation in the study, central laboratory testing will continue every 14 days (± 3 days) after the Early Termination Visit until the ALC is above the lower limit of normal.

- Chemistry:

  Full chemistry panel at Screening: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, HbA1c, albumin, alkaline phosphatase, creatinine, ALT, AST, gamma glutamyltransferase (GGT), total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein, C-reactive protein

  - All other visits: blood urea nitrogen, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, total bilirubin, conjugated bilirubin, C-reactive protein. Of note, C-reactive protein will not be disclosed to preserve the blind.

- Urinalysis: Leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
- The central laboratory will analyze routine blood samples. 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 at Screening in females of childbearing potential. Urine β-hCG will be performed in females of childbearing potential at each scheduled visit. Between scheduled visits up until the 90-day Safety Follow-up Visit, monthly home urine pregnancy tests should be performed by the patient. If a urine pregnancy test result is positive, the Investigator will instruct the patient to suspend further study dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including after the 90-day Safety Follow-up visit, if needed.
- Serology testing will be performed at Screening to determine the patient's immune status with respect to the following viral infections:

  VZV

  - A VZV titer will be performed to determine if the patient has immunity (positive IgG result to *Varicella Zoster* virus). If VZV antibody titer is negative, the patient may choose to receive VZV vaccination in order to qualify for the study. If the patient receives a VZV vaccination, randomization can occur at a minimum of 30 days after vaccination has been completed.

  HIV

  - A HIV antibody test will be performed. Patients testing positive for HIV (ELISA test result, confirmed by Western blot) will be excluded from the trial.

  HAV

  - An anti-hepatitis A virus (HAV) antibody (anti-HAV IgM) test will be performed. Patients testing positive will be excluded from the trial, unless they are indicative of prior hepatitis A that is considered cured and accompanied by normal liver transaminase values.

  HBV

  - Anti-hepatitis surface (HBs) antigen and anti-hepatitis B core (HBc) antigen test will be performed
  - Patients who test positive for HBs antigen will be excluded from the trial.
  - For patients who test positive only for antibody to HBc antigen, an HBV DNA test must be performed.
  - If the HBV DNA test is negative (without anti-viral therapy) and the liver function tests (LFTs) are normal, the patient will be eligible for this trial. These patients will undergo periodic monitoring for HBV DNA during the trial.

  HCV

  - A HCV antibody (anti-HCV IgG or IgM test) will be performed.

- Patients testing positive for HCV antibody and a positive confirmatory test will be excluded from the trial.

12.2. Adverse Events and Serious Adverse Events

12.2.1. 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 12.2.7.

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 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.

12.2.2. 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 are 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.

12.2.3. 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.

12.2.4. 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.

12.2.5. 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/assent is signed through the last visit. 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 and procedures. Data entry must be completed within 24 hours from the time the trial site personnel first learned of the event.

[redacted]

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.

12.2.5.1. 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.

12.2.6. Adverse Events of Special Interest

Potential AEs that may be a consequence of $S1P_1$ modulation will be closely monitored during the trial. These AEs include bradycardia, heart conduction abnormalities (2nd degree and higher AV block), macular edema, malignancy, serious or opportunistic infection, pulmonary effects, and hepatic effects. An independent DSMB for the trial will perform quarterly safety reviews starting after the first patient is dosed.

Special considerations regarding monitoring for these events are as follows:

- Bradycardia and heart conduction abnormalities (eg, symptomatic bradycardia, 2nd degree AV block, QT prolongation):
  - Patients will be closely monitored in the clinic after their first dose of the initial dose escalation regimen for a period of 6 hours after treatment. Electrocardiograms will occur predose and at Hour 6 following dosing, with more frequent assessments if clinically indicated. Resting pulse and blood pressure in the sitting position will be assessed predose and then hourly for 6 hours following dosing. See the monitoring guidelines in Section 12.1.10 for further details.
  - Investigators should be particularly cautious with patients who have a pulse rate < 55 bpm prior to administration of the investigational drug. Atropine IV is recommended as the first line treatment of bradycardia, up to a maximum daily dose of 3 mg. In general, the common guidelines for treatment of bradycardia (eg, Advanced Cardiac Life Support guidelines) should be followed as appropriate.
- Pulmonary effects
  - Any condition that might affect the outcome of pulmonary function testing including infection, respiratory symptoms, occupational exposures (including asbestos) and cigarette smoking needs to be collected before PFT testing and transcribed to the pulmonary function tests eCRF page. If patients have decline in PFT values (FEV1 and/or FVC) below 50% of the predicted values, treatment

should be discontinued. If a patient discontinues due to respiratory AE, the Investigator should ensure that the patient has adequate evaluations as clinically indicated by a pulmonologist (consider PFTs, chest X-ray or high resolution computed tomography, based on findings of the other exams) at the time of the AE. For patients with pulmonary nodules, lung biopsy should be considered (Cryptococcus pneumonia and pulmonary TB have been reported with fingolimod). Further evaluations will be conducted until such time as resolution is confirmed or no further improvement is expected by the Investigator (based on a follow-up period of not less than 3 months).

