RPC01-2201

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

January 16, 2020

Statistical Analysis Plan

Version 1.5

Prepared by:

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Statistical Therapeutic Area Head

Signature [redacted]

Printed Name [redacted] Date 16 Jan 2020

Lead Clinical Research Physician / Clinical Research Physician / Medical Affairs Physician

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Printed Name _____ Date 16 Jan 2020

Lead Product Safety Physician / Medical Affairs Physician (if applicable)

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Printed Name [redacted]

Date 1/16/2020

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Signature _____

Printed Name _____ Date _____

Lead Clinical Research Physician / Clinical Research Physician / Medical Affairs Physician

Signature [redacted]

Printed Name [redacted] Date 1/16/20

SPONSOR: CELGENE INTERNATIONAL II SÀRL

[redacted]	27.01.2020
Signature of Celgene International II Sàrl Representative	**dd mmm yyyy**
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LIST OF ABBREVIATIONS

Table 1. Abbreviations

Abbreviation or Specialist Term	Definition
5-ASA	5-Aminosalicylic acid
6-MP	6-Mercaptopurine
AE	Adverse event
AESI	Adverse event(s) of special interest
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-TNF	Anti-tumor necrosis factor
AP	Abdominal Pain
AST	Aspartate aminotransferase
AV	Atrioventricular
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CRO	Contract Research Organization
CRP	C-reactive protein
DLCO	Diffusion capacity of the lung for carbon monoxide
DM	Data management
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
FEV_1	Forced expiratory volume at 1 second
FVC	Forced vital capacity
GHAS	Geboes Histology Activity Score
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
ITT	Intent to treat
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
ms	Milliseconds
NRI	Non-responder imputation
OC	Observed cases
OCT	Optical coherence tomography
PFT	Pulmonary function test (FEV1, FVC, and DLCO)
PK	Pharmacokinetic
PT	Preferred term
PYE	patient-years of exposure
RHI	Robarts Histopathology Index
SAE	Serious adverse event
SD	Standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	Stool Frequency
SAP	Statistical analysis plan
SBP	Systolic blood pressure

SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SE	Standard error
SI	Standard international
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USA	United States of America
VZV	varicella-zoster virus
WBC	white blood cell
WHODrug	World Health Organization Drug classification dictionary

1. ADMINISTRATIVE STRUCTURE

1.1. Sponsor and Oversight

This trial is being conducted under the sponsorship of Celgene. The clinical monitoring and data management (DM) are being performed under contract with IQVIA, and statistical analyses are being performed under contract with PPD, LLC, with oversight from Celgene.

1.2. Data Quality Assurance

The Clinical Operations, DM, and Biostatistics departments at the contract research organizations (CRO) will collaborate internally and with the sponsor to ensure that the data collected and analyzed for this trial are of the highest quality possible and meet the data standards set for the trial. This will be accomplished in part through programmed edit checks which will be reviewed by the statisticians, programmers and other team members on an ongoing basis to evaluate whether any checks need to be added or any existing checks need to be modified. In addition, periodic reviews of listings of accumulating data, assessment of data query trends and resulting retraining of trial site personnel will be performed to further ensure data quality.

2. INTRODUCTION

[redacted]

[redacted]

[redacted]

[redacted]

3. OBJECTIVES

3.1. Induction Period Primary Objective

To assess endoscopic improvement following treatment with RPC1063.

3.2. Extension Period Primary Objective

To characterize the long term safety of continued dosing of RPC1063.

4. INVESTIGATIONAL PLAN

4.1. Overall Trial Design and Plan

Approximately 60 patients with moderately to severely active Crohn's disease will be enrolled into this trial. Patients who complete the Induction Period will have the opportunity to receive continued treatment with RPC1063 in the Extension Period, provided that the investigator determined using clinical judgement, that the patient should continue into the Extension Period. All patients in the Extension Period will continue to receive RPC1063 1.0 mg daily and may continue 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.

The safety of patients will be monitored by collection of treatment-emergent AEs, AEs of special interest (AESI), serious adverse events (SAEs), AEs leading to discontinuation of investigational drug, physical examinations, vital signs measurements, ECG results, optical coherence tomography (OCT) examinations, 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 90days for collection of safety data, including lymphocyte recovery, and for the assessment of their disease status.

4.2. Endpoints and Endpoint Definitions

The Simple Endoscopic Score for Crohn's Disease (SES-CD) assesses the degree of inflammation and will be used to evaluate the primary efficacy endpoint. The SES-CD reflects the assessment of mucosal lesions in CD, and grades lesions by location (rectum, left colon, transverse colon, right colon and ileum) using ulcer size, extent of ulcerated surface, extent of affected surface, and presence/type of narrowing. Additional details and scoring algorithms can be found in Appendix 2.

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 typically 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 along with

the data handling details for deriving the average daily scores (including the sub-scores) over the 7 day period are noted in Appendix 3.

The severity of Crohn's disease is defined based on CDAI score as follows: mild with CDAI score of ≥150 to <220, moderate with CDAI score of ≥220 to ≤450 and severe with a CDAI score of >450.

4.2.1. Definitions

Table 2. Key Terms

Term	Definition
SES-CD	The sum of the scores for the 5 segments composed of the sum of 4 separate components that include: Size of ulcers, Extent of ulcerated surface, Extent of affected surface and the presence and type of narrowing. The 4 components are evaluated for each of the accessible segments and are scored as 0 to 3. The segments include: rectum, sigmoid & left colon, transverse colon, right colon and the ileum. The range of SES-CD scores is 0 – 12 for each segment, and 0 – 56 for the overall SES-CD score, with larger scores indicating greater severity of disease.
CDAI	The weighted sum of the 8 components: Number of liquid or soft stools for 7 days, Abdominal pain for 7 days, general well-being for 7 days, presence of complications, taking diarrhea medication, abdominal mass, hematocrit and percentage deviation from standard weight. The typical range of CDAI score is 0 to > 600.
PRO2	The *weighted* sum of two items that separately contribute to the derivation of two CDAI sub-scores: PRO2 = SF*7*2 + AP*7*5. See Table 10, Appendix 3 for details.
SF/AP	The *unweighted* sum of two items that separately contribute to the derivation of two CDAI sub-scores: SF/AP = SF + AP. See Table 10, Appendix 3 for details. NOTE: This definition is included for reference only; in some clinical trials for Crohn's disease, this has been used for various endpoints.
SF&AP	SF & AP Remission, defined as Average daily stool score ≤ 3 points AND average daily abdominal pain score ≤ 1 point
GHAS	Geboes Histology Activity Score
RHI	Robarts Histopathology Index

