A PHASE 2, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PARALLEL-GROUP STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF INDUCTION THERAPY WITH RPC1063 IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

Test Drug: RPC1063
Protocol Number: RPC01-202
Study Phase: Phase 2
IND/EudraCT number: 115,243/2012-003123-38
Date and Version: 03 May 2019 (Version 10.0)
Replaces Version: 29 May 2018 (Version 9.0)

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1. SIGNATURES

Protocol RPC01-202, Version 10.0, was approved by:

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{See appended electronic signature page}

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Senior Director, Clinical Research & Development

Date

Sponsor: Celgene International II Sàrl

9 May 2019

Signature of Celgene International II Sàrl Representative

Date

Olivia Fière
Director Clinical Operations
Celgene International
Switzerland

Printed Name of Celgene International II Sàrl Representative

Declaration of Investigators

I have read and agree to the protocol RPC01-202 entitled 'A Phase 2, multi-center, randomized, double-blind, placebo-controlled parallel-group study to evaluate the clinical efficacy and safety of induction therapy with RPC1063 in patients with moderately to severely active ulcerative colitis' dated 03 May 2019 (Version 10.0). I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

_____ _____

Print Name Title

_____ _____

Signature Date

2. SYNOPSIS

NAME OF SPONSOR: Celgene International II Sàrl (CIS II)	**PROTOCOL No.:** RPC01-202
NAME OF STUDY TREATMENT: RPC1063	
TITLE OF STUDY: A Phase 2, multi-center, randomized, double-blind, placebo-controlled parallel-group study to evaluate the clinical efficacy and safety of induction therapy with RPC1063 in patients with moderately to severely active ulcerative colitis	
PLANNED NUMBER OF STUDY CENTERS: It is planned to initiate approximately 80 study centers to enroll patients in North America, Europe, and Asia Pacific.	
PHASE OF DEVELOPMENT: 2	
PLANNED STUDY DATES: The planned duration of the study is from October 2012 through December 2019.	
OBJECTIVES: **Primary Objective:** The primary objective of the study is to compare the efficacy of RPC1063 vs placebo for induction of clinical remission at Week 8 in patients with moderately to severely active ulcerative colitis (UC) **Secondary Objectives:** The secondary objectives are to: • Compare the efficacy of RPC1063 vs placebo at weeks 8 and 32 as measured by clinical response, clinical remission, and mucosal healing • Compare the overall safety and tolerability of RPC1063 vs placebo for the duration of the study [redacted]	
STUDY DESIGN AND METHODOLOGY: Study RPC01-202 is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients with moderately to severely active UC. This study includes 3 periods (Screening, Induction, and Maintenance) and an optional Open-Label Treatment Period (OLP). Following the 5-week Screening Period, eligible patients will be randomized and enter the 9-week placebo-controlled Induction Period (IP). Patients who are responders at Week 8 will continue on their assigned treatment in the 24-week Maintenance Period (MP). Non-responders at Week 8 have the option to enter the OLP. Patients who complete the MP will be given the option to participate in the OLP. Patients that enter the MP and experience disease relapse will also have the option to enter the OLP. The study will include both patients that have received anti-TNF therapy and those that have not. It is anticipated that approximately 50% of the patients included in the study will have received anti-TNF therapy. Induction Period (IP): The IP will serve as a dose-finding study to assess the efficacy and safety of RPC1063 for the induction of clinical response, remission, and mucosal healing in patients with moderately to severely active UC. The IP will last 9 weeks and consists of dose escalation over 8 days followed by the full dose for 8-weeks. Approximately 180 patients will be randomized in a 1:1:1 ratio to receive 1 of 3 treatment regimens: • RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) daily oral capsule • RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) daily oral capsule • Placebo daily oral capsule	

The randomization will be stratified by prior anti-TNF therapy experience (yes versus no).

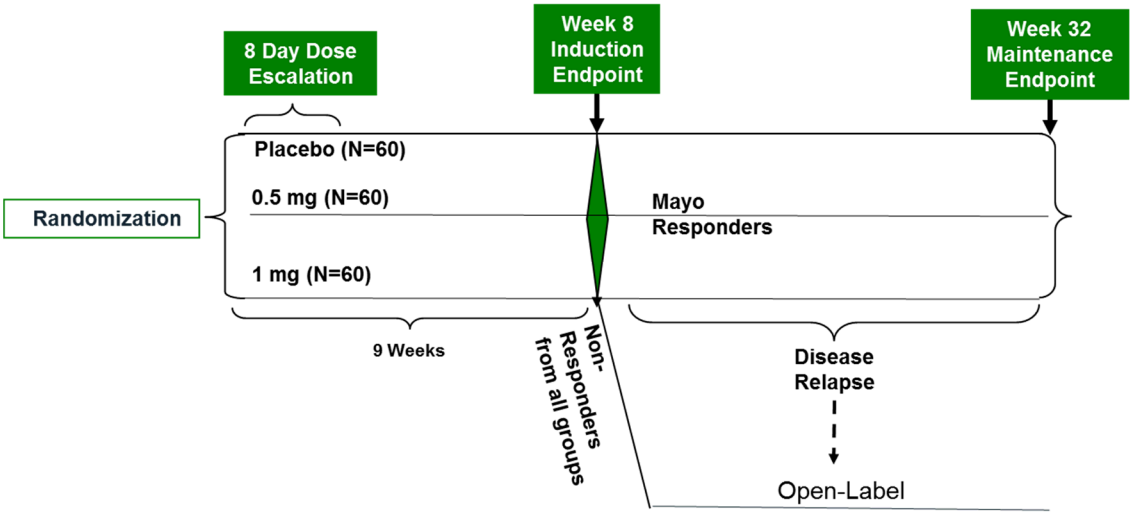
For patients randomized to one of the active treatment groups, there will be an 8-day dose escalation regimen in the IP consisting of 4 days of treatment with RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg), followed by 3 days of treatment with RPC1063 0.5 mg, followed by the assigned treatment level.

Maintenance Period (MP): All patients who complete the IP and are responders at Week 8 of the IP will enter the 24-week MP. Patients will continue to receive the same investigational drug in the MP as received during the IP, and individual patient treatment will remain blinded until all patients have reached Week 32. The last visit in the MP will occur at Week 32. Patients who complete the MP will be given the option to participate in the OLP. Patients that enter the MP and experience disease relapse will have the option to enter the OLP.

Disease relapse is defined as when all of the following criteria are met:

- An increase in UC disease activity as defined by an increase in partial Mayo score of ≥ 2 points compared to the Week 8 partial Mayo score with an absolute partial Mayo score ≥ 4 points
- An endoscopic subscore of ≥ 2 points
- Exclusion of other causes of an increase in disease activity unrelated to underlying UC (e.g., infections, change in medication)

Open-Label Treatment Period (OLP): Patients who complete the IP and are non-responders at Week 8 and those that complete the MP or experience disease relapse during the MP will have the option to enter the OLP. All patients in the OLP will receive daily study treatment with RPC1063 1 mg. There will be an 8-day dose escalation regimen consisting of 4 days of treatment with RPC1063 0.25 mg, followed by 3 days of treatment with RPC1063 0.5 mg, followed by RPC1063 1 mg. Patients who have not shown clinical improvement 8 weeks after initiation of the OLP should discontinue from the study. Eligible patients will be transitioned into the Phase 3 open-label extension UC Study RPC01-3102 and will be able to immediately enter the study (without completing the 30-day or 90-day Safety Follow-up Visits). The OLP will continue for up to 6 years or until marketing approval of RPC1063 for UC in the country of the clinical site (estimated to be in 2019), or completed transition of patients to Study RPC01-3102, or until the Sponsor discontinues the development program.



Safety Monitoring/Follow-up:

Potential adverse events (AEs) of interest that may be a consequence of sphingosine 1-phosphate 1 receptor 1 ($S1P_1$) modulation will be closely monitored during the study. These AEs include bradycardia, heart conduction abnormalities, pulmonary toxicity, macular edema, cutaneous malignancy, serious or

opportunistic infection and hepatotoxicity. A Data Monitoring Committee (DMC) for the study will perform safety reviews periodically, approximately four times a year until the end of the Maintenance Period.

The safety of patients will be monitored by collection of treatment-emergent AEs, serious adverse events (SAEs), physical exams, vital signs, Holter monitoring, electrocardiograms (ECGs), pulmonary function tests, optical coherence tomography (OCT), blood chemistry and hematology panels, coagulation panels, and urinalysis at baseline and various time points during the study. White blood cell (WBC) counts and lymphocyte counts will be monitored centrally (and will not be provided to the site) to prevent potential unblinding of the Investigator. Patients who discontinue from treatment due to lack of response, AEs, or other reasons, even if alternative treatment is given, will be followed for 90 days for collection of safety data and for the assessment of their disease status.

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Inclusion Criteria:

1. Male or female patients aged 18 to 75 years, inclusive
2. Have had UC diagnosed at least 2 months prior to screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence
3. Have active UC confirmed on endoscopy with ≥ 15 cm involvement
4. Have active UC defined as Mayo score of 6-12 inclusive with endoscopic subscore of ≥ 2
5. Have undergone colonoscopy or sigmoidoscopy within the past 2 years for extent of disease, and if the UC has been present for > 10 years, have had a colonoscopy with biopsy to rule out dysplasia
6. Female patients of childbearing potential:

   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
   - placement of an intrauterine hormone-releasing system
   - bilateral tubal occlusion
   - vasectomised partner
   - sexual abstinence

   Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.
7. Must be currently receiving treatment with at least 1 of the following therapies:
   a. Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide) for at least 6 weeks with the dose stable for at least 3 weeks prior to screening endoscopy
   b. Prednisone (doses ≤ 30 mg) or equivalent for at least 4 weeks and receiving a stable dose for at least 2 weeks
8. 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
9. All patients aged 45 or over must have had a colonoscopy to screen for adenomatous polyps within 5 years prior to the first dose of investigational drug or must have had a colonoscopy at screening to assess for polyps. The adenomatous polyps must be removed prior to their first dose of investigational drug.
10. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments

11. Patients must have documentation of positive Varicella Zoster virus (VZV) IgG antibody status or complete VZV vaccination at least 30 days prior to randomization
12. Documentation of no evidence of chronic lung disease or tuberculosis (TB) on a chest X-ray completed within the 6 months prior to screening. If a chest X-ray was not done in the 6 months preceding the Screening visit, it may be performed during the Screening visit

Exclusion Criteria:

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 evidence of fulminant colitis, toxic megacolon or bowel perforation
   - Previous total colectomy
   - Have 4 or more of the following:
     - Temp > 38°C
     - Heart rate (HR) > 110 (bpm)
     - Focal severe or rebound abdominal tenderness
     - Anemia (hemoglobin [Hgb] < 8.5 g/dL)
     - Transverse colon diameter > 5 cm on plain X-ray
2. Diagnosis of Crohn's disease or indeterminate colitis or the presence or history of a fistula consistent with Crohn's disease
3. Have positive stool culture for pathogens (O+P, bacteria) or positive test for *C. difficile* at screening. If *C. difficile* is positive, the patient may be treated and retested
4. Have had treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 16 weeks of screening
5. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin (hCG) measured during screening
6. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric or other major systemic disease making implementation of the protocol or interpretation of the study difficult or that would put the patient at risk by participating in the study
7. Clinically relevant cardiovascular conditions, including history or presence of:
   i. 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
   ii. Prolonged QTcF interval (QTcF > 450 msec males, > 470 msec females), or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome)
   iii. Patients with other pre-existing stable cardiac conditions who have not been cleared for the study by an appropriate cardiac evaluation by a cardiologist
8. Resting HR less than 55 beats per minute (bpm) when taking vitals as part of a physical exam at Screening
9. History of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c > 7% , or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy
10. History of uveitis
11. Known active bacterial, viral, fungal, mycobacterial infection or other infection (including TB or atypical mycobacterial disease [but excluding fungal infection of nail beds]) 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 prior to screening
12. History of recurrent or chronic infection (e.g., hepatitis B or C, human immunodeficiency virus [HIV], syphilis, TB); recurring urinary tract infections are allowed
13. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved)
14. History of alcohol or drug abuse within 1 year prior to randomization

15. History of or currently active primary or secondary immunodeficiency

Exclusions Related to Medications:

16. History of treatment with a biologic agent within 5 half-lives of that agent prior to randomization
17. History of treatment with an investigational agent within 5 half-lives of that agent prior to randomization
18. History of treatment with topical rectal 5-ASA or steroids within 2 weeks of screening
19. Receipt of a live vaccine or attenuated live vaccine within 4 weeks prior to randomization
20. Previous treatment with lymphocyte-depleting therapies (e.g., Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
21. Previous treatment with D-penicillamine, leflunomide or thalidomide
22. Previous treatment with natalizumab or fingolimod
23. History of treatment with intravenous immune globulin (IVIg), plasmapheresis, within 3 months prior to randomization
24. Planned concurrent treatment with immunosuppressive agents (e.g., azathioprine, 6-MP, or methotrexate) after randomization. Subjects receiving azathioprine, 6-MP or methotrexate at screening must discontinue treatment with these agents prior to dosing with investigational drug.
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. Treatment with any of the following drugs or interventions within the corresponding timeframe:

    - At randomization
      - CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) or inducers (eg, rifampicin)
    - Two weeks prior to randomization
      - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)

Exclusions Related to Laboratory Results:

27. Serum creatinine > 1.4 mg/dL for women or > 1.6 mg/dL for men
28. 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
29. Platelet count < 100,000/μL
30. Hgb < 8.5 g/dL
31. Neutrophils < 1500 /μL
32. Absolute WBC count < 3500/μL
33. Absolute lymphocyte count < 800/μL
34. ECG showing any clinically significant abnormality (e.g., acute ischemia, any significant heart conduction abnormality [e.g., left bundle branch block])
35. Forced expiratory volume at 1 second (FEV_1) or forced vital capacity (FVC) < 70% of predicted values at screening

NUMBER OF PATIENTS: Approximately 180 patients will be randomly assigned 1:1:1 on Day 1 to 1 of 3 treatment regimens (approximately 60 per treatment group)

STUDY TREATMENTS:

IP

On Day 1, patients will be randomly assigned 1:1:1 to 1 of 3 treatment regimens through Week 8:

- RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) oral capsule daily
- RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) oral capsule daily
- Matching placebo oral capsule daily

For patients randomized to one of the active treatment groups, there will be an 8-day dose escalation regimen in the IP consisting of 4 days of treatment with RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg), followed by 3 days of treatment with RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg), followed by the assigned treatment level for at least 8 weeks.

MP

Patients will continue to receive the same investigational drug in the MP as received during the IP, and individual patient treatment will remain blinded until all patients have reached Week 32.

OLP

All patients in the OLP will receive daily oral study treatment with RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg). There will be an 8-day dose escalation regimen consisting of 4 days of treatment with RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg), followed by 3 days treatment with RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg), followed by RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg).

DURATION OF TREATMENT:

IP: 9 weeks

MP: 24 weeks

OLP: Up to 6 years (or until marketing approval, or completed transition of patients to Study RPC01-3102, or discontinuation of the development program)

STUDY EVALUATIONS
Efficacy Endpoints:

Primary Efficacy Endpoint:

- The primary endpoint is the proportion of patients in clinical remission at Week 8, defined as a Mayo score of ≤ 2 points and with no individual subscore of > 1 point

Secondary Efficacy Endpoints:

- Proportion of patients with a clinical response at Week 8, defined as a reduction from baseline in Mayo score of ≥ 3 points and ≥ 30%, and a decrease from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point
- Change from baseline in Mayo score at Week 8
- Proportion of patients with mucosal healing at Week 8, defined by an endoscopy subscore of ≤ 1 point
- Proportion of patients in clinical remission at Week 32 defined as Mayo score of ≤ 2 points with no individual subscore of > 1 point
- Proportion of patients with a clinical response at Week 32, defined as a reduction from baseline in Mayo score of ≥ 3 points and ≥ 30%, and a decrease from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point
- Proportion of patients with mucosal healing at Week 32, defined as an endoscopy subscore of ≤ 1 point
- [redacted] patients with histologic remission at Week 8 as determined by a Geboes index score < 2.0

Safety Endpoints:

- The incidence and type of AEs, SAEs, AEs leading to discontinuation of investigational drug, target AEs of special interest, laboratory abnormalities, vital signs, ECG, and physical exam abnormalities

Pharmacokinetic (PK) and Pharmacodynamic (PD) Endpoints:

- PK assessments will include PK sampling to determine plasma concentration of RPC1063 and active metabolites at scheduled assessments during the treatment period.
- Absolute lymphocyte count (ALC) derived from blinded hematology laboratory results

- Plasma protein biomarkers (cytokines, chemokines, other inflammatory proteins)
- Stool culture for fecal biomarkers – fecal lactoferrin and calprotectin
- Total immunoglobulins (Igs) - IgA, IgG, IgM

[redacted]

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4. LIST OF ABBREVIATIONS

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ACLS	Advanced Cardiac Life Support
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC_{0-24}	area under the plasma concentration-versus-time curve from time 0 to 24 hours
AV	Atrioventricular
AZA	Azathioprine
BCRP	Breast Cancer Resistance Protein
BP	blood pressure (systolic/diastolic)
CFR	Code of Federal Regulations
Cl/F	total clearance
C_{max}	observed values for maximum concentration
CMH	Cochran-Mantel-Haenszel
CRO	clinical research organization
CRP	C-reactive protein
DDI	Drug-drug interaction
DLCO	diffusion capacity of the lung for carbon monoxide
DMC	Data Monitoring Committee
EAE	experimental autoimmune encephalomyelitis
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
FEV_1	forced expiratory volume at 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GMP	Good Manufacturing Practice
HBcAg	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HR	heart rate
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN β-1a	interferon beta-1a

Ig	Immunoglobulin
IND	Investigational New Drug
IP	Induction Period
IRB	Independent Review Board
ITT	intent-to-treat
IUD	Intrauterine device
IUS	Interuterine-hormone releasing system
IV	intravenous/ly
IVIg	intravenous immune globulin
IVRS	Interactive Voice Response System
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MITT	modified intent-to-treat
MMF	mycophenolate mofetil
MP	Maintenance Period
MS	multiple sclerosis
OCT	optical coherence tomography
OLP	Open-Label Period
PD	pharmacodynamic(s)
PFTs	pulmonary function tests ($FEV_{1,}$ FVC and DLCO)
PK	pharmacokinetic(s)
PP	per protocol
PQC	Product Quality Complaint
PT	prothrombin time
PTT	partial thromboplastin time
PVG	pharmacovigilance
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RBC	red blood cell
RDC	remote data capture
RPR	rapid plasma regain
$S1P_1$	sphingosine 1-phosphate 1 receptor
SAE	serious adverse event
SAP	Statistical Analysis Plan
t½	terminal half-life
TB	Tuberculosis
T_{max}	time of maximum concentration
TNBS	trinitrobenzene sulfonic acid
TNF	tumor necrosis factor
TQT	thorough QT
UC	ulcerative colitis
ULN	upper limit of normal
US/USA	United States/United States of America
VZV	varicella zoster virus
WBC	white blood cell

WMA	World Medical Association
WOCBP	women of child-bearing potential

5. ETHICS

5.1. Ethics Committee

In Europe, this study will be conducted in compliance with independent ethics committee (IEC) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) E6 Guidelines, in accordance with applicable regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10). In addition this study will adhere to all local regulatory requirements, and requirements for data protection.

In the United States (US), this study will be conducted in compliance with institutional review board (IRB) and ICH GCP Guidelines - including Title 21 Part 56 of the United States of America (USA) Code of Federal Regulations (CFR) relating to IRBs and GCP as described in the United States Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B(R3)), and with ICH regulations regarding scientific integrity (E4, E8, E9 and E10).
In addition this study will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a trial/study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC for the study protocol/amendment(s), written informed consent form, any consent form updates, patient recruitment procedures (e.g., advertisements), and any written information to be provided to patients and a statement from the IRB/IEC that they comply with GCP requirements. The IRB/IEC approval must identify the protocol version as well as the documents reviewed.

5.2. Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 (R1); FDA CFR (21 CFR § 50, 56, 312)), applicable version of the Declaration of Helsinki and all applicable regulatory requirements.

5.3. Patient Information and Consent

The Investigator will explain the benefits and risks of participation in the study to each patient, the impartial witness and obtain written informed consent. Written informed consent must be obtained prior to the patient entering the study and before initiation of any study related procedure (including administration of investigational drug).

The Sponsor or their designee will provide a sample informed consent form, based on the elements of informed consent in Section 18.1. The final version-dated form must be agreed to by the IRB/IEC and will contain all elements in the sample form, in language readily understood by the patient. In the event 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. Each patient's original consent form, personally signed and dated by the patient or witness, and by the person who conducted the

informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled patients with a copy of their signed informed consent.

The consent form may need to be revised during the study 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 (21CFR 56.108(a)(4)). Those patients who are presently enrolled and actively participating in the study should be informed of the change if it might relate to the patients' willingness to continue their participation in the study (21CFR 50.25(b)(5)). The FDA does not require re-consenting of patients that have completed their active participation in the study, or of patients who are still actively participating when the change will not affect their participation, for example when the change will be implemented only for subsequently enrolled patients.

The Investigator should, with the consent of the patient, inform the patient's primary physician about participation in the clinical study.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator(s):

This is a multi-center study. There will not be a leading/coordinating Investigator assigned.

Monitoring and Evaluation Committee(s):

This study will use an independent Data Monitoring Committee (DMC, see Section 13.13).

Clinical Laboratories:

Central laboratories will be used for this study:

PPD Global Central Labs
Kleine Kloosterstraat 19
B-1932 Zaventem – Belgium
Tel. +32 2 725 21 27
Fax. +32 2 725 21 02

PPD Global Central Labs
61 Science Park Road
#02-12/14, The Galen
Singapore Science Park II
Singapore 117525
Tel: +6565946210
Fax: +65 65946201

PPD Global Central Labs
Global Central Labs
2 Tesseneer Drive
Highland Heights, KY, USA 41076-9167
Tel: +1-859-781-8877
Fax: +1-859-781-9310

PK Laboratory:

ICON Development Solutions, LLC

8282 Halsey Road, Whitesboro, NY, USA 13492

Tel: +1-315-768-2540

Fax: +1-315-736-2460

Central Colonoscopy Evaluation:

Independent central evaluation will be performed for this study by:

Robarts Clinical Trials

Robarts Research Institute

100 Perth Drive

London, Ontario, Canada

N6A 5K8

Central Electrocardiogram (ECG) Reading:

Central ECG reading will be performed for this study by:

BioClinica Inc. (formerly CoreLab Partners, Inc.)

100 Overlook Center

Princeton, NJ 08540, US

Clinical Research Organizations (CRO):

PPD Development, LLC.

929 North Front Street

Wilmington, NC 28401

Tel: 910-251-0081

Fax: 910-762-5820

ClinStar, a PRA Company

4130 ParkLake Avenue, Suite 400

Raleigh, NC 27612, USA

Tel.: 919-786-8200

Fax: 919-786-8201

Central IRB:

Quorum IRB

1601 Fifth Ave

Seattle, WA, 98101

Study Medical Monitor/Medical Expert:

Ernesto Oviedo-Orta, MD, PhD, MBA

[redacted]

Clinical Study Supply Management:

For Europe:

Almac Clinical Service Ltd.
9 Charlestown Road
Seagoe Industrial Estate
Craigavon
BT63 5PW
United Kingdom

For the US:

Almac Clinical Services LLC
25 Fretz Road
Souderton
PA 18964

Almac Clinical Services LLC
4204 Technology Drive
Durham, NC 27704

8. STUDY OBJECTIVES AND ENDPOINTS

8.1. Study Objectives

8.1.1. Primary Study Objective

The primary objective of the study is to compare the efficacy of RPC1063 vs placebo for induction of clinical remission at Week 8 in patients with moderately to severely active UC.

