STATISTICAL ANALYSIS PLAN

Title: A Phase 2, multi-center, randomized, double-blind, placebo-controlled parallel-group study to evaluate the clinical efficacy and safety of induction therapy with RPC1063 in patients with moderately to severely active ulcerative colitis

Protocol: RPC01-202

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LIST OF ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte count
ANCOVA	analysis of covariance
BP	blood pressure (systolic/diastolic)
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRO	clinical research organization
CSR	clinical study report
DBP	diastolic blood pressure
DLCO	Diffusing capacity of the lung for carbon monoxide
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
FEV_1	forced expiratory volume at 1 second
FVC	forced vital capacity
HBcAg	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotrophin
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IP	Induction Period
ITT	intent-to-treat
IV	intravenous/ly
IVRS	interactive voice response system
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MITT	modified intent-to-treat
MP	Maintenance Period
OCT	optical coherence tomography
OLP	Open-Label Period
PD	pharmacodynamic(s)
PFTs	pulmonary function tests (includes FEV_1, FVC, DLCO)
PK	pharmacokinetic(s)
PP	per protocol
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan

SBP	systolic blood pressure
SD	standard deviation
UC	ulcerative colitis
ULN	upper limit of normal
VZV	varicella zoster virus
WBC	white blood cell
WOCBP	women of child bearing potential

1. INTRODUCTION

[redacted] 2014

- ICH Guidance on Statistical Principles for Clinical Trials (E9)

2. PURPOSE OF ANALYSES

[redacted] analysis plan will be developed to guide analyses of heart rate data collected from the Holter monitors.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

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

3.1.2. Secondary Objectives

The secondary objectives are to:

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

3.1.3. Exploratory Objectives

[redacted]

[redacted]

3.2. Endpoints

3.2.1. Efficacy Endpoints

Primary Efficacy Endpoint:

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

Key Secondary Efficacy Endpoints (rank ordered):

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

Other Secondary Efficacy Endpoints:

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

[redacted]

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

3.2.2. Safety Endpoints

- The incidence and type of Adverse Events (AEs), Serious Adverse Events (SAEs), AEs leading to discontinuation of study treatment, target AEs of special interest, laboratory abnormalities, vital signs, electrocardiograms (ECG), and physical exam abnormalities

3.2.3. PK and PD Endpoints

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

4. STUDY DESIGN

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

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

The study will include both patients that have received anti-TNF therapy and those that have not. It is anticipated that approximately 50% of the patients included in the study will have received anti-TNF therapy.

The study design is shown in Figure 1.

Induction Period (IP)

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

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

- RPC1063 0.5 mg oral capsule daily
- RPC1063 1.0 mg oral capsule daily
- Placebo oral capsule daily

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

For patients randomized to one of the active treatment groups, there will be an 8 day dose titration regimen in the IP consisting of 4 days of treatment with RPC1063 0.25 mg, followed by 3 days treatment with RPC1063 0.5 mg, followed by the assigned treatment level for approximately 8 weeks.

Maintenance Period (MP)

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

the MP will occur at Week 32. Patients who complete the MP will be given the option to participate in the OLP. Patients that enter the MP and experience disease relapse will have the option to enter the OLP.

Optional Open-Label Treatment Period (OLP)

Patients who complete the IP and are non-responders at Week 8 and those that complete the MP or experience disease relapse during the MP will have the option to enter the OLP. All patients in the OLP will receive daily study treatment with RPC1063 1.0 mg. There will be an 8 day dose titration regimen consisting of 4 days of treatment with 0.25 mg RPC1063, followed by 3 days treatment with RPC1063 0.5 mg, followed by RPC1063 1.0 mg. Patients who are non-responders 8 weeks after initiation of the OLP should discontinue from the study. The OLP will continue until the last patient who enters the OLP portion of the study has completed 20 weeks of treatment in the OLP.