- Hepatic effects
  - If patients have elevations in the LFTs (ALT or/and AST) ≥3 times the ULN, a retest should be performed as soon as possible but not later than 14 days after the original test. Upon confirmation of the abnormality, retests should be performed weekly until the elevated LFT decreases to below 3 times the ULN. At any time, if any of the following occur and there are no apparent alternative causes for the finding, the investigational drug must be permanently discontinued:
    - ALT or AST > 8x ULN or
    - ALT or AST > 5x ULN with confirmation, within 2 weeks or
    - ALT or AST > 3x ULN and (total bilirubin > 2x ULN) or
    - ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

  The Investigator should establish causality

  After discontinuation due to elevation of ALT or AST > 5x ULN or concurrent elevations of ALT or AST > 3x ULN and bilirubin > 2x ULN, further liver function evaluation should be performed (for example, coagulation panel and alkaline phosphatase) in consultation with the Medical Monitor.

- Macular edema
  - For patients with abnormal OCT findings or with visual signs or symptoms of new onset macular edema that develop following initiation of treatment, a general ophthalmologic examination including eye history, visual acuity, and dilated ophthalmoscopy will also be performed
  - Investigational drug must be discontinued in any patient who has a confirmed diagnosis of macular edema that is of new onset since Baseline
  - Patients with a diagnosis of macular edema must be followed up monthly and more frequently if needed based on the ophthalmologist's judgment

- Malignancies
  - Because RPC1063 is an immunomodulator, patients should be carefully monitored for malignancies (including dermatologic malignancy)
  - The Investigator will complete a dermatological examination for monitoring of the potential development of new cutaneous malignancies during the trial. Patients with any suspicious finding noted during the examination will be referred to an appropriately qualified dermatologist for evaluation and treatment, if warranted
- Serious or opportunistic infections
  - TB, serious bacterial infections, systemic fungal infections, viral infections such as herpes infections (including herpes zoster and disseminated herpes simplex) and protozoan infections will be considered AEs of special interest

12.2.7. 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. The reporting of AEs will begin at Induction Day 1 post first dose for all randomized patients. The reporting of SAEs for any patient will begin from the time written informed consent/assent is signed through the last visit, as detailed in Section 12.2.5. 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 each patient and provide further information to the CRO on the patient's condition. During the trial, all AEs/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.

12.2.8. Treatment of 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 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 do not need to be recorded as AEs in the eCRF; only in the case of any AEs associated with the overdose should these be reported on relevant AE/SAE sections in the eCRF.

12.2.9. Procedures in Case of Pregnancy

If a urine pregnancy test is positive, the patient will be instructed to suspend further study 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 to confirm the result.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product 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/assent 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.

12.2.10. Data Safety Monitoring Board

An independent DSMB will be charged with monitoring accumulating safety data from the trial, as well as general aspects of trial conduct.

The committee will meet periodically during the trial (approximately 4 times each year) to review aggregate analyses by treatment group concerning enrollment, treatment compliance, adherence to follow-up schedule, and safety data from the trial. The DSMB may recommend modifying or stopping the trial early due to safety concerns based on data reviews.

The blinding plan to assure that all personnel involved in the conduct of the trial remain blinded to the results of interim reviews will be specified in the DSMB Charter.

[redacted]

12.4. 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.

13. PLANNED STATISTICAL METHODS

13.1. Determination of Sample Size

Induction Period:

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

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

Table 5: Sample Size and Corresponding Precision

Total Sample Size	Sample Size by Treatment		Precision: Half-Width of a 95% Confidence Interval for Treatment Difference (Ozanimod Versus Placebo)	
	Ozanimod	Placebo	Clinical Remission Δ=10% (16% versus 6%)	Clinical Response Δ=25% (57% versus 32%)
30	20	10	21.8%	36.1%
60	40	20	15.4%	25.6%
90	60	30	12.6%	20.9%
120	80	40	10.9%	18.1%
150	100	50	9.7%	16.2%

[redacted]

Maintenance Period (adult patients):

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

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

13.2. Statistical Methods

13.2.1. General Considerations

For the purposes of statistical analyses, the IP and the MP will be treated as two independent trials. The analysis of the IP will formally evaluate the efficacy and safety of RPC1063 1 mg vs. placebo as an induction therapy and the analysis of the MP will formally evaluate the efficacy and safety of RPC1063 1 mg vs. placebo as a maintenance therapy.