Table 3. Key Endpoints

Category or Shorthand	Label	Definition
Endoscopy	Endoscopic Change	SES-CD change from baseline
	Endoscopic Response-25	SES-CD decrease from baseline of ≥ 25%
	Endoscopic Response-50	SES-CD decrease from baseline of ≥ 50%
	Endoscopic Remission	SES-CD ≤ 4 points and a SES-CD decrease from baseline ≥ 2 points with no SES-CD sub-score > 1 point
CDAI	CDAI Change	CDAI change from baseline
	SF Change	SF Change from baseline
	AP Change	SF Change from baseline
	CDAI Clinical Response	CDAI decrease from baseline of ≥ 100 points
	CDAI Clinical Remission	CDAI score of <150
PRO2	PRO2 Clinical Response	PRO2 CD decrease ≥ 50%
SF&AP	SF & AP Remission	Average daily stool score ≤ 3 points AND average daily abdominal pain score ≤ 1 point
Histology	GHAS Change	GHAS change from baseline
	GHAS Remission	No active inflammation in any measured segment; see Appendix 4 for details
	RHI Change	RHI change from baseline
	RHI Response - by Segment	RHI segment score decrease ≥ 50%
	RHI Remission- by Segment	No active inflammation in a measured segment
	RHI Remission	No active inflammation in any measured segment; see Appendix 4 for details
	Global RHI Score	A weighted sum of the worst of each of the four disease components across the four colonic segments; see Appendix 4 for details
Mucosal Healing	RHI Mucosal Healing	Endoscopic Remission combined with RHI Remission
Biomarkers	CRP Change	C-reactive protein change from baseline
	CRP Response-10	C-reactive protein < 10 mg/L
	FCP Change	Fecal calprotectin change from baseline
	FCP Response-250	Fecal calprotectin < 250 mcg/g

4.2.2. Efficacy Endpoints for Induction Period

Primary Efficacy Endpoint

- Endoscopic Change

Other Efficacy Endpoints

- Category: Endoscopy

  - Proportion of patients with Endoscopic Response-25
  - Proportion of patients with Endoscopic Response-50
  - Proportion of patients with Endoscopic Remission
- Category: CDAI
  - CDAI Change
  - SF Change
  - AP Change
  - Proportion of patients with CDAI Clinical Response
  - Proportion of patients with CDAI Clinical Remission
- Category: PRO2
  - Proportion of patients with PRO2 Clinical Response
- Category: SF&AP
  - Proportion of patients with SF&AP Remission
- Category: Histology
  - GHAS Change
  - Proportion of patients with GHAS Remission
  - RHI Change
  - Global RHI Score Change
  - Proportion of patients with RHI Response - by segment among non-RHI remitters at Baseline
  - Proportion of patients with RHI Remission
  - Proportion of patients with RHI Remission - by segment
  - Proportion of patients with RHI Remission - by segment among non-RHI remitters at Baseline
- Category: Mucosal Healing
  - Proportion of patients with RHI Mucosal Healing
- [redacted]

– [redacted]

4.2.3. Efficacy Endpoints for Extension Period

The efficacy endpoints for the induction period listed above in section 4.2.2 will be evaluated for all extension visits.

In addition, proportion of patients achieving remission and remaining corticosteroid-free in the prior 12 weeks will be evaluated at each time point of Week 36, Week 48, and Week 52, among the patients who received corticosteroids for CD at baseline. This analysis will be performed for CDAI Remission and SF&AP Remission.

Clinical Remission (Based on CDAI) at both Week 12 and Week 52 will also be summarized. Following efficacy graphs will be presented.

- CDAI change from Baseline (Observed) showing mean and 95% CI at each scheduled visit up to Week 52, overall and by Biologic Exposed vs. Biologic Naïve
- CDAI (Observed) showing mean and 95% CI at each scheduled visit up to Week 160, overall and by Biologic Exposed vs. Biologic Naïve
- Bar graph of CDAI Clinical Response (NRI) at Week 12 and Week 52, overall and by Biologic Exposed vs. Biologic Naïve
- Bar graph of CDAI Clinical Response (Observed) at Week 12 and Week 52, overall and by Biologic Exposed vs. Biologic Naïve
- Bar graph of CDAI Clinical Remission (NRI) at Week 12 and Week 52, overall and by Biologic Exposed vs. Biologic Naïve
- Bar graph of CDAI Clinical Remission (Observed) at Week 12 and Week 52, overall and by Biologic Exposed vs. Biologic Naïve
- Bar graph of Endoscopic Response-50 (Paired Segments, NRI) at Week 12 and Week 52, overall and by Biologic Exposed vs. Biologic Naïve
- Bar graph of Endoscopic Response-50 (Paired Segments, Observed) at Week 12 and Week 52, overall and by Biologic Exposed vs. Biologic Naïve
- Stool frequency change from Baseline (Observed) showing mean and 95% CI at each scheduled visit up to Week 52, overall and by Biologic Exposed vs. Biologic Naïve
- Stool frequency (Observed) showing mean and 95% CI at each scheduled visit up to Week 160, overall and by Biologic Exposed vs. Biologic Naïve

- Abdominal Pain change from Baseline (Observed) showing mean and 95% CI at each scheduled visit up to Week 52, overall and by Biologic Exposed vs. Biologic Naïve
- Abdominal Pain (Observed) showing mean and 95% CI at each scheduled visit up to Week 160, overall and by Biologic Exposed vs. Biologic Naïve

4.2.4. Safety Endpoints

The incidence, severity, relationship and type of TEAEs, SAEs, AEs leading to discontinuation of investigational drug, and AEs of special interest; clinically meaningful changes from baseline for 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

[redacted]

5. GENERAL STATISTICAL CONSIDERATIONS

All efficacy and safety data will be listed by patient. Listings will be sorted by patient number and visit/study day.

Continuous data will be summarized using descriptive statistics: number of patients (n), mean, standard deviation (SD), standard error (SE), median, minimum and maximum.

Categorical data will be summarized using the number and percent of patients. When count or frequency data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. The denominator for percentages will be the number of patients within the population of interest, unless otherwise stated. Denominator for percentages in demographic and baseline categories will use the number of non-missing values. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places.

Additional rounding rules are 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; and
- If the original value has 2 or more decimal places: mean, median, CIs, and SD will all have 3 decimal places.

Minimum and maximum will always have the same decimal places as the original measure, up to a maximum of 3 decimal places.

Unless otherwise indicated, values that are collected with "<" sign and a numerical bound will be analyzed as half the numerical bound, without the sign in tables and figures. Values that are collected with ">" sign and a numerical bound will be analyzed as the numerical bound, without the sign. In listings, these data will be reported as collected, with the sign.

5.1. Sample Size

The sample size of approximately 60 patients for the Induction Period has been chosen to enable estimates of response and remission rates with reasonable precision. To give this some context, if we assume a remission rate of 15% and a response rate of 30%, it is estimated that half-width of the 95% CI around the proportion of patients in response and remission, respectively, would be 12.8% and 16.4% for a 30 patient study. For a 60 patient study, on the other hand, the same half-widths would be 9.0% and 11.6%.

5.2. Randomization, Stratification, and Blinding

This is a non-randomized, unstratified, unblinded, single-arm, open-label trial.

5.3. Statistical Hypotheses and Multiple Endpoint Handling

No statistical hypothesis testing will be performed in this trial.