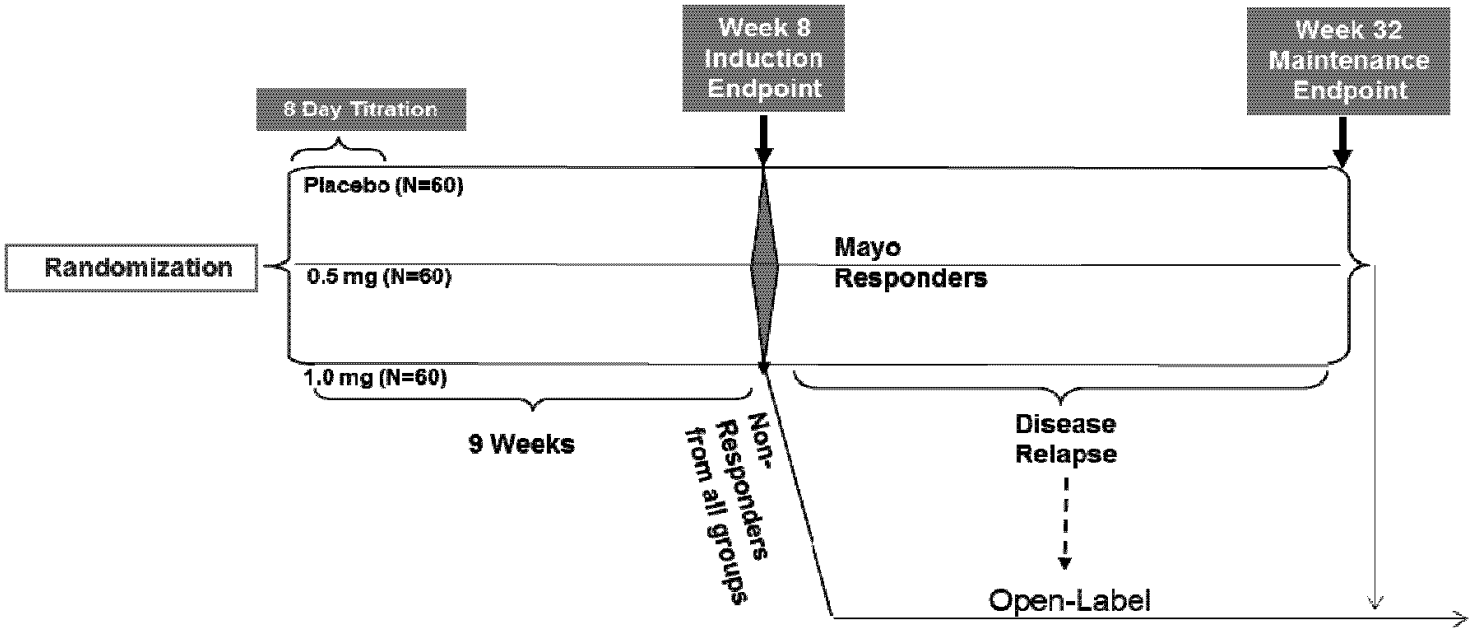
Safety Monitoring/Follow-up

Potential adverse events (AEs) of interest that may be a consequence of sphingosine 1-phosphate 1 receptor 1 (S1P1R) modulation will be closely monitored during the study. These AEs include bradycardia and heart conduction abnormalities, pulmonary toxicity, macular edema, cutaneous malignancy, serious or opportunistic infection and hepatotoxicity. A Data Monitoring Committee (DMC) for the study will perform safety reviews periodically, approximately four times a year.

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

Patients who discontinue from treatment due to lack of response, AEs, or other reasons, even if alternative treatment is given, will be followed for 30 days for collection of safety data, including lymphocyte recovery, and for the assessment of their disease status.

Figure 1: Study Schematic



5. DEFINITIONS

5.1. Time Point Definitions

Study Day for Induction and Maintenance Periods

All visit data will be assigned a study day, from the Visit 1 in the Induction Period according to the following rules:

- Visit 1 Day will be designated as Day 1
- All other days after Day 1: Study Day = (Visit Date – Visit 1 Date + 1)
- All other days before Day 1: Study Day = (Visit Date – Visit 1 Date)

Study days for evaluations occurring during the Screening visit will be negative numbers (e.g., "–7"), no Day 0 is defined for this study.

Study Day for the Open Label Period

All visit data will be assigned a study day, from the Visit 1 in the Open Label Period according to the following rules:

- OLP Day 1 will be designated as Day 1
- All other days after OLP Day 1: Open Label Day = (Visit Date – Open Label Visit 1 Date + 1)
- All other days before OLP Day 1: Open Label Day = (Visit Date – Open Label Visit 1 Date)

Baseline Measurement

There will be two baseline definitions:

Baseline: The latest assessments completed prior to initial study drug administration will be used as the Baseline measurement for all analyses for the IP and MP. It will also be used as the Baseline measurement for efficacy analyses for the OLP.

Treatment Baseline: The last assessment prior to initial administration of RPC1063 will be used as the Baseline measurement for safety analyses for the OLP.

Visits

Visits identifiers on the study electronic case report forms (eCRFs) will be used.

5.2. Efficacy Assessments

5.2.1. Flexible Sigmoidoscopy/Colonoscopy

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

5.2.2. Mayo Score

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

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

1. Stool frequency[a]
   - 0 = Normal number of stools for this patient
   - 1 = 1 to 2 stools more than normal
   - 2 = 3 to 4 stools more than normal
   - 3 = 5 or more stools more than normal
2. Rectal bleeding[b]
   - 0 = No blood seen
   - 1 = Streaks of blood with stool less than half the time
   - 2 = Obvious blood with stool most of the time
   - 3 = Blood alone passes
3. Findings on endoscopy
   - 0 = Normal or inactive disease
   - 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
   - 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
   - 3 = Severe disease (spontaneous bleeding, ulceration)
4. Physician's global assessment[c]
   - 0 = Normal
   - 1 = Mild disease
   - 2 = Moderate disease
   - 3 = Severe disease

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

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

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

The Mayo score will be derived at all visits when an endoscopy is performed. For these visits, the Mayo score will be derived using the endoscopy subscore and the non-endoscopy subscores performed at the same nominal visits, even if the assessments have different dates. The baseline Mayo score will be derived from the most recent endoscopy subscore (Item 3) completed during Screening and the last non-missing non-endoscopy subscores (i.e., Items 1, 2, and 4) prior to initial study drug administration.

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

Mayo scores are calculated using:

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

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

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

Using the full Mayo score:

Clinical Remission is defined as a Mayo score of ≤ 2 points and no individual subscore > 1 point

Clinical Response is defined when all of the following criteria are met:

- Reduction in Mayo score of ≥ 3 points
- Reduction in Mayo score of ≥ 30%
- Reduction in Rectal Bleeding subscore of ≥ 1 point OR a Rectal Bleeding subscore of ≤ 1 point

Mucosal Healing is defined as an Endoscopic subscore of ≤ 1 point

Using the partial Mayo score:

Clinical Remission is defined as a partial Mayo score of ≤ 2 points and no individual subscore > 1 point

Clinical Response is defined when all of the following criteria are met:

- Reduction in partial Mayo score of ≥ 2 points
- Reduction in partial Mayo score of ≥ 30%
- Reduction in Rectal Bleeding subscore of ≥ 1 point OR a Rectal Bleeding subscore of ≤ 1 point

5.3. Safety Definitions

AE or SAE Onset Date

AE and SAE onset or start dates are reported in the AE eCRFs.

AE or SAE End Date

AE and SAE end dates are reported in the AE eCRFs.

AEs and SAEs

AEs will be recorded from the time written informed consent is signed through the Follow-up visit (last dose + 30 days).

An AE or SAE will be regarded as treatment-emergent if it has a start date during or after the first study drug administration or if it worsened or if the relationship to study drug changed from unrelated to related after the first study drug administration. UC disease relapse and related symptoms will be monitored as study endpoints, but will not be recorded as AEs unless they meet the definition of an SAE.

All AEs or SAEs meeting these criteria with a start date up to and including 30 days following the last dose of treatment with the study drug will be considered treatment-emergent.

Treatment Related AEs

For summary purposes, all AEs classified by the Investigator on the AE eCRF as “possible”, “probable” or “related” will be considered treatment related AEs. If the relationship to study drug is unknown or missing, the AE will be considered to be treatment related.

Duration of AEs

The duration of an AE will be calculated as:

Duration = (AE End Date – AE Onset Date) + 1

5.4. Other Definitions

Age

Age (in years) will be calculated from the date of birth to the date of informed consent. Age will be reported as an integer.

Study Drug

Study drug refers to RPC1063 0.5 mg, RPC1063 1.0 mg, or Placebo oral capsules as well as the titration doses.