All efficacy and safety data will be listed by patient. Baseline for the IP is defined as the last observed measurement prior to the Day 1 receipt of investigational drug. Baseline for the MP is defined as the last observed measurement prior to the first dose of investigational drug following randomization into the MP. All safety and efficacy endpoints will be summarized by treatment group.

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.

13.2.2. Analysis Populations

All patient populations will be defined and documented prior to database lock. The following analysis populations will be used in the statistical analysis:

- Intent-to-Treat (ITT) population: The ITT population will consist of:
  - **Induction Period Cohort 1:** All randomized adult patients from Cohort 1 of the IP of the trial who received at least 1 dose of investigational drug (RPC1063 or placebo)
  - **Induction Period Cohort 2:** All enrolled adult patients from Cohort 2 of the IP of the trial who received at least 1 dose of investigational drug (RPC1063)

    [redacted]
  - **Maintenance Period:** All randomized patients who received at least 1 dose of investigational drug (RPC1063 or placebo) in the MP

  The ITT populations will be used as the primary population for all efficacy parameters. Patients who prematurely withdraw from the trial for any reason and for whom an assessment is not performed for any reason will still be included in the ITT analyses. Patients who receive an incorrect investigational drug from that which was randomized will be summarized in the treatment group according to the intended randomization.
- Per Protocol (PP) population: The PP population will consist of all patients in the ITT populations who adhere to the protocol. This population will be used in sensitivity analyses of the primary and key secondary endpoints to evaluate the influence of major protocol violators and protocol deviators on the primary

results. Patients may be excluded from this population if they violate the eligibility criteria or significantly deviate from the trial plan. Specific reasons for warranting exclusion from this population will be documented prior to database lock and may include, but are not limited to, investigational drug noncompliance > 20%, receiving incorrect investigational drug for more than 1 week in the IP or more than 1 month in the MP, and missing more than 2 visits while still on the trial.

- Safety population: The Safety population will consist of all patients who receive at least 1 dose of investigational drug. This population will be used for all summaries of safety data. Patients randomized to placebo who receive any amount of RPC1063 will be summarized in the RPC1063 1 mg group. Patients randomized to RPC1063 who receive only placebo for all doses will be summarized in the placebo group, otherwise they will be summarized in the RPC1063 1 mg group.

13.3. 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, randomized, dosed, completing the IP, not completing the IP by reason for dropout, completing the MP, and not completing the MP by reason for dropout will be summarized for the ITT population. Patient demographics will be summarized for the ITT population and will include age, sex, race, ethnicity, height, weight, and body mass index.

Baseline characteristics will be summarized for the ITT population and will include age at UC symptom onset, age at UC diagnosis, years since UC symptom onset, years since UC diagnosis, prior anti-TNF use, corticosteroid use at Screening, concomitant UC medication use at Baseline, each component of the Mayo score, the Complete Mayo Score, [redacted]

Compliance with randomized 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.

13.4. Efficacy

13.4.1. Induction Period (Adult Patients)

Cohort 1 (double-blind RPC1063 1 mg once daily or placebo) will be used to formally assess the efficacy endpoints in the IP of the trial.

As Cohort 2 (open-label RPC1063 1 mg once daily) does not have a placebo control, no efficacy endpoints will be formally examined for the IP; however, the efficacy measures shown in Section 6.2.1 will be summarized and described.

13.4.1.1. Induction Period Primary Efficacy Analysis (Adult Patients)

The primary analysis of proportion of patients in clinical remission (Three-component Mayo definition) at Week 10 will be carried out on the ITT population using a two-sided Cochran-Mantel-Haenszel (CMH) test at the 5% level of significance, stratified by corticosteroid use at screening (yes or no), and prior anti-TNF use (yes or no). Results will be expressed as number of patients in remission, remission percentages, weighted difference in remission percentages, odds ratio, and associated 95% confidence intervals (CIs) and p-values.