5.4. Analysis Populations

All patients who are enrolled in the Induction Period and receive at least one dose of investigational drug will comprise both the Intent-to-Treat (ITT) population and the Safety population. Because this is a single arm open label study, these two analysis populations are indistinguishable. This population will be used to summarize all efficacy and safety data for both Induction and Extension Periods.

5.5. Other Important Considerations

5.5.1. Definition of Baseline

Unless otherwise specified, baseline is defined as the last observation collected on or before the receipt of first dose of Investigational Product (IP). Calculation of Change and Percent Change from Baseline are done according to the following:

- Change from Baseline to any trial Week t (C_t) is calculated as follows:
  - $C_t = M_t - M_B$, where:
    - M_t is the measurement of interest at Week t
    - M_B is the measurement of interest at Baseline
- Percent change from Baseline to any trial Week t (P_t) is calculated as follows:
  - $P_t = 100*(C_t/M_B)$

NOTE: If M_B =0 or missing then percent change from Baseline will not be determined.

5.5.2. Study Day Calculation for Reporting Purposes

The following conventions will be used to calculate study day for reporting purposes:

- Study Day = date of measurement – first dose date +1, if date of measurement is on or after the first dose date.
- Study Day = date of measurement – first dose date, if date of measurement is prior to the first dose date.
- Study Day 1 is the first dose date of the Induction Period, and no Study Day 0 is defined.

5.5.3. Visit Windows

The analysis time point assignment for the post-baseline visits will be assigned based on the analysis windows described in Table 4 below for the following items:

- Efficacy (please see Protocol Table 2 for a description of what study elements are considered to belong to the Efficacy category; it is also noted that not all Efficacy elements are considered in this SAP, please see the endpoints in Sections 4.2.2, 4.2.3, and 12)
- 12-lead ECG
- Vital signs
- Hematology
- Blood chemistry
- Pregnancy test
- Urinalysis
- Physical examination
- Pulmonary function test
- Optical coherence tomography

Adverse events and coagulation panel data will not be windowed.

If multiple assessments are available within a range, then the one closest to the target day will be used for that analysis time point. If multiple assessments are same distance, but on different sides of the target day, then the latter one will be used. If multiple assessments are available on the same day, then the average of these assessments will be used, except for the lab and ECG data for which the assessment at a later time of the same day will be used.

Table 4. Analytic Visit Windows

Visit	Ideal Analysis Day[a]	Visit Window
Baseline	1	<= 1
Week 4	29	2 – 42
Week 8	57	43 – 70
Week 12	85	71 – 98
Week 24	169	99 –– 210
Week 36	253	211 – 294
Week 48	337	295 - 350
Week 52	365	351 - 392
Week 64	449	393 - 490
Week 76	533	491 - 574
Week 88	617	575 - 658

Week 100	701	659 - 742
Week 112	785	743 - 826
Week 124	869	827 - 910
Week 136	953	911 - 994
Week 148	1037	995 - 1078
Week 160	1121	>= 1079
Safety Follow-up Day 30	30	≤ 60
Safety Follow-up Day 75 and Day 90	90	≥ 61

[a]Except for the visits recorded as safety follow-up visits, the reference date will be the date of the first dose of IP in the study, and the relative day is calculated date of assessment/collection – date of the first dose of IP + 1 if the date of assessment/collection is on or after the date of the first dose of IP, or date of assessment/collection – date of the first dose of IP if the date of assessment/collection is before the date of the first dose of IP. The reference date for the visits recorded as safety follow-up visits will be the date of the last dose of IP in the study, and the relative day is calculated date of assessment/collection – date of the last dose of IP.

Applying above visit window rules will be done after distinguishing treatment visits and follow-up visits by CRF visit labels.

For all study elements to which the above table applies, the last available assessment will be derived as the last value on treatment, whether scheduled or unscheduled.

5.5.4. Handling of Missing and Partial Data

For all proportion-based efficacy endpoints, patients with missing efficacy data and the responses after treatment failure will be considered non-responders (NRI) in the primary analyses.

Treatment failures at Week 12 and Week 52 will be determined based on the rules listed in Section 9.1. In all analyses where NRI is used, responses of the patients who are treatment failures at Week 12 will be imputed as non-responder at Week 12 and onwards. In addition, responses of the patients who are treatment failures at Week 52 will be imputed as non-responder at Week 52 and onwards.

Continuous efficacy endpoints will not be imputed.

Sensitivity analyses on missing data on selected endpoints are detailed in the efficacy analyses sections 9.1 and 9.2.

With the exception of partial dates, missing demographic, disposition, baseline characteristics, medical history, and safety data will be analyzed using observed data only, without imputation. For

partial dates, the algorithms for imputation will vary depending upon the parameter; the details can be found in Appendix 1.

5.5.5. Handling of Missing Segmental Scores for SES-CD, GHAS, and RHI

The analyses of change from baseline and the defined responder analyses for SES-CD, GHAS, and RHI, as applicable, will exclude the segments non-evaluable or missing at baseline, regardless of whether or not they become evaluable post-baseline. In addition, any missing segment scores (in the presence of at least 1 non-missing segmental SES-CD score) of SES-CD will be imputed by non-missing score used in the previous visit. This methodology is the primary analysis and will also be referred to as "complete cases" or "paired segments" as only segments scored at both baseline and the repeat endoscopy will be assessed. Exploratory analyses of the SES-CD scores based on available data without any adjustments or imputation will also be performed.

6. PATIENT DISPOSITION

A summary of disposition of all screened patients will be generated and will include the following information:

- Number and percentage of enrolled patients in the Safety Population
- Number and percentage of enrolled patients in the ITT Population
- Number and percentage of enrolled patients dosed and not dosed
- Number and percentage of enrolled patients discontinuing during Induction, with reasons
- Number and percentage of enrolled patients discontinuing after Induction but prior to Extension, with reasons
- Number and percentage of enrolled patients who completed Week 12 and continued into Extension
- Number and percentage of enrolled patients discontinuing during Extension up to and including Week 52, with reasons
- Number and percentage of enrolled patients discontinuing during Extension after Week 52, with reasons
- Number and percentage of enrolled patients who completed Week 52
- Number and percentage of enrolled patients ongoing and completing the Protocol (Week 160)

Only the primary reason for discontinuation will be tabulated.

The reasons for Screen Failure will be separately tabulated according to the relevant Inclusion / Exclusion criteria. The number and percentage of ITT patients by Region, Country, and Site will be tabulated.

7. DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND MEDICAL HISTORY

7.1. Demographics and Baseline Characteristics

The demographics and baseline characteristics will be presented using descriptive statistics for the ITT population.

Tabulated demographic characteristics will consist of

- Sex
- Age
- Age Category
- Ethnicity
- Race
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI, kg/m^2)

A patient's age in years is calculated using the integer part of the difference in number of days between the date of informed consent and date of birth divided by 365.25 or is recorded directly on the eCRF. The number and percentage of patients in the following age categories will be presented: 18-29, 30-39, 40-49, 50-59, 60-69, 70-75, < 65, ≥ 65, < median, and ≥ median.