8.1.2. Secondary Study Objectives

The secondary objectives are to:

- Compare the efficacy of RPC1063 vs placebo at weeks 8 and 32 as measured by clinical response, clinical remission, and mucosal healing
- Compare the overall safety and tolerability of RPC1063 vs placebo for the duration of the study

[redacted]

8.2. Endpoints

8.2.1. Efficacy Endpoints

Primary Efficacy Endpoint:

- The primary endpoint is the proportion of patients in clinical remission at Week 8, defined as a Mayo score of ≤ 2 points and with no individual subscore of > 1 point

Secondary Efficacy Endpoints:

- Proportion of patients with a clinical response at Week 8, defined as a reduction from baseline in Mayo score of ≥ 3 points and ≥ 30%, and a decrease from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point
- Change from baseline in Mayo score at Week 8
- Proportion of patients with mucosal healing at Week 8, defined by an endoscopy subscore of ≤ 1 point

- Proportion of patients in clinical remission at Week 32 defined as Mayo score of ≤ 2 points with no individual subscore of > 1 point
- Proportion of patients with a clinical response at Week 32, defined as a reduction from baseline in Mayo score of ≥ 3 points and ≥ 30%, and a decrease from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point
- Proportion of patients with mucosal healing at Week 32, defined by an endoscopy subscore of ≤ 1 point

[redacted]

- [redacted]
- [redacted] at Week 8 as determined by a Geboes index score < 2.0 (Geboes 2000)

8.2.2. Safety Endpoints

- The incidence and type of AEs, SAEs, AEs leading to discontinuation of investigational drug, target AEs of special interest, laboratory abnormalities, vital signs, ECG, and physical exam abnormalities

8.2.3. PK and PD Endpoints

- PK assessments will include PK sampling to determine plasma concentration of RPC1063 and active metabolites at scheduled assessments during the treatment period (see Table 1 [IP and MP] and Table 2 [OLP] Schedule of Events)
- Absolute lymphocyte count (ALC) derived from blinded hematology laboratory results
- Plasma protein biomarkers (cytokines, chemokines, other inflammatory proteins)
- Stool analysis for fecal biomarkers – fecal lactoferrin and calprotectin
- Total immunoglobulins (Igs) - IgA, IgG, IgM

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan

Study RPC01-202 is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients with moderately to severely active UC.

This study includes 3 periods (Screening, Induction, and Maintenance) and an optional Open-Label Treatment Period (OLP). Following the 5-week Screening Period, eligible patients will be randomized and enter the 9 week placebo-controlled IP. Patients who are responders at Week 8 will continue on their assigned treatment in the 24-week MP. Non-responders at Week 8 have the option to enter the OLP. Patients who complete the MP will be given the option to participate in the OLP. Patients that enter the MP and experience disease relapse will also have the option to enter the OLP.

The study will include both anti-TNF patients as well as anti-TNF naïve patients. It is anticipated that approximately 50% of the patients enrolled will have had prior anti-TNF therapy experience.

The study design is shown in Figure 1. Assessments and procedures are outlined in Table 1 for the IP and MP and Table 2 for the OLP. Assessments are described in Section 11.

Induction Period (IP)

The IP will serve as a dose-finding study to assess the efficacy and safety of RPC1063 for the induction of clinical response, remission, and mucosal healing in patients with moderately to severely active UC. The IP will last 9 weeks and consists of dose escalation over 8 days followed by the full dose for 8 weeks.

Approximately 180 patients will be randomized in a 1:1:1 ratio to receive 1 of 3 treatment regimens:

- RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) daily oral capsule
- RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) daily oral capsule
- Placebo daily oral capsule

The randomization will be stratified by prior anti-TNF therapy experience (yes or no).

For patients randomized to one of the active treatment groups, there will be an 8-day dose escalation regimen in the IP consisting of 4 days of treatment with RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg), followed by 3 days of treatment with RPC1063 0.5 mg, followed by the assigned treatment level for at least 8 weeks.

Maintenance Period (MP)

All patients who complete the IP and are responders (see Section 13.8) at Week 8 of the IP will enter the 24-week MP. Patients will continue to receive the same investigational drug in the MP as received during the IP, and individual patient treatment will remain blinded until all patients have reached Week 32. The last visit in the MP will occur at Week 32. Patients

who complete the MP will be given the option to participate in the OLP. Patients that enter the MP and experience disease relapse will have the option to enter the OLP.

Optional Open-Label Treatment Period (OLP)

Patients who complete the IP and are non-responders at Week 8 and those that complete the MP or experience disease relapse during the MP will have the option to enter the OLP. All patients in the OLP will receive daily study treatment with RPC1063 1 mg. There will be an 8-day dose escalation regimen consisting of 4 days of treatment with RPC1063 0.25 mg, followed by 3 days of treatment with RPC1063 0.5 mg, followed by RPC1063 1 mg.

Patients who have not shown clinical improvement 8 weeks after initiation of the OLP should discontinue from the study. Eligible patients will be transitioned into the Phase 3 open-label extension UC Study RPC01-3102 and will be able to immediately enter the study (without completing the 30-day or 90-day Safety Follow-up Visits). The OLP will continue for up to 6 years, or until marketing approval of RPC1063 for UC in the country of the clinical site (estimated to be in 2019), or completed transition of patients to Study RPC01-3102, or until the Sponsor discontinues the development program.

Safety Monitoring/Follow-up

Potential AEs of interest that may be a consequence of $S1P_1$ modulation will be closely monitored during the study. These AEs include bradycardia, heart conduction abnormalities, pulmonary toxicity, macular edema, cutaneous malignancy, serious or opportunistic infection, and hepatotoxicity. A DMC for the study will perform safety reviews periodically, approximately 4 times a year until the end of the Maintenance Period.

The safety of patients will be monitored by collection of treatment-emergent AEs, SAEs, physical exams, vital signs, Holter monitoring and ECGs, PFTs, optical coherence tomography (OCT), blood chemistry and hematology panels, coagulation panels, and urinalysis at baseline and at various time points during the study. White blood cell (WBC) counts and lymphocyte counts will be monitored centrally (and will not be provided to the site) to prevent potential unblinding of the Investigator.

Patients who discontinue from treatment due to lack of response, AEs, or other reasons, even if alternative treatment is given, will be followed for 90 days for collection of safety data and for the assessment of their disease status.

9.1.1. Study Schematic and Schedule of Events

Figure 1: Study Schematic

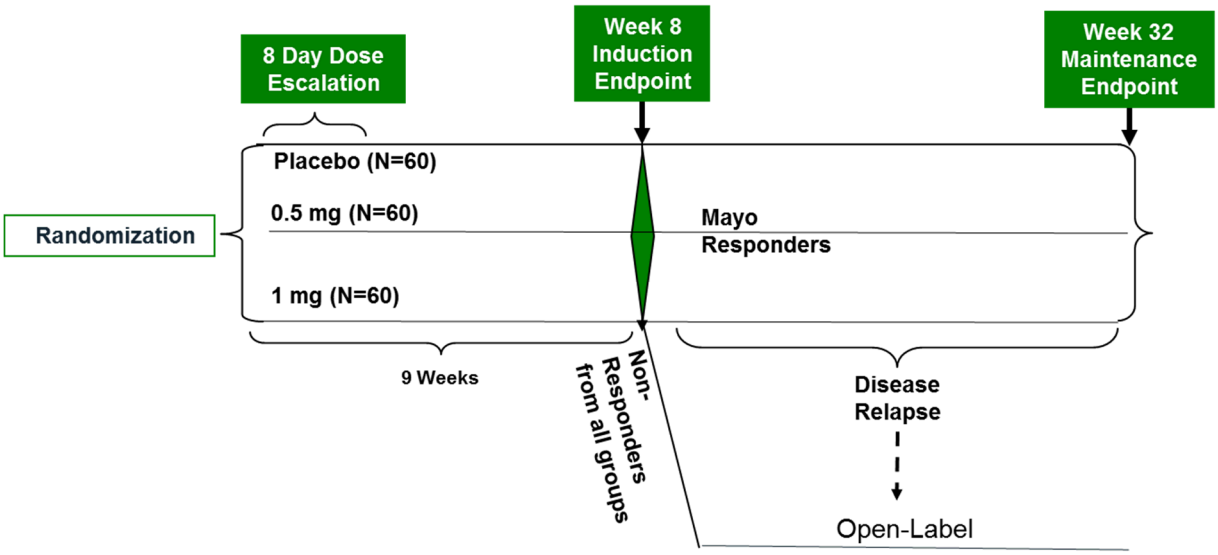

Table 1: Schedule of Assessments and Procedures for Induction and Maintenance Periods

	Study Procedures	Screening	Induction Period (IP)			Maintenance Period (MP)			Safety Follow-up	
			Dose Escalation	Assigned Dose						
			Visit 1[a,b,c]	Visit 4[b,d]	Visit 5[b,d]	Relapse Visit	Visit 6[b]	End of Study Visit/ET		
			Dose Escalation Day 1	Week 4	Week 8		Week 20	Week 32		
		Day -35 to 0	Dose Escalation Day 1	Day 36±3	Day 64±3	Day 1OLP	Day 148±3	Day 232±3	Last dose + 30 days ± 7 days	Last dose + 90 ± 10 days[r]
	Informed consent	X				Patients not in response or who do not maintain response within this time period should follow the assessments and timings provided in the OLP table (Table 2)				
	Inclusion/exclusion criteria	X	X							
	Demographics	X								
	Medical history[e]	X	X							
	TB screening[f]	X								
	Chest X-ray[f] (if not done in previous 6 months)	X								
	Total immunoglobulins (Igs) - IgA, IgG, IgM	X						X		
	Viral serology[g]	X								
	Stool culture[h]	X								
	Randomization		X							
	Dispense investigational drug		X	X	X		X			
	Administer investigational drug at clinic		X							
	Review drug compliance			X	X		X	X		
	Prior and concomitant medications	X	X	X	X		X	X	X	X
SAFETY ASSESSMENTS	Adverse events	X	X	X	X		X	X	X	X
	12-Lead ECG	X	X[a]		X			X		
	Holter monitoring		X							
	Vital signs	X	X[a]	X	X		X	X		
	Clinical laboratory tests									
	Hematology[s]	X	X	X	X		X	X	X	
	Blood chemistry	X	X	X	X		X	X	X	

	Study Procedures	Screening	Induction Period (IP)			Maintenance Period (MP)			Safety Follow-up	
			Dose Escalation	Assigned Dose						
			Visit 1[a,b,c]	Visit 4[b,d]	Visit 5[b,d]	Relapse Visit	Visit 6[b]	End of Study Visit/ET		
			Dose Escalation Day 1	Week 4	Week 8		Week 20	Week 32		
		Day -35 to 0	Dose Escalation Day 1	Day 36±3	Day 64±3	Day 1OLP	Day 148±3	Day 232±3	Last dose + 30 days ± 7 days	Last dose + 90 ± 10 days[r]
	Pregnancy test (WOCBP only)[i]	X	X	X	X		X	X	X	X
	Coagulation panel	X						X		
	Urinalysis	X			X		X	X		
	Physical examination[j]	X	X[k]		X[k]		X[k]	X	X[k]	
	Pulmonary function tests[l]	X[l]			X[l]			X		
	Optical coherence tomography	X						X		
PK AND PD ASSESSMENTS	Stool collection for fecal biomarkers	X			X			X	X	
	Inflammatory biomarkers plasma sampling	X			X			X	X	
	PK blood sampling[m]		X	X	X		X	X	X	X
EFFICACY ASSESSMENTS	Endoscopy[n]	X			X[o]			X		
	Mayo scoring									
	Mayo diary	X[p]	X	X	X		X	X		
	Mayo full clinical score	X			X			X		
	Mayo partial clinical score		X[q]	X			X			
	Patient diary to support mayo clinical score	X	X	X	X		X	X		
	Colonic biopsy	X			X			X		

Key: ALC = absolute lymphocyte count; ET = Early Termination; IP = Induction Period; MP = Maintenance Period; OCT = optical coherence tomography; OLP = Open-Label Period;PD = pharmacodynamic; PK = pharmacokinetic; TB = tuberculosis; WOCBP = women of child-bearing potential.