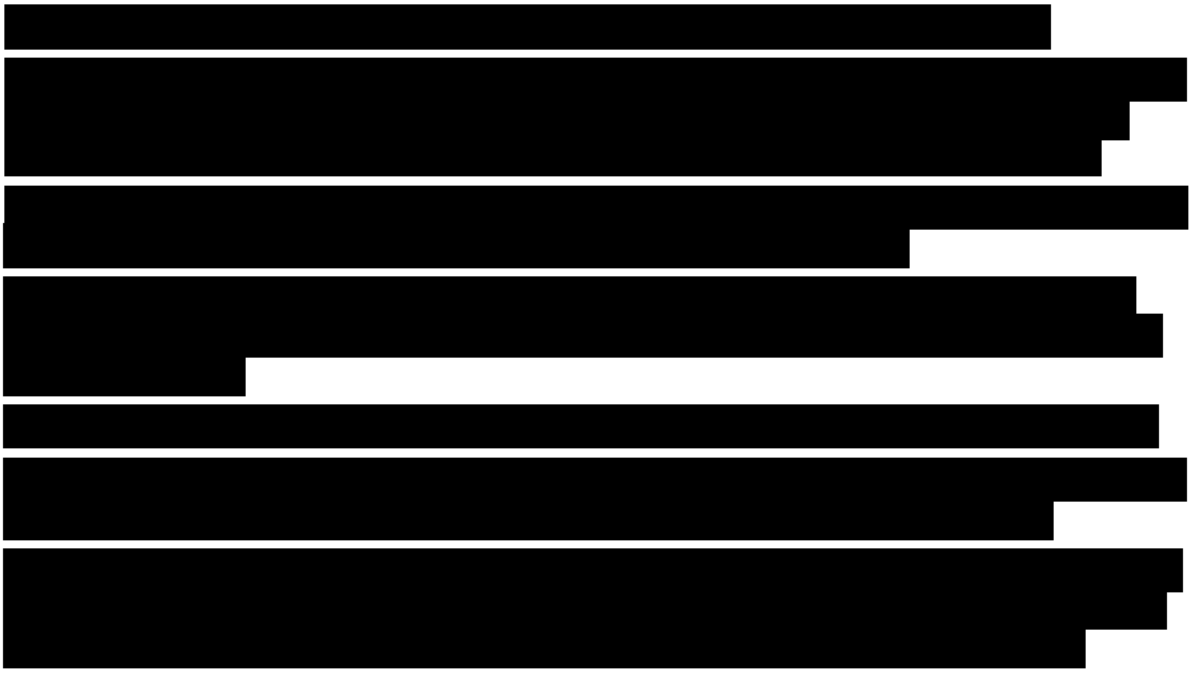
The primary analysis will be repeated on the PP population and on key subgroups of the ITT population including, but not limited to, patients with and without prior anti-TNF experience and patients with and without prior corticosteroid use. These will be considered sensitivity/supportive analyses only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

[redacted]

13.4.1.2. Induction Period Secondary Efficacy Analysis (Adult Patients)

The 3 key secondary endpoints will be tested in order in a closed, hierarchical testing procedure in order to control the overall Type I error rate for multiple endpoints. If the primary endpoint is statistically significant, the proportion of patients with a clinical response (Three-component Mayo definition) at Week 10 will be tested at the 5% level of significance. If that endpoint is significant, then the proportion of patients with endoscopic improvement at Week 10 will be tested at the 5% level of significance. This testing procedure will continue through each of the 3 key secondary endpoints until an endpoint fails to reach statistical significance, after which all subsequent key secondary endpoints will be considered exploratory. Endpoints listed as other secondary endpoints (Section 6.2.2) will be tested in a nonhierarchical fashion without adjustments for multiplicity.

[redacted]



13.4.2. Maintenance Period (Adult Patients)

Patients with a clinical response at Week 10 will be eligible to enter the MP. Patients who received RPC1063 1 mg and showed a clinical response during the IP (both Cohort 1 and Cohort 2) will be randomized in a double-blind manner to receive either RPC1063 1 mg or placebo in a 1:1 ratio. Patients randomized to placebo in Cohort 1 who demonstrate a clinical response during the IP will continue to receive placebo in the MP. Patients from either Cohort who do not show a clinical response may enter an optional Open-Label Extension trial, if appropriate.

MP endpoints are listed in Section 6.2.4.

13.4.2.1. Maintenance Period Primary Efficacy Analysis

The primary analysis of proportion of patients in clinical remission (Three-component Mayo definition) at Week 42 (52 weeks total treatment) will be carried out on the ITT population using a two-sided CMH test at the 5% level of significance, stratified by clinical remission status at Week 10 of the IP (yes or no), and corticosteroid use at Week 10 of the IP (yes or no). Results will be expressed as number of patients in remission, remission percentages, weighted difference in remission percentages, odds ratio, and associated 95% CIs and p-values.