Tabulated demographic characteristics will consist separately of region (North America, Europe), country (Canada, Hungary, Poland, USA, Ukraine) and history of tobacco/nicotine use (current, former, never).

7.2. Medical History

7.2.1. General Medical History

Medical history other than Crohn's disease (CD) will be summarized for the ITT population and will display the number and percentage of patients with a significant history for each body system.

7.2.2. Crohn's Disease History

The following CD history parameters will be summarized for the ITT population using descriptive statistics:

- Age at CD symptom onset (yr)
- Age at CD diagnosis (yr)
- Years since CD symptom onset
- Years since CD diagnosis
- Years since CD diagnosis category (0 - <2, 2 - <5, 5 - <10, 10 - <15, and ≥15)
- CDAI score at baseline
- CDAI score at baseline category (<330 and ≥330)

- Baseline Stool Frequency (daily average)
- Baseline Abdominal Pain (daily average)
- Category of days available for stool frequency and abdominal pain calculations (< 3, 3-6, >=7)
- SES-CD at baseline
- SES-CD at baseline category (< 12 and ≥ 12; ≥ median, < median)
- Baseline PRO2
- Baseline SF&AP
- Prior Corticosteroid use (Y/N)
- Prior Immunomodulator use (Y/N)
- Prior Biologics use (Y/N)
- Prior 5-ASA use (Y/N)
- Prior CD surgery History (Y/N)
- Baseline Fecal Calprotectin (microgram/g)
- Baseline Fecal Calprotectin (microgram/g) category (<250 and ≥250)
- Baseline CRP (mg/L)
- Baseline CRP (mg/L) category (<10 and ≥ 10)
- Baseline Enterocutaneous and/or Perianal Fistulas (Y/N)
- Draining Fistulas (Y/N)
- Non-Draining Fistulas (Y/N)
- Closed Fistulas (Y/N)
- Biological Response (Biologic Primary Non-responder vs All Others)
- Disease Location (Ileum only; Colon only; Ileocolonic (Ileum and Colon))
- Prior CD Surgery (Y/N)

Incomplete diagnosis dates will be imputed as detailed Appendix 1.

7.2.3. Anti-TNF/Biologic Treatment History

The following Anti-TNF/Biologic treatment history parameters will be summarized for the ITT population using descriptive statistics:

- Number and percentage of patients with any Prior Anti-TNF or other Biologic Medications for the treatment of Crohn's Disease
- Previously Treated patients that took Medications Prior to Study Entry, with the number and percentage of patients having type of response (Primary Non-Responder, Secondary Non-Responder, Intolerant) and Length of time (<=1 year; >1 year and <=2 years; > 2 years) separately tabulated
    - Infliximab
    - Adalimumab
    - Certolizumab Pegol
    - Vedolizumab
    - Other

7.3. Protocol Deviations

Deviations from the protocol will be recorded appropriately and tabulated at the end of the study. Protocol deviations may be classified into, but not necessarily limited to, the following categories:

- Inclusion/exclusion criteria deviation
- Patients deemed to have needed to be withdrawn but were not withdrawn
- Incorrect treatment or dose
- Prohibited medication use
- Treatment non-compliance
- Procedure non-compliance

Tabulation and listing of deviations will be done according to ICH E3 [2]. Classification of deviations as important protocol violations (which may alternatively be described as "major deviations") will be done according to Section 10.2 of ICH E3 and will be decided on a case-by-case basis by the Sponsor.

8. TREATMENTS, MEDICATIONS AND NON-TRIAL MEDICAL PROCEDURES

8.1.1. Prior and Concomitant Medications

[redacted]

8.1.2. Non-Trial Medical Procedures

Non-Trial medical procedures will only be listed.

[2] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

8.2. Investigational drug

All patients entering the Induction Period will initiate a 7-day dose titration regimen. This regimen will consist of RPC1063 0.25 mg starting on Study Day 1 for 4 days (1 capsule per day), then RPC1063 0.5 mg starting on Study Day 5 for 3 days (2 capsules per day), followed by RPC1063 1.0 mg beginning on Study Day 8 (1 capsule per day). Patients entering the Extension Period will continue with RPC1063 1.0 mg (1 capsule per day).

8.2.1. Extent of Exposure

Extent of exposure will be summarized for the Safety Population and will include the following:

- Duration of Exposure (Person-Years)
- Number of capsules administered

These outcomes are derived using data as collected in the EDC system. Duration of Exposure in person-years is calculated per-patient as ((Date of Last Dose – Date of First Dose) + 1)/365.25. The number of capsules administered per-patient is directly obtained from the EDC system.

8.2.2. Investigational Drug Compliance

Drug Compliance will be summarized for the Safety Population and will include the following:

- Number of capsules expected
- RPC1063 Compliance Rate

These outcomes are derived using data as collected in the EDC system. Number of capsules expected is directly determined per-patient based on the number of capsules and bottles dispensed to the patient. The RPC1063 compliance rate is calculated per-patient as (number of capsules taken)/(number of capsules expected) x 100. The number of capsules taken is computed as the difference between the number of capsules dispensed at the previous visit and the number of capsules returned to the site at the following visit.

9. EFFICACY ANALYSIS

Unless otherwise stated, the ITT analysis population will be used for efficacy analyses. Due to the open-label nature of the trial and the lack of a control group, efficacy data at all scheduled visits will be summarized and no formal statistical hypothesis testing will be performed.

Certain related endpoints relying on the same fundamental measurement may result in analyses that are continuous in one case and categorical in another case. For example, CDAI scores are the fundamental measurement for the CDAI Change from Baseline endpoint that is described in Section 9.3, and CDAI Change from Baseline is a continuous analysis. On the other hand, CDAI scores are the fundamental measurement for the CDAI Clinical Remission endpoint described in Section 9.4, and the proportion of remitters at a given visit is a categorical analysis.

All efficacy endpoints will be tabulated by scheduled visit.

9.1. Treatment Failure Rules

Final Treatment Failure status will be determined by internal clinical review using the following rules:

1. Any protocol-prohibited change in CD medications including the following:
    a. Post-baseline initiation of, or increase in, corticosteroids to treat worsening CD to a dose greater than the maximum daily dose taken between the Screening and Baseline visits
    b. Prolonged course of systemic corticosteroids > 14 days for treatment of disease other than CD
    c. Initiation of an immune-suppressing therapy including 6-mercaptopurine (6-MP), azathioprine, anti-TNF agents, or vedolizumab
    d. Post-baseline initiation of antibiotics to treat worsening of CD/disease flare
2. Surgical resection of small intestine or colon during the study as a treatment of CD-related symptoms
3. Endoscopic dilation treatment for CD-associated stricture(s) during the study

Treatment failures at Week 12 and Week 52 will be determined by using the above rules. Treatment failure status will be used as a criterion in NRI. Patients identified as Treatment Failures will be listed.

