1. CLINICAL TRIAL PROTOCOL

Protocol Title:	A Phase 2, Multi-Center, Open-Label Induction Trial with Extension Period to Assess Endoscopic Improvement and Changes in Intestinal and Serum Biomarkers in Patients with Moderately to Severely Active Crohn's Disease Receiving Oral RPC1063 as Induction Therapy
Protocol Number:	RPC01-2201
Version and Date:	5.0 dated 24 May 2019
Replaces Version:	4.0 dated 29 May 2018
Investigational Product:	RPC1063
IND No.:	126,740
EudraCT No.:	2015-002025-19
Trial Phase:	2
Sponsor:	[redacted]
Sponsor Medical Monitor:	W. Jerry Liu, MD [redacted]

CONFIDENTIAL

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SIGNATURES

PROTOCOL TITLE: A Phase 2, Multi-Center, Open-Label Induction Trial with Extension Period to Assess Endoscopic Improvement and Changes in Intestinal and Serum Biomarkers in Patients with Moderately to Severely Active Crohn's Disease Receiving Oral RPC1063 as Induction Therapy

PROTOCOL NO: RPC01-2201

{See appended electronic signature page}

Signature | Date

[redacted]

[redacted]

Sponsor: Celgene International II Sàrl

Signature of Celgene International II Sàrl Representative	Date

Printed Name of Celgene International II Sàrl Representative

2. SYNOPSIS

Sponsor/Company: Celgene International II Sàrl		
Investigational Product: RPC1063		
Name of Active Ingredient: RPC1063		
Trial Title:	A Phase 2, Multi-Center, Open-Label Induction Trial with Extension Period to Assess Endoscopic Improvement and Changes in Intestinal and Serum Biomarkers in Patients with Moderately to Severely Active Crohn's Disease Receiving Oral RPC1063 as Induction Therapy	
Brief Title:	Open-Label Endoscopic Improvement Trial of RPC1063 for Moderate to Severe Crohn's Disease	
Protocol No:	RPC01-2201	
Investigators:	Approximately 60-80	
Regions:	North America, Europe	
Trial Duration: 3 years		**Phase:** 2

Objectives:

Induction Period

Primary:

- To assess endoscopic improvement following treatment with RPC1063

Secondary:

- To characterize clinical improvement, response, and remission following treatment with RPC1063
- To assess changes in intestinal and blood biomarkers following treatment with RPC1063 by characterizing the following:
  - Intestinal mucosa histopathologic disease activity
  - Select cellular, protein, and molecular biomarkers in the intestinal mucosa and blood
- To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of RPC1063
- To assess the safety of RPC1063

Extension Period

Primary:

- To characterize the longer term safety of continued dosing of RPC1063

Secondary:

- To characterize endoscopic improvement at Week 52
- To characterize the histopathological changes of the intestinal mucosa at Week 52
- To characterize the effect of RPC1063 in maintaining clinical improvement over time

Methodology:

This is an open label trial comprised of 2 periods – a 12 week Induction Period and an Extension Period (148 weeks). Eligible patients will enter into the trial through the Induction Period and those who complete the Induction Period will have the opportunity to enter into the Extension Period.

Induction Period:

Patient eligibility will be determined during a 5-week Screening Period prior to first dose of investigational drug. All eligible patients will complete a 7-day dose escalation regimen consisting of 4 days of treatment with RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) daily followed by 3 days of treatment with RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) daily, with the final

RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) daily dose to be reached on Day 8. Patients will then continue on open label at RPC1063 1 mg/day during the Induction Period for 11 weeks. At Week 12 patients will be evaluated for endoscopic and clinical response/remission.

Patients who complete the Induction Period will have the opportunity to receive continued treatment with RPC1063 in the Extension Period. Investigators should assess patient's clinical status at the end of the Induction Period and, using clinical judgment, determine if the patient should continue into the Extension Period or withdraw from the trial and receive alternative therapy.

Extension Period:

All patients will receive RPC1063 1 mg daily dose in the Extension Period and may receive treatment through Week 160. During the Extension Period, the investigator should continue to assess the patient's clinical status and based on clinical judgment determine if the patient should continue or withdraw from the trial and receive alternative therapy.

Patients who complete the Week 160 visit may have the option to immediately enter (without completing the 30-day and 90-day Safety Follow-up Visits) the open-label extension Phase 3 Crohn's disease Study [redacted].

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Male or female patients aged 18 to 75 years, inclusive
2. Diagnosis of Crohn's disease for at least 2 months (prior to Screening) by clinical endoscopic evidence and corroborated by a histology report (Note: histopathology may be performed during Screening if no prior report is readily available)
3. Crohn's disease Activity Index score of 220 to 450 inclusive with an SES-CD score of ≥ 6. (If disease isolated to ileum, the requirement will be a SES-CD score ≥ 4)
4. Average daily stool score ≥ 4 points and/or an average daily abdominal pain score of ≥ 2 points
5. Patients must meet one of the following criteria:
    - Have an inadequate response or loss of response to at least one of the following Crohn's disease treatments:
        - Aminosalicylates, oral aminosalicylates ≥2.4 g/day or ≥3 g/day sulfasalazine for at least 4 weeks
        - Corticosteroids, oral prednisone ≥ 30 mg or budesonide ≥ 9 mg for at least 2 weeks or an equivalent (to oral prednisone) of intravenous corticosteroid for 1 week
        - Immunomodulators, oral azathioprine ≥ 1.5 mg/kg or 6-mercaptopurine 0.75 mg/kg (documentation of therapeutic level of 6-thioguanine is also acceptable) or methotrexate ≥ 12.5 mg/week for at least 8 weeks
        - Biologic therapy (TNFα antagonist or vedolizumab only) at an approved labeled dose used for induction therapy for at least 4 weeks or recurrence of disease activity despite scheduled maintenance therapy. (Biologic therapy exposed patients will be capped at 50% of total enrolled patients)
    - And/or have been intolerant to any of the above mentioned therapies (e.g., unable to achieve doses, dose levels, or treatment durations because of treatment related side effects and/or laboratory abnormalities)
6. The following background therapies for Crohn's disease will be permitted on a stable dose:
    - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide) at a stable dose for at least 3 weeks prior to Screening endoscopy

- Prednisone (doses ≤ 20 mg per day) or equivalent at a stable dose for at least 2 weeks prior to Screening endoscopy
- Budesonide therapy at a stable dose (dose ≤ 9 mg per day) for at least 2 weeks prior to Screening endoscopy
- Antibiotics used for the treatment of Crohn's disease (i.e., ciprofloxacin, metronidazole) at a stable dose for at least 2 weeks prior to Screening endoscopy

7. 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 endoscopy score
8. 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
   - complete sexual abstinence

   Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

   Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for female subjects of childbearing potential. The Investigator will educate all FCBP about the different options of contraceptive methods or abstinence as appropriate. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).
9. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
10. Must have documentation of positive *Varicella zoster* virus (VZV) immunoglobulin G (IgG) antibody status or complete VZV vaccination at least 30 days prior to first dose of investigational drug
11. For patients at high risk (i.e., family history, disease duration) for colonic malignancy, documented evidence of having had a surveillance colonoscopy within the last 2 years or according to local medical guidelines to evaluate for polyps, dysplasia, or malignancy. If no recent history of surveillance colonoscopy, this can be done as part of colonoscopy performed during Screening

Diagnosis and Main Criteria for Exclusion:

Exclusions Related to General Health:

1. Diagnosis of ulcerative colitis or indeterminate colitis
2. Crohn's disease isolated to the stomach, duodenum, jejunum, or peri-anal region, without colonic or ileal involvement
3. Known strictures or stenosis leading to symptoms of obstruction
4. Current stoma or need for ileostomy or colostomy
5. Extensive small bowel resection (>100 cm) or known diagnosis of short bowel syndrome

6. Suspected or diagnosed intra-abdominal or perianal abscess that has not been appropriately treated
7. Currently require or are anticipated to require surgical intervention for Crohn's disease during the Induction Period
8. Currently receiving total parenteral nutrition
9. Positive stool culture for pathogens (ova and parasites, bacteria) or positive test for *Clostridium difficile* (C. difficile) at Screening. Patients may be treated and retested but must have negative stool culture for pathogens (ova and parasites, bacteria) within 30 days prior to first dose of investigational drug and 60 days prior to first dose of investigational drug for C. difficile
10. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin (hCG) measured during Screening

11. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric or other major systemic disease making implementation of the protocol or interpretation of the trial difficult or that would put the patient at risk by participating in the trial
12. Clinically relevant cardiovascular conditions, including history or presence of:
    - Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea
    - 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)
    - Resting HR < 55 beats per minute (bpm) when taking vitals as part of a physical examination at Screening
    - Mobitz type 2nd degree or 3rd degree AV block
13. History of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c > 9%, or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy
14. History of uveitis or known macular edema
15. Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis [TB] or atypical mycobacterial disease [but excluding fungal infection of nail beds, minor upper respiratory tract infections and minor skin infections]) or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 30 days of Screening or oral antibiotics within 14 days of Screening.
16. History or known presence of recurrent or chronic infection (e.g., hepatitis A, B, or C, human immunodeficiency virus (HIV); recurrent urinary tract infections are permitted.
17. 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)
18. Past or current evidence of colonic dysplasia
19. History of alcohol or drug abuse within 1 year prior to first dose of investigational drug
20. History of or currently active primary or secondary immunodeficiency

Exclusions Related to Medications:

21. History of treatment with a biologic agent within 5 elimination half-lives of that agent prior to first dose of investigational drug
22. History of treatment with an investigational agent within 5 elimination half-lives of that agent prior to first dose of investigational drug
23. History of treatment with topical rectal 5-ASA or steroids within 2 weeks of Screening
24. History of primary non-response to two approved biologic therapies used for the treatment of Crohn's disease