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

In addition to the primary analysis of MP clinical remission at Week 42 (52 weeks total treatment) using the Three-component Mayo definition described in Section 6.2.1, the following alternative definitions of remission will be explored as sensitivity analyses:

- Rectal Bleeding Subscore ≤ 1 point and Stool Frequency Subscore ≤ 1 point and Endoscopy Subscore ≤ 1 point
- Rectal Bleeding Subscore = 0 points and change from Baseline in Stool Frequency Subscore ≤ 0 points (same or improved) and Endoscopy Subscore ≤ 1 point
- Partial Mayo Score of ≤ 2 points with none of the associated 3 subscores > 1 point

13.4.2.2. Maintenance Period Secondary Efficacy Analysis

The 6 key secondary endpoints (Section 6.2.4) will be tested in order in a closed, hierarchical testing procedure in order to control the overall Type I error rate for multiple endpoints. If the primary endpoint is statistically significant, the proportion of patients with a clinical response (Three-component Mayo definition) at 52 weeks will be tested at the 5% level of significance. If that endpoint is significant, then the proportion of patients with endoscopic improvement at 52 weeks will be tested at the 5% level of significance. This testing procedure will continue through each of the 6 key secondary endpoints until an endpoint fails to reach statistical significance, after which all subsequent key secondary endpoints will be considered exploratory. Endpoints listed as other secondary endpoints (Section 6.2.4) will be tested in a nonhierarchical fashion without adjustments for multiplicity.

[redacted]

13.4.2.4. Handling Missing Data

For proportion-based primary and key secondary efficacy endpoints, patients with missing Week 10 efficacy data for the IP and/or patients with missing Week 42 (52 weeks total treatment) efficacy data for MP will be considered non-responders using non-responder

imputation (NRI). Sensitivity analyses around missing data may include tipping-point analysis, missing data imputed using multiple imputation (MI) and analyzing observed cases with no imputation.

For continuous efficacy endpoints, missing data analysis may be performed using a multiple imputation (MI) method and observed cases with no imputation.

13.4.3. Safety Analyses

All safety analyses will be carried out on the Safety population.

Adverse events will be monitored during the trial and the data analyzed with respect to incidence within each treatment group as well as severity and potential relationship of the AEs to investigational drug. Adverse events with onset on, or after the first dose of investigational drug or with onset prior to the first dose of investigational drug 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 lowest and to the highest on-trial value in and out of the normal range as well as by visit. Changes from Baseline to each visit for each 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.

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

OCT parameters will be summarized.

[redacted]

13.5. Pharmacokinetic Analyses

Population PK analyses will use the PK data from this trial combined with data from other Phase 2 and Phase 3 trials to assess the influence of patient covariates on the exposure of RPC1063 and other relevant active metabolites. Exposure-response analysis may also be performed as appropriate. Results on population PK and exposure-response will be reported in separate, stand-alone reports.

13.6. Interim Analyses

No interim analyses for efficacy are planned during the conduct of either trial period.

13.7. Induction Period Analysis

The data from the IP in Cohort 1 will be cleaned, unblinded, and analyzed after the last Cohort 1 patient has had their last IP visit. The data from Cohort 2 will be cleaned and summarized after the last Cohort 2 patient has had their last Cohort 2 visit.

[redacted]

The treatment blind for the MP will not be broken until the end of the study.

13.8. End of Study Analysis

The data from MP will be cleaned, unblinded, and analyzed after the last Maintenance patient has had their last MP visit.

13.9. Treatment Failure Rules

Treatment failure rules (TFR) will be applied to the primary analyses of all efficacy endpoints. Patients will be considered to have failed treatment if any of the following occur:

- Any protocol-prohibited change in medications including:
  - Post-Baseline initiation of, or increase in total daily dose level higher than the maximum dose taken between the Screening and Baseline visits in:
    - Corticosteroids or 5-ASA dose to treat UC
    - Prolonged course of systemic corticosteroids > 14 days for treatment of disease other than UC
  - Initiation of an immune suppressing therapy including 6-mercaptopurine (6-MP), azathioprine, anti-TNF agents, vedolizumab or tofacitinib
- A colectomy (partial or total) or an ostomy

[redacted]

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Monitoring

The Sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical trial. CRO monitors will work in accordance with CRO 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.

14.2. 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 daily diary information directly into an electronic diary, and this will be considered a source document. [redacted]

All data entered by the site staff must be entered in English. The eCRFs should 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.

14.3. 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. 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 Standard Operating Procedures (SOPs).

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 center visits post-enrollment
- Routine center monitoring
- Ongoing center 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.

15.2. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the patient. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately.

[redacted]

16. ETHICS

16.1. Institutional Review Board or Independent Ethics Committee

An Independent Ethics Committee should approve the final protocol, including the final version of the ICF, assent form, 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 informed consent and/or assent 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 and/or assent form 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 informed consent/assent 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.

16.2. Ethical Conduct of the Trial

This trial will be conducted and the informed consent and/or assent 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.

16.3. Patient Information and Informed Consent/Assent

The Investigator will explain the benefits and risks of participation in the trial to each patient (or patient's parent/legal guardian), and/or the impartial witness and obtain written informed consent/assent. Written informed consent/assent 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/assent form for each patient, signed and dated by the patient, patient's parent/legal guardian, or witness, and by the person who conducted the informed consent/assent discussion. The Investigator will supply all enrolled patients with either a copy of their signed informed consent/assent or, depending upon local requirements, a second original informed consent/assent, signed by both parties.