9.2. Handling Endoscopy Data

9.2.1. SES-CD, GHAS, and RHI Related Endpoints

For the primary analysis of SES-CD score along with the sub-scores, only segments evaluated or imputed at both baseline and post-baseline will be summarized as described in section 5.5.5 Handling of Missing Segmental Scores for SES-CD, GHAS, and RHI. This will be referred to as either "Complete Case" or "Paired Segment" analysis. For example, if the rectum and left colon were evaluated at baseline and segments for the rectum, left colon, transverse colon and right colon were evaluated or imputed at Week 12, only the rectum and left colon at baseline and the rectum and left colon at Week 12 would be used to derive SES-CD and the change from baseline to Week 12 in this table.

SES-CD score will also be determined based on all available segments at a given visit without adjusting for the segments available at Baseline. These scores will be referred to as "Robarts Observed Scores".

9.2.2. GHAS and RHI Related Endpoints (exploratory efficacy endpoints)

The sub-scores and total scores for GHAS and RHI will follow the same approach as the SES-CD related endpoints except the imputation of missing segments as they are based on the same concept of evaluating 5 segments as described above.

9.3. Continuous Efficacy Endpoints

For continuous efficacy endpoints, the number of patients (n), mean, standard deviation (SD), standard error (SE), median, minimum and maximum will be presented for the actual values and change from baseline at all scheduled visits. It is noted that percent change from baseline may be displayed for certain endpoint variations, based on the TFL shell specifications. 95% CI presented in efficacy graphs will be computed using the t distribution.

All continuous efficacy endpoints will be tabulated by scheduled visit. This includes (see Table 3) Endoscopic Change, CDAI Change, GHAS Change, RHI Change, CRP Change, and FCP Change. Per Section 5.5.3, efficacy data will be associated with Visits according to analytic visit windows.

In all cases, the primary analysis will be based on observed cases.

The list of continuous efficacy endpoints is shown in Table 5 below:

Table 5. Continuous Endpoints and Imputation Methods

Continuous Efficacy Endpoints	Method(s)
Endoscopic Change (Paired Segments, Total Score)	OC
CDAI Change	OC
SF Change	OC
AP Change	OC
GHAS Change from Baseline (Paired Segments, Total Score)	OC
RHI Change from Baseline (Paired Segments, Total Score)	OC
C-RP Change from Baseline	OC
FCP Change from Baseline	OC
Global RHI Score	OC

9.4. Proportion-based Efficacy Endpoints

For binary categorical efficacy endpoints, the number and percentage of patients achieving the endpoint will be presented, along with a 95% Clopper-Pearson exact confidence interval. This will be done for Weeks 12 and 52 only.

The primary analysis for a given endpoint will be based on non-responder imputation (NRI). Sensitivity analyses around missing data will be observed case analysis.

All proportion-based efficacy endpoints will be tabulated by scheduled visit. The list of proportion-based efficacy endpoints and methods are shown in Table 6 below:

Table 6. Categorical Endpoints and Imputation Methods

Categorical Efficacy Endpoints	Method
Endoscopic Response-25 (Paired Segments)	NRI, OC
Endoscopic Response-25 (Robarts Observed)	NRI,OC
Endoscopic Response-50 (Paired Segments)	NRI, OC
Endoscopic Response-50 (Robarts Observed)	NRI, OC
Endoscopic Remission (Paired Segments)	NRI, OC
Endoscopic Remission (Robarts Observed)	NRI, OC
CDAI Clinical Response	NRI, OC
CDAI Clinical Remission	NRI, OC
PRO2 Clinical Response	NRI
SF&AP Clinical Remission	NRI, OC
GHAS Remission	NRI, OC
RHI Remission	NRI, OC
RHI Mucosal Healing	NRI, OC
RHI Response - by Segment	NRI, OC
RHI Remission by Segment	NRI, OC
C-RP Response-10	NRI, OC
FCP Response-250	NRI, OC

*Note: Endoscopic responses will be determined using both complete cases (paired segments) and Robarts observed scores (all segments) of the SES-CD assessment at Weeks 12 and 52.

For the primary analysis of the endoscopic response and endoscopic remission scores using SES-CD from complete cases, only the sub-scores from segments evaluated or imputed at both baseline and post-baseline (i.e., Paired Segments) will be used to sum the SES-CD for deriving the response as described above in Section 5.5.5. For example, if the segments for the rectum and left colon were evaluated at baseline and segments for the rectum, left colon, transverse colon and right colon were evaluated or imputed at Week 12, only the rectum and left colon sub-scores at Week 12 would be used to derive endoscopic response at Week 12 in this table.

Exploratory subgroup analyses on the select endpoints listed in Section 9.5 will be conducted.

[redacted]

[redacted]

10. SAFETY ANALYSIS

All analyses of safety data will be conducted using the Safety population. Statistical hypothesis testing will not be performed on any safety results. No imputation of missing safety data will be performed except in the case of missing AE onset dates (Appendix 1).

10.1. Adverse Events

A TEAE is any reaction, side effect, or other untoward event, regardless of relationship to investigational drug, which occurs any time during or after the first dose of investigational drug, until 90 days following the last dose of investigational drug.

For an event to be a TEAE, it must meet one of the following conditions:

- Begins on Study Day 1, during or after ingestion of the first dose of investigational drug;
- Begins after Study Day 1; or

- Begins before Study Day 1 and worsens in severity during or after the Study Day 1 ingestion of investigational drug.

AEs with unknown onset dates or unknown end dates will be counted as having occurred during the investigational drug period (i.e., as TEAEs) unless the event resolves before Study Day 1.

Only TEAEs will be presented in AE tables, according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 18.1, system organ class (SOC), and PT. Any AEs that occur prior to Study Day 1 without worsening in severity on or after Study Day 1 should be recorded on the medical history eCRF and will be summarized as part of medical history.

Summaries of incidence of TEAEs will include only one occurrence of a PT per patient, i.e., multiple occurrences of the same PT will be counted only once. As with the PT, multiple occurrences of TEAEs within the same SOC will be counted only once for that SOC.

10.1.1. Incidence of Treatment Emergent Adverse Events

In the tables showing incidence by SOC and PT, SOCs will be sorted by the alphabetical order and PTs will be sorted within SOC in descending order of incidence. For tables showing incidence by PT only, the PTs will be sorted in descending order of incidence.

An overall summary of TEAEs will show the number and percentage of the patients experiencing TEAEs in following categories

- At least one TEAE
- At least one Moderate or Severe TEAE
- At least one Severe TEAE
- At least one Possible, Probable or Related TEAE
- At least one Related TEAE
- At least one Serious TEAE
- At least one Possible, Probable or Related Serious TEAE
- At least one Related Serious TEAE
- At least one TEAE Leading to Discontinuation of Study Drug
- At least one TEAE Leading to Study Withdrawal
- Death
- Death - Possible, Probable or Related to Study Drug

The incidence of all TEAEs along with number of events will be presented by SOC and PT and, separately by PT only and sorted in descending order of number of patients experiencing the TEAE.