25. Receipt of a live vaccine or live attenuated vaccine within 4 weeks prior to Screening
26. Previous treatment with lymphocyte-depleting therapies (e.g., Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
27. Treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 16 weeks of Screening
28. Previous treatment with D-penicillamine, leflunomide, or thalidomide
29. Previous treatment with natalizumab or fingolimod
30. History of treatment with intravenous immune globulin (IVIg), plasmapheresis, within 3 months prior to first dose of investigational drug
31. Planned concurrent treatment with immunosuppressive agents (e.g., azathioprine, 6-MP, or methotrexate) after enrollment. Patients receiving azathioprine, 6-MP or methotrexate at Screening must discontinue treatment with these agents prior to first dose of investigational drug.
32. Chronic non-steroidal anti-inflammatory drug (NSAID) use (Note: occasional use of NSAIDs and acetaminophen [eg, headache, arthritis, myalgias, or menstrual cramps] and aspirin up to 325 mg/day is permitted)
33. Treatment with Class Ia or Class III anti-arrhythmic drugs, or treatment with two or more agents in combination known to prolong PR interval
34. Treatment with any of the following drugs or interventions within the corresponding timeframe:

    - At Day 1
      - CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) or inducers (eg, rifampicin)
    - Two weeks prior to Day 1
      - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)

Exclusions Related to Laboratory Results:

35. Serum creatinine > 1.4 mg/dL for women or > 1.6 mg/dL for men
36. 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
37. Platelet count < 100,000/µL
38. Hgb < 8.5 g/dL
39. Neutrophils < 1500/µL
40. Absolute WBC count < 3500/µL
41. Absolute lymphocyte count < 800/µL
42. Electrocardiogram (ECG) showing any clinically significant abnormality (e.g., acute ischemia, any significant heart conduction abnormality [e.g., left bundle branch block])
43. Forced expiratory volume at 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values at Screening

Test Product, Dose, and Mode of Administration:

Induction Period:

All patients will receive RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) capsule orally starting with a 7-day dose escalation regimen of RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) daily on Days 1 through 4 and RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) daily (administered as two RPC1063/ozanimod HCl 0.25 mg [equivalent to ozanimod 0.23 mg] capsules) on Days 5 through 7, continuing with RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) daily through Week 12.

Extension Period:

All patients will receive RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) capsule orally once daily through Week 160.

Reference therapy, dosage and mode of administration: Not applicable

Duration of treatment:

Induction Period: 12 weeks

Extension Period: 148 weeks

Endpoints:

Definitions

Endoscopic

Response: SES-CD decrease from baseline of ≥ 50%

Remission: SES-CD ≤ 4 points and a SES-CD decrease ≥ 2 points with no SES-CD sub-score > 1 point

CDAI

Clinical Response: CDAI reduction from baseline of ≥ 100 points

Clinical Remission: CDAI score of < 150

PRO2

Clinical Response: PRO2 decrease ≥ 50%

Clinical Remission: Average daily stool score ≤ 3 points AND average daily abdominal pain score ≤ 1 point

Mucosal Healing

Endoscopic remission plus histologic improvement

Induction Period

Primary Efficacy Endpoint:

- Change in SES-CD from baseline at Week 12

Other Efficacy Endpoints:

- Change in CDAI score from baseline at Week 12
- Proportion of patients with clinical remission based on CDAI at Week 12
- Proportion of patients with clinical response based on CDAI at Week 12
- Proportion of patients with clinical remission based on PRO2 definitions at Week 12
- Proportion of patients with clinical response based on PRO2 definitions at Week 12
- Proportion of patients with endoscopic remission based on SES-CD definitions at Week 12
- Proportion of patients with endoscopic response based on SES-CD definitions at Week 12
- Change in intestinal mucosa histopathologic features and disease activity
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Improvement in perianal and enterocutaneous fistulas at Week 12 in those patients with fistulas at baseline

Extension Period

Efficacy Endpoints:

- Proportion of patients in endoscopic remission based on SES-CD definitions at Week 52
- Proportion of patients in endoscopic response based on SES-CD definitions at Week 52
- Proportion of patients in clinical remission based on CDAI at Week 52
- Proportion of patients in clinical response based on CDAI at Week 52
- Proportion of patients in clinical remission based on PRO2 definitions at Week 52
- Proportion of patients in clinical response based on PRO2 definitions at Week 52
- Proportion of patients in clinical remission at Week 52 based on CDAI and PRO2 definitions who are off corticosteroids of those on corticosteroids at baseline
- Proportion of patients in clinical remission based on CDAI over time
- Proportion of patients in clinical response based on CDAI over time
- Proportion of patients in clinical remission based on PRO2 definitions over time
- Proportion of patients in clinical response based on PRO2 definitions over time
- Change in intestinal mucosa histopathologic features, histologic disease activity, and biomarkers over time
- Change in fecal calprotectin and serum C-reactive protein (CRP) levels over time
- Improvement in perianal and enterocutaneous fistulas in those patients with fistulas at baseline over time

Pharmacokinetic and Pharmacodynamic Endpoints

- Plasma concentration of RPC1063 and active metabolites at scheduled assessments during the treatment period
- Absolute lymphocyte count (ALC) derived from hematology laboratory results
- Peripheral immune cell phenotype determined by Flow cytometry

Safety:

The incidence, severity, relationship and type of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), AEs leading to discontinuation of investigational drug, and AEs of special interest, and clinically meaningful changes from baseline on clinical laboratory measures, vital signs, ECG, and physical examinations will be assessed.

The safety of patients will be monitored by collection of treatment-emergent AEs, serious adverse events (SAEs), physical examinations, vital sign measurements, ECG results, optical coherence tomography (OCT), pulmonary function tests (PFTs), and clinical laboratory tests. Patients who discontinue from treatment due to lack of response, AEs, or other reasons, even if alternative treatment is given, will complete an Early Termination Visit and will be followed for 90 days for collection of safety data and for the assessment of their disease status.

Statistical Methods:

Induction and Extension Period Efficacy

This is an open-label, single-arm trial. As such, there are no hypothesis tests on the data collected in this trial. In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using number of patients (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Safety

All treatment-emergent AEs will be coded and tabulated by system organ class and preferred term. Adverse events will be monitored during the trial and the data analyzed with respect to incidence as well as severity and potential relationship of the AEs to investigational drug. The incidence of AEs, SAEs, AEs of special

interest, and AEs leading to discontinuation will be summarized and presented in descending order of frequency. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual patient values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from baseline will be produced. The change from baseline for each of the vital signs and ECG parameters will be summarized. The incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

Sample Size Justification

The sample size of 60 patients has been chosen to enable estimates of response and remission rates with reasonable precision. Assuming a remission rate of 15% and a response rate of 30%, it is estimated that the confidence interval (half-widths of the 95% CI) around the proportion of patients in response and remission will be 12.8% and 16.4% for 30 patients and 9.0% and 11.6% for 60 patients.

Version and Date: 5.0 dated 24 May 2019

3. TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this protocol.

Table 1: Abbreviations

Abbreviation or Specialist Term	Definition
5-ASA	5-Aminosalicylic acid
6-MP	6-Mercaptopurine
ADR	Adverse drug reaction
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-TNF	Anti-tumor necrosis factor
AST	Aspartate aminotransferase
AV	Atrioventricular
AZA	Azathioprine
BCRP	Breast Cancer Resistance Protein
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CFR	Code of Federal Regulations
CI	Confidence interval
CRO	Contract Research Organization
CRP	C-reactive protein
DDI	Drug drug interaction
DLCO	Diffusion capacity of the lung for carbon monoxide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
Early Term	Early termination
FEV_1	Forced expiratory volume at 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Definition
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	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine-hormone releasing system
IV	Intravenous
IVIg	Intravenous immune globulin
LAM	Lactational amenorrhea method
LFT	Liver function test
MMF	Mycophenolate mofetil
NASH	Nonalcoholic steatohepatitis
NSAID	Nonsteroidal anti-inflammatory drug
OCT	Optical coherence tomography
PD	Pharmacodynamic
PE	Physical examination
PFT	Pulmonary function test (FEV_1, FVC, and DLCO)
PK	Pharmacokinetic
PQC	Product Quality Complaint
RT-PCR	Reverse transcription polymerase chain reaction
$S1P_1$	Sphingosine 1-phosphate 1 receptor
SAE	Serious adverse event

Abbreviation or Specialist Term	Definition
SD	Standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
TB	Tuberculosis
TGFβ	Transforming growth factor beta
TNFα	Tumor necrosis factor alpha
UC	Ulcerative colitis
ULN	Upper limit of normal
VZV	Varicella Zoster Virus
WBC	White blood cell
WOCBP	Women of child-bearing potential

6. TRIAL OBJECTIVES AND ENDPOINTS

6.1. Trial Objectives

6.1.1. Induction Period Primary Objective

To assess endoscopic improvement following treatment with RPC1063

6.1.2. Induction Period Secondary Objectives

- To characterize clinical improvement, response, and remission following treatment with RPC1063
- To assess changes in intestinal and blood biomarkers following treatment with RPC1063 by characterizing the following:
  - Intestinal mucosa histopathologic disease activity
  - Select cellular, protein, and molecular biomarkers in the intestinal mucosa and blood
- To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of RPC1063
- To assess the safety of RPC1063

6.1.3. Extension Period Primary Objective

To characterize the longer term safety of continued dosing of RPC1063

6.1.4. Extension Period Secondary Objectives

- To characterize endoscopic improvement at Week 52
- To characterize the histopathological changes of the intestinal mucosa at Week 52
- To characterize the effect of RPC1063 in maintaining clinical improvement over time

6.2. Endpoints

6.2.1. Induction Period Endpoints

Patients in the Induction Period will be assessed for the following efficacy endpoints:

Primary Efficacy Endpoint

- Change in SES-CD score from baseline at Week 12.