6. STATISTICAL METHODS

This section presents the statistical approaches that are anticipated for the analysis of study data. These approaches may at times require modifications due to unanticipated features of the data. Any modifications that are not in the final SAP are considered to be post-hoc and will be detailed in the CSR.

6.1. General Analysis Approach

Unless otherwise noted, all summaries of data by treatment group during the IP/MP and the OLP will include the following three groups:

1) Placebo
2) RPC1063 0.5 mg
3) RPC1063 1.0 mg

The following conventions will be used for all data presentations and analyses unless otherwise specified.

- Appropriate descriptive statistics will be computed and displayed (by time point and other key variables as appropriate) for both continuous and categorical variables. For continuous variables, descriptive statistics will include n (the number of patients with non-missing data), mean, standard deviation (SD), median, and minimum and maximum values. For categorical data, the number and percentage of patients within each category will be presented. The denominator for percentages will be based on the number of patients with non-missing data appropriate for summary purposes. Unless otherwise noted, all percentages will be presented to one decimal place.
- Individual data listings of all data represented on the eCRF and from the clinical laboratory will be presented. Sort order for data listings will be treatment, site-patient number, visit, and assessment period where appropriate.
- Version 9.1 (or higher) of the SAS® statistical software package will be used to provide all tables, figures, data listings, and analyses.

- There are approximately 70 study sites in this study. Due to the large number of study sites and the small numbers of patients per site, the analysis of efficacy endpoints will not include adjustments for study site.

Further analysis and reporting conventions are described in Section 7.

6.2. Coding Dictionaries

Adverse events will be coded using version 15.0 or later of the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary, Enhanced, September 1, 2012 or later.

6.3. Data Management

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

6.4. Missing values

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

For calculation of the Mayo score for the efficacy endpoints, at least 2 of the 4 subscores must be available to calculate the total Mayo score. A missing subscore(s) will be carried forward from the most recent previous visit for which the subscore is available. The endoscopy subscore is not considered missing if the Investigator endoscopic subscore is available. If more than 2 subscores are missing, then the Mayo score will be considered missing.

For calculation of the partial Mayo score for the efficacy endpoints, at least 2 of the 3 subscores must be available to calculate the partial Mayo score. The missing subscore will be carried forward from the previous visit. If more than 1 subscore is missing, then the partial Mayo score will be considered missing.

For the primary analysis, as well as for the analyses of all key secondary efficacy endpoints that are defined as proportions, patients who have missing Mayo or partial Mayo scores at the specified time point will be classified as nonresponders.

One of the key secondary efficacy endpoints (change in Mayo score) is a quantitative endpoint. For the key secondary analysis of this variable, missing values will be replaced by the last observation carried forward (LOCF). If no post-Baseline observation is available to carry forward, then the average score for the observed values within the same treatment group will be used, rounded to the nearest integer.

6.5. Sample Size

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

The sample size is justified with respect to the comparison of remission rates at the end of the IP between an RPC1063 group and the placebo group. Based on the use of a two-sided test at the alpha=0.05 level of

significance, and assuming a placebo remission rate of 10%, a sample size of 60 patients per group will provide 80% power to detect an improvement in the remission rate of 21 percentage points or larger (i.e., an active group remission rate of 31% or larger).

6.6. Study Blinding, Patient Identification and Replacement of Patients

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

Patients will be assigned a unique patient number and will only be identified by their patient number and their initials on all study documentation.

Patients who discontinue from the study following randomization will not be replaced.

6.7. Enrollment and Randomization Procedures

A patient is considered enrolled in the study when the informed consent form is signed at the screening visit.

Patients will be randomized into the study on Day 1 using the IVRS system.

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

6.8. Analysis Populations

The following analysis populations will be used in the statistical analysis. Analysis population membership will be determined prior to unblinding.

Intent-to-Treat (ITT) Population: The ITT population will consist of all randomized patients who received at least 1 dose of study treatment, with treatment assignment designated according to randomized treatment. This will be the primary population for the analysis of efficacy endpoints.

Per Protocol (PP) Population: The PP population will consist of the subset of the ITT population, excluding those patients who have had a major protocol violation. Major protocol violations will include all violations that would significantly impact assessment of safety and efficacy of the compound and will be finalized in advance of data lock and primary analyses. Violation of any of the following three inclusion criteria related to UC specific disease activity would exclude a patient from the PP population:

- Must have a confirmed diagnosis of UC by endoscopic and histologic evidence
- Must have a baseline Mayo score of 6-12 inclusive with endoscopic subscore of >=2
- Must have a baseline endoscopy with >= 15 cm involvement

Poor study drug compliance will also exclude the patient from the PP population. Poor study drug compliance is defined as taking less than 80% or more than 120% of study treatment during the entire treatment period.

The patients excluded from the PP population will be fully defined and documented with reasons for exclusion prior to database lock.

Safety Population: The Safety population will consist of all patients receiving any study treatment. All patients in the Safety population will be analyzed according to the highest dose of RPC1063 actually received and not according to the treatment they are randomized to receive, in the event there is a discrepancy.

6.9. DMC

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

The committee will meet periodically, approximately four times a year during the study, to review unblinded aggregate analyses by treatment group concerning enrollment, treatment compliance, adherence to follow-up schedule, and safety data from the trial. The DMC may recommend modifying or stopping the trial early due to safety concerns based on data reviews. The DMC will also review the Primary Endpoint (Week 8 Induction) and make recommendations taking into account both the efficacy results and the safety profile.

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

6.10. Final Analyses and Reporting

The primary analysis will be carried out when all patients have completed (or would have been eligible to complete) the IP of the study. The randomized treatment groups will be unblinded for both the IP and MP for the primary analysis. At the time of the primary analysis, the database will be locked for all visits through Week 8 and the available Mayo score data will be cleaned for all visits beyond Week 8. Data will continue to accrue for the MP and OLP visits. For this primary analysis, the safety analyses will be summarized for the IP only.

Final database lock will occur when all patients have completed the study and all data during the assessment periods has been monitored. In addition, no database may be locked, randomization code unblinded, or analyses completed (other than analyses for the DMC) until this SAP has been approved. All analyses outlined in the protocol and in this SAP (other than analyses conducted for the DMC) will be carried out after:

- The SAP has been approved
- All analysis populations are determined

Further exploratory analyses not necessarily identified in this SAP may be performed to support the CSR. Any post-hoc or unplanned analyses performed and not identified in this SAP will be clearly identified in the CSR.