10.1.2. Relationship of Adverse Events to Investigational drug

A summary of TEAEs by relationship to investigational drug will be presented in a table by incidence of occurrence. The potential relationships are “Unrelated”, “Unlikely”, “Possible”, “Probable”, and “Related”. A treatment-related TEAE is a TEAE with any relation to investigational drug other than “Unrelated” or “Unlikely”. In the TEAE by relationship table, if a

patient reports multiple occurrences of the same TEAE, only the most related occurrence will be presented. TEAEs that are missing relationship will be presented in the summary table as "Probable" but will be presented in the data listing with a missing relationship. A summary of treatment-related TEAEs by SOC and PT will also be presented.

10.1.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The potential severity levels are "Mild", "Moderate", and "Severe". TEAEs will be classified by severity. In the TEAE severity table, if a patient reported multiple occurrences of the same TEAE, only the most severe occurrence will be presented. TEAEs that are missing severity will be presented in summary tables as "Severe" but will be presented in the data listing with a missing severity. A summary of severe TEAEs by SOC and PT will also be presented.

10.1.4. Serious Adverse Events

Criteria for determining SAEs are defined in the protocol.

A summary of treatment-emergent SAEs will be presented by SOC and PT, and also by SOC and PT and relationship to study drug. SAEs will also be listed separately.

10.1.5. Adverse Events Leading to Treatment Discontinuation

All TEAEs reported with an investigational drug action taken as "Permanently discontinued" will be summarized in a table by PT, and a listing excluding deaths will be presented.

10.1.6. Death

All patient deaths during this trial will be collected and presented in a listing. The information that is presented will include, at minimum, the date of first dose, date of last dose, date of last visit, date of death, cause of death, and relationship to study drug.

10.1.7. Adverse Events of Special Interest

Target treatment emergent adverse events of special interest (AESIs) will be closely monitored in the trial. AESIs include bradycardia and heart conduction abnormalities (e.g., symptomatic bradycardia, 2nd degree AV block, QT prolongation), pulmonary effects (significant decline in forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and diffusing capacity of the lung for carbon monoxide [DLCO] measurements), hepatic effects (confirmed liver function test (LFT) elevations > 3x ULN), macular edema based on abnormal OCT findings or visual signs/symptoms of new onset or worsening macular edema, serious or opportunistic infections and malignancies.

AESIs will be summarized by SOC and PT and presented in a listing.

10.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the standard international (SI) units provided by the central lab. Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together.

Summary tables for hematology, chemistry, and urinalysis including actual values and change and percent change values from Baseline will be presented for clinical laboratory tests collected as numeric values. These summaries will be provided for each visit, highest value, lowest value, and last value.

Hematology and blood chemistry values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory. Categorical urinalysis values will be flagged as "normal" or "abnormal". Categorical laboratory data will be summarized using shift tables where appropriate.

Laboratory data collected at unscheduled visits will be included in listings and will contribute to tables showing changes from Baseline to highest value, lowest value, and last value. The results from safety follow-up visit will not be included in the calculations of highest, lowest, and last values.

10.2.1. Hematology

The following laboratory tests will be included in hematology summary tables:

- Absolute Lymphocyte Count
- Basophils
- Basophils/Leukocytes
- Eosinophils
- Eosinophils/Leukocytes
- Ery. Mean Corpuscular HGB Concentration
- Ery. Mean Corpuscular Hemoglobin
- Ery. Mean Corpuscular Volume
- Erythrocytes
- Hematocrit
- Hemoglobin
- Leukocytes
- Lymphocytes
- Lymphocytes/Leukocytes
- Mean Platelet Volume
- Monocytes
- Monocytes/Leukocytes
- Neutrophils
- Neutrophils/Leukocytes
- Platelets

Actual values, change from baseline, and percent change from baseline will be summarized by visit. Shift tables from baseline, by visit, will be presented. The proportion of patients with abnormalities in Absolute Lymphocyte Count (ALC; ALC < 200 cells/uL; ALC < 500 cells/uL), Absolute Neutrophil Count (ANC; ANC < 1000 cells/uL), and Total WBC (WBC > 20,000 cells/uL) will be presented overall and by visit.

10.2.2. Blood Chemistry

The following laboratory tests will be included in the blood chemistry summary tables:

- Alanine Aminotransferase
- Albumin
- Alkaline Phosphatase
- Amylase
- Aspartate Aminotransferase
- blood Urea Nitrogen
- C-Reactive Protein
- Conjugated Bilirubin
- Creatinine
- Gamma Glutamyl Transferase
- Glucose
- Total Bilirubin

Actual values, change from baseline, and percent change from baseline will be summarized by visit. Shift tables from baseline, by visit, will be presented. The proportion of patients with abnormalities in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) will be presented overall and by visit. Abnormalities in both ALT and AST will be presented for the following categories:

- > 1 x ULN;
- ≥ 2 x ULN;
- ≥ 3 x ULN;
- ≥ 4 x ULN;
- ≥ 5 x ULN;
- ≥ 8 x ULN; and
- ≥ 10 x ULN

A listing will present abnormal chemistry values for all patients.

10.2.3. Coagulation-related parameters

Coagulation panel results (central laboratory) will be summarized continuously for the Screening and Early Termination visits. A listing of abnormal coagulation-related parameters will be provided.

10.2.4. Urinalysis

The following laboratory tests will be included in the urinalysis:

- Specific Gravity
- pH
- Bilirubin
- Glucose
- Ketones
- Leukocytes
- Blood
- Protein
- Urobilinogen
- Urine Color and Appearance
- Nitrate
- Leukocyte Esterase

Actual values, change from baseline, and percent change from baseline will be summarized by visit for pH and Specific Gravity. Shift tables from baseline, by visit, will be presented for Bilirubin, Glucose, Ketones, Leukocytes, Occult Blood, Protein, Specific Gravity, Urobilinogen, and pH.

A listing of urinalysis values will be presented.

10.2.5. Pregnancy Testing and Serology Testing

Serum β-human chorionic gonadotropin (i.e., serum beta hCG) will be collected at Screening for females of childbearing potential. Between scheduled visits, monthly urine pregnancy tests (i.e., urine beta hCG) should be conducted by females of childbearing potential, and if the urine test is positive at the scheduled visit, it should be confirmed with a serum beta hCG test.

Serology testing will be collected at Screening for all patients and will include immunoglobulin G (IgG) antibodies to varicella-zoster virus (VZV), human immunodeficiency virus (HIV), immunoglobulin M (IgM) antibodies to hepatitis A virus (HAV), surface antigen of the hepatitis B virus (HBsAG), anti-hepatitis B core total antibodies (anti-HBc total), hepatitis B virus deoxyribonucleic acid (HBV DNA), and anti-hepatitis C virus (HCV) IgG/IgM.

Serum pregnancy, urine pregnancy, and serology results will be listed only.

10.3. Vital Sign Measurements

The following vital signs measurements will be collected for Day 1 (Baseline, Hour 1, Hour 2, Hour 3, Hour 4, Hour 5, and Hour 6, Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, Week 52, and all visits subsequent to Week 52 according to the Protocol-defined schedule of vital signs assessments:

- Heart Rate (sitting; ‘HR’)
- Systolic Blood Pressure (sitting; ‘SBP’)
- Diastolic Blood Pressure (sitting; ‘DBP’)

The baseline value for a given patient in any tabulation or listing will be the lowest pre-dose value observed on Day 1.