Footnotes to Table 1

a. The duration of Visit 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 (±10 minutes) postdose. A further 12-lead ECG will be performed at the end of the observation period.
b. Study visits should be scheduled in the morning, where possible, and on study visit days patients should be instructed to withhold the dose until the study visit and the dose should be administered during the visit.
c. Just prior to dosing at Visit 1, patients will begin 24-hours of Holter monitoring. Patients will not be expected to remain on site for the 24-hour duration as monitoring will continue at home.
d. IP Week 4 and IP Week 8 occur 4 and 8 weeks, respectively, following the completion of dose escalation, ensuring 8 weeks of dosing at the assigned dose.
e. Medical history will include smoking history. The Day 1 medical history can be abbreviated, noting events that occurred between Screening and Day 1.
f. Screening for TB will include a review of past history, current physical exam, A chest X-ray will be obtained for those subjects who do not have a chest X-ray within 6 months prior to screening and either a tuberculin skin test or a QuantiFERON® gold test for TB.
g. Serology testing will be performed at screening to determine the patient's immune status with respect to the following viruses: varicella zoster virus (VZV), human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antigen (HBcAg) IgM, anti-hepatitis C virus (HCV) IgG or IgM, should be assessed at screening in all patients.
h. 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.
i. For females of childbearing potential only, serum beta human chorionic gonadotropin (hCG) at screening is required, and a urine beta hCG 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 RPC1063 dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including after the 90-day Safety Follow-up Visit, if needed.
j. At screening includes height and weight, and Visits 1, 5, 6, End-of-Study, and 30-day Safety Follow-up Visit includes weight only. A complete PE will be performed at screening and End-of-Study. The complete physical examination will include a full examination of the skin for lesions as well as a check for visual symptoms (i.e., blurred vision or decreased visual acuity).
k. An interim physical examination will be conducted at Visits 1, 5, 6, and 30-day Safety Follow-up Visit. The interim PE will include areas with previously noted abnormalities and/or that are associated with any new complaints from the patient. The interim PE will also include a check for visual symptoms (i.e., blurred vision or decreased visual acuity).
l. DLCO, if applicable, will be done at Screening and End of Study/ET.
m. Blood samples for PK evaluation are to be taken up to 15-30 minutes prior to investigational drug (pre-dose) and just prior to discharge from the clinic (6-8 hours post dose) on Day 1. Blood samples on Week 4 and 20 should be taken 2-6 hours after dosing. Blood samples on Week 8 and 32 will be trough level, taken just prior to dose administration. 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 AE resulting in unblinding, discontinuation, or SAE.
n. At screening a colonoscopy will be required if the patient has had UC ≥ 10 years but has not had a colonoscopy within 1 year of the screening date. If the patient has had a colonoscopy within 1 year of the screening date a flexible sigmoidoscopy may be used. Endoscopy must be completed within 21 days of randomization. This procedure can also be used to determine the endoscopy subscore component of the Mayo Score.
o. At Visit 5, sigmoidoscopy should be performed either on day of visit or no more than 7 days prior to the visit date.
p. At screening patients will be issued with a Mayo diary and will be trained in the completion of the diary.
q. The Mayo partial clinical score on Day 1 should be combined with the Central endoscopic read in order to assess the patient for "Mayo Score" entrance criteria.
r. The 90-day Safety Follow-up Visit should be conducted as a clinic visit. However, if the patient is not available for a clinic visit, a telephone call follow-up should be performed (with at least 3 attempts within the visit window) to record the pregnancy test result, concomitant medications, and AEs, including information regarding relationship of the AE to RPC1063.
s. If ALC is confirmed < 200 cells/μL, the Investigator will temporarily discontinue investigational drug and then consult the Medical Monitor. Laboratory testing will be repeated weekly until ALC is > 500 cells/μL. For patients whose ALC level is confirmed < 200 cells/μL and has not reached the acceptable range (ALC > 500 cells/μL) during the study, laboratory testing will be repeated at the 90-day Safety Follow-up Visit.

Table 2: Schedule of Assessments and Procedures for the Optional Open-Label (OLP) Period

		Open-Label Period (OLP)					Safety Follow-up[m]	
		Dose Escalation	Assigned Dose (1 mg)					
		Visit 1OLP[a,b,c]	Visit 4OLP[b,d]	Visit 5OLP[b,d]	Additional OLP Visits[e]	End of Open-label Visit/ET[e]		
	Study Procedures	Dose Escalation Day 1	Week 4OLP	Week 8OLP	12-week Intervals	End of Study		
		Dose Escalation Day 1OLP	Day 36 ± 3 OLP	Day 64 ± 3 OLP	Day (last visit calculated from Day 1 + 84) ± 14 OLP	Day of last dose	Last dose + 30 ± 7 days	Last dose + 90 ± 10 days[n]
	Dispense investigational drug	X	X	X	X	X[m]		
	Administer investigational drug at clinic	X						
	Review drug compliance		X	X	X	X		
	Prior and concomitant medications	X	X	X	X	X	X	X
SAFETY ASSESSMENTS	Total immunoglobulins (Igs) - IgA, IgG, IgM					X		
	Adverse events	X	X	X	X	X	X	X
	12-Lead ECG	X[a]				X		
	Holter monitoring	X						
	Vital signs	X[a]	X	X	X	X		
	Clinical laboratory tests							
	Hematology[o]		X	X	X	X	X	
	Blood chemistry		X	X	X	X	X	
	Pregnancy test (WOCBP only)[f]		X	X	X	X	X	X
	Coagulation panel					X		
	Urinalysis			X		X		
	Physical examination[g]			X[h]		X[g]	X[h]	
	Pulmonary function tests[i]					X		
	Optical coherence					X		

		Open-Label Period (OLP)						
		Dose Escalation	Assigned Dose (1 mg)					
	Study Procedures	Visit 1OLP[a,b,c]	Visit 4OLP[b,d]	Visit 5OLP[b,d]	Additional OLP Visits[e]	End of Open-label Visit/ET[e]	Safety Follow-up[m]	
		Dose Escalation Day 1	Week 4OLP	Week 8OLP	12-week Intervals	End of Study		
		Dose Escalation Day 1OLP	Day 36 ± 3 OLP	Day 64 ± 3 OLP	Day (last visit calculated from Day 1 + 84) ± 14 OLP	Day of last dose	Last dose + 30 ± 7 days	Last dose + 90 ± 10 days[n]
	tomography							
PK AND PD ASSESSMENTS	Stool collection for fecal biomarkers			X		X	X	
	Inflammatory biomarkers plasma sampling			X		X	X	
	PK blood sampling[j]			X		X	X	X
EFFICACY ASSESSMENTS	Endoscopy				X[k]	X[l]		
	Mayo scoring							
	Mayo diary		X	X	X	X		
	Mayo full clinical score				X[k]	X		
	Mayo partial clinical score		X	X	X			
	Patient diary to support Mayo clinical score		X	X	X	X		
	Colonic biopsy				X[k]	X		

Key: ALC = absolute lymphocyte count; ET = Early Termination; OCT = optical coherence tomography; OLP = Open-label Period; PD = pharmacodynamic; PK = pharmacokinetic; WOCBP = women of child-bearing potential.

Footnotes to Table 2

a. The duration of Visit 1OLP 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 (±10 minutes) postdose. Another 12-lead ECG will be performed at the end of the observation period.

b. Study visits should be scheduled in the morning, where possible, and on study visit days patients should be instructed to withhold the dose until the study visit and the dose should be administered during the visit.

c. Just prior to dosing at Visits 1OLP, patients will begin 24- hours of Holter monitoring. Patients will not be expected to remain on site for the 24-hour duration as monitoring will continue at home.
d. Visit 4OLP and Visit 5OLP occur 4 and 8 weeks, respectively, following the completion of dose escalation, ensuring 8 weeks of dosing at the assigned dose.
e. Patients who continue past Week 8 in the OLP will have the Additional OLP Visit assessments performed at 12-week intervals throughout the OLP. The OLP will continue for up to 6 years, or until marketing approval of RPC1063 for UC in the country of the clinical site (estimated to be in 2019), or the completed transition of patients to Study RPC01-3102, or until the Sponsor discontinues the development program.
f. For females of childbearing potential only, serum beta human chorionic gonadotropin (hCG) at screening is required and a urine beta hCG is required at each visit. Between scheduled visits, monthly urine pregnancy tests should be performed by the patient. If a urine pregnancy test is positive, the Investigator will instruct the patient to suspend further RPC1063 dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including after the 90-day Safety Follow-up Visit, if needed.
g. Includes weight. The complete physical examination will include a full examination of the skin for lesions as well as a check for visual symptoms (i.e., blurred vision or decreased visual acuity).
h. An interim physical examination will be conducted at Visit 5OLP and 30-day Safety Follow-up Visit. The interim PE will include areas with previously noted abnormalities and/or that are associated with any new complaints from the patient. The interim PE will also include a check for visual symptoms (i.e., blurred vision or decreased visual acuity).
i. DLCO, if applicable, will be done at End of Open-Label/ET.
j. The PK blood sample on Week 8 should be trough level, taken just prior to dose administration. The blood sample on End of Open-label Visit/ET should be taken 2-6 hours after dosing. 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 AE resulting in unblinding, discontinuation, or SAE.
k. For patients who continue past Week 8 in the OLP, an endoscopy will be performed at Week 56OLP and a full Mayo score will be calculated at that time.
l. At End of Open-Label or ET Visit sigmoidoscopy should be performed either on day of visit or no more than 7 days prior to the visit date.
m. For patients who are entering the open-label extension UC Study RPC01-3102 at a date other than the End of Study visit, investigational drug will be dispensed in this study. For patients who are immediately entering (at the End of Study visit) the open-label extension UC Study RPC01-3102, investigational drug will be dispensed in Study RPC01-3102.
n. The 90-day Safety Follow-up Visit should be conducted as a clinic visit. However, if the patient is not available for a clinic visit, a telephone call follow-up should be performed (with at least 3 attempts within the visit window) to record the pregnancy test result, concomitant medications, and AEs, including information regarding relationship of the AE to RPC1063.
o. If the ALC is confirmed below 200 cells/μL, the Investigator will temporarily discontinue investigational drug and then consult the Medical Monitor. Laboratory testing will be repeated weekly until ALC is > 500 cells/μL. For patients whose ALC level is confirmed < 200 cells/μL and has not reached the acceptable range (ALC > 500 cells/μL) during the study, laboratory testing will be repeated at the 90-day Safety Follow-up Visit.

9.1.2. Additional Information

9.1.2.1. Adverse Events of Special Interest

Investigators should identify AEs that are in the following categories for AESIs. AESIs fall into a number of categories based on the safety observations from the potential pharmacologic effects of S1P modulators. These target AEs of special interest will be closely monitored in the RPC01-202 study. These AEs include serious or opportunistic infections, cardiac events (bradycardia and heart conduction abnormalities), pulmonary events (dyspnea and clinically significant wheezing) ophthalmic events (macular edema), dermatologic events (cutaneous malignancies), and hepatic events (liver function test [LFT] elevation). Further details on monitoring of these AEs are provided in Section 11.5.

9.2. Dose Rationale

[redacted]

[redacted]

9.3. Study Design Rationale

[redacted]

9.4. Study Duration

The study duration from first patient enrolled to last patient last visit is estimated to be approximately 32 months. The enrollment period is estimated to last approximately 18 months. Patients who complete the MP and then participate in the OLP of the study are anticipated to receive a minimum of 12 months of treatment.

9.5. Study Population

Eligible patients will be 18 to 65 years of age, inclusive, with a diagnosis of active UC (Mayo score 6-12).

9.5.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following inclusion criteria:

1. Males or female patients aged 18 to 75 years, inclusive
2. Have had UC diagnosed at least 2 months prior to screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence
3. Have active UC confirmed on endoscopy with $\geq$ 15 cm involvement
4. Have active UC defined as Mayo score of 6-12 inclusive with endoscopic subscore of ≥ 2
5. Have undergone colonoscopy or sigmoidoscopy within the past 2 years for extent of disease, and if the UC has been present for > 10 years, have had a colonoscopy with biopsy to rule out dysplasia

6. Female patients of childbearing potential:

   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
   - vasectomised partner
   - sexual abstinence

   Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

7. Must be currently receiving treatment with at least 1 of the following therapies:
   a. Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide) for at least 6 weeks with the dose stable for at least 3 weeks prior to screening endoscopy
   b. Prednisone (doses $\leq$ 30 mg) or equivalent for at least 4 weeks and receiving a stable dose for at least 2 weeks
8. 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
9. All patients aged 45 years or over must have had a colonoscopy to screen for adenomatous polyps within 5 years of their first dose of investigational drug or must have had a colonoscopy at screening to assess for polyps. The adenomatous polyps must be removed prior to their first dose of investigational drug.
10. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
11. Patients must have documentation of positive Varicella Zoster virus (VZV) IgG antibody status or complete VZV vaccination at least 30 days prior to randomization
12. Documentation of no evidence of chronic lung disease or tuberculosis (TB) on a chest X-ray completed within the 6 months prior to screening. If a chest X-ray was not done in

the 6 months preceding the Screening visit, it may be performed during the Screening visit

9.5.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at time of randomization or at the time point specified in the individual criterion listed:

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 evidence of fulminant colitis, toxic megacolon or bowel perforation
   - Previous total colectomy
   - Have 4 or more of the following:
     - Temp > 38°C
     - HR > 110 (bpm)
     - Focal severe or rebound abdominal tenderness
     - Anemia (hemoglobin [Hgb] < 8.5 g/dL)
     - Transverse colon diameter > 5 cm on plain X-ray
2. Diagnosis of Crohn's disease or indeterminate colitis or the presence or history of a fistula consistent with Crohn's disease
3. Have positive stool culture for pathogens (O+P, bacteria) or positive test for *C. difficile* at screening. If *C. difficile* is positive, the patient may be treated and retested
4. Have had treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 16 weeks of screening
5. Pregnancy, lactation, or a positive serum beta-hCG measured during screening
6. Clinically relevant, hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric or other major systemic disease making implementation of the protocol or interpretation of the study difficult or that would put the patient at risk by participating in the study
7. Clinically relevant cardiovascular conditions, including history or presence of:
   i. 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
   ii. Prolonged QTcF interval (QTcF > 450 msec males, > 470 msec females), or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome)

iii. Patients with other pre-existing stable cardiac conditions who have not been cleared for the study by an appropriate cardiac evaluation by a cardiologist

8. Resting HR less than 55 beats per minute (bpm) when taking vitals as part of a physical exam at Screening
9. History of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c > 7%, or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy
10. History of uveitis
11. Known active bacterial, viral, fungal, mycobacterial infection or other infection (including TB or atypical mycobacterial disease [but excluding fungal infection of nail beds]) 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 prior to screening
12. History of recurrent or chronic infection (e.g., hepatitis B or C, HIV, syphilis, TB); recurring urinary tract infections are allowed
13. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved)
14. History of alcohol or drug abuse within 1 year prior to randomization
15. History of or currently active primary or secondary immunodeficiency

Exclusions Related to Medications:

16. History of treatment with a biologic agent within 5 half-lives of that agent prior to randomization
17. History of treatment with an investigational agent within 5 half-lives of that agent prior to randomization
18. History of treatment with topical rectal 5-ASA or steroids within 2 weeks of screening
19. Receipt of a live vaccine or attenuated live vaccine within 4 weeks prior to randomization
20. Previous treatment with lymphocyte-depleting therapies (e.g., Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
21. Previous treatment with D-penicillamine, leflunomide or thalidomide
22. Previous treatment with natalizumab or fingolimod
23. History of treatment with intravenous immune globulin (IVIg), plasmapheresis, within 3 months prior to randomization
24. Planned concurrent treatment with immunosuppressive agents (e.g., azathioprine, 6-MP, or methotrexate) after randomization. Subjects receiving azathioprine, 6-MP or methotrexate at screening must discontinue treatment with these agents prior to dosing with investigational drug.

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. Treatment with any of the following drugs or interventions within the corresponding timeframe:
    - At randomization
        - CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) or inducers (eg, rifampicin)
    - Two weeks prior to randomization
        - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)

Exclusions Related to Laboratory Results:

27. Serum creatinine > 1.4 mg/dL for women or > 1.6 mg/dL for men
28. 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
29. Platelet count < 100,000/µL
30. Hgb < 8.5 g/dL
31. Neutrophils < 1500 /µL
32. Absolute WBC count < 3500/µL
33. Absolute lymphocyte count < 800/µL
34. ECG showing any clinically significant abnormality (e.g., acute ischemia, any significant heart conduction abnormality [e.g., left bundle branch block])
35. FEV_1or FVC < 70% of predicted values at screening

9.6. Treatment

9.6.1. Treatments Administered

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

During the IP, patients will be randomly assigned in a 1:1:1 ratio on Day 1 to one of following 3 treatment regimens as set out in Table 3:

- RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) daily oral capsule
- RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) daily oral capsule
- Placebo daily oral capsule

Capsule dosing: dosing will be once daily in the morning, if possible, with or without food.

On days of study visits, patients should be instructed to withhold the dose until the office visit, and dose will be administered during the visit.

9.6.2. Study Treatment After 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. If the patient is ill and unable to take a dose, 2 days without treatment is acceptable, otherwise the patient will contact the Investigator. If the patient misses more than 7 consecutive doses for any reason, Day 1 cardiac monitoring procedures will be performed on the first day that the patient resumes dosing. Holter monitoring will not be performed. 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 may include an additional dose escalation schedule if deemed appropriate.

Patients will continue to receive the same investigational drug in the MP as received during the IP, and individual patient treatment will remain blinded until all patients have reached Week 32.

9.6.3. Study Treatment Formulation

[redacted]

9.6.4. Study Treatment Labeling and Packaging

[redacted]

[redacted]

9.6.5. Blinding of Study Treatment

Investigational medicinal product and placebo capsules will be identical in physical appearance. The treatment each patient will receive will not be disclosed to the Investigator, study center personnel, patient, Sponsor and their representatives. The treatment codes will be held according to an Interactive Voice Response System (IVRS). Further instructions will be provided in a separate IVRS manual.

For details of the emergency procedure for unblinding of individual patients see Section 9.12, below.

9.6.6. Study Treatment Storage and Accountability

Study treatment should not be used for purposes other than as defined in this protocol.

9.6.6.1. Study Treatment Storage

RPC1063 and placebo capsules should be stored at room temperature (approximately 25°C [77°F], excursions permitted 15°C to 30°C [59°F to 86°F]) in a dry location. The inactive ingredients used in the formulations are slightly hygroscopic; therefore, all bottles contain a ½-gram desiccant canister and should be kept tightly sealed when drug product is not being dispensed.

9.6.6.2. Study Treatment Accountability

All supplies of investigational drug 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 relating to investigational drug supplies received during the study. 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 Almac and the Study Monitor immediately. Copies of the investigational drug accountability records will be provided by each Investigator for inclusion in the Trial Master File after database lock. The Study 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 investigational drug only to the identified patients of this study, according to the procedures described in this study protocol. After the end of the study, the Study Monitor will ensure that all unused investigational drug and all medication containers can be destroyed on-site as long as proper documentation is supplied. The Study Monitor will perform final accountability, package, seal, and prepare for shipment. If destruction on-site is not possible then medication and all medication containers will be returned to Almac 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 Study Center File.

[redacted]

During Dose Escalation

A summary of the cardiac monitoring during dose escalation is presented in Table 4.

Table 4: Cardiac Monitoring During Dose Escalation

Procedure	Cardiac Monitoring			
	Day 1/1OLP			
	Pre-dose	Hourly for 6 hours	At Hour 6	Continuous Monitoring for 24 hours
Vital signs	X	X		
12-lead ECG	X[1]		X	
Holter monitoring[2]				X[3]
Assess Discharge Criteria[4]			X	

1 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.
2 Begin at least 15 minutes predose and continue for 24 hours after dose.
3 Holter monitoring will be performed on Day 1/1OLP.
4 See Section 9.6.7.2 for discharge criteria. Additional observation should be instituted until the finding has resolved in the following situations: HR 6 hours post-dose is < 45 bpm; HR 6 hours post-dose is at the lowest value post-dose; ECG 6 hours post-dose shows new onset second degree or higher AV block; the ECG 6 hours post-dose shows a prolonged QTcF interval (> 450 msec males, > 470 msec females).

There is no provision for dose adjustments in this study. Patients who cannot tolerate investigational drug must be withdrawn from the study.

9.7. Withdrawal of Patients from Study Treatment and/or the Study

9.7.1. Discontinuation of Study Treatment

Patients will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The Investigator will provide a written explanation in the source documentation to be entered on the appropriate electronic case report form (eCRF) page describing the reason for discontinuation. If a patient withdraws before completion, every effort should be made to complete the assessments at the 30-day and 90-day Safety Follow-up Visits.

A patient may discontinue the study for the following medical or administrative reasons:

- Investigator decision

  The Treating Investigator may discontinue investigational drug if it is determined that it is not in the patient's best interest to receive further treatment. The Medical Monitor should be promptly notified of the decision.

- Adverse Event/Intercurrent illness

  A patient may be discontinued from the study if, in the judgment of the Investigator, the patient develops an adverse event such as an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies withdrawal from the study.

- Lack of Efficacy/Worsening Disease
- If the patient becomes pregnant

- Noncompliance

  After consultation between the Investigator, the Medical Monitor, and the Sponsor when appropriate, a patient may be discontinued from the study for failure to comply with protocol requirements.

- Patient chooses to discontinue investigational drug.

  The patient may choose to discontinue investigational drug but has not withdrawn consent. In this case it is expected that the ET and 30-day and 90-day Safety Follow-up Visits would be completed.

- Patient withdrawal of consent

  Every effort should be made within the bounds of safety and patient choice to have each patient complete the study. If a patient withdraws consent, the only additional study data to be collected will be the follow-up of SAEs as mandated by the protocol.

- Sponsor termination or suspension of the study.

All patients who discontinue investigational drug and who have not withdrawn consent should complete an Early Termination Visit and the 30-day and 90-day Safety Follow-up Visits for the collection of safety data and to assess their disease status (see Table 1 and Table 2). For subjects 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 it is above the lower limit of normal.

The reason for discontinuation of investigational drug will be recorded in the clinical records and the patient's eCRF.

9.7.2. Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any one of the following reasons:

- The patient withdraws consent.
- The patient is unwilling or unable to comply with the protocol.
- Patient's safety is affected, assessed by the Treating Investigator and/or the Medical Monitor

The reason for the patient's withdrawal from the study must be recorded in the clinical records and the patient's eCRF.

9.8. Prior and Concomitant Therapy

[redacted]

[redacted]

9.10. 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 study. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused investigational drug at the end of the study. 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.

Overall study non-compliance is defined as taking less than 80% or more than 120% of investigational drug during the entire treatment period.

At each visit, previously dispensed investigational drug capsules will be collected by the Investigator and compliance assessed. Patients will record missed doses in a diary that will be reviewed periodically by site staff and the Clinical Monitor. Patients exhibiting poor compliance as assessed by medication counts (i.e., 2 or more missed medication days in 1 week) and response to the question "Did you take your medication regularly?" should be counseled on the importance of good compliance to the study 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 study.

9.11. Assignment to Treatment

Patients must provide proper informed consent before any study procedures are performed (refer to Section 5.3 for further details regarding obtaining patients informed consent). At the time of consent, the patient is enrolled in the study. Patients will be randomized into the IP of the study on Day 1 after all screening and baseline assessments have been completed and the Investigator has verified that the patient is eligible per the inclusion (Section 9.5.1) and exclusion criteria (Section 9.5.2).

Randomization will be performed through an IVRS (further instructions will be provided in a separate IVRS manual). Treatment groups are described in Section 9.6.1.

Patients will be stratified by anti-TNF treatment (yes vs no) and will be randomized 1:1:1 to receive placebo, RPC1063 0.5 mg, or RPC1063 1 mg.

9.12. Unblinding Procedures for Individual Patients

A patient's treatment group assignment blind will not be broken until the end of the study unless medical treatment of that patient depends upon knowing whether the patient is receiving active drug. 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. Prior to unblinding, the investigator should first attempt to contact the Medical Monitor to discuss the medical emergency and the reason for wanting to unblind. The treatment assignment will be unblinded through an IVRS. Reasons for treatment unblinding must 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 or SAE resulting in unblinding, or discontinuation.

10. STUDY SCHEDULE

The study design is shown in Figure 1. Assessments and procedures are outlined in Table 1 for the IP and MP and Table 2 for the OLP. Assessments are described in Section 11.

It is recommended that the study visits are scheduled in the morning. On days of study visits, patients should be instructed to withhold the dose until the office visit, and the dose will be administered during the visit.

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

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 pre-dose PK sampling
- Physical examination
- Efficacy assessments

10.1. Screening Period

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) and Table 2 (OLP) are to be performed by the Principal Investigator or a qualified designee.

Written, signed, and dated informed consent from the patient prior to the performance of any study-related procedures must be obtained by the Principal Investigator or designee (refer to Section 5.3 for further details regarding obtaining patients informed consent). A copy of the signed informed consent must be given to the patient for his/her records.

10.2. Screening Failures and Rescreening of Patients

A screen failure is defined as a patient who has given informed consent, and failed to meet the inclusion and/or exclusion criteria. Patients who fail to meet the inclusion/exclusion criteria can be rescreened.

10.3. Induction Period (IP) and Maintenance Period (MP)

Eligible patients will be randomized to treatment group on Day 1. Visits, assessments, and procedures will be performed as per the Schedule of Events in Table 1. Guidelines for dose escalation (Day 1) are provided in Section 9.6.7.