Other Efficacy Endpoints

- Change in CDAI score from baseline at Week 12
- Proportion of patients with clinical remission based on CDAI at Week 12
- Proportion of patients with clinical response based on CDAI at Week 12
- Proportion of patients with clinical remission based on PRO2 definitions at Week 12

- Proportion of patients with clinical response based on PRO2 definitions at Week 12
- Proportion of patients with endoscopic remission based on SES-CD definitions at Week 12
- Proportion of patients with endoscopic response based on SES-CD definitions at Week 12
- Change in intestinal mucosa histopathologic features and disease activity
- [redacted]
- Improvement in perianal and enterocutaneous fistulas at Week 12 in those patients with fistulas at baseline

6.2.2. Extension Period Efficacy Endpoints

Patients in the Extension Period will be examined for the following efficacy endpoints:

- Proportion of patients in endoscopic remission based on SES-CD definitions at Week 52
- Proportion of patients in endoscopic response based on SES-CD definitions at Week 52
- Proportion of patients in clinical remission based on CDAI at Week 52
- Proportion of patients in clinical response based on CDAI at Week 52
- Proportion of patients in clinical remission based on PRO2 definitions at Week 52
- Proportion of patients in clinical response based on PRO2 definitions at Week 52
- Proportion of patients in clinical remission at Week 52 based on CDAI and PRO2 definitions who are off corticosteroids of those on corticosteroids at baseline
- Proportion of patients in clinical remission based on CDAI over time
- Proportion of patients in clinical response based on CDAI over time
- Proportion of patients in clinical remission based on PRO2 definitions over time
- Proportion of patients in clinical response based on PRO2 definitions over time

- Change in intestinal mucosa histopathologic features, histologic disease activity, and biomarkers over time
- Change in fecal calprotectin and serum C-reactive Protein levels over time
- Improvement in perianal and enterocutaneous fistulas in those patients with fistulas at baseline over time

6.2.3. Safety Endpoints

The incidence, severity, relationship and type of TEAEs, SAEs, AEs leading to discontinuation of investigational drug, and AEs of special interest, and clinically meaningful changes from baseline on clinical laboratory measures, vital signs, electrocardiograms (ECGs), and physical examination will be assessed.

Safety assessments will include the following:

- Collection of AEs
- Physical examinations
- Vital sign measurements
- ECG results
- Optical coherence tomography
- Pulmonary function tests (PFTs) (FEV_1, FVC, and diffusion capacity of the lung for carbon monoxide [DLCO], where available)
- Clinical laboratory tests

6.2.4. Pharmacokinetic and Pharmacodynamic Endpoints

Pharmacokinetic and PD endpoints will include the following:

- [redacted]
- [redacted]
- [redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Trial Design

This Phase 2, multi-center, open-label trial, to be conducted in North America and Europe, is designed to assess the endoscopic improvement, clinical response/remission, and changes in intestinal and blood biomarkers in patients with moderately to severely active Crohn's disease receiving RPC1063 as induction therapy. The trial comprises 2 periods: Induction (12 weeks) and Extension (148 weeks). Patients will be entered into the trial through the Induction Period. A central reader will calculate the SES-CD for eligibility and assessment of the primary endpoint to ensure objectivity.

The safety of patients will be monitored by collection of treatment-emergent AEs, serious adverse events (SAEs), physical examinations, vital sign measurements, ECG results, optical coherence tomography (OCT), pulmonary function tests (PFTs), and clinical laboratory tests.

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

7.1.1. Induction Period

The trial will enroll approximately 60 patients with moderately to severely active Crohn's disease. Patient eligibility will be determined during a 5-week Screening Period. All patients who meet eligibility criteria and enter into the trial will complete a 7-day dose escalation regimen consisting of 4 days of treatment with RPC1063/ozanimod HCl 0.25 mg (equivalent to ozanimod 0.23 mg) daily followed by 3 days treatment with RPC1063/ozanimod HCl 0.5 mg (equivalent to ozanimod 0.46 mg) daily (administered as two 0.25 mg capsules), with the final dose level of RPC1063/ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) daily dose to be reached on Day 8. Patients will then continue on RPC1063 1 mg daily during the Induction Period for 11 weeks. At Week 12 patients will be evaluated for endoscopic and clinical response/remission.

Patients who complete the Induction Period will have the opportunity to receive continued treatment with RPC1063 in the Extension Period. Investigators should assess patient's clinical status at the end of the Induction Period and, using clinical judgment, determine if the patient should continue into the Extension Period or withdraw from the trial and receive alternative therapy.

Induction Period visit schedule and procedures, including early termination and safety follow-up, are provided in Table 2.

7.1.2. Extension Period

All patients will receive RPC1063 1 mg daily dose in the Extension Period and may receive treatment through Week 160. During the Extension Period, the investigator should continue to assess the patients clinical status and based on clinical judgment determine if the patient should continue or withdraw from the trial and receive alternative therapy. Extension Period visit schedule and procedures, including early termination and safety follow-up, are provided in Table 3.

Patients who complete the Week 160 visit may have the option to immediately enter (without completing the 30-day or 90-day Safety Follow-up Visits) the open-label extension Phase 3 CD Study [redacted].

7.2. Criteria for Trial Termination

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

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

7.3. Schedule of Events

The visit schedule and procedures for the Induction Period and Extension Period are provided in Table 2 and Table 3, respectively.

Table 2: Schedule of Events for Induction Period

		Screening	Induction Period				Early Term Visit	Safety Follow-up	
			Dose Escalation	1 mg Dose					
			Visit I1	Visit I2	Visit I3	Visit I4			
		Screening	Day 1[a,b]	Week 4[b]	Week 8[b]	Week 12[b,c]			
	Trial Procedures	Day-35 to 0	Day 1	Day 28±3	Day 56±3	Day 84±3		Last Dose +30 ±3 days	Last Dose +90 ±10 days[r]
	Informed consent	X							
	Inclusion/exclusion criteria	X	X						
	Demographics	X							
	Medical history[d,e]	X	X						
	Viral serology[f]	X							
	Stool culture[g]	X							
	Dispense investigational drug		X	X	X	X			
	Administer investigational drug at clinic		X	X	X	X			
	Review drug compliance			X	X	X	X		
	Prior and concomitant medications	X	X	X	X	X	X	X	X
	Medical procedures (non-trial)		X	X	X	X	X	X	
Efficacy Assessments	CDAI patient diary	X[h]	X	X	X	X	X		
	CDAI clinical score	X[h]	X	X	X	X	X		
	Colonoscopy	X[h]				X[i]	X[j]		
	SES-CD	X[h]				X	X		
	Colonic biopsy	X				X	X[j]		

			Induction Period				Early Term Visit	Safety Follow-up	
			Dose Escalation	1 mg Dose					
			Visit I1	Visit I2	Visit I3	Visit I4			
		Screening	Day 1[a,b]	Week 4[b]	Week 8[b]	Week 12[b,c]			
	Trial Procedures	Day-35 to 0	Day 1	Day 28±3	Day 56±3	Day 84±3		Last Dose +30 ±3 days	Last Dose +90 ±10 days[r]
	[redacted]	X			X	X	X		
	Enterocutaneous and perianal fistula drainage[k]	X				X	X		
PK and PD Assessments	[redacted]		X	X	X	X			
	PK blood sampling[l]		X	X	X	X	X	X	X
	Flow cytometry		X			X[m]	X		
Safety Assessments	Adverse events		X	X	X	X	X	X	X
	12-Lead ECG	X	X[n]			X	X		
	Vital signs	X	X	X	X	X	X	X	
	Hematology[s]	X	X	X	X	X	X	X	
	Blood chemistry	X	X	X	X	X	X	X	
	Pregnancy test (WOCBP only)[o]	X	X	X	X	X	X	X	X
	Coagulation panel	X					X		
	Urinalysis	X		X		X	X		
	Physical examination[p]	X	X	X	X	X	X	X	
	Pulmonary function tests[q]	X				X	X		
	Optical coherence tomography	X		X		X	X		

[a] The duration of Day 1 Visit will be approximately 7 hours.
[b] Trial visits should be scheduled in the morning, where possible, and on trial visit days patients should be instructed to withhold the dose until the trial visit . The dose should be administered during the visit.
[c] Patients should continue taking investigational drug while it is being determined if they qualify for the Extension Period. Those who do not qualify should return for their Early Term Visit as soon as is practical but no later than 4 weeks after their Week 12 visit.
[d] Medical history will include smoking and Crohn's disease history. Day 1 medical history can be abbreviated, noting events that occurred between Screening and Day 1.
[e] Active TB must be ruled out according to local medical practices.
[f] Serology testing will be performed at Screening to determine the patient's immune status with respect to the following viruses: Human immunodeficiency virus (HIV) antibodies, anti-hepatitis A virus IgM, hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antigen (HBcAg) IgM, anti-hepatitis C virus (HCV) IgG or IgM. In addition, patients must have documentation of positive Varicella Zoster Virus (VZV) IgG antibody status or complete VZV vaccination at least 30 days prior to first dose of investigational drug.
[g] At Screening the stool sample will be used to rule out serious infection and should include evaluation for C. difficile toxin as well as ova and parasitic examination.
[h] During Screening the CDAI clinical score, SES-CD and colonoscopy must be completed within 14 days of Day 1. Patients should also begin completing the CDAI patient diary during this time. At Screening, patients will be issued a CDAI diary and will be trained in the completion of the diary.
[i] Week 12 colonoscopy should be performed either on day of visit or no more than 7 days prior to the visit date.
[j] Colonoscopy does not need to be performed at the Early Term visit if one was completed within 8 weeks of the Early Term visit.
[k] Enterocutaneous and perianal fistula drainage assessment will only be performed on patients with fistulas at baseline.
[l] Blood samples for PK evaluation are to be taken up to 15-30 minutes prior to investigational drug administration (pre-dose) and just prior to discharge from the clinic (6-8 hours post-dose) on Day 1. Blood samples at subsequent visits will be trough level, taken just prior to investigational drug administration. The actual time of investigational drug administration for all visits with PK evaluation will be recorded. The blood sample at the 30-day and 90-day Safety Follow-Up Visit can be collected at any point during the visit. An additional PK sample will be obtained for patients with any AE resulting in discontinuation or SAE.
[m] Week 12 flow cytometry analysis will only be performed for patients with a baseline sample (Day 1).
[n] Prior to first dose of investigational drug, a 12-lead ECG will be performed. After the dose, patients will have hourly vital signs recorded at 1, 2, 3, 4, 5, and 6 hours post-dose. A second 12-lead ECG will be performed at the end of the observation period.
[o] For females of childbearing potential only, serum beta hCG is required at screening and a urine beta hCG is required at each visit. Between scheduled visits up until the 90-day Safety Follow-up Visit, monthly 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. Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for female subjects of childbearing potential. The Investigator will educate all FCBP about the different options of contraceptive methods or abstinence as appropriate. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).
[p] The screening physical examination (PE) includes height and weight, other visits include weight. A complete PE will be performed at Screening and end of trial visit (Week 12 or Early Term). The complete PE 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). An interim PE may be performed at all other visits. The interim PE will include areas with previously-noted abnormalities and those 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).
[q] DLCO, if locally available, will be done at Screening and Early Term.
[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 AEs to RPC1063.
[s] If ALC is confirmed < 200 cells/µL, the Investigator will temporarily discontinue investigational drug. 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.