Two separate continuous tabulations will be generated: for Study Day 1, actual values and change from baseline will be summarized continuously for Baseline, Hour 1, Hour 2, Hour 3, Hour 4, Hour 5, Hour 6, and Hour 7. Separately, for the post-baseline visits, the actual values and change from baseline will be summarized continuously for Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, Week 52, and all visits subsequent to Week 52 according to the Protocol-defined schedule of vital signs assessments.

For Study Day 1, Heart Rate will be summarized categorically for the following categories for Day 1 for Hours 1, 2, 3, 4, 5, 6, and Minimum Overall:

- >= 65
- 60-64
- 55-59
- 50-54
- 45-49
- 40-44
- 35-39
- < 35

The proportion of patients requiring extended cardiac monitoring beyond Day 1, Hour 6, based on the criteria in Section 12.1.9. Guidelines for Monitoring Patients Taking Their First Dose of RPC1063 in the protocol , will be summarized categorically and will also be presented in a listing showing the criteria triggering a subject to be included in the listing. A listing of vital signs for the subjects who required extended cardiac monitoring per protocol criteria will be presented.

The number and percentage of patients who meet the criteria for clinically relevant abnormalities for HR, SBP, and DBP will be summarized by visit. The criteria for clinically relevant abnormalities are shown in the following table. All increases and decreases are relative to pre-dose on Day 1.

Table 7. Vital Sign Abnormality Cutoffs

Vital Sign	Criteria for Abnormalities
HR	> 120 bpm < 45 bpm
SBP	> 180 mmHg < 90 mmHg
DBP	> 105 mmHg < 50 mmHg

10.4. Electrocardiogram

The following ECG values will be included for summarization:

- QTcB – Bazett's Correction
- QTcF – Fridericia's Correction
- PR Duration
- QRS Duration
- QT Duration
- RR Duration
- Ventricular Rate

QTcF is the primary measure of corrected QT, with Bazett's correction serving as a supportive measure. For all ECG measurements, actual values and change from baseline will be summarized continuously by visit.

The proportion of patients with ECG outliers will be presented overall and by visit. For this analysis, the categories defined below will be used:

- QT > 480 milliseconds (ms), QT > 500 ms, Female: QTcF > 470 ms, and Male: QTcF > 450 ms
- PR < 120 ms, PR > 200 ms

The interpretation of ECG results will be presented by visit ('Normal', 'Abnormal, not clinically significant', 'Abnormal, clinically significant').

ECG abnormalities upon first dose of study drug will be summarized categorically, with the types of abnormalities sorted alphabetically within each time point.

10.5. Pulmonary Function Testing

The following pulmonary function test outcomes will be summarized continuously:

- Largest forced expiratory volume in 1 second (i.e., FEV_1)
- Percent of predicted FEV_1
- Largest forced vital capacity (i.e., FVC)
- Percent of predicted FVC
- DLCO corrected for hemoglobin

The actual value, change, and percent change will be summarized by visit. It is noted that the percent predicted value for a given outcome is the ratio of the original value relative to the predicted value, reported as a percentage.

DLCO is collected at the local lab for each site where available, 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

An abnormality is defined as percent predicted FEV1 < 70% and <80% of baseline or percent predicted FVC < 70% and <80% of baseline. Abnormalities will be summarized by number and percent by visit and shift tables.

A listing of pulmonary abnormalities will be provided.

10.6. Physical Examination

Physical examination results will be listed only.

10.7. Other Assessments

A summary table of number and percent of patients with dermatological abnormalities by visit will be presented. This table will further include summary of last available value, and an overall summary. Listings of dermatological abnormalities and abnormalities found during optical coherence tomography (OCT) will be provided.

Listings of abnormalities in visual acuity and dilated ophthalmoscopy will be provided.

11. INTERIM ANALYSIS

11.1. Interim Analysis

Due to the open-label nature of this study, there is no formal interim analysis of efficacy for this trial (i.e., no p-values will be produced and no adjustment for Type I error rates is needed).

However, accumulating efficacy and safety results may be summarized and presented at various Congresses, Proceedings, Conferences, or in scholarly journals in an ongoing manner. Also, data may be periodically extracted and summarized for inclusion in regulatory filings, annual safety reports, or abbreviated safety CSRs.

11.2. Data Safety Monitoring Board

An overall summary that may include disposition, safety, and efficacy data from the trial may be presented to an independent DSMB as needed.

12. CLARIFICATIONS/CHANGES TO THE PROTOCOL PLANNED ANALYSES

The primary purpose of this section is to modify and/or clarify items specified in the Protocol [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, Version 5.0, dated May 29, 2019], as follows:

- GHAS and RHI and related endpoints are added to Section 4.2.1
- Protocol Section 6.2. Endpoints

  A treatment failure criteria is defined Section 9.1. Patients identified as Treatment Failures will be listed and a sensitivity analysis of the endoscopic endpoints undertaken.

- Protocol Section 6.2.1 Induction Endpoints (i.e., Week 12)
  - [redacted]
    - [redacted]
    - [redacted]
  - The intestinal mucosa histopathologic features and disease activity endpoints have been revised to reflect two specific measures: the Geboes Histology Activity Score (GHAS) and the Robarts Histopathology Index (RHI)
- Protocol Section 6.2.2 Extension Endpoints (i.e., Week 52)
  - Per Section 4.2.3, all Induction Period endpoints will be replicated for the Extension Period
  - Section 4.2.3 describes additional endpoints for the Extension Period not applicable to the Induction period
  - The endpoints and analyses in Section 9.5 are not discussed in the Protocol
- [redacted]
  - [redacted]

- Protocol Section 13.2 Statistical Methods
  - 13.2.1 General Considerations
    - Imputation for missing efficacy data will be performed as follows:
      - NRI will be used to impute missing binary endpoints and the responses after treatment failure as non-responder. Sensitivity analyses will include observed cases only for select endpoints.
      - Continuous efficacy endpoints will not be imputed.
    - Missing segmental scores for SES-CD, GHAS, and RHI are described in detail in section 5.5.5.
    - There will be no imputation for the safety observations.
- Protocol Section 13.3 Disposition, Demographics, and Baseline Characteristics
  - Treatment compliance will be summarized continuously with respect to the number of capsules taken versus the number of capsules expected. Total dose will not be summarized and categories of compliance will not be considered.
  - Extent of exposure will be summarized with respect to duration of exposure and number of capsules administered
- Protocol Section 13.5 Safety Analysis
  - The overall summary of TEAE's will be repeated by study period (Day 1 through Day 85; Day 86 through Day 365; ≥ Day 366) to show the timing of adverse event onset
- Protocol Section 13.6 Pharmacokinetic Analyses
  - Pharmacokinetic analyses will be governed by a supplemental analysis plan. Inclusion of the results of these analyses in the CSR is discretionary.

[redacted]

[redacted]

APPENDIX 1. IMPUTATION OF PARTIAL AND MISSING DATES

Incomplete Dates of CD Symptom and CD Diagnosis

If day is missing, day will be set to 15th of the month.