The consent form/assent 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/assent of the patient, the Investigator should inform the patient's primary physician about participation in the clinical trial.

16.4. Patient Data Protection

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

16.5. Investigator Obligations

This trial will be conducted in accordance with the 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 IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

16.6. 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 he/she has read, understands 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 center where the Investigator has not signed the protocol.

17. DATA HANDLING AND RECORD KEEPING

17.1. 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.

17.2. Retention of Records

It is the Investigator's responsibility to maintain essential trial documents (protocol and protocol amendments, completed eCRFs, signed ICFs/assent forms, 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 Harmonisation (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 product. 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.

18. 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 site will be set forth in the Clinical Trial Agreement.

Appendix 2: Investigator Responsibilities

Per Good Clinical Practices 21 CFR 312.53

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/assent 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 21 CFR 312.60

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/assent of each human patient to whom the drug is administered, **except as provided in 21 CFR 50.23.**

Appendix 3: BENEFIT RISK ASSESSMENT

POTENTIAL BENEFITS

Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disorder that involves the surface mucosa, the crypt epithelium, and the submucosa of the colon [redacted] 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 [redacted]

Patients with UC suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever [redacted] The pathology of 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 [redacted] Toxic megacolon commonly requires an urgent colectomy to avoid perforation, peritonitis, and sepsis. Colectomy is curative, and patients with refractory UC may undergo colectomy as a treatment option. Within 10 years of diagnosis, 19.9% of adults with UC had undergone colectomy. [redacted]

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 [redacted]

The overall goal of treatment for patients with active UC is to induce and maintain remission and to induce and maintain mucosal healing [redacted] 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 [redacted] 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 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 [redacted]

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 precluding long-term use.

[redacted]

[redacted]

For those patients who are unresponsive to, or intolerant of corticosteroids, immunomodulators including azathioprine (AZA), 6-mercaptopurine (6-MP), and cyclosporine [redacted] or biologics (such as infliximab) are used to induce and/or maintain remission [redacted] However, these medications have multiple limitations including toxicities. 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 has increased with the recognition of these potentially severe complications. Infliximab is indicated for pediatric UC but comes with potential risks, and 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. [redacted]

Ozanimod is a small molecule compound that selectively binds with high affinity to sphingosine 1-phosphate receptors 1 and 5. Ozanimod is extensively metabolized in humans with up to 13 metabolites identified in plasma, urine, and feces, including 2 active selective major metabolites and 1 inactive major metabolite found in human plasma at steady state. [redacted]

Many cell types express S1P1, including vascular endothelial cells, brain cells, and lymphocytes. 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 [redacted] Given the immune-mediated inflammation in Crohn's disease, prevention of circulation of disease-exacerbating, self-reactive lymphocytes to the gut is likely to have salutary immunomodulatory effects with a consequent dampening of disease processes.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of ozanimod.

[redacted]

[redacted]

The current study is designed to evaluate the benefit-risk profile of ozanimod in subjects with moderately to severely active UC. The trial is composed of 2 periods: Induction and Maintenance. Patients will enter into the trial through the Induction Period (IP) [redacted] Cohort 1 admitted 645 adult patients randomized in a 2:1 ratio to receive either ozanimod 0.92 mg or placebo once daily in a double-blind fashion, stratified by corticosteroid use at Screening and prior anti-TNF use. Cohort 2 admitted 367 adult patients to open label ozanimod. [redacted] The primary endpoint of the study is the proportion of adult patients in clinical remission at Week 10. Adult patients from Cohort 1 or Cohort 2 with clinical response at the end of the IP will proceed through to the MP. Patients who participate in this trial may qualify to participate in an optional Open-Label Extension trial.

[redacted]

POTENTIAL RISKS AND PRECAUTIONS

As of 20 December 2018, an estimated 4520 subjects have received ozanimod with over 8000 person-years of exposure in a clinical development program including relapsing multiple sclerosis (RMS) and IBD patients. The Phase 1 clinical studies have shown ozanimod to have adequate safety and tolerability, linear PK, and dose-dependent PD effects on lymphocyte counts. The safety and tolerability results from the Phase 2 and Phase 3 studies in RMS, the Phase 2 study in UC, and the ongoing Phase 2 study in CD suggest that ozanimod at doses of 0.46 and 0.92 mg daily is well tolerated and has a good safety profile in subjects with RMS, in subjects with moderately to severely active UC, and in subjects with moderately to severely active CD.