Abbreviations: AE = adverse event; ALC = absolute lymphocyte count; CDAI = Crohn's Disease Activity Index; DLCO = diffusion capacity of the lung for carbon monoxide; Early Term = Early Termination; ECG = electrocardiogram; PD = pharmacodynamic; PK = pharmacokinetic; SES-CD = Simple Endoscopic Score for Crohn's disease; TB = tuberculosis; WOCBP = women of child-bearing potential

Table 3: Schedule of Events for Extension Period

	Trial Procedures	Extension Period																
		Treatment															Safety Follow-up	
		E1[a,b]	E2[b]	E3[b]	E4[b]	E5[b]	E6[b]	E7[b]	E8[b]	E9[b]	E10	E11	E12	E13	E14[b]	Early Term		
		W12	W 24	W 36	W 48	W 52	W 64	W 76	W 88	W 100	W 112	W 124	W 136	W 148	W 160			
		Day 84 ±3	Day 168 ±7	Day 252 ±7	Day 336 ±3	Day 364 ±3	Day 448 ±7	Day 532 ±7	Day 616 ±7	Day 700 ±7	Day 784 ±7	Day 868 ±7	Day 952 ±7	Day 1036 ±7	Day 1120 ±7	Day of Early Term	Last dose +30 ±3 days	Last dose +90 ±10 days[j]
	Dispense investigational drug	See Week 12 of the Induction Period	X	X	X	X	X	X	X	X	X	X	X	X	X[k]			
	Administer investigational drug at clinic		X	X	X	X	X	X	X	X	X	X	X	X	X			
	Review drug compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments	CDAI patient diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	CDAI clinical score		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Colonoscopy					X[c]										X[d]		
	SES-CD score					X										X[d]		
	Colonic biopsy					X										X[d]		
	[redacted]		X			X									X	X		

	Trial Procedures	Extension Period																
		Treatment															Safety Follow-up	
		E1[a,b]	E2[b]	E3[b]	E4[b]	E5[b]	E6[b]	E7[b]	E8[b]	E9[b]	E10	E11	E12	E13	E14[b]	Early Term		
		W12	W 24	W 36	W 48	W 52	W 64	W 76	W 88	W 100	W 112	W 124	W 136	W 148	W 160			
		Day 84 ±3	Day 168 ±7	Day 252 ±7	Day 336 ±3	Day 364 ±3	Day 448 ±7	Day 532 ±7	Day 616 ±7	Day 700 ±7	Day 784 ±7	Day 868 ±7	Day 952 ±7	Day 1036 ±7	Day 1120 ±7	Day of Early Term	Last dose +30 ±3 days	Last dose +90 ±10 days[j]
	Enterocutaneous and perianal fistula drainage[e]		X			X									X	X		
PK and PD Assessments	[redacted]		X			X									X	X	X	
	PK blood sampling[f]		X			X									X	X	X	X
Safety Assessments	Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	12-Lead ECG					X										X		
	Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Hematology[l]		X	X	X	X		X		X		X		X		X	X	
	Blood chemistry		X	X	X	X		X		X		X		X		X	X	
	Urine pregnancy test[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Urinalysis			X		X		X		X		X		X		X		
	Physical Examination[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Pulmonary function test[i]		X			X					X				X	X		

	Trial Procedures	**Extension Period**															
		Treatment														**Early Term**	**Safety Follow-up**	
		E1[a,b]	**E2**[b]	**E3**[b]	**E4**[b]	**E5**[b]	**E6**[b]	**E7**[b]	**E8**[b]	**E9**[b]	**E10**	**E11**	**E12**	**E13**	**E14**[b]			
		W12	**W 24**	**W 36**	**W 48**	**W 52**	**W 64**	**W 76**	**W 88**	**W 100**	**W 112**	**W 124**	**W 136**	**W 148**	**W 160**			
		Day 84 ±3	Day 168 ±7	Day 252 ±7	Day 336 ±3	Day 364 ±3	Day 448 ±7	Day 532 ±7	Day 616 ±7	Day 700 ±7	Day 784 ±7	Day 868 ±7	Day 952 ±7	Day 1036 ±7	Day 1120 ±7	Day of Early Term	Last dose +30 ±3 days	Last dose +90 ±10 days[j]
	Optical coherence tomography					X					X				X	X		

[a] The duration of Visit E1 will be approximately 3 hours.
[b] Trial visits should be scheduled in the morning, when possible. At trial Visits Week 24, 52 and at Week 160, patients should be instructed to withhold the dose until the trial visit and the dose should be administered during the visit.
[c] At Week 52, a colonoscopy should be performed either on the day of visit or no more than 7 days prior to the visit date.
[d] Colonoscopy, biopsy, and SES-CD score do not need to be performed at the Early Term visit if the Early Term Visit occurs within 8 weeks of the Week 12 colonoscopy or after the Week 52 colonoscopy assessment.
[e] Enterocutaneous and perianal fistula drainage assessment will only be performed on patients with fistulas at baseline.
[f] Blood samples at each visit will be trough level, taken just prior to investigational drug administration. The actual time of investigational drug administration for all visits with PK evaluation will be recorded. The blood sample at the Follow-up visit can be collected at any point during the visit. An additional PK sample will be obtained for patients with any AE resulting in discontinuation or SAE.
[g] For females of childbearing potential only, serum beta hCG is required at screening and a urine beta hCG is required at each visit. Between scheduled visits up until the 90-day Safety Follow-up Visit, monthly 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. Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for female subjects of childbearing potential. The Investigator will educate all FCBP about the different options of contraceptive methods or abstinence as appropriate. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).
[h] A complete PE will be performed at Week 160 or Early Term, whichever is applicable. The complete PE 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). An interim physical examination may be performed at all other visits; weight will be recorded at all visits. The interim PE will include areas with previously-noted abnormalities and those 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 locally available, will be done at Week 52 and Early Term.
[j] 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 AEs to RPC1063.

[k] For eligible patients who are entering the Phase 3 open-label extension CD Study RPC01-3204 at a future date (not on visit Week 160), investigational drug will be dispensed in this study. For eligible patients who are immediately entering the Phase 3 open label extension CD Study RPC01-3204 on the same day as visit Week 160, investigational drug will be dispensed in Study RPC01-3204.

[l] If ALC is confirmed < 200 cells/μL, the Investigator will temporarily discontinue investigational drug. 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.

Abbreviations: AE = adverse event; ALC = absolute lymphocyte count; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; DLCO = diffusion capacity of the lung for carbon monoxide; Early Term = Early Termination; ECG = electrocardiogram; PK = pharmacokinetic; PD = pharmacodynamic; SES-CD = Simple Endoscopic Score for Crohn's disease

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

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

1. Male or female patients aged 18 to 75 years, inclusive
2. Diagnosis of Crohn's disease for at least 2 months (prior to Screening) by clinical endoscopic evidence and corroborated by a histology report (Note: histopathology may be performed during Screening if no prior report is readily available).
3. Crohn's disease Activity Index score of 220 to 450 inclusive with an SES-CD score of ≥ 6. (If disease isolated to ileum, the requirement will be a SES-CD score ≥ 4.)
4. Average daily stool score ≥ 4 points and/or an average daily abdominal pain score of ≥ 2 points.
5. Patients must meet one of the following criteria:
   - Have an inadequate response or loss of response to at least one of the following Crohn's disease treatments :
     - Aminosalicylates, oral aminosalicylates ≥2.4 g/day or ≥3 g/day sulfasalazine for at least 4 weeks
     - Corticosteroids, oral prednisone ≥30 mg or budesonide ≥9 mg for at least 2 weeks or an equivalent (to oral prednisone) of intravenous corticosteroid for 1 week
     - Immunomodulators, oral azathioprine ≥ 1.5 mg/kg or 6-mercaptopurine 0.75 mg/kg (documentation of therapeutic level of 6-thioguanine is also acceptable) or methotrexate ≥ 12.5 mg/week for at least 8 weeks
     - Biologic therapy (TNFα antagonist or vedolizumab only) at an approved labeled dose used for induction therapy for at least 4 weeks or recurrence of disease activity despite scheduled maintenance therapy. (Biologic therapy exposed patients will be capped at 50% of total enrolled patients)
   - And/or have been intolerant to any of the above mentioned therapies (e.g., unable to achieve doses, dose levels, or treatment durations because of treatment related side effects and/or laboratory abnormalities)
6. The following background therapies for Crohn's disease will be permitted on a stable dose:
   - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide) at a stable dose for at least 3 weeks prior to Screening endoscopy
   - Prednisone (doses ≤ 20 mg per day) or equivalent at a stable dose (dose ≤ 9 mg per day) for at least 2 weeks prior to Screening endoscopy
   - Budesonide therapy at a stable dose for at least 2 weeks prior to Screening endoscopy

- Antibiotics used for the treatment of Crohn's disease (i.e., ciprofloxacin, metronidazole) at a stable dose for at least 2 weeks prior to Screening endoscopy

7. 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 endoscopy score
8. 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
   - complete sexual abstinence

   Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

   Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for female subjects of childbearing potential. The Investigator will educate all FCBP about the different options of contraceptive methods or abstinence as appropriate. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).
9. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
10. Must have documentation of positive *Varicella zoster* virus (VZV) immunoglobulin G (IgG) antibody status or complete VZV vaccination at least 30 days prior to first dose of investigational drug
11. For patients at high risk (i.e., family history, disease duration) for colonic malignancy, documented evidence of having had a surveillance colonoscopy within the last 2 years or according to local medical guidelines to evaluate for polyps, dysplasia, or malignancy.