If month is missing, month and day will be set to July 1st.

If either imputation above results in a date < informed consent, then impute it as the date of informed consent -1.

Adverse Event

All AE onset dates must be entered on the eCRF as complete dates. In the rare case that all or part of an AE onset date is missing but an AE resolution date is present and after first dose date then the AE onset date will be imputed as follows:

Table 8. Adverse Event Date Imputation Rules

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Date of first dose
year = year of first dose	Missing	Non-missing	Set month to month of first dose
year = year of first dose	Missing	Missing	Set month and day to those of first dose
year < year of first dose	Missing	Non-missing	set month to December
year < year of first dose	Missing	Missing	set month and day to December 31
year > year of first dose	Missing	Non-missing	set month to January
year > year of first dose	Missing	Missing	set month and day to January 1
year = year of first dose	Month = month of first dose	Missing	Set day as day of 1st dose
year = year of first dose	Month < month of first dose	Missing	Set day as last day of onset month
year = year of first dose	Month > month of first dose	Missing	Set day as first day of onset month
year < year of first dose	Non-missing	Missing	Set day as last day of onset month
year > year of first dose	Non-missing	Missing	Set day as first day of onset month

If AE resolution date is present and prior to first dose date, no need to impute incomplete AE start date, as the AE is not treatment emergent and the event should be in the medical history.

Prior and Concomitant Medications

- If year and month are present and day is missing then set day to first day of month for start date, and set day to last day of month for end date

- If year and day are present and month is missing then set month to January for start date, and set month to December for end date
- If year is present and month and day are missing then set month and day to January 1 for start date, and set month and day to December 31 for end date
- Completely missing dates will not be imputed

If start date is completely missing and end date is not prior to the first dose, then the medication will be classified as concomitant; if the end date is missing, then the medication will be classified as concomitant. Medications for which the start and end dates are completely missing will be classified as concomitant.

APPENDIX 2. SIMPLE ENDOSCOPIC SCORE FOR CROHN'S DISEASE (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 narrowings. Each of these components are scored on a scale of 0 to 3 as outlined below:

Table 9. 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

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. Sub-scores for each segment will be derived and used to create SES-CD.

SES-CD sub-scores

- SES-CD rectum
- SES-CD left colon
- SES-CD transverse colon
- SES-CD right colon
- SES-CD ileum

APPENDIX 3. CDAI SCORE CALCULATIONS

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 typically range from 0 to approximately 600, with higher scores indicating greater disease activity. The 8 components used to assess the CDAI, their weighting factors and calculation rules are noted in the table below. The number of stools, abdominal pain and general well-being are patient-reported outcomes which will be entered daily into an e-diary by patients. The Hematocrit component will be coming from the lab data and the other 4 components will be entered by the site at each visit.

Table 10. Score calculations, weights, and rules associated with CDAI, its components, and associated endpoints

Item	Weight	Algorithm
Number of liquid or soft stools (CDAI sub-score)	2	• Use the most recent 7 days prior to the visit date in Rave EDC database; excluding the day prior and the day of the endoscopy, as applicable. • *Define: SF = average daily stool score = average of the number of liquid/soft stools for the available days in the 7-day window* • If there are less than 3 days with non-missing values, then set SF to missing • If there are 7 days of data available, then the CDAI sub-score is equal to the sum of the 7 days*2; otherwise, the CDAI sub-score is equal to the average daily stool score*7*2; as a formula, this is written as CDAI sub-score = SF*7*2 in both cases
Abdominal pain (CDAI sub-score)	5	• Use the most recent 7 days prior to the visit date in Rave EDC database; excluding the day prior and the day of the endoscopy, as applicable. • *Define: AP = average daily abdominal pain score = average of the abdominal pain level for the available days in the 7-day window* • If there are less than 3 days with non-missing values, then set AP to missing

		• If there are 7 days of data available, then the CDAI sub-score is equal to the sum of the 7 days*5; otherwise, the CDAI sub-score is equal to the average daily abdominal pain score*7*5; as a formula, this is written as CDAI sub-score = AP*7*5 in both cases
General well-being (CDAI sub-score)	7	• Use the most recent 7 days prior to the visit date in Rave EDC database; excluding the day prior and the day of the endoscopy, as applicable. • *Define: GW = average daily general well-being score = average of the general well-being level for the available days in the 7-day window* • If there are less than 3 days with non-missing values, then set GW to missing • If there are 7 days of data available, then the CDAI sub-score is equal to the sum of the 7days*7; otherwise, the CDAI sub-score is equal to the average daily general well-being score *7*7; as a formula, this is written as CDAI sub-score = GW*7*7 in both cases
Presence of complications* (CDAI sub-score)	20	• Sum=Total of the number of checked complications • CDAI sub-score = Sum * 20.
Taking diarrhea meds* (CDAI sub-score)	30	• Variable: Yes=1; No=0 • CDAI sub-score = Variable * 30
Abdominal mass* (CDAI sub-score)	10	• Variable: No=0; Questionable=2; Definite=5 • CDAI sub-score = Variable * 10
Hematocrit (CDAI sub-score)	6	• Hematocrit (HCT) is obtained from the Hematology lab panel and can be found in the SDTM LB domain

		• If HCT is missing, use the last non-missing value immediately preceding the time point; if the immediately preceding time point value is missing too, then set to missing • Men: CDAI sub-score = (47 - HCT) * 6 • Women: CDAI sub-score = (42 - HCT) * 6 • If CDAI sub-score is < 0, it will be recorded as 0
Percentage deviation from standard weight (CDAI sub-score)	1	• The standard weight table was provided by Celgene to ERT for integration into the SitePro tablet algorithms (height in cm and weight in kg); ERT created four conversion tables which will be used in statistical analysis so that the %deviation from standard weight is automatically calculated by the ERT system, which allows ERT to calculate estimated CDAI scores embedded in their monthly SitePro.sas7bdat datasets. It is noted that these are CDAI estimates only and not for use in production TFLs. • If weight is missing, use the last non-missing %deviation from standard weight value immediately preceding the time point; if the immediately preceding time point value is missing too, then set %deviation from standard weight to missing • CDAI sub-score = %deviation from standard weight; it should be >=-10 (i.e., -10, -9; if calculated value is <-10, it will be recorded as -10) in all cases
CDAI (CDAI endpoint)	n/a	• CDAI endpoint = sum of the above 8 CDAI sub-scores. If any of the 8 sub-scores are missing, then the CDAI endpoint score is missing.
PRO2 (CDAI associated endpoint)	n/a	• PRO2 = *weighted* sum of SF and AP = SF*7*2 + AP*7*5. If either SF or AP are missing, then PRO2 is missing.
SF/AP (CDAI associated endpoint – included only for reference)	n/a	• SF/AP = *unweighted* sum of SF and AP = SF + AP. If either SF or AP are missing, then SF+AP is missing.

*: The visit date that is used to calculate the relative study day will be taken from Rave, instead of the system generated date in Sitepro.