No important risks have been identified associated with ozanimod treatment. Important potential risks based on experience with non-selective sphingosine 1-phosphate (S1P) agonists include symptomatic bradycardia, atrioventricular conduction disorder, liver injury, macular edema, Progressive Multifocal Leukoencephalopathy (PML), Posterior Reversible Encephalopathy Syndrome (PRES), embryofetal toxicity in exposed pregnant females, malignancies, infections, and pulmonary effects.

ptomatic Bradycardia, Atrioventricular Conduction disorder:

Initiation of ozanimod may result in transient reductions in heart rate. In active-controlled MS clinical trials, after the initial dose of ozanimod 0.23 mg, the greatest mean reduction from baseline in heart rate of 1.2 beats per minute (bpm) occurred at Hour 5 on Day 1, returning to near baseline at Hour 6. Heart rates below 40 bpm were not observed. Initiation of ozanimod without dose escalation may result in greater reductions in heart rate.

Ozanimod studies exclude subjects with severe untreated sleep apnea or recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure or have a history or presence of second-degree atrioventricular block Type II or third-degree AV block or sick sinus syndrome unless the subject has a functioning pacemaker. Subjects will be excluded from the study if they are being treated with Class Ia or Class III anti-arrhythmic drugs or with 2 or more agents in combination known to prolong PR interval.

On Day 1 of treatment, the protocol requires cardiac monitoring of the subjects for 6 hours after the first dose of investigational product and provides guidelines for extended monitoring and treatment if bradycardia. Subjects will be discontinued for clinically important bradycardia or AV conduction block as described in the protocol.

Liver Injury:

Elevations of aminotransaminases, primarily ALT and GGT, may occur in subjects receiving ozanimod.

In active-controlled multiple sclerosis (MS) clinical trials, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of subjects treated with ozanimod 0.92 mg and 1.3% of subjects on interferon (IFN) β-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of subjects on ozanimod and 3.1% of subjects on IFN β-1a. The median time to elevation 3-fold the ULN was 6 months. The majority (79%) continued treatment with ozanimod with values returning to < 3 times the ULN within approximately 2-4 weeks.

A similar pattern of ALT elevations has been seen in UC and CD studies. As of 20Dec2018, no cases of severe drug-induced liver injury were reported with ozanimod in RMS, UC, or CD clinical trials.

Liver function tests and hepatobiliary AEs will be closely monitored within the clinical trials, including for patients who develop symptoms suggestive of hepatic disease. Repeat testing, stopping, and drug discontinuation rules have been provided to address elevations in liver enzymes.

Macular Edema:

In the active-controlled MS clinical trials with ozanimod, macular edema was observed in one (0.1%) subject with ozanimod 0.92 mg and 3 (0.3%) subjects with ozanimod 0.46 mg, all of whom had preexisting risk factors.

Subjects with a history of uveitis, Type 1 diabetes mellitus, and uncontrolled Type 2 diabetes mellitus were excluded from clinical trials with ozanimod. During the study, OCT will be used to screen for macular edema. Subjects who present with visual symptoms of macular edema should be evaluated by the investigator and, if confirmed, treatment with ozanimod should be discontinued. Study drug must be discontinued in any subject who has a confirmed diagnosis of macular edema that is of new onset.

Progressive Multifocal Leukoencephalopathy (PML):

PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically only occurs in subjects who are immunocompromised, and that usually leads to death or severe disability.

JCV infection resulting in PML has been observed in subjects treated with MS therapies and has been associated with some risk factors (eg, polytherapy with immunosuppressants, severely immunocompromised subjects). No cases of PML were identified in clinical trials with ozanimod. Should symptoms present that are suggestive of PML, investigators should hold ozanimod and perform appropriate diagnostic evaluation. If confirmed, treatment with ozanimod should be discontinued.

Posterior Reversible Encephalopathy Syndrome (PRES):

In controlled clinical trials with ozanimod, one case of PRES was reported in a subject with Guillain-Barré syndrome. A relationship of PRES to ozanimod is uncertain. It has been observed with other S1P receptor modulators. If PRES is suspected, treatment with ozanimod should be discontinued by the investigator.

Embryofetal Toxicity in Exposed Pregnant Females:

There are no adequate and well-controlled studies in pregnant women. In animals, findings at similar exposure levels included embryo- fetal death, abnormal/delayed ossification, and abnormalities of the viscera and large blood vessels. There have been no reports of teratogenicity in the ozanimod clinical trials.

The use of ozanimod is not recommended during pregnancy and in women of childbearing potential not using contraception. Women of child-bearing potential should use effective contraception during treatment and for a minimum of 90 days after stopping treatment and must stop study treatment in the event of a diagnosis of pregnancy.

Malignancy:

Nonclinical testing found no carcinogenic effect through extensive genetic toxicology testing, in vivo carcinogenicity studies, and assessment of proliferative lesions in the general toxicology studies. The overall incidence of malignancies observed for patients on ozanimod is generally comparable to rates reported in the literature and health authority medical reviews for an age-matched population. The malignancies reported do not demonstrate any particular pattern and are not typical of those observed in an immunosuppressed population.