If no recent history of surveillance colonoscopy, this can be done as part of colonoscopy performed during Screening

8.2. Patient Exclusion Criteria

Candidates will be excluded from entering the trial if any of the following exclusion criteria exist at time of enrollment or at the time point specified in the individual criterion listed:

Exclusions Related to General Health:

1. Diagnosis of ulcerative colitis or indeterminate colitis
2. Crohn's disease isolated to the stomach, duodenum, jejunum, or peri-anal region, without colonic or ileal involvement
3. Known strictures or stenosis leading to symptoms of obstruction
4. Current stoma or need for ileostomy or colostomy
5. Extensive small bowel resection (>100 cm) or known diagnosis of short bowel syndrome
6. Suspected or diagnosed intra-abdominal or perianal abscess that has not been appropriately treated
7. Currently require or are anticipated to require surgical intervention for Crohn's disease during the Induction Period
8. Currently receiving total parenteral nutrition
9. Positive stool culture for pathogens (ova and parasites, bacteria) or positive test for *Clostridium difficile* (C. difficile) at Screening. Patients may be treated and retested but must have negative stool culture for pathogens (ova and parasites, bacteria) within 30 days prior to first dose of investigational drug and 60 days prior to first dose of investigational drug for C. difficile
10. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin (hCG) measured during Screening
11. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric or other major systemic disease making implementation of the protocol or interpretation of the trial difficult or that would put the patient at risk by participating in the trial
12. Clinically relevant cardiovascular conditions, including history or presence of:
    - Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea
    - 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)

- Resting HR less than 55 beats per minute (bpm) when taking vitals as part of a physical examination at Screening
- Mobitz type 2nd degree or 3rd degree AV block

13. History of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c > 9%, or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy
14. History of uveitis or known macular edema
15. Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis [TB] or atypical mycobacterial disease [but excluding fungal infection of nail beds, minor upper respiratory tract infections and minor skin infections]) or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 30 days of Screening or oral antibiotics within 14 days of Screening.
16. History or known presence of recurrent or chronic infection (eg, hepatitis A, B, or C, human immunodeficiency virus (HIV); recurrent urinary tract infections are permitted.
17. 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)
18. Past or current evidence of colonic dysplasia
19. History of alcohol or drug abuse within 1 year prior to first dose of investigational drug
20. History of or currently active primary or secondary immunodeficiency

Exclusions Related to Medications:

21. History of treatment with a biologic agent within 5 elimination half-lives of that agent prior to first dose of investigational drug
22. History of treatment with an investigational agent within 5 elimination half-lives of that agent prior to first dose of investigational drug
23. History of treatment with topical rectal 5-ASA or steroids within 2 weeks of Screening
24. History of primary non-response to two approved biologic therapies used for the treatment of Crohn's disease
25. Receipt of a live vaccine within 4 weeks prior to Screening
26. Previous treatment with lymphocyte-depleting therapies (e.g., Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
27. Treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 16 weeks of Screening
28. Previous treatment with D-penicillamine, leflunomide, or thalidomide
29. Previous treatment with natalizumab or fingolimod

30. History of treatment with intravenous immune globulin (IVIg), plasmapheresis, within 3 months prior to first dose of investigational drug
31. Planned concurrent treatment with immunosuppressive agents (e.g., azathioprine, 6-MP, or methotrexate) after enrollment. Patients receiving azathioprine, 6-MP or methotrexate at Screening must discontinue treatment with these agents prior to first dose of investigational drug.
32. Chronic non-steroidal anti-inflammatory drug (NSAID) use (Note: occasional use of NSAIDs and acetaminophen [eg, headache, arthritis, myalgias, or menstrual cramps] and aspirin up to 325 mg/day is permitted)
33. Treatment with Class Ia or Class III anti-arrhythmic drugs) or treatment with two or more agents in combination known to prolong PR interval
34. Treatment with any of the following drugs or interventions within the corresponding timeframe:
    - At Day 1
      - CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) or inducers (eg, rifampicin)
    - Two weeks prior to Day 1
      - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)

Exclusions Related to Laboratory Results:

35. Serum creatinine > 1.4 mg/dL for women or > 1.6 mg/dL for men
36. 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
37. Platelet count < 100,000/µL
38. Hgb < 8.5 g/dL
39. Neutrophils < 1500/µL
40. Absolute WBC count < 3500/µL
41. Absolute lymphocyte count < 800/µL
42. Electrocardiogram showing any clinically significant abnormality (e.g., acute ischemia, any significant heart conduction abnormality [e.g., left bundle branch block])
43. Forced expiratory volume at 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values at Screening

8.3. Trial Discontinuation

Patients will be encouraged to complete the trial; 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 eCRF page describing the reason for discontinuation.

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

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

- Physician decision: The Investigator must discontinue investigational drug if it is determined that it is not safe or in the patient's best interest to receive further treatment. The Medical Monitor should be promptly notified of the decision
- Non-compliance with investigational drug: After consultation between the Investigator, the Medical Monitor, or Clinical Monitor, and the Sponsor when appropriate, a patient may be discontinued from the trial for failure to comply with dosing regimen as specified by the protocol
- Non-compliance with protocol/protocol deviation: A patient fails to follow protocol procedures, or other event or decision that stands in contrast to the guidelines set in the protocol
- Adverse event: A patient must be discontinued from investigational drug if, in the judgment of the Investigator or if specified in the protocol, the patient develops an AE such as an intercurrent illness or complication that justifies discontinuation of investigational drug
- Lack of efficacy: Decision by the patient and/or the Investigator to discontinue treatment due to a lack of expected or desired effect related to a therapy
- Withdrawal by Patient: The patient may choose to discontinue investigational drug at any time. Every effort should be made within the bounds of safety and patient choice to have each patient complete the Early Termination Visit and 30-day and 90-day Safety Follow-up Visits. If a patient withdraws consent, the only additional trial data to be collected will be the follow-up of SAEs as mandated by the protocol
- Pregnancy: If the patient becomes pregnant investigational drug must be discontinued (see Section 12.2.11)
- Trial termination by Sponsor
- Other

All patients who discontinue the trial should complete an Early Termination Visit (see Table 2 and Table 3). 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. With the exception of patients who withdraw consent or are lost to follow-up, patients should complete the 30-day and 90-day Safety Follow-up Visits for the collection of safety data and to assess their disease status. Alternative treatment for CD can be started, if needed, after the Early Termination Visit.

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

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

Patients who withdraw from the trial will not be replaced.

9. TRIAL TREATMENTS

The Investigator must ensure that the investigational drug will be used only in accordance with the protocol. Investigational drug should not be used for purposes other than as defined in this protocol.

9.1. Treatments Administered

[redacted]

9.1.1. Instructions for Missed Dose(s) of RPC1063 Capsules

[redacted]

9.1.2. Induction Period

Patients will receive RPC1063 1 mg oral capsule daily for 11 weeks after the 7-day dose escalation (12 weeks total duration).

9.1.3. Extension Period

All patients will receive RPC1063 1 mg capsule orally once daily for 148 weeks.

9.2. Selection of Dose in the Trial

The selected dose of 1 mg/day of RPC1063 is primarily based on the results from the Phase 2 dose finding induction trial in UC (RPC01-202). The 1 mg/day dose demonstrated better efficacy than the 0.5 mg/day dose across various clinical and endoscopic endpoints. Furthermore, the expected magnitude of pharmacodynamics effect on peripheral lymphocyte reduction and an acceptable safety profile was observed.

A dose escalation over the first 7 days (0.25 mg/day on Days 1 to 4 and 0.5 mg/day [administered as two 0.25 mg capsules] on Days 5 to 7) will be implemented, as results from RPCS 001 and preliminary results from RPC01-202 indicate that use of a dose escalation

regimen mitigates the magnitude of reduction in HR. Preliminary evidence from these trials suggest that patients who increase their dose progressively over the first week are less likely to have a clinically meaningful decrease in HR or blood pressure; therefore, a dose escalation starting with 0.25 mg RPC1063 for the first 4 days of dosing followed by 0.5 mg (administered as two 0.25 mg capsules) on Days 5 through 7 before progressing to the 1 mg/day dose will be used.

9.3. Method of Assigning Patients to Treatment Groups

Not applicable.

9.4. Selection and Timing of Dose for Each Patient

Patients will self-administer RPC1063 orally once-daily. Investigational drug should be taken at approximately the same time each day with or without food.

9.5. Prior and Concomitant Treatments

All treatments, other than RPC1063, being taken by the patients on entry into the trial or at any time during the trial including through the 90-day Safety Follow-up Visit, are regarded as concomitant medications and must be documented on the appropriate section of the eCRF. A history of all prior medications needs to be documented to at least 4 weeks prior to trial participation. A history of previous treatments for CD needs to be documented.

Patients who are receiving oral 5-ASA, oral corticosteroids, or purified medicinal probiotics at screening must keep their prescribed dosage steady through Week 8 and can only be discontinued or reduced in dose if Investigator judgment requires it because of toxicity or medical necessity. After Week 8 these medications can be discontinued or reduced as medically indicated. Oral 5-ASA, oral corticosteroids, or purified medicinal probiotics should not be started during the first 12 weeks of the study in patients who were not receiving them during screening. Ideally, patients receiving 5-ASA or purified medicinal probiotics should maintain a stable dose throughout the trial. Patients not receiving oral 5-ASA, oral corticosteroids, or purified medicinal probiotics at screening can only begin dosing with these medications if Investigator judgment requires it because of medical necessity.

9.5.1. Steroid Taper

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

Corticosteroids may be tapered starting from Week 12 for patients entering the Extension Period. Patients receiving prednisone at a dose of > 10 mg/day (or equivalent) may have their dose reduced at a rate of 5 mg per week until a 10 mg/day dose is achieved. Patients receiving prednisone at doses of ≤ 10 mg/day (or equivalent), or once a 10 mg/day dose (or equivalent) is achieved by tapering, may have their dose reduced at a rate of 2.5 mg/week until discontinuation. Beginning at Week 12, patients receiving budesonide may taper their dose at a rate of 3 mg every 3 weeks. For patients who do not tolerate a corticosteroid taper without recurrence of clinical symptoms of either CD or steroid withdrawal, the corticosteroid dose may be increased (up to the dose at trial entry if required), but tapering may be tried again.