10.4. Open-Label Period (OLP)

Patients who complete the IP and are non-responders at Week 8 and those that complete the MP or experience disease relapse during the MP will have the option to enter the OLP. Patients must

start the OLP within 2 weeks of their Week 8 Induction Visit, Disease Relapse visit in the MP or Week 32 MP visit. Visits, assessments, and procedures will be performed as per the Schedule of Events in Table 2. Guidelines for monitoring patients during dose escalation (Day 1OLP) are provided in Section 9.6.7.

The OLP will continue for up to 6 years or until marketing approval of RPC1063 for UC in the country of the clinical site (estimated to be in 2019), or completed transition of patients to Study RPC01-3102, or until the Sponsor discontinues the development program.

10.5. Early Termination

For patients who discontinue the study for any reason, every attempt should be made to complete the assessments detailed in the End of Period/Early Termination (ET) visit and the 30-day and 90-day Safety Follow-up Visits for the collection of safety data and for the assessment of their disease status (Table 1 [IP and MP] and Table 2 [OLP]). With the exception of patients who withdraw consent or are lost to follow-up, central laboratory testing of ALC will continue every 14 days (± 3 days) after permanent discontinuation of RPC1063 until it is above the lower limit of normal for patients who discontinue treatment or complete the trial.

10.6. Unscheduled Relapse Assessment Visit

If during the MP or OLP 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 [IP and MP] and Table 2 [OLP]).

10.7. Study Stopping Rules

The Sponsor has the right to terminate the study prematurely for safety reasons. In addition, the Sponsor may terminate the study prematurely 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 study.

The IEC or IRB and the Regulatory Authorities will be informed in writing about any premature termination of the study.

11. METHODS OF ASSESSMENT

The study design is shown in Figure 1. Assessments and procedures are outlined in Table 1 for the IP and MP and Table 2 for the OLP.

11.1. Efficacy Assessments

11.1.1. Flexible Sigmoidoscopy/Colonoscopy

To ensure quality data and standardization, the same endoscopist should be used throughout the study wherever possible. Colonoscopies will be read blinded to treatment allocation at a centralized reading facility, Robarts Clinical Trials.

11.1.2. Mayo Score

The Mayo score is a standardized, accepted, numerical scale used to evaluate disease severity in people with UC.

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

1. Stool frequency [a]

   0=Normal number of stools for this patient

   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, mild 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.

Partial Mayo scores are calculated using data from Items 1, 2 and 4 only.

Mayo scores are calculated using:

1. The Stool frequency and rectal bleeding data form the most recent consecutive 3-day period prior to the visit, excluding the following:
    a. The day medications for constipation, diarrhea, or bowel irregularity are taken
    b. The day(s) of a procedure or preparation for a procedure (e.g., enemas, other laxative, clear liquid diet) that would affect bowel frequency or blood content of the stool
    c. The 48 hours following use of anti-motility agents (i.e., loperamide)
    d. The 48 hours following endoscopy

Disease relapse is defined as when all of the following criteria are met:

- An increase in UC disease activity as defined by an increase in partial Mayo score of ≥ 2 points compared to the Week 8 partial Mayo score with an absolute partial Mayo score ≥ 4 points
- An endoscopic subscore of ≥ 2 points
- Exclusion of other causes of an increase in disease activity unrelated to underlying UC (e.g., infections, change in medication).

11.2. Clinical Safety Assessments

Physical Examination

A complete physical examination will include evaluation of heart, lung, head and neck, abdominal, neurological, full examination of the skin for lesions, and extremities. An interim (or brief) physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the patient. In addition, patients will be questioned on visual symptoms (i.e., blurred vision or decreased visual acuity) during both the complete and interim physical examinations.

All significant findings that are present at screening must be reported on the relevant medical history/current medical conditions eCRF. Significant findings made after randomization that meet the definition of an AE must be recorded on the AEs eCRF.

Height and Weight

Height will be measured at screening. Weight will be monitored throughout the study.

Vital Signs

Heart rate and blood pressure (systolic and diastolic) will be assessed per the Schedule of Events (Table 1 and Table 2).

When obtaining the predose HR and BP during dose escalation (Day 1/1OLP), the patient should rest in the supine position for at least 15 minutes before measurement to establish an accurate baseline measurement. After the patient has been supine for at least 15 minutes, HR and BP will be measured 3 times. An automated validated device can 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. The repeat HR and BP measurements will be made at 2-minute intervals. The lowest predose value of supine HR and BP (based on the systolic BP) should be taken as the baseline measure and used for comparison to postdose values. Orthostatic blood pressure will then be measured once with the patient in the standing position (after standing for 2 minutes). A sudden, significant fall in BP (> 20 mmHg) between 2 and 5 minutes after standing from the supine position will be interpreted as orthostatic hypotension and will be documented in the patient chart and eCRF.

Post-baseline HR and BP measurements should be taken after the patient has been supine for at least 5 minutes. HR and BP will be measured once using an automated validated device. Any clinically relevant change from baseline should be confirmed on repeat measures. Orthostatic blood pressure will then be measured in the same manner with the patient in the standing position (after standing for 2 minutes). A sudden, significant fall in BP (> 20 mmHg) between 2 and 5 minutes after standing from the supine position will be interpreted as orthostatic hypotension and will be documented in the patient chart and eCRF.

ECG

12-lead ECG to be performed after the patient has been resting quietly for at least 10-15 minutes.

Digital ECG devices will be provided to each clinical site by the central ECG laboratory for the duration of the study. The screening ECG report from the central reader must be available to confirm patient eligibility before randomization. A 12-lead ECG will be performed before and 6 hours after the first dose of investigational drug administration, while the patient is at the clinic.

Detailed instructions describing the process for recording and transmission of the digital ECGs will be outlined in the study-specific manual and provided to the site before the start of the study. Stand-alone ECGs will be obtained, printed, photocopied to preserve the ink if necessary, and kept at the site as source documentation.

ECG & Holter Monitoring

Dual function Digital ECG devices that are capable of capturing both stand-alone ECGs and Holter data will be provided to each clinical site by the central ECG laboratory for the duration of the study. Detailed instructions describing the process for recording and transmission of the digital ECGs and Holter data will be outlined in the study-specific manual and provided to the site before the start of the study.

Stand Alone/Static ECGs

Static ECGs will be captured at intervals as defined in the schedule of assessments (Section 9.1.1). The 12-lead ECG will be performed after the patient has been resting quietly in a supine position for at least 10-15 minutes. The screening 12-lead ECG report from the central reader must be available to confirm patient eligibility before randomization. Six hour post dose ECG will be evaluated by the treating physician or the central reader to confirm if extended monitoring is required. Simultaneously the ECGs will be printed out locally, photocopied to preserve the ink if necessary, and kept at the site as source documentation.

Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Only clinically significant abnormalities should be reported in the medical history/current medical conditions or AE CRF. Clinically significant findings must be discussed with the Medical Monitor before enrolling the patient in the study.

Continuous 12-lead Holter Monitoring

24 hour continuous cardiac monitoring (12 lead digital Holter monitoring) will be captured at Day 1/1OLP. Holter monitoring will start at least 15 minutes prior to dose and complete at least 24 hours post dose administration. Patients should be in the supine position prior to Holter application through the capture of the static pre-dose 12-lead ECG as well as for the acquisition of the 6 hour post dose 12-lead ECG. Holter analysis parameters will be described in the operations document.

Pulmonary Function Tests

Pulmonary function tests including FEV_1, FVC and DLCO, if applicable, measurements will be performed as scheduled Table 1 and Table 2. These tests will be performed at a qualified pulmonary function laboratory or respiratory department. 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).

Ophthalmological Examination

OCT will be performed at scheduled times as outlined in Table 1 and Table 2.

Monitoring of AEs and SAEs

Throughout the course of the study, every effort must be made to remain alert to possible AEs or SAEs. Refer to Section 12 for definitions of AEs/SAEs, monitoring, and reporting. Refer to Section 11.5 for monitoring of AEs of special interest.

Monitoring of Concomitant Therapy

The use of concomitant medication and procedures will be monitored throughout the study. Refer to Section 9.8 for prohibited concomitant therapies.

11.3. Laboratory Safety Assessments

Analysis of samples will be conducted centrally by PPD Global Lab. Wherever possible during the Induction and Maintenance Period, Investigators should not send laboratory samples to their local labs as this may lead to unblinding of the treatment assignment given RPC1063's MoA (retention of systemic lymphocytes). Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a laboratory manual.

Additional and repeat laboratory safety testing may be performed at the discretion of the Investigator.

The following laboratory tests will be performed to assess the safety profile of RPC1063, as outlined in Table 1 and Table 2:

- Routine safety laboratory tests:
  - Hematology – red blood cell (RBC) count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, Hgb, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Total and differential WBC counts will not be provided to the Investigator to maintain the treatment blind during the Induction and Maintenance Period. These parameters and alerts for these parameters will be monitored by the PPD Safety Surveillance team.
  - Blood chemistry - sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, ALT, AST, gamma glutamyltransferase (GGT), amylase, total bilirubin, conjugated bilirubin and CRP. CRP results will not be reported until completion of the study to maintain the treatment blind during the Induction and Maintenance Period. Abnormal laboratory parameters inconsistent with clinical presentation of UC or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value ($\geq$ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic).
  - Urinalysis - leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
- Routine blood samples will be analyzed by the central laboratory. Blood samples taken at the screening visit are to be in the fasting state. Blood samples taken at subsequent visits are recommended to be in the fasting state. 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 study laboratory manual. The results of the analysis will be made available to

each site by the central laboratory, at the earliest, 48 hours after receipt of the samples 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. Abnormal laboratory values should not be recorded on the AE eCRF; however, any diagnoses (or signs or symptoms if a diagnosis is not possible) associated with the abnormal findings should be recorded on the AE eCRF.
- Pregnancy test: serum beta-hCG must be performed at screening in women of childbearing potential. Urine beta-hCG will be performed in women 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 RPC1063 dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including after the 90-day Safety Follow-up Visit, if needed.
- Coagulation panel: prothrombin time (PT) and partial thromboplastin time (PTT). To be performed as scheduled in Table 1 and Table 2.
- Serology testing will be performed at screening to determine the patient's immune status with respect to several viruses; testing will be as follows:
  - anti-VZV IgG
  - HIV antibodies
  - HBsAg and HBcAg IgM
  - anti-HCV IgG or IgM

Patients who are negative for VZV IgG antibodies at screening can undergo vaccination and be randomized 30 days after appropriate VZV vaccination has been completed. Patients testing positive for HIV, or for serological markers of acute or chronic hepatitis B or C, will be excluded from the study unless they are indicative of prior hepatitis B vaccination or cured hepatitis B and accompanied by normal liver transaminase values.

- TB infection: to be assessed using review of the patients' medical history, current physical exam, current screening chest X-ray (if past chest X-rays within 6 months prior to screening is not available) and either a purified protein derivative skin test or a QuantiFERON® Gold test for TB. Patients with a positive purified protein derivative may use a QuantiFERON® Gold test to confirm the absence of active or latent TB.

11.4. PK and PD Assessments

PK samples will be shipped to PPD Global Central Labs. Details of the procedures to be followed for sample collection, storage, and shipment will be documented in a separate PK Laboratory Manual.