Infections:

Ozanimod causes a dose-dependent reduction in peripheral lymphocyte count because of reversible retention of lymphocytes in lymphoid tissues. In the controlled RMS trials, mean absolute lymphocyte counts during treatment with ozanimod were approximately 45% of baseline values. Ozanimod may therefore increase the susceptibility to infections. In the Phase 3 RMS program, 0.4% of subjects on 0.46 mg ozanimod and 3.3% of subjects on 0.92 mg ozanimod developed ALC below 0.2 x 10^9/L with no distinct pattern of timing. An association between ALC < 0.2 x 10^9/L and serious or opportunistic infections was not detected; however, an increased risk of infection cannot be ruled out.

In active-controlled completed RMS clinical trials, the overall rate of infections (35%) with Ozanimod was similar to that of IFN β-1a. Ozanimod treatment was associated with a higher frequency of viral upper respiratory tract infections, urinary tract infections, and herpes zoster. The overall rate of serious infections was similar between ozanimod (1%) and IFN β-1a (0.8%) in active-controlled MS clinical trials (also refer to protocol Section 6.2.5).

Phase 2 UC and CD data follow a similar pattern.

After discontinuing ozanimod 0.92 mg, the median time to recovery of peripheral blood lymphocytes to the normal range was 30 days, with approximately 90% of subjects recovering within 90 days.

Vaccinations

No clinical data are available on the efficacy and safety of vaccinations, including live attenuated, in subjects taking ozanimod. The use of live attenuated vaccines is to be avoided during treatment with ozanimod and for 90 days after treatment discontinuation.

[redacted]

Pulmonary Effects:

Pulmonary function is known to be affected by fingolimod, a non-selective S1P receptor modulator, and increased collagen or fibrin deposition in the lung as has been reported in toxicology studies with fingolimod. In nonclinical studies, ozanimod did not induce smooth muscle hypertrophy, and no effect on respiratory function was observed with ozanimod administration in rodents. In patients with multiple sclerosis, the pulmonary data indicate that mild reductions in FEV1 and DLCO occurred early in treatment with ozanimod 1 mg but were not clinically meaningful and did not progress. Pulmonary effects are not considered to be a risk associated with ozanimod treatment.

Subjects with a forced expiratory volume at 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values at screening are excluded from the study. Subjects will be evaluated if either parameter falls below 70% of predicted and below 80% of baseline and will be discontinued if an FEV1 or FVC < 50% of predicted values develops during the study.

Drug/Drug Interactions:

Co-administration of ozanimod is not recommended with MAO inhibitors (clinical interaction has not been studied), BCRP inhibitors (may increase exposure to ozanimod metabolites), or Class Ia and Class III anti-arrhythmic drugs (not studied). Patients should be monitored when co-administering ozanimod with strong CYP2C8 inhibitors as the risk of adverse reactions may be greater (may increase ozanimod metabolite exposure). Ozanimod can be co-administered with calcium channel blockers or beta blockers (except sotalol, which also has class III activity) but should not be used simultaneously with two or more agents known to slow heart rate or delay AV conduction (eg, combination of a beta blocker and non-dihydropyridine calcium channel blockers). For detailed information on drug-drug interaction study results, refer to the Investigator's Brochure, Edition 11, section 6.3.5.1.

Addition of Adolescents

Protocol Amendment 6 includes the addition of adolescent subjects. Examination of the toxicity of ozanimod in juvenile rats identified the same effects as in adult rats (decreased peripheral blood lymphocytes, increased lung weights, and increased alveolar macrophages) with no unexpected findings. There are no drug-related risks identified specific to adolescents.

Adolescent patients with delayed growth or delayed pubertal development and who will not maintain a stable dose of corticosteroids through Week 10 are excluded from the study.

CONCLUSIONS

Based on the Investigator's Brochure (edition 11), the overall investigational benefit-risk balance of ozanimod remains unchanged. Currently available information supports an acceptable benefit-risk profile for ozanimod when used in accordance with the dosing and safety monitoring outlined in the study protocol.

The Phase 2 Induction and Maintenance study results in subjects with moderately to severely active ulcerative colitis suggested clinical and endoscopic benefit. In addition, the safety results suggest that ozanimod is well tolerated and is consistent with that observed in other patient populations. The overall data to date suggests that this ozanimod study has a potentially favorable benefit-risk profile for patients with moderate to severe ulcerative colitis.

In conclusion, based on current data available and the safety monitoring/management specified in the protocol it is considered safe to proceed with the proposed study in the patient population at the dose regimen specified in the protocol.