9.5.2. Allowed Medications

All prior medications (including over-the-counter medications) administered 30 days prior to the first dose of investigational drug and any concomitant therapy administered to the patient during the course of the trial (starting at the date of informed consent) until 90 days after the final dose of investigational drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures and/or past biologic exposure relating to CD should be recorded. Any medication that is considered necessary for the patient's health and that is not expected to interfere with the evaluation of or interact with investigational drug may be continued during the trial (see Table 4).

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

9.5.3. Concomitant Medications Prohibited Through the 30-Day Safety Follow-up Visit

[redacted]

[redacted]

Table 4: Examples of Prohibited Cardiac Medications (Systemic Use)

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

9.5.4. Concomitant Medications Between the 30-Day Safety Follow-up Visit and the 90-Day Safety Follow-up Visit

[redacted]

9.6. Medical Care of Patients after End of Trial

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

9.7. Treatment Compliance

It is the Investigator's responsibility to ensure that patients are correctly instructed on how to take their investigational drug and that each patient is fully compliant with their assigned dosage regimen. Records of investigational drug used and intervals between visits will be kept during the trial. Drug accountability will be noted by the Clinical Monitor during site visits and at the completion of the trial. Patients will be asked to return all unused medication at the end of the

trial. The investigational drug should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained as described in Section 10.3.

Overall trial 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, or by a qualified individual under the Investigator's supervision, and compliance assessed. Patients exhibiting poor compliance as assessed by medication counts (i.e., 2 or more missed medication days in 1 week) and their response to a medication compliance question at each visit should be counseled on the importance of good compliance to the trial dosing regimen. Patients who are persistently non-compliant (<80% or >120%) should be discussed with the Medical Monitor to determine whether they should be withdrawn from the trial.

9.8. Blinding

This is an open-label trial without randomization.

10. INVESTIGATIONAL DRUG MATERIALS AND MANAGEMENT

10.1. Investigational Drug

[redacted]

10.2. Packaging and Labeling

RPC1063 capsules will be packaged in 30 cc white high-density polyethylene bottles (35 capsules per bottle, apart from the dose escalation kits), closed with a 28 mm child resistant screw-cap that is induction sealed. The labeling of investigational drug will be in accordance with GCP and any other local regulatory requirements.

10.3. Investigational Drug Accountability

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

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

The Investigator will provide the investigational drug only to the identified patients of this trial, according to the procedures described in this trial protocol. After the end of the trial, the Clinical Monitor will perform final accountability, package, seal, and prepare for shipment. Investigational drug and all medication containers will be returned to the clinical supply distribution vendor and documentation will be returned to the CRO. The CRO will verify that a final report of investigational drug accountability is prepared and maintained in the Investigator's Trial Center File.

11. ASSESSMENT OF EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS

11.1. Efficacy Assessments

11.1.1. Primary Efficacy Assessments

The SES-CD will be used to evaluate the primary efficacy endpoint.

11.1.2. SES-CD

The simple endoscopy score (SES-CD) assesses the degree of inflammation. The SES-CD assesses the following 4 components: size of ulcers, ulcerated surface, affected surface, and presence of narrowing. Each of these components are scored on a scale of 0 to 3 as outlined in Table 5.

In the SES-CD, each of these 4 components are assessed in the five segments of the ileum and colon: ileum, right, transverse, left (descending and sigmoid), and rectum. The SES-CD is the sum of the individual scores of each of the components across the five segments. Mild CD is defined as an SES-CD ≥3 but less than 7 points. Moderate to severely active CD is defined as an SES-CD of ≥7 points.

To ensure quality data and standardization, the same endoscopist should be used throughout the trial wherever possible. Colonoscopies will be read at a centralized reading facility. Each patient who enters into the trial will have colonic biopsies obtained during colonoscopy (see Table 2 and Table 3). Details regarding the biopsies are provided in the biopsy manual.

Table 5: Definitions of Simple Endoscopic Score for Crohn's Disease

	SES-CD Values			
Variable	**0**	1	**2**	**3**
Size of ulcers	None	Aphthous ulcers (< 0.5 cm)	Large ulcers (0.5 to 2 cm)	Very large ulcers (>2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

11.1.3. Crohn's Disease Activity Index

The Crohn's Disease Activity Index (CDAI) is a composite score that is used to measure the clinical activity of Crohn's disease. The CDAI uses a questionnaire with responses scored numerically and weighted. Scores range from 0 to approximately 600, with higher scores indicating greater disease activity. The 8 components used to assess the CDAI and their weighting factors are noted in Table 6. The definitions of mild, moderate, and severe Crohn's disease are provided in Table 7.

Patient-reported outcomes (stool frequency and abdominal pain components of the CDAI Score and general well-being), and the other CDAI components will be collected in an electronic diary. Patients will complete the stool frequency, abdominal pain and general well-being components of the CDAI from the patient's first screening visit and will continue throughout the trial.

Patients will be instructed on the use and completion of questions on the electronic diary.

The diary entries will be reviewed by site personnel during screening (prior to dosing, if applicable) and during all trial visits. The stool frequency and abdominal pain diary entries preceding each trial visit will be used to calculate the CDAI score and will be calculated using the stool frequency and the abdominal pain data from the most recent 7 day period, or at least 3 days within that 7 day period, prior to the visit, excluding the following:

- One day prior to the start of a procedure or preparation for a procedure that would affect stool frequency
- The day(s) of a procedure or preparation for a procedure that would affect stool frequency

Because the colonoscopy preparations can interfere with the assessment of other clinical parameters, diary entries used to calculate the CDAI score will not correspond to day(s) of bowel preparation or endoscopy.

Table 6: CDAI Assessment

Clinical or Laboratory Variable	**Weighting Factor, ×**
Number of liquid or soft stools each day for 7 days	2
Abdominal pain (graded from 0-3 on severity) each day for 7 days	5
General well-being, assessed from 0 (well) to 4 (terrible) daily for 7 days	7
Presence of complications*	20
Taking diphenoxylate/atropine, loperamide, or opiates for diarrhea	30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	10
Hematocrit 47-HCT in men and 42-HCT in women	6
Percentage deviation from standard weight	1
Total Score	

*One point each is added for each set of complications: arthritis or arthralgia; iritis or uveitis; erythema nodosum, pyoderma gangrenosum, aphthous stomatitis; anal fissure, fistula or perirectal abscess; other bowel-related fistula; febrile (fever) episode over 100 degrees during the past week

Table 7: Crohn's Disease Severity Definitions

Severity	CDAI Score
Mild	150-220
Moderate	220-450
Severe	>450

11.1.4. PRO2

The PRO2 is a composite score based on 2 components of the CDAI, the number of liquid or soft stools/day for 7 days and the abdominal pain (rated on a scale of 0-3) assessed for 7 days (Khanna 2015). The components of the score and their relative weightings are included in Table 8.

Table 8: PRO 2 Assessment

Component	Weighting, x
Number of liquid or soft stools/day for 7 days	2
Abdominal pain (0-3) for 7 days	5

The PRO2 assessment will utilize the two components of the CDAI: number of liquid or soft stools and abdominal pain.

11.1.5. Un-weighted Stool Frequency and Abdominal Pain

Stool Frequency as described in Table 8 will be obtained and calculated without a weighting factor for use as part of the inclusion criteria (4). Abdominal pain will also be obtained and calculated without a weighting factor for use as part of the inclusion criteria (4). These un-weighted patient reported assessments will also be used as efficacy endpoints (Section 11.1.7).

11.1.6. Other Efficacy Measures

11.1.6.1. Enterocutaneous and Perianal Fistula Drainage Assessment

Fistulas will be characterized as actively draining and open or closed. Based on physical examination, a fistula will be considered open if an investigator can express purulent material from the fistula with application of gentle pressure (Present 1999).

11.1.7. Efficacy Definitions

Endoscopic

Response: SES-CD decrease from baseline of ≥ 50%

Remission: SES-CD ≤ 4 points and a SES-CD decrease ≥ 2 points with no SES-CD sub-score > 1 point

CDAI

Clinical Response: CDAI reduction from baseline of ≥ 100 points

Clinical Remission: CDAI score of < 150

PRO2

Clinical Response: PRO2 decrease ≥50%

Clinical Remission: Average daily stool score ≤ 3 points AND average daily abdominal pain score ≤ 1 point

Mucosal Healing: Endoscopic remission plus histologic improvement

11.2. Pharmacokinetics and Pharmacodynamics

11.2.1. Pharmacokinetics and Pharmacodynamics

Pharmacokinetic samples will be shipped to the central laboratory. Details of the procedures to be followed for sample collection, storage, and shipment will be documented in a separate laboratory manual. The actual time of investigational drug administration for all visits with PK evaluation will be recorded on the dosing log.

The following PK and PD assessments will be performed on the visit days specified in Table 2 and Table 3 to determine the safety profile of RPC1063:

- Standard PK sampling: Samples on trial will be collected prior to dose administration (trough samples) and 6 to 8 hours after dose administration, as indicated in the Schedule of Assessments footnotes.
- Intestinal mucosa: immunohistochemistry and/or in situ hybridization (IHC/ISH) for example CD20, CD4, CD8, Foxp3, α4β7, CCR7, IFNα, IL17
- Intestinal mucosa: transcript profiling (mRNA) for example IFN signature, T cell exhaustion signature, outcome signature, S1PR pathway
- [redacted]
- [redacted]

11.2.2. Flow Cytometry

Flow cytometry samples will be collected as specified in Table 2.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety will be evaluated by the incidence, severity, relationship and type of AEs, SAEs, AEs leading to discontinuation of investigational drug, and AEs of special interest; and clinically meaningful changes from baseline in clinical laboratory test results, vital signs, ECGs, and physical examinations.

12.1.1. Physical Examination

A complete physical examination will include evaluation of heart, lung, head and neck, abdomen, skin, and extremities. All significant findings that are present at baseline must be reported on the relevant medical history/current medical conditions eCRF. Significant findings made after enrollment that meet the definition of an AE must be recorded on the AEs eCRF.

12.1.2. Vital Signs

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

Patients will be carefully monitored after the first dose of investigational drug with a 6-hour post-dose monitoring period of hourly recording of pulse and blood pressure as described in Section 12.1.9.