The following PK and PD assessments will be performed on the visit days specified in Table 1 and Table 2 to determine the safety profile of RPC1063:

- Standard PK sampling: PK samples are to be taken predose and 6-8 hours after dosing on Day 1. Samples on study will either be trough samples, taken prior to dose administration or will be collected 2 to 6 hours after dose administration, as indicated in the Schedule of Events footnotes.
- Stool culture for fecal biomarkers – fecal lactoferrin and calprotectin, which are tests sensitive to the identification of intestinal inflammation
- Plasma protein biomarker analysis (cytokines, chemokines, other inflammatory proteins)
- Total Igs: IgA, IgG, IgM

11.5. Monitoring of Patients With Adverse Events of Special Interest

Several of the AEs noted in fingolimod clinical studies may be a consequence of $S1P_1$ stimulation and will therefore be closely monitored in the RPC01-202 study. These AEs include:

a. Bradycardia and heart conduction abnormalities. Dose-related transient, reversible bradycardia and first degree atrioventricular block were reported primarily as first dose effects in fingolimod studies. The HR reduction observed with sphingosine-1-receptor agonists is an expected effect of S1PR modulation and appears to be conducted through the same pathway as vagus nerve stimulation. In addition, these negative chronotropic effects of $S1P_1$ agonists appear to attenuate over time secondary to S1PR desensitization and internalization on cardiac myocytes (Kovarik 2008). This effect appears to occur with increasing exposure to investigational drug; thus, gradual dose escalation of the dose of RPC1063 over several days may mitigate against larger reductions in HR.

b. Pulmonary toxicity. An initial sharp decrease followed by a slow progressive decline over time in FEV1 was observed in fingolimod clinical studies. Nonclinical toxicity studies with RPC1063 have revealed the potential for pulmonary toxicity at doses considerably higher than the pharmacologically active dose. Pulmonary function tests including FEV1, FVC, and DLCO, if applicable, will be measured in all patients. All efforts should be made to obtain DLCO assessments and exceptions based on lack of equipment must be pre-approved by the Sponsor. Every patient whose PFTs are abnormal will be followed 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).

c. Hepatotoxicity. Fingolimod caused frequent, reversible liver enzyme elevations greater than 3-fold above the ULN in up to 12% of patients; this was a significant cause of cessation of therapy. In this study, clinical blood chemistry analyses to assess LFTs will be performed. Every patient whose LFTs are abnormal will be followed until values return to baseline.

d. Macular edema. Instances of serious macular edema were reported in fingolimod renal transplant studies, and a 0.8% incidence was reported as an SAE in fingolimod

(1.25 mg dose) MS clinical studies. Nonclinical studies with RPC1063 have not revealed eye-related toxicities. In this study, OCT will be performed in all patients at baseline and the end of study visits or early termination. In addition, patients will be questioned about visual signs or symptoms at each study visit and instructed to inform the investigator if they develop symptoms between visits. For patients with symptoms of macular edema, OCT and ophthalmologic examination including dilated ophthalmoscopy will also be performed. Every patient whose ophthalmic evaluations reveal abnormalities will be followed until values return to baseline.

e. Opportunistic or serious infections. TB, serious bacterial infections, systemic fungal infections, viral infections such as herpes infections (including herpes zoster and disseminated herpes simplex) and protozoal infections should be reported as adverse events of special interest.

Overall, the following procedures should be followed:

- Vital signs will be assessed in supine and standing position at every visit. A sudden, significant fall in BP (> 20 mmHg) between 2 and 5 minutes after standing from the supine position will be interpreted as orthostatic hypotension and will be documented in the patient chart and eCRF.
- 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. ECGs will occur predose and at Hour 6 following dosing, with more frequent assessments as clinically indicated; vital signs, including orthostatic BP assessment, will be assessed predose and then hourly for 6 hours following dosing.
- Clinicians should be particularly mindful of patients who have a low HR at baseline (spontaneously or through drug induced ß-receptor blockade), 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. Furthermore, the common guidelines for treatment of bradycardia (e.g., Advanced Cardiac Life Support-ACLS guidelines) should be followed as appropriate:
  - In case of clinical symptoms or hypotension, administration of atropine 1 mg, repeated administration in 3-5 minutes.
  - If HR and/or BP remain unresponsive, consider administration of dopamine drip 5-20 μg/kg/min or epinephrine drip 2-10 μg/min.
  - Performance of transcutaneous pacing may also be considered
  - In the setting of decreased BP, isoproterenol should be avoided or used with caution.
- 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 (FEV_1 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).

- If patients have elevations in LFTs (ALT or/and AST) greater than 3 times the ULN, a retest should be performed within 14 days whenever possible. Upon confirmation of the abnormality, retests should be performed weekly until the elevated LFT decreases below 3 times the ULN. If the LFTs increase is confirmed to be above 5 times the ULN the investigational drug must be permanently discontinued.
- Study drug must be discontinued in any patient who has a diagnosis of macular edema. Patients with a diagnosis of macular edema must be followed up monthly or more frequently if needed based on the ophthalmologist's judgment. Further ophthalmological evaluations will be conducted until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than 3 months). If the patient does not show definite signs of improvement on examination 6 to 8 weeks after discontinuation of investigational drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated.
- Examination of the skin for lesions will be performed as part of the physical examination at screening and at the end of study. If skin lesions are noted, the patient will be referred to a dermatologist for evaluation and follow-up care.

12. SAFETY DEFINITIONS, MONITORING, AND REPORTING

Throughout the study, the Investigator will remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the patient, and appropriate medical intervention should be provided if necessary.

At the signing for the informed consent form, patients should be given names and telephone numbers of site staff for reporting AEs and medical emergencies.

12.1. Adverse Events

The AE definitions and reporting procedures provided in this protocol comply with current CFR 21 Part 312.32. An AE is any untoward medical occurrence that does not necessarily have a causal relationship with the investigational medicinal product. An AE can therefore be any unfavorable or unintended sign, including an abnormal laboratory finding, symptom or disease temporally associated with the use of an investigational medicinal product whether or not considered related to the investigational medicinal product.

UC disease relapse and related symptoms will be monitored as study endpoints, but will not be recorded as AEs.

AEs will be monitored throughout the entire study including the 90-day Safety Follow-up Visit. Investigators will ask the patient at each visit if they have experienced any untoward occurrence since the last study visit. All AEs will be recorded on the eCRFs provided: a description of the event, severity, time of occurrence, duration, any action (e.g., treatment and follow-up tests), and the outcome should be provided along with the Investigator's assessment of the relationship to the investigational drug.

AEs will be recorded from the time written informed consent is signed until 90 days following the last dose of treatment with the investigational drug.

If known, the event diagnosis should be recorded, in preference to the listing of individual signs or symptoms. AEs must be graded as being mild, moderate, or severe and their approximate duration given. Definitions of severity are as follows:

Mild: an AE usually transient in nature and generally not interfering with normal activities;

Moderate: an AE that is sufficiently discomforting to interfere with normal activities;

Severe: an AE that is incapacitating and prevents normal activities.

Even if the Investigator feels there is no relationship to the investigational drug, all AEs MUST be recorded in the eCRF. 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 (e.g., 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 (e.g., 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.

12.2. Serious Adverse Events

A SAE is any untoward medical occurrence or effect that fulfills the following criteria:

- Results in death
- Is life-threatening (NOTE: the term "life-threatening" 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 hospitalization or prolongation of existing inpatient hospitalization

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality/birth defect
- Important medical events not captured by the above but which may, for example, require medical intervention to prevent one of the outcomes above.

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 may 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.

12.3. Reporting of Serious Adverse Events

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

Any SAE which occurs to any patient from the time written informed consent is signed through the last visit must be reported by the Investigator. 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 product, must also be reported. Any SAE that is ongoing when the patient completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status or the patient is lost to follow-up.

Any AE considered serious by the Investigator or Sub-Investigator or that meets serious criteria should be reported to PPD Pharmacovigilance (PVG) using the remote data capture (RDC) system. Data entry must be completed within 24 hours from the time the study site personnel first learned of the event.

In the event that RDC entry is not possible (e.g., system failure or access problems), the study site should complete the paper SAE report form and fax the form to PPD PVG within 24 hours of awareness of the event. The RDC system should be updated as soon as it is available.

Contact information for the PPD Pharmacovigilance Center:

SAE Hotline: +44 1223 374240

SAE Fax line: +44 1223 374102

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.

12.4. Monitoring of Patients with Adverse Events

Investigators must carefully monitor each patient for AEs. This includes clinical laboratory variables. Assessments must be made of the seriousness, severity, and relationship to the

administration of the investigational drug. After the initial AE/SAE report the Investigator is required to follow up proactively each patient and provide further information to PPD on the patient's condition. During the study, all AE/SAEs should be followed up until resolved, stabilized, or returned to baseline status or patient is lost to follow-up, unless the event is considered by the Investigator to be unlikely to resolve due to the patient's underlying disease.

12.5. Procedures to be followed in the Event of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. For abnormal laboratory test values related to AEs of special interest, refer to Section 11.5.

12.6. Clinical Laboratory Parameters and Abnormal Laboratory Test Results

Clinically significant changes, in the judgment of the Investigator, in laboratory parameters (abnormalities) will be recorded as AEs.

During the treatment period, all Total WBC and WBC differential results will be blinded. 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 lymphocyte count [ALC] < 200 cells/µL
- Absolute neutrophil count [ANC] < 1000 cells/µL
- Total WBC > 20,000 cells/µL

If the repeat values also exceed these limits, the Investigator will be informed that the patient's results for the abnormal parameter have fallen below the acceptable threshold.

If ANC or total WBC counts are confirmed below the acceptable limits, the Medical Monitor will contact the treating investigator to request close monitoring for risk of serious infection and appropriate follow-up, at the discretion of the investigator.

If the ALC is confirmed < 200 cells/µL, the Investigator will temporarily discontinue investigational drug and then consult with the Medical Monitor. Laboratory testing will be repeated weekly until ALC is > 500 cells/µL.

When ALC has returned to > 500 cells/µL, the treatment may be reinitiated at the Investigator's discretion (Section 9.6.2 for instructions on resuming treatment after missing doses). For patients whose ALC level is confirmed < 200 cells/µL and has not reached the acceptable range (ALC > 500 cells/µL) during the study, laboratory testing will be repeated at the 90-day Safety Follow-up Visit.

If patients have elevations in ALT and/or AST ≥ 3x the upper limit of normal (ULN), a retest should be performed as soon as possible but not later than 14 days after the original test. If the abnormality is confirmed, weekly testing should continue until ALT and AST are < 3x ULN. If the ALT and/or AST stabilizes at a level > 3x ULN, the Medical Monitor may agree to less

frequent testing. The Investigator should establish causality. In addition, the confirmed elevation > 3x ULN is an adverse event of special interest (see Section 11.5) and should be reported by the Investigator.

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 INR > 1.5) 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.

12.7. Abnormal Clinical Safety Findings

Clinically significant changes, in the judgment of the Investigator, will be recorded as AEs.

12.8. Treatment of Overdose of Study Treatment

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

12.9. Procedures in Case of Pregnancy

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

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

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be

handled as AEs. All outcomes of pregnancy must be reported to the Sponsor and/or its designee. In cases of live birth, the infant will be followed for up to a year.

13. DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data management and statistical analysis of this study will be performed by PPD.

13.1. Data Management

An eCRF will be used for the current study, and a data management plan will be prepared by the CRO, PPD.

13.2. Sample Size Estimation

Approximately 300 patients will be screened to ensure that 180 patients are randomized in the IP, assuming a 40% screen failure rate. Patients will be enrolled in a 1:1:1 randomization with approximately 60 patients assigned per treatment arm.

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

A meaningful change or clinical improvement (defined in this study as the incremental increase in the proportion of patients obtaining remission in response to a medication compared to placebo), is dependent upon both the impact of the disease and the impact of the medication on the patient's health and well-being. Key factors that need to be considered include: the consequences of the disease, the efficacy and safety profile of the therapy, and the efficacy and safety profile of alternative treatments.

UC is a disease with a profound impact on the patient's health and well-being with chronic diarrhea, blood loss, abdominal pain and loss of income. Current therapies for moderately to severely active UC have significant limitation related to their efficacy, safety, or convenience.

We have chosen remission as the primary endpoint of this study since to obtain remission requires patients to be free of symptoms and have significant resolution of their disease activity. Patients who obtain remission have a notable improvement in their health and quality of life.

Obtaining remission, this clinically important endpoint, is a notable medical achievement; therefore, a moderate increase of 15-20% in the proportion of patients in remission would be meaningful for patients with moderate to severely active UC.

13.3. Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Tables, listings, and figures shells will also be provided.

13.4. Randomization

Patients will be randomized into the study on Day 1 using an IVRS provided by PPD.

Patients will be randomized 1:1:1 to receive placebo, RPC1063 0.5 mg, or RPC1063 1 mg. The randomization will be stratified by anti-TNF therapy (yes vs no).

Treatment groups are described in Section 9.6.1.

13.5. Analysis Populations

The following analysis populations will be used in the statistical analysis:

Intent-to-Treat (ITT): The ITT population will consist of all randomized patients. The primary efficacy analysis will be carried out in the intent-to-treat population, with treatment assignment designated according to randomized treatment.

Modified Intent-to-Treat (MITT): The MITT population will consist of all randomized patients who received at least 1 dose of investigational drug, with treatment assignment designated according to randomized treatment.

Per Protocol (PP): The PP population will consist of the subset of the ITT population, excluding those patients who have had a major protocol violation. These will be defined prospectively, in advance of data lock and primary analyses, in the final SAP, by the (aggregate results blinded) project statistician.

PK: The PK population will consist of patients who have at least one baseline and one post-baseline PK assessment.

Safety: The Safety population will consist of all patients receiving any investigational drug and safety analyses will be carried out on this population according to treatment actually received.

13.6. Demographic and Baseline Data

Demographic and baseline data will be summarized by treatment group. Frequency distributions and summary statistics will be presented.