6.11. Patient Disposition

The number and percentage of patients who signed the informed consent form, who were randomized, in each analysis population, who completed the study, who completed the IP, MP, and OLP will be summarized by treatment group. The number and percentage of patients who withdrew from the study and their reasons for withdrawal in each period will be tabulated by treatment group. All percentages will be based on the number of subjects in the ITT population. Disposition data will also be presented in a listing.

6.12. Demographics and Baseline Characteristics

The demographics and baseline characteristics will be presented in a table. The demographic characteristics consist of age, age category, sex, race, ethnicity, weight, height, body mass index (BMI), smoking history, and stratification factors. Age, weight, height, BMI, years as a smoker, and numbers of cigarettes, cigars, and pipes smoked per week will be summarized using the descriptive statistics. The number and percentage of patients in each age category (18-29, 30-39, 40-49, 50-59, 60-69, and 70-75, and < median, ≥ median) and in each race category (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other) will be reported. The number and percentage of patients who have ever smoked, are current smokers, and who smoke each type of tobacco product will be reported. The summaries will be presented for the ITT population. Listings will be provided for demographic and baseline characteristic data.

6.13. General Medical History

Medical history information will be collected at the Screening Visit and on Day 1 (Visit 1).

Medical history will be summarized for the ITT population and will display the number and percentages of subjects with a significant history for each body system. Significant medical history included specific details will also be listed

6.14. Ulcerative Colitis Disease History

The following UC disease history parameters will be summarized using descriptive statistics:

- Age at UC diagnosis
- Years since UC diagnosis
- Mayo score at Baseline (using the central endoscopy score)
- Mayo score subgroup proportions using the central endoscopy score (< 8 vs. ≥ 8)
- Mayo score at Baseline (using the investigator endoscopy score)
- Mayo component scores at Baseline (stool frequency, rectal bleeding, physician's global assessment, investigator endoscopy score, central endoscopy score)
- Extent of disease (limited to left side of colon or extensive).

For partial UC diagnosis dates, the following imputation methods will be applied:

- If month and year are present but day is missing, then the day will be set to the 15th
- If year is present but not month and day, month and day will be set to July 1st
- If either imputation above results is a date >= the date of informed consent, then impute the date as informed consent date – 1.

UC disease history will also be listed.

6.15. Protocol Deviations

Deviations and violations from the protocol will be recorded appropriately. If a patient was allowed to continue in the study, this will be recorded. According to the recommendations in the ICH guidelines, the protocol deviations will be classified into, but not necessarily limited to, the following categories:

- Inclusion/exclusion criteria deviation
- Prohibited medication use
- Incorrect treatment or dose
- Treatment non-compliance
- Procedure non-compliance
- Safety observation

Classification of deviations as major protocol violations, and decisions regarding exclusion of patients and/or patient data from the statistical analyses, will be decided on a case-by-case basis without knowledge of the treatment assigned and before database lock by the project statistician with input from the clinical study team. All protocol deviations will be presented in a summary table by protocol deviation category and treatment. Major protocol violations will be summarized separately. A listing of protocol deviations will also be presented that identifies those patients excluded from analyses.

6.16. Dosing Compliance

6.17. Treatment Compliance

[redacted]

6.18. Prior and Concomitant Medications

All treatments being taken by the subjects on entry to the study or at any time during the study in addition

[redacted]

6.19. Efficacy Analyses

Analysis of all efficacy endpoints will primarily be based on the ITT population with treatment failure rules applied. Patients will be considered to have failed treatment if they have protocol-prohibited changes in concomitant UC medications, including an increase in corticosteroid dose from baseline to treat UC or a prolonged course of systemic corticosteroids >7 days for treatment of disease other than UC; initiation of an immune suppressing therapy including 6-MP or azathioprine or anti-TNF agents; a colectomy (partial or total) or an ostomy; or have discontinued study agent for lack of therapeutic effect before the week 8 evaluations. Patients with a treatment failure will be considered not to have achieved the dichotomous end points; and for continuous end points, their last values will be carried forward for all

visits subsequent to the time of treatment failure. Treatment failure rules will supersede other data handling rules.

The efficacy endpoints will also be analyzed in the PP population.

6.19.1. Endpoints

Efficacy analyses include clinical remission, clinical response, mucosal healing, and changes in Mayo score.

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

6.19.2. Primary Efficacy Analysis

The primary analysis will be carried out when all patients have completed (or would have been eligible to complete) the IP of the study (Week 8).

The primary endpoint of proportion of patients in clinical remission at Week 8 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by prior anti-TNF therapy experience (yes or no). The primary analysis will use the data from the 1 mg dose and placebo groups and compare the remission rates in these two groups using a two-sided test at the 0.05 level of significance. The second comparison for the primary endpoint will be the comparison of remission rates between the 0.5 mg group and the placebo group. The CMH p-value and the relative risk along with its 95% CI will be provided for each treatment group. In addition, the treatment difference and associated 95% CI will also be provided.

6.19.3. Secondary Efficacy Analyses

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

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

Provided that all previously specified tests are statistically significant ($p < 0.05$), each of these comparisons will be assessed using a two-sided test at the 0.05 level of significance. However, if a comparison is not statistically significant, then all subsequent comparisons will be considered exploratory.

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

Actual and change from baseline in Mayo scores over time will be plotted.

6.19.4. Exploratory Efficacy Analyses

6.19.5. Sensitivity Analyses

Sensitivity analyses will be carried out to assess homogeneity of the results for the primary and key secondary endpoints across geographical regions. In these analyses, geographic region will be categorized as North America, Europe, and Asia Pacific. For proportion endpoints, these analyses will be carried out using logistic regression models including effects for treatment group, prior anti-TNF therapy experience, geographic region, and the interaction between treatment group and geographic region. If interactions cannot be excluded, results will be summarized by geographic region. Similarly, quantitative endpoints will be analyzed using ANCOVA models as described previously, with the addition of effects for geographic region and the interaction between treatment group and geographic region.

Sensitivity analyses of the primary and key secondary endpoints will be carried out to investigate the impact of missing data on the efficacy conclusions. All sensitivity analyses will be conducted in the ITT population. The primary and secondary efficacy analyses will be repeated using the following missing data methods:

- Analyses using LOCF (except change in Mayo score)
- Analyses of observed cases (i.e., using only observed data, with no imputation for missing data)
- Multiple imputation model-based methods

Finally, each of the primary and key secondary endpoint analyses will be repeated using clinical endpoints derived from the Mayo score using the investigator endoscopy interpretation.

6.19.6. Other Efficacy Analyses

6.19.6.1. Mayo Score at Week 32

The analyses will be performed for all available Week32 data at the time of database lock as described in Section 6.10.

- Proportion of patients in clinical remission at Week 32
- Proportion of patients in clinical response at Week 32
- Change in Mayo score from baseline at Week 32
- Proportion of patients with mucosal healing at Week 32

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

Actual and change from baseline in partial Mayo scores over time will be plotted.

6.19.6.2. Mayo Score at the End of OLP

The analyses will be carried out when all patients have completed (or would have been eligible to complete) the OLP of the study. The mayo score will be summarized using descriptive statistics.

6.19.6.3. Partial Mayo Score

Partial Mayo score at all visits will be analyzed as follows:

- Proportion of subjects in clinical remission based on the partial Mayo score at each visit through last available
- Proportion of subjects in clinical response based on the partial Mayo score at each visit through last available
- Change in partial Mayo score from baseline at each visit through last available

The endpoints that are defined as proportions will be analyzed using the same type of methodology as described for the primary analysis. Analyses of all proportion endpoints using the CMH test will be

completed using the data from the two groups being compared. Quantitative secondary endpoints such as change in Mayo score will be analyzed using ANCOVA models with effects for treatment group and prior anti-TNF therapy experience, and with the baseline value of the corresponding endpoint included as a covariate. All analyses will be carried out using two-sided test at the 5% level of significance.

6.19.6.4. Endoscopy Data Availability

The counts and percentages of available endoscopy data from both Central reader and Investigator interpretation will be summarized at each visit (Baseline, Week 8, Week 32, and End of Study/ET).

6.20. Safety Analysis

All summaries of Safety data will use the Safety population. All data collected during the IP, MP and OLP will be summarized by treatment group. Statistical hypothesis testing will not be performed on any safety results.

6.20.1. Adverse Events

For presentation, adverse event verbatim text will be coded into MedDRA System Organ Class (SOC) and preferred term. For all AE summaries, if a patient has more than one AE within a preferred term, the patient is counted once in that preferred term at the maximum severity and closest relationship to study material or dosing procedure. If a patient has more than one AE within a system organ class, the patient is similarly counted once in that system organ class.

All AE safety summaries by treatment group will separately summarize the incidence of events in the placebo group, each RPC1063 dose group, and RPC1063 dose groups combined.

An overview of AEs will be tabulated by treatment group. The number and percentage of patients in each treatment group will be summarized for the following categories:

- any treatment-emergent AEs
- any SAEs
- treatment-related AEs
- treatment-related SAEs
- mild, moderate and severe AEs
- AEs with a start date during IP
- AEs with a start date during MP
- AEs with a start date during OLP
- AEs leading to study discontinuation
- AEs leading to study drug discontinuation

The following AE tables refer to AEs that are reported at any time during the study. The number and percentage of unique patients reporting each treatment-emergent AEs will be summarized by SOC, preferred term, and treatment group. A similar table will also be prepared separately for SAEs. Further, the number of treatment-emergent AEs and SAEs, categorized by SOC, preferred term, maximum severity (mild, moderate, or severe), and treatment group will be summarized. In addition, the number of treatment-emergent AEs and SAEs, categorized by system organ class, preferred term, relationship to study drug, and treatment group will be summarized. Finally, the incidence of AEs by preferred term only will be summarized, sorted by descending frequency in the combined RPC1063 group. All AE tables with both SOC and preferred term will be sorted by SOC alphabetically and then by preferred term in descending AE frequency in the combined RPC1063 treatment group. All of these AE and SAE tables will also be repeated for AEs that are reported with start dates during the IP, during the MP, and during the OLP.

AEs with start dates during a follow-up period will be categorized with the previous study phase.

For AE and SAE tables summarizing maximum severity, patients reporting an event more than once with varying severity will be counted only once with the maximum severity within each system organ class/preferred term. For AE and SAE tables summarizing AEs by drug relationship patients will be counted only once, in the category of the strongest relationship to study drug within each system organ class/preferred term.

AEs of special interest will also be summarized by treatment group. The MedDRA SOC and preferred terms that refer to these AEs will be identified by the clinical study team and the project statistician prior to study unblinding and database lock. Treatment-emergent AEs of special interest are defined as AEs related to the following abnormalities:

- Infections
- Bradycardia and heart conduction abnormalities.
- Pulmonary toxicity as measured by the following Pulmonary Function Test (PFT) parameters: FEV_1, FVC, and DLCO.
- Hepatotoxicity which will be assessed by clinical blood chemistry liver function tests.
- Macular edema
- Cutaneous malignancy.

Complete listings of all AEs will be provided. For each AE, the corresponding severity, relationship to study drug, seriousness (yes/no), and available start and stop dates of the event will be specified.

In addition, data listings of all SAEs, AEs leading to discontinuation, and a listings of deaths will also be provided, displaying details of the death captured on the eCRF. Serious adverse event narratives will be provided for the CSR.

6.20.2. Physical Examinations

A complete physical examination will include evaluation of heart, lung, head and neck, abdominal, neurological, skin, and extremities. An interim (or brief) physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the patient.

Abnormal physical examination findings at each visit will be listed.

6.20.3. Height and Weight

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

6.20.4. Vital Signs

Heart rate (HR) and systolic/diastolic blood pressure (BP) will be assessed at scheduled times as outlined in protocol.

After the patient has been supine for at least 15 minutes, HR and BP will be measured 3 times using an automated validated device. The repeat HR and BP measurements will be made at 2-minute intervals. The lowest predose HR and BP (based on Systolic BP) will be taken as the baseline measure and used as comparison to postdose values. BP will then be measured in the same manner with the patient in the standing position. A sudden, significant fall in BP (> 20 mmHg) between 2 and 5 minutes after standing from the supine position will be interpreted as orthostatic hypotension and will be documented in the patient chart and eCRF.

After the first dose of study treatment, patients will be carefully monitored during a 6-hour post-dose monitoring period of hourly recording of HR (supine) and BP (supine and orthostatic). During the 6-hour post-dose monitoring on Day 1, after the patient has been supine for at least 5 minutes, HR and BP will be measured once using an automated validated device. Any clinically relevant change from baseline should be confirmed on repeat measures. Blood pressure will then be measured in the same manner with the patient in the standing position. The same orthostatic hypotension criteria stated above will be applied.

Heart rate and systolic and diastolic blood pressure will be summarized using descriptive statistics at each timepoint by treatment group. BP measurements will be summarized separately in the supine and orthostatic positions. Any clinically significant changes will be recorded as AEs or SAEs.

For patients participating in cardiac monitoring on Day 5, a summary table will be provided that summarizes the hourly change from pre-dose assessment through hour 6 at each of the baseline and Day 5, visits by treatment group for heart rate and blood pressure.

Box plots will be provided to display the distribution of HR and BP. In addition, line plots will be created to display the change from baseline over the entire study period and change from pre-dose in HR and BP for the baseline and Day 5visits.

The number and percentage of subjects with clinically relevant abnormalities will be presented by treatment group. The criteria for clinically relevant abnormalities are shown in the following table.

Table 1. Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38^{o}C and an increase from pre-dosing of at least 1^{o}C
Heart Rate	>120 beats per minute post-baseline, or
	an increase from pre-dosing of more than 20 beats per minute, or
	<45 beats per minute post-baseline, or
	a decrease from pre-dosing of more than 20 beats per minute
Systolic Blood Pressure	>180 mmHg post-baseline, or
	an increase from pre-dosing of more than 40 mmHg, or
	<90 mmHg post-baseline, or
	a decrease from pre-dosing of more than 30 mmHg
Diastolic Blood Pressure	>105 mmHg post-baseline, or
	an increase from pre-dosing of more than 30 mmHg, or
	<50 mmHg post-baseline, or
	a decrease from pre-dosing of more than 30 mmHg

All vital sign measurements will also be listed.

6.20.5. Electrocardiograms (ECGs) and Holter Monitoring

Stand Alone/Static ECGs

Static ECGs will be captured at intervals as defined in the schedule of assessments. The 12-lead ECG will be performed after the patient has been resting quietly in a supine position for at least 15 minutes. ECGs will be captured at scheduled times as outlined in the protocol.

Summary tables including actual values and change from baseline values will be presented for ECG results. Any clinically significant changes will be recorded as AEs or SAEs.

ECG results including morphology parameters will also be listed.

Continuous 12-lead Holter Monitoring

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

Any clinically significant changes will be recorded as AEs or SAEs.

6.20.6. Laboratory Assessments

Laboratory tests include the following:

- Hematology – red blood cell (RBC) count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin (Hgb), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Total and differential WBC counts will not be provided to the Investigator to maintain the treatment blind. These parameters and alerts for these parameters will be monitored by the PPD Safety Surveillance team.
- Blood chemistry - sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, alanine aminotransferase, aspartate transaminase, gamma glutamyltransferase, amylase, total bilirubin, conjugated bilirubin.
- Urinalysis - leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
- Pregnancy test: serum beta-hCG must be performed at screening in women of childbearing potential; urine beta-hCG will be performed at each visit, and if positive, do not dose, and confirm with a serum pregnancy test.
- Coagulation panel: prothrombin time and partial thromboplastin time.
- Serology testing will be performed at screening to determine the patient's immune status with respect to several viruses; testing will be as follows:
    - anti-VZV IgG

- HIV antibodies
- anti-hepatitis A virus IgM
- HBsAg and HBcAg IgM
- anti-HCV IgG or IgM

Hematology, blood chemistry, and coagulation test results will be summarized at each study visit by treatment group for visits during the IP and MP and for all patients during the OLP. Changes from Visit 1 to the End of Study Visit will be summarized by treatment group.

Subjects with abnormalities in hematology assessments, defined as absolute lymphocyte count (ALC) <200 cells/uL, absolute neutrophil count (ANC) < 500 cells/uL as well as ANC <1000 cells/uL and total WBC >20,000 cells/uL will be summarized for each treatment group.

In addition, the change and percent change from baseline in CBC with Differential will be summarized for each treatment group.
The incidence of subjects with abnormalities in Liver Function Tests (SGPT/ALT, SGOT/AST, and GGT) will be summarized overall and at each visit for each treatment group for the following categories:

- > 1 x upper limit of normal (ULN)
- ≥ 2 x ULN
- ≥ 3 x ULN
- ≥ 4 x ULN
- ≥ 5 x ULN

Shift tables will summarize changes from relevant Baseline by treatment group for visits during the IP, MP, and the OLP. Changes from Day 1 to visits during the OLP will be summarized for all patients.

All clinical laboratory results will also be listed. Laboratory values that are outside the normal range will be flagged high (H) or low (L). All out of range values will be identified in the listing.

Plasma protein biomarker results (cytokines, chemokines, other inflammatory proteins) may not be available at the time of database lock and thus may be analyzed at a later time.

6.20.7. Pulmonary Function Tests

Pulmonary function tests (PFTs) including FEV_1, FVC, and DLCO, if applicable, measurements will be performed as scheduled in the protocol. These tests will be performed at a high qualified pulmonary function laboratory or respiratory department.

A minimum of 3 acceptable maneuvers will be performed at each visit. The acceptability criteria are a satisfactory start of test and a satisfactory end of test. The largest FVC and the largest FEV_1 will be recorded, after examining the data from all of the acceptable curves, even if the 2 values do not come from the same curve.

For FEV1 and FVC, summary tables for actual value, change, percent change, percent predicted, change in percent predicted, and percent change in percent predicted will be produced. For DLCO summary tables for actual value, change, and percent change will be produced. DLCO is collected at the local lab

for each site, so results may be collected in domestic or SI units. DLCO results in domestic units (mL/min/mmHg) will be converted to SI units (mmol/min/kPa) prior to analysis using the following conversion factor: DLCO in SI units = (DLCO in domestic units) / 2.986.

Line plots of FEV1, FVC, and DLCO results over time will be presented. PFT test results will also be listed.

6.20.8. Ophthalmological Examination

Optical Coherence Tomography (OCT) will be performed at scheduled times as outlined in protocol.

Any clinically significant changes will be recorded as AEs or SAEs. OCT details will also be listed.

6.20.9. Dermatological Examination

Dermatological evaluations will be performed Screening, the End of Study Visit, Visit 1OLP, and the End of OLP Visit as part of the physical examination.

A certified dermatologist will perform dermatological evaluations if abnormal results are found on the physical examination. Any clinically significant changes will be recorded as AEs or SAEs. Dermatological examination abnormalities by visit will be presented and dermatological examination details will be listed.

6.21. PD Analysis

In addition to summarizing the actual values and change from baseline in Absolute lymphocyte count (ALC) specified as part of the Hematology analysis, percent change in ALC will also be summarized by treatment group. Actual value, change, and percent change in ALC over time will also be plotted.

7. REPORTING CONVENTIONS

The following reporting conventions will be adopted for the tables, listings, and figures. These conventions will enhance the review process and help to standardize presentation with common notations.

- All tables and data listings will be presented in Landscape Orientation, unless presented as part of the text in a CSR, in Courier New, 10 point font.
- Figures will be presented in Landscape Orientation, unless Portrait Orientation suggests that the information presented is easier to interpret.
- Legends will be used for all figures with more than one variable or item displayed.
- Lines should be wide enough to see the line after being copied.
- Specialized text styles, such as bolding, italics, borders, shading text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal characters are allowed (e.g., μ,α,β).
- Capital letters will be used throughout all tables, figures, and data listings.
- A standard header on each page will contain information to include the sponsor name ("Receptos, Inc.") and study identifier ("Protocol RPC01-202").
- The ICH numbering convention will be used for all tables, listings, and figures.
- All footnotes will be left justified and at the bottom of a page.
- Missing values (other than date values) for both numeric and character variables will be presented as blanks in a table or data listing. Missing date/month/year will be presented as dash ('-') for each space.
- All date values will be presented as DDMMMYYYY (e.g., 29AUG2009) format. A four-digit year is preferred for all dates.
- All observed time values will be presented using a 24-hour clock HH:MM format (e.g., 01:35). Seconds should only be reported if they were measured as part of the study.
- Time durations will be reported in mixed HHh MMm notation (e.g., 5h 32m). The use of decimal notation to present time durations should be avoided (e.g., 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures, and data listings will have the name of the program and a date/time stamp on the bottom of each output.
- Each table, figure, and data listing will have "Page x of y" presented on the top right-hand side of each page.
- Additional rounding rules as follows:

- If the original value has 0 decimal places: mean, median, and CIs will have one decimal place and SD will have 2 decimal places
- If the original value has 1 decimal place: mean, median, and CIs will have 2 decimal places and SD will have 3 decimal places
- If the original value has 2 or more decimal places: mean, median, CIs, and SD will all have 3 decimal places

- All calculated percentages between 1% and 99% will be rounded to one decimal place. A percentage of 100% will be reported as 100%. Any computation of percentage that results in 0% will be reported as 0 as the number of responses and no percentage will be reported. All categories whose counts are zero will be displayed for the sake of completeness.
- P-values will be rounded to four decimal places. If a p-value is less than 0.0001, it will be reported as "<0.0001". If a p-value is greater than 0.9999, it will be reported as ">0.9999".

8. DEVIATIONS FROM PROTOCOL

The analyses of the following endpoints specified in the protocol are not performed due to collected samples have not been analyzed at the time of database lock.

- Proportion of patients with histologic Remission at Week 8 for exploratory objectives and exploratory efficacy endpoints.
- Plasma protein biomarkers (cytokines, chemokines, other inflammatory proteins) as PD endpoint.

STATISTICAL ANALYSIS PLAN – OPEN LABEL PERIOD ADDENDUM

Title: A Phase 2, multi-center, randomized, double-blind, placebo-controlled parallel-group study to evaluate the clinical efficacy and safety of induction therapy with RPC1063 in patients with moderately to severely active ulcerative colitis

Protocol: RPC01-202

Sponsor: Celgene International II Sàrl (see appended signature page)
Rue du Pré-Jorat 14
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Tel: + 41 32 864 69 01

Date: October 15, 2019

Status: Addendum to Version 2.0

CONFIDENTIAL

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LIST OF ABBREVIATIONS

AE	adverse event
DEF	definition
DMC	data monitoring committee
IP	Induction Period
ITT	intent-to-treat
MP	Maintenance Period
NRI	Non-responder imputation
OLP	Open-Label Treatment Period
SAE	serious adverse event
SAP	statistical analysis plan
UC	ulcerative colitis

1. Introduction

[redacted]

Label Treatment Period (OLP) as in the Core Period and are detailed in SAP Version 2.0.

2. Study Design

[redacted]

3. Analysis Cohorts

- Intent-to-Treat (ITT) Analysis Cohorts will be labeled by randomized treatment in the parent study for all subjects who received at least one dose of RPC1063 1mg in OLP.
- Safety Analysis Cohorts will be labeled by actually received treatment in the parent study for all subjects who received east one dose of RPC1063 1mg in OLP.

4. DMC

There were no DMC reviews planned for the OLP.

5. Patient Disposition

Patient disposition information will only include subjects who participated the OLP.

6. OLP Baseline

Baseline for efficacy analyses:

Core baseline: The last assessment prior to/on first dose date in Core Period.

The full set of the efficacy endpoints will be derived based on Core baseline.

Baseline for safety analyses:

The adverse events (AEs) will be summarized per Section 8.

For non-AE safety endpoints, definition of Baseline will not change (SAP v2.0 Section 5.1)

7. Efficacy Analyses

The efficacy measurements will be summarized by parent study treatment group at each OLP visit in the OLP ITT population. Non-responder imputation (NRI) will be used as the primary method for addressing missing binary outcomes. No treatment failure rule will be applied in the OLP, as per its defined in Section 6.19 (SAP v2.0).

7.1. Endpoints

Complete Mayo score: The Full Mayo score in SAP v2.0.

The 9-point Mayo score: The sum of the Rectal Bleeding subscore, Stool Frequency subscore, and the Endoscopy subscore. The 9-point Mayo score has a range of 0-9 points.

OLP Efficacy Endpoints

Clinical Remission

- Four-component Mayo clinical remission: Complete Mayo score of <=2 points with no individual subscore of >1 point
- Three-component Mayo clinical remission: Rectal bleeding subscore=0 and stool frequency subscore <=1 (and a decrease of >=1 point from the baseline stool frequency subscore), and endoscopy subscore <=1

Clinical Response

- Four-component Mayo clinical response: Reduction from baseline in complete Mayo score of >=3 points and reduction from baseline in complete Mayo score of >=30%, and (reduction in rectal bleeding subscore of >=1 point or a rectal bleeding subscore of <=1 point)
- Three-component Mayo clinical response: Reduction from baseline in the 9-point Mayo score of >=2 points and Reduction from baseline in the 9-point Mayo score >=35%, and (reduction from baseline in the rectal bleeding subscore of >=1 point or a rectal bleeding subscore of <=1 point).

Mucosal Healing

- Mucosal Healing is defined as an Endoscopic subscore of ≤ 1 point
- Mucosal healing (alternative definition): Endoscopy subscore of <=1 point and a Geboes index score <2.0

Histological remission

- Histological remission is defined as Geboes index score < 2.0.

Analysis visit windows defined in Section 7.3 will be applied on all efficacy analyses.

7.2. Mayo Score at the End of OLP

The analyses will be carried out when all patients have completed (or would have been eligible to complete) the OLP of the study. The mayo score will be summarized using descriptive statistics.

The proportion of patients in clinical remission, clinical response, and with mucosal healing will be descriptively summarized at each visit window defined in Section 7.3 in the OLP ITT population.

The proportion of patients in partial Mayo clinical remission and in partial Mayo clinical response will be descriptively summarized for each OLP visit in the OLP ITT population.

The proportion of patients in clinical remission (for all bullet definitions listed in Section 7.1), in clinical response (for all bullet definitions listed in Section 7.1), and with mucosal healing will also be descriptively summarized as described above in the same subgroups as the Core period in the OLP ITT population.

- Prior anti-TNFα use (yes vs. no)
- Age (< median vs. ≥ median)
- Sex (Female vs. Male)
- Disease localization (Left side vs. Extensive)
- Baseline disease activity (Mayo score using the central endoscopy read ≤ 8 vs. > 8)

The proportion of patients in clinical remission (for all definitions), in clinical response (for all definitions), and with mucosal healing will be descriptively summarized as described above in the OLP ITT population using:

- Observed cases
- NRI

7.3. Visit Windows

Post-OLP-Baseline visits (scheduled or unscheduled) during OLP will be mapped to an analysis visit based on the windowing algorithm below. If a visit cannot be mapped to any analysis visit, then the analysis visit will be set to missing and the data of interest will be excluded from summaries. If multiple visits containing the same data of interest can be mapped to the same analysis visit, the visit closest to the target day will be used in the analysis. In the event that two or more visits are equidistant to the target day, the later visit will be used in the analysis. If the two visits are on the same day, then the visit with the worst result will be used in the analysis.

Visit	Target Day	Analysis Visit Window for partial Mayo score	Analysis Visit Window for Complete Mayo Score, 9-point Mayo Score and Geboes Index
		(+/- 6 weeks)	(+/- 24 weeks)
Day 1OLP	1	N/A	N/A
Week 4OLP	36	(19-50)	N/A
Week 8OLP	64	(51 - 106)	N/A
Week 20OLP	148	(107 - 190)	N/A
Week 32OLP	232	(191 - 274)	N/A
Week 44OLP	316	(275 - 358)	N/A
Week 56OLP	400	(359 - 442)	(232 - 568)
Week 68OLP	484	(443 - 526)	N/A
Week 80OLP	568	(527 - 610)	N/A
Week 92OLP	652	(611 - 694)	N/A

Week 104OLP	736	(695 - 778)	(569 - 904)
Week 116OLP	820	(779 - 862)	N/A
Week 128OLP	904	(863 - 946)	N/A
Week 140OLP	988	(947 - 1030)	N/A
Week 152OLP	1072	(1031 - 1114)	(905 - 1240)
Week 164OLP	1156	(1115 - 1198)	N/A
Week 176OLP	1240	(1199 - 1282)	N/A
Week 188OLP	1324	(1283 - 1366)	N/A
Week 200OLP	1408	(1367 - 1450)	(1241 - 1576)
Week 212OLP	1492	(1451 - 1534)	N/A
Week 224OLP	1576	(1535 - 1618)	N/A
Week 236OLP	1660	(1619 - 1702)	N/A
Week 248OLP	1744	(1703 - 1786)	(1577 - 1912)
Week 260OLP	1828	(1787 - 1870)	N/A
Week 272OLP	1912	(1871 - 1954)	N/A
Week 284OLP	1996	(1955 - 2038)	N/A
Week 296OLP	2080	(2039 - 2122)	(1913 - 2248)
Week 308OLP	2164	(2123 - 2206)	N/A
Week 320OLP	2248	(2207 - 2290)	N/A

8. Safety Analyses

AEs will be recorded from the time written informed consent is signed through the 90-day safety Follow-up visit to ensure adequate collection of adverse events that could be associated with investigational drug.

Treatment-emergent adverse events include adverse events that started between the date of first dose of OLP and 90-day safety Follow-up visit after the date of last dose.

9. Guideline on Missing Date Imputation

The following missing data imputation rules will be applied to the OLP analyses.

Medication Dates:

If the start date of medication is completely missing in which the day, month, and year are all unknown or only the day is known, then the start date will not be imputed.

For the partial start date of medication,

- If the year is present and the month and day are missing or the year and day are present and the month is missing, set month and day to January 1.
- If the year and month are present and the day is missing, set day to 1st day of month.
- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.

If the end date of medication is completely missing which the day, month, and year are all unknown or only the day is known, then the end date will not be imputed.

For the partial end date of medication,

- If the year is present and the month and day are missing or the year and day are present and the month is missing, set month and day to December 31.
- If the year and month are present and the day is missing, set day to last day of the month.

Adverse Event Dates:

If the adverse event onset date is completely missing, is set to date of first dose.

If year is missing, set it as the year of first dose.

If year is present but (month and/or day) are missing:

- If year = year of first dose, then set missing month and/or day to month and/or day of first dose
- If year < year of first dose, then set missing month and/or day to December and/or 31.
- If year > year of first dose, then set missing month and/or day to January and/or 1.

If month and year are present but day is missing:

- If year = year of first dose and if month = month of first dose, then set day of first dose
- If month < month of first dose, then set day to last day of the month
- If month > month of first dose, then set day to first day of the month
- If year < year of first dose, then set day to last day of the month
- If year > year of first dose, then set day to first day of the month

For all other cases, set to date of first dose.

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30 Dec 2019	
Signature of Celgene International II Sàrl Representative Olivia Fière Senior Director Global Clinical Trial Management	**dd mmm yyyy**
Printed Name of Celgene International II Sàrl Representative	