12.1.3. Electrocardiogram

The 12-lead digital ECG devices will be provided to each clinical site by the central ECG laboratory for the duration of the trial. Detailed instructions describing the process for recording and transmission of the digital ECGs will be outlined in the trial-specific manual and provided to the site before the start of the trial. Paper versions of ECG tracings recorded at the times specified in the schedule of assessments (Section 7.3, Table 2, and Table 3) will be printed and photocopied to preserve the ink if necessary, and kept at the site as source documentation.

ECG will be performed after the patient has been resting quietly in a supine position. The screening ECG report from the central reader must be available to confirm patient eligibility before enrollment. Electrocardiograms will be performed on Day 1 for all patients while in the clinic before the first dose of investigational drug administration and after the 6-hour post-dose vital signs assessment. The 6-hour post-dose ECG will be evaluated by the treating physician, with input if needed from a local cardiologist or a central reader to confirm if extended monitoring is required. Additional ECG monitoring will be performed on Days 5 and 8 if cardiac issues are identified on the prior day of dose escalation, as described in Section 12.1.9.

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

12.1.4. Ophthalmological Examination

An OCT will be performed as scheduled in Table 2 and Table 3. If there is a suspicion of new onset or worsening macular edema, then general retinal examinations, including eye history, visual acuity, and dilated ophthalmoscopy will be obtained. A general ophthalmologist can do the examination, although a retinal specialist would be preferred to do the examinations wherever possible.

12.1.5. Pulmonary Function Tests

Pulmonary function tests including forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) will be performed as scheduled in Table 2 and Table 3. In addition, diffusion capacity of carbon monoxide (DLCO) measurements will be performed where locally available. DLCO will not be required at sites where there is no local testing facility. These tests will be performed at a qualified pulmonary function laboratory or respiratory department. Refer to the American Thoracic Society/European Respiratory Society guidelines for standardization of spirometry and single breath determination of carbon monoxide uptake in the lung (MacIntyre 2005; Miller 2005a; Miller 2005b).

12.1.6. Height and Weight

Height will be measured at Screening only; weight will be measured at each visit.

12.1.7. Monitoring of Adverse Events and Serious Adverse Events

Throughout the course of the trial, every effort must be made to remain alert to possible AEs or SAEs. Refer to Section 12.2 for definitions of AEs/SAEs, monitoring and reporting. Refer to Section 12.2.7 for AEs of special interest.

12.1.8. Monitoring of Concomitant Therapy

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

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

On Day 1 of treatment for Induction, careful cardiac monitoring of the patients is required. The Investigator is responsible for monitoring the patient following the first intake of the investigational drug, as well as managing bradycardia symptoms should they occur. The Investigator must review the baseline pre-dose ECG, pulse, and blood pressure during the 6-hour monitoring period, post-dose ECG, and assess discharge status at the time specified in Table 2. Baseline pre-dose ECG should be provided by the site and be available for comparison to the post-dose ECG in order to determine if criteria requiring extended monitoring are met.

Resting pulse and blood pressure in the sitting position will be measured at the times specified in Table 2 (by the Investigator, an assisting nurse, or other medically qualified staff member). When obtaining the pulse and blood pressure before the first dose, the patient should be allowed to rest in a seated position at least 10 minutes before taking measurements. The pulse and sitting blood pressure measurements should be repeated 2 additional times (before the first dose of investigational drug only). The lowest pre-dose value of sitting pulse and blood pressure (based on systolic blood pressure) will be recorded in the case report form and serve as baseline for

comparison to post-dose values. The repeat measurements will be made at approximately 2-minute intervals. For the hourly measurements after investigational drug administration, pulse and sitting blood pressure will be measured once and recorded in the eCRF.

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

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

1. The pulse 6 hours post-dose is < 45 bpm
2. The pulse 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum PD effect on the heart may not yet have occurred)
3. The ECG 6 hours post-dose shows new onset second degree or higher AV block
4. The ECG 6 hours post-dose shows a prolonged QTcF interval (> 450 msec for males, > 470 msec for females)

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

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

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

12.1.10. Clinical Laboratory Evaluations

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

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

- Hematology - RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, mean platelet volume, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Total WBC and all differential WBC counts will be provided to the site in this open-label trial.

  During the treatment period, WBC differential results will be available to the Investigator. Reductions in ALC levels is a known pharmacodynamic effect of RPC1063. If any of the following results are observed, the Investigator will be asked to repeat the laboratory tests within approximately 7 days:

  – Absolute neutrophil count [ANC] < 1000 cells/µL

  – Absolute lymphocyte count [ALC] < 200 cells/µL

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

  If the ALC is confirmed below the 200 cells/µL, 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, treatment may be reinitated at Investigator's discretion (Section 9.1.1 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.

- Chemistry

  – Full chemistry panel at Screening: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, HDL and LDL, C-reactive protein.

  – All other visits - blood urea nitrogen, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, amylase, total bilirubin, conjugated bilirubin, C-reactive protein

- Urinalysis - leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, urobilinogen, urine color and appearance, and nitrate and leukocyte esterase

- The central laboratory will analyze routine blood samples. Details regarding collection of samples, shipment of samples, reporting of results, laboratory reference ranges, and alerting abnormal values will be supplied to the site before site initiation in a trial laboratory manual. The results of the analysis will be made available to each site by the central laboratory.

- Investigators will be asked to comment on those abnormalities on the respective laboratory result page, including a notation of the clinical significance of each

abnormal finding in the patient's source documents. The laboratory sheets will be filed with the patient's source documents.

- Pregnancy test: serum 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.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, which that does not necessarily have a causal relationship with the investigational treatment. 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 (ICH E2A, II.A.1).

AEs will be monitored throughout the entire trial 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 trial 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.

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

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

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

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

12.2.2. Definition of Serious Adverse Events

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

- Results in death
- Is life-threatening

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

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

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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

12.2.3. Assessment of Adverse Event Severity

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

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

12.2.4. Assessment of Adverse Event Relationship to Investigational Drug

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

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

Unrelated: those AEs which are clearly and incontrovertibly due to extraneous causes (concurrent drugs, environment, etc) and do not meet the criteria for drug relationship listed under Unlikely, Possible, Probable, or Related.

Unlikely: An AE may be considered unlikely if it includes at least the first two features:

- It does not follow a reasonable temporal sequence from administration of the drug
- It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient

- It does not follow a known pattern to the suspected drug
- It does not reappear or worsen when the drug is re-administered

Possible: An AE may be considered possible if it includes at least the first two features:

- It follows a reasonable temporal sequence from administration of the drug
- It could readily have been produced by the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient
- It follows a known response pattern to the suspected drug

Probable: An AE may be considered probable if it includes at least the first three features:

- It follows a reasonable temporal sequence from administration of the drug
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient
- It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug (eg, bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc)
- It follows a known pattern of response to the suspected drug

Related: An AE may be considered related if it includes all of the following features:

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

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

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

12.2.5. Reporting of Serious Adverse Events

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

The Investigator will report any SAE that occurs to any patient from the time written informed consent is signed through the last visit. All SAEs that occur within 90 days of the last dose of treatment with the investigational drug, whether or not considered related to the investigational

product, must also be reported. Any SAE that is ongoing when the patient completes the trial or discontinues from the trial will be followed by the Investigator until the event has resolved, stabilized, or returned to Baseline status.

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

The SAE hotline numbers are as follows:

[redacted]

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

12.2.6. Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

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

12.2.7. Adverse Events of Special Interest

Adverse events (AEs) of special interest include bradycardia, heart conduction abnormalities (2nd degree and higher AV block), macular edema, malignancy, serious or opportunistic infection, pulmonary effects, and hepatic effects.

Special considerations regarding monitoring for these events are as follows:

- Bradycardia and heart conduction abnormalities (eg, symptomatic bradycardia, 2nd degree AV block, QT prolongation):
  - Patients will be closely monitored in the clinic after their first dose of the initial dose escalation regimen for a period of 6 hours after treatment. Electrocardiograms will occur pre-dose and at Hour 6 following dosing, with more frequent assessments if clinically indicated. Resting pulse and blood pressure in the sitting position will be assessed pre-dose and then hourly for 6 hours following dosing. See the monitoring guidelines in Section 12.1.9 for further details.
  - Investigators should be particularly mindful of patients who have a pulse rate < 55 bpm prior to administration of the investigational drug. Dose should be withheld for patients who have a pulse rate of <55 bpm prior to administration of investigational drug. Atropine IV is recommended as the first line treatment of

bradycardia, up to a maximum daily dose of 3 mg. In general, the common guidelines for treatment of bradycardia (eg, Advanced Cardiac Life Support guidelines) should be followed as appropriate.

- Patients should be discontinued from participation in the trial if any of the below are present:
  - Mobitz type II 2nd degree AV block **or**
  - 3rd degree AV block **or**
  - Symptomatic bradycardia that is non-responsive to intervention (e.g., atropine or isoproterenol) and lasting ≥ 24 hours (i.e., across the entire dosing interval)

- Pulmonary effects
  - Any condition that might affect the outcome of pulmonary function testing including infection, respiratory symptoms, occupational exposures (including asbestos) and cigarette smoking needs to be collected before PFT testing and transcribed to the pulmonary function tests eCRF page. If patients have decline in PFT values (FEV1 and/or FVC) below 50% of the predicted values, treatment should be discontinued. If a patient discontinues due to respiratory AE, the Investigator should ensure that the patient has adequate evaluations as clinically indicated by a pulmonologist (consider PFTs, chest X-ray or high resolution computed tomography, based on findings of the other exams) at the time of the AE. For patients with pulmonary nodules, lung biopsy should be considered (Cryptococcus pneumonia and pulmonary TB have been reported with fingolimod). Further evaluations will be conducted until such time as resolution is confirmed or no further improvement is expected by the Investigator (based on a follow-up period of not less than 3 months).

- Hepatic effects
  - If patients have elevations in the LFTs (ALT or/and AST) ≥3x 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.
  - 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, or right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

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.

– Evaluation of alternative causes for the liver test abnormalities could include any of the following:
  - Acute viral hepatitis
  - Alcoholic or autoimmune hepatitis
  - Hepatobiliary disorders
  - NASH
  - Cardiovascular causes
  - Concomitant treatments

- Macular edema
  – For patients with abnormal OCT findings or with visual signs or symptoms of new onset or worsening macular edema that develop following initiation of treatment, a general ophthalmologic examination including eye history, visual acuity, and dilated ophthalmoscopy will also be performed
  – Investigational drug must be discontinued in any patient who has a confirmed diagnosis of clinically significant macular edema that is of new onset or worsened since baseline
  – Patients with a diagnosis of macular edema must be followed up monthly and more frequently if needed based on the ophthalmologist's judgment
- Malignancies
  – Because RPC1063 is an immunomodulator, patients should be carefully monitored for infections and malignancies (including dermatologic malignancy)
  – The treating Investigator will complete a dermatological examination for monitoring of the potential development of new cutaneous malignancies during the trial. Patients with any suspicious finding noted during the examination will be referred to an appropriately qualified dermatologist for evaluation and treatment, if warranted
- Serious or opportunistic infections
  – TB, serious bacterial infections, systemic fungal infections, viral infections such as herpes infections (including herpes zoster and disseminated herpes simplex) and protozoan infections should be reported as AEs

- During the treatment period if a serious infection or a serious opportunistic infection is identified, investigational drug should be suspended until the patient has received appropriate treatment and has had resolution of the infection. Investigational drug can be restarted at the Investigator's discretion after assessment of the patient's clinical status (See Section 9.1.1 for instructions on resuming treatment after missing doses)
- Patients withdrawn from the trial as a result of the above will be followed until lymphocyte levels return to the patient's pre-treatment baseline or to the central laboratory's Lower Limit of Normal, whichever is lower

12.2.8. Monitoring of Patients with Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

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

12.2.9. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) for the trial will at a minimum perform quarterly safety reviews starting after the first patient is dosed.

12.2.10. Treatment of Overdose of Investigational Drug

An overdose is any dose of investigational drug given to a patient or taken by a patient that exceeds the dose described in the protocol. There is no information regarding overdose with RPC1063. Any overdose, with or without associated AEs, must be promptly reported to the CRO's Medical Monitor or other designated Drug Safety Center. Overdoses do not need to be recorded as AEs in the eCRF; only in the case of any AEs associated with the overdose should these be reported on relevant AE/SAE sections in the eCRF.

12.2.11. 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 trial.

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

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

13. PLANNED STATISTICAL METHODS

13.1. Determination of Sample Size

Induction:

The sample size of 60 patients has been chosen to enable estimates of response and remission rates with reasonable precision. Assuming a remission rate of 15% and a response rate of 30%, it is estimated that the confidence interval (half-widths of the 95% CI) around the proportion of patients in response and remission will be 12.8% and 16.4% for 30 patients and 9.0% and 11.6% for 60 patients.

13.2. Statistical Methods

13.2.1. General Considerations

All efficacy and safety data will be listed by patient and summarized. Baseline is defined as the last observed measurement prior to the Induction Period Day 1 receipt of investigational drug.

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

There will be no imputation for missing efficacy or safety observations

13.2.2. Analysis Populations

All patient populations will be defined and documented prior to database lock. Due to the open-label, non-randomized nature of the trial design, the intent-to-treat (ITT) and safety populations will be the same: all enrolled patients who receive at least one dose of RPC1063. These populations will be used as the primary populations for all efficacy and safety parameters.

13.3. Disposition, Demographics and Baseline Characteristics

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

Baseline characteristics will be summarized for and will include age at CD symptom onset, age at CD diagnosis, years since CD symptom onset, years since CD diagnosis, baseline CDAI score, baseline SES-CD score, baseline PRO2 score, prior anti-TNF use, and prior corticosteroid use.

Compliance with investigational drug will be summarized and will include the number of patients estimated to be < 80% compliant, 80 to 100% compliant, and > 100% compliant. The total dose and average daily dose will also be summarized.

13.4. Induction and Extension Efficacy

As there are no hypothesis tests on the data collected in this trial, all efficacy endpoints will be reported using descriptive statistics. Proportions of patients in response and proportions of patients in remission will include 95% confidence intervals.

13.5. Safety Analyses

Adverse events will be monitored during the trial and the data analyzed with respect to incidence as well as severity and potential relationship of the AEs to investigational drug. Adverse events with onset on, or after the first dose of investigational drug or with onset prior to the first dose of investigational drug that increase in severity on, or after the first dose of investigational drug will be considered treatment-emergent. All treatment-emergent AEs will be coded and tabulated by system organ class and preferred term. Incidence of AEs, SAEs, AEs of special interest, and AEs leading to discontinuation will be summarized and presented in descending order of frequency.

Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual patient values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from baseline will be produced. The change from baseline for each of the vital signs and ECG parameters will be summarized. Incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

13.6. Pharmacokinetic Analyses

[redacted]

13.7. Interim Analyses

No formal interim analysis is planned.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Monitoring

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

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

14.2. Data Management/Coding

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

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

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

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

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

14.3. Quality Assurance and Inspections

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Study Monitor and Source Data Verification

According to the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

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

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

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

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

15.2. Product Quality Complaint

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

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

16. ETHICS

16.1. Institutional Review Board or Independent Ethics Committee

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

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

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

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

16.2. Ethical Conduct of the Trial

This trial will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (48th General Assembly, Somerset West, Republic of South Africa, October 2008 [or current version]), the applicable guidelines for Good Clinical Practice (GCP; CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the trial will be conducted.

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

16.3. Patient Information and Consent

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

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

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

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

16.4. Patient Data Protection

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

16.5. Investigator Obligations

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

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

16.6. Protocol Signatures

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

17. DATA HANDLING AND RECORD KEEPING

17.1. Inspection of Records

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

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

17.2. Retention of Records

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

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

18. PUBLICATION POLICY, FINANCING, AND INSURANCE

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

[redacted]

20. APPENDIX: INVESTIGATOR SIGNATURE

PROTOCOL TITLE: A Phase 2, Multi-Center, Open-Label Induction Trial with Extension Period to Assess Endoscopic Improvement and Changes in Intestinal and Serum Biomarkers in Patients with Moderately to Severely Active Crohn's Disease Receiving Oral RPC1063 as Induction Therapy

PROTOCOL NO: RPC01-2201

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

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

This document summarizes the changes to Protocol RPC01-2201 from Version 4.0 (dated 29 May 2018) to Version 5.0 (dated 24 May 2019).

21. OVERVIEW OF KEY CHANGES

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

- New contact information
- Change to safety follow up from 75 days to 90-day (±10 days) Safety Follow-up Visit to ensure adequate collection of adverse events that could be associated with investigational drug. The timing of the visit is based on the estimated time needed to clear the major active metabolites of RPC1063 in the vast majority of patients (ie, 5 half-lives of CC112273 and CC1084037 and accounting for variation of half-life duration in a human population).
- Extended requirements for contraception in females after treatment discontinuation from the 75-day Safety Follow-up Visit to the 90-day Safety Follow-up Visit.
- Updated description of RPC1063 to include major active metabolite CC1084037compound background

22. DETAILS OF CHANGES FROM THE PRIOR PROTOCOL VERSION

For each change to the protocol text, Table 9 provides the location of the change, the original text, the revised text, and the rationale for the change. Minor editorial changes are not identified.

Table 9: Specific Changes to Protocol RPC01-2201 from Version 4.0 (29 May 2018) to Version 5.0 (24 May 2019)

Protocol Section(s)	Original Text	Revised Text or New Text	Rationale
Protocol Synopsis, Section 7, Table 2, Section 8, Section 9, Section 12,	75-day Safety Follow-up Visit	90-day Safety Follow-up Visit	[redacted]
Title Page	[redacted]	[redacted]	
Signature Page	[redacted]	[redacted]	

Protocol Section(s)	Original Text	Revised Text or New Text	Rationale
Section 5.2 RPC1063	RPC1063 is a small molecule compound that selectively and potently activates the sphingosine 1-phosphate 1 receptor ($S1P_1$) and $S1P_5$ receptor ($S1P_5$), although it is more selective towards $S1P_1$ over $S1P_5$. In vitro, RPC1063 has little activity on the other S1P receptors, showing half maximal effective concentration (EC_{50}) > 10,000 nM for S1P2, > 5000 nM for $S1P_3$, and > 2000 nM for $S1P_4$. RPC1063 is extensively metabolized in humans with up to 13 metabolites identified in plasma, urine, and feces, including 1 major active metabolite (CC112273) in plasma. The RPC1063 metabolites, CC112273, RP101988, RP101075, and RP101442, show a similar potency and selectivity profile to RPC1063.	RPC1063(ozanimod) is a sphingosine 1-phosphate receptor modulator, which binds with high affinity selectively to sphingosine 1-phosphate receptor subtypes 1 and 5. RPC1063 causes lymphocyte retention in lymphoid tissues. The mechanism by which RPC1063 exerts therapeutic effects in CD (Crohn's disease) is unknown but may involve the reduction of lymphocyte migration into the central nervous system. RPC1063 is 10-fold more selective for $S1P_1$ relative to $S1P_5$ and has little activity on other S1P receptors ($S1P_2$, $S1P_3$, and $S1P_4$). RPC1063 is extensively metabolized in humans to form a number of circulating active metabolites. In vitro, RPC1063 and its active metabolites demonstrated similar activity and selectivity for $S1P_1$ and $S1P_5$. In humans, approximately 94% of circulating total active drug exposure is represented by RPC1063 (6%), CC112273 (73%), and CC1084037 (15%).	[redacted]
Protocol Synopsis, Table 2, Section 8.1		Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for female subjects of childbearing potential. The Investigator will educate all FCBP about the different options of contraceptive methods or abstinence as appropriate. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).	[redacted]

Protocol Section(s)	Original Text	Revised Text or New Text	Rationale
Protocol Synopsis, Section 8.1	Male patients: Must agree to use a latex condom during sexual contact with women of childbearing potential while participating in the study until completion of the 75-day Safety Follow-up Visit.	Removed text	[redacted]
Protocol Synopsis, Section 8.1	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	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 •complete sexual abstinence	[redacted]