13.7. Patient Disposition

Patient disposition will be summarized and summary statistics presented.

13.8. Efficacy Analysis

13.8.1. Endpoints

Efficacy analyses include clinical remission, clinical response, mucosal healing, and histological remission, which are defined as follows:

- Clinical remission: Mayo score of ≤ 2 points and with no individual subscore of > 1 point
- Clinical response: a reduction from baseline in Mayo score of ≥ 3 points and ≥ 30%, and a decrease from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point
- Mucosal healing: an endoscopy subscore of ≤ 1 point
- Histological remission: Geboes index score < 2.0

Endoscopy images will be obtained during each endoscopy and will be sent to Robarts Clinical Trials for central reading and determination of the Mayo endoscopy score. The result of the central reading of the endoscopy will be used to ensure patient eligibility prior to enrollment and to calculate the Mayo Score at the times indicated in the schedule of events. The Mayo score used for clinical endpoints in the study will utilize the Mayo endoscopy score derived from the central reader.

13.8.2. Primary Efficacy Analysis

The primary efficacy analysis will be completed based on the ITT population for the IP. The primary analysis will be carried out when all patients have completed (or would have been eligible to complete) the IP of the study.

The primary endpoint of clinical remission at Week 8 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by prior anti-TNF therapy experience. The primary analysis will use the data from the 1 mg dose and placebo groups and compare the remission rates in these 2 groups using a two-sided test at the alpha=0.05 level of significance.

13.8.3. Key Secondary Analyses

If the primary efficacy analysis is statistically significant ($p < 0.05$), then additional confirmatory tests using the ITT population will be performed in the following prespecified order:

- Proportion of patients in clinical remission at Week 8: 0.5 mg dose versus placebo
- Proportion of patients in clinical response at Week 8: 1 mg dose versus placebo
- Proportion of patients in clinical response at Week 8: 0.5 mg dose versus placebo
- Change in Mayo score from baseline at Week 8: 1 mg dose versus placebo
- Change in Mayo score from baseline at Week 8: 0.5 mg dose versus placebo
- Proportion of patients with mucosal healing at Week 8: 1 mg dose versus placebo
- Proportion of patients with mucosal healing at Week 8: 0.5 mg dose versus placebo
- Proportion of patients in clinical remission at Week 32: 1 mg dose versus placebo
- Proportion of patients in clinical remission at Week 32: 0.5 mg dose versus placebo
- Proportion of patients in clinical response at Week 32: 1 mg dose versus placebo
- Proportion of patients in clinical response at Week 32: 0.5 mg dose versus placebo
- Change in Mayo score from baseline at Week 32: 1 mg dose versus placebo
- Change in Mayo score from baseline at Week 32: 0.5 mg dose versus placebo
- Proportion of patients with mucosal healing at Week 32: 1 mg dose versus placebo
- Proportion of patients with mucosal healing at Week 32: 0.5 mg dose versus placebo

Provided that all previously specified tests are statistically significant ($p < 0.05$), each of these comparisons will be assessed using a two-sided test at the alpha = 0.05 level of significance.

However, if a comparison is not statistically significant, then all subsequent comparisons will be considered exploratory.

Secondary endpoints that are defined as proportions will be analyzed using the same type of methodology as described for the primary analysis. Analyses of all proportion endpoints using the CMH test will be completed using the data from the two groups being compared. Quantitative secondary endpoints will be analyzed using analysis of covariance (ANCOVA) models with effects for treatment group (three levels) and prior anti-TNF therapy experience, and with the baseline value of the corresponding endpoint included as a covariate. All secondary analyses will be carried out using two-sided test at the 5% level of significance.

13.8.4. Exploratory and Sensitivity Analyses

[redacted]

13.9. Pharmacokinetics

PK analyses will be detailed in a separate plan.

13.10. Safety

The incidence of treatment-emergent AEs will be summarized for each treatment group overall, by severity, and by relationship to investigational drug. SAEs will be presented by treatment group and by relationship to investigational drug. Summary tables will present incidence estimates and individual event rates by system organ class as well as within each system organ class. Patients experiencing an event more than once with varying severity will be counted only once with the maximum severity within each system organ class/preferred term. For incidence of relationship to investigational drug, patients will be counted only once, in the category of the strongest relationship to investigational drug within each system organ class/preferred term. Laboratory values, vital signs, ECG, and PFT data will be presented in appropriate summary tables.

13.11. Missing Data

For the primary analysis, as well as for the analyses of all key secondary efficacy endpoints that are defined as proportions, patients who do not provide data at the specified time point will be classified as nonresponders.

The Mayo score used for clinical endpoints in the study will utilize the Mayo endoscopy score derived from the central reader. In the case that a central endoscopic result is missing and the endoscopic subscore read by the Investigator will be utilized.

One of the key secondary efficacy endpoints (change in Mayo score) is a quantitative endpoint. For the key secondary analyses of this variable, missing values will be replaced by the least favorable observed change observed in the placebo group.

Sensitivity analyses of the primary and key secondary endpoints will be carried out to investigate the impact of missing data on the efficacy conclusions. These will include analyses of completed cases, observed cases, and multiple imputation model-based methods.

13.12. Interim Analysis

No interim analysis is planned for this study.

13.13. Data Monitoring Committee

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

The committee will meet periodically, approximately four times a year during the study, to review unblinded aggregate analyses by treatment group concerning enrollment, treatment compliance, adherence to follow-up schedule, and safety data from the trial until the end of the

Maintenance Period. The DMC may recommend modifying or stopping the trial early due to safety concerns based on data reviews.

The blinding plan to assure that all Sponsor personnel and all personnel involved in the conduct of the study remain blinded to the results of reviews will be specified in the DMC Charter.

14. MONITORING PROCEDURES (QUALITY ASSURANCE)

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfill these obligations and to maintain current of study progress, the Sponsor's monitors or representatives will visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted in order to assess patient enrolment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

14.1. Routine Monitoring

Sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study patients considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the Study Monitor.

Whenever a patient name is revealed on a document that is to be collected for the Sponsor the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the patient number as identification.

14.2. Inspections and Auditing Procedures

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor/CRO immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

14.3. 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. You can do so by emailing customercomplaints@celgene.com or by contacting the Celgene Customer Care Center (1-888-423-5436).

15. STUDY MANAGEMENT AND MATERIALS

15.1. Electronic Case Report Forms

An eCRF will be used to store and transmit patient information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed, and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by examining personnel or the study coordinator. The eCRF must be completed as soon as possible after any patient evaluation or communication. If data is to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to Study Monitors and other regulatory auditors.

15.2. Data Collection

During each study visit, a physician participating in the study will maintain progress notes in the patient's medical records to document all significant observations. At a minimum, these notes will contain: the date of the visit and the corresponding day or visit in the study schedule (e.g., screening, Day 1, Day 28, etc.); general condition and status remarks by the patient, including any *significant* medical findings; the severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is study drug-related; changes in concomitant medications or dosages; and a general reference to the procedures completed; and the signature or initials of all physicians making an entry in the medical record (progress notes).

In addition, any contact with the patient via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialed and dated on the day the change is made by the Investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

15.3. Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed informed consent for each patient shall be filed with records kept by the Investigator and a copy shall be given to the patient.

15.4. Record Maintenance

All data derived from the study will remain the property of the Sponsor.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of patients, source documents, eCRFs and investigational drug inventory must be kept on file.

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The Sponsor or their representative will notify the Principal Investigator of these events.

Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor, and will provide the Sponsor the opportunity to collect such records.
The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives and regulatory authorities.

If an Investigator moves, withdraws from an investigation or retires the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

15.5. Confidentiality

All information obtained during the conduct of the study with respect to the patient's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each patient's anonymity is maintained. On eCRFs and other documents submitted to the Sponsor or the CRO, patients must not be identified by name. Instead, patients will only be known by their initials and by the unique patient number allocated to them in order to ensure confidentiality on all study documentation. Patients will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure patient safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the US FDA to review patients' medical records as they relate to this study. Only the patient's unique number on the eCRFs will identify him/her, but their full names may be made

known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

Documents that are not for submission to the Sponsor or the CRO (e.g., consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO, and auditing by regulatory authorities. No documents identifying patients by name will leave the investigative site and patient identity will remain confidential in all publications related to the study.

16. ADMINISTRATION PROCEDURES

16.1. Regulatory Approval

The Sponsor or their appointed agents will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No patient may enter the study until this approval has been obtained. A copy of the approval (where one is provided, according to local country requirements) will be provided to the Investigator and to the IRB(s)/IEC(s).

16.2. Protocol Amendments

In accordance with ICH Topic E 6 (R1) Guideline for GCP the Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and documented approval from the IRB/IECs of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study patients, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IRB/IECs assuming this responsibility. The Investigator must await IRB/IEC approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to patients. In these cases, the IRB/IEC must be notified within 5 days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB/IEC, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IRB/IEC, the Investigator, and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the patient, the currently approved written informed consent form will require modification. The modified informed consent form must also be reviewed and approved by the Sponsor, appropriate regulatory authorities, and the IRB/IEC. In such cases, repeat informed consent must be obtained from patients enrolled in the study before participation continues.

16.3. Protocol Adherence and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the patient requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-Investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the patient

should continue in the study. The Investigator, the Sponsor, and the Medical Monitor will document this decision.

16.4. Publication Policy

After completion of the study, the Investigator(s) may prepare a joint publication with the Sponsor. The Investigator(s) must undertake not to submit any part of the data from this protocol for publication without the prior consent of the Sponsor.

16.5. Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated.

16.6. Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly. Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 part 54.

16.7. Insurance, Indemnity and Compensation

The Sponsor undertakes to maintain an appropriate clinical study insurance policy.

Deviations from the study protocol - especially the prescription of a dose other than that scheduled in the study protocol, other modes of administration, other indications, and longer treatment periods - are not permitted and shall not be covered by the statutory patient insurance scheme.

16.8. Discontinuation of the Study

This study may be terminated by the Sponsor. The study may also be terminated prematurely at any time when agreed to by both the Investigators and the Sponsor as being in the best interests of patients, and justified on either medical or ethical grounds. In terminating the study, the Sponsor, the CRO (PPD) and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

16.9. Study Center File Management

The Investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but will not be limited to, the information listed below:

1. Investigator's Brochure;
2. Current, signed version of the protocol and any previous versions of the protocol;
3. Protocol amendments (if applicable);

4. Operations Manual (if applicable);
5. Current informed consent form (blank) and any previous versions of the informed consent form;
6. Curricula Vitae of Investigator(s) and sub-Investigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug [IND] regulations), signed by all Principal Investigators. The names of any sub-Investigators must appear on this form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations;
7. Documentation of IRB/IEC approval of the protocol, the informed consent form, any protocol amendments, and any informed consent form revisions;
8. All correspondence between the Investigator, IRB/IEC, and the Sponsor/CRO relating to study conduct;
9. Lab certification(s);
10. Monitoring log;
11. Study drug invoices;
12. Signature list of all staff completing eCRFs; and
13. Signature list of all staff completing drug accountability summaries.

18. APPENDIX

18.1. Appendix 1: Elements of Informed Consent

ELEMENTS OF INFORMED CONSENT

Both the informed consent discussion and the written informed consent form and any other written information to be provided to patients should include explanations of the following:

- That the study involves research.
- The purpose of the study.
- The study treatment(s) and the probability for random assignment to each treatment.
- The study procedures to be followed including all invasive procedures.
- The patient's responsibilities.
- Those aspects of the study that are experimental.
- The reasonably foreseeable risks or inconveniences to the patient and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the patient, the patient should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
- The compensation and/or treatment available to the patient in the event of study-related injury.
- The anticipated prorated payment, if any, to the patient for participating in the study.
- The anticipated expenses, if any, to the patient for participating in the study.
- That the patient's participation in the study is voluntary and that the patient may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the patient is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the patient's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the patient or the patient's legally acceptable representative is authorizing such access.
- That records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the patient's identity will remain confidential.
- That the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the study.
- The person(s) to contact for further information regarding the study and the rights of study patients, and whom to contact in the event of study-related injury.
- The foreseeable circumstances and/or reasons under which the patient's participation in the study may be terminated.

- The expected duration of the patient's participation in the study.
- The approximate number of patients involved in the study.

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UserName: Oviedo-Orta, Ernesto (eoviedoorta)
Title: Sr Director, Clinical R&D, I&I
Date: Sunday, 05 May 2019, 02:39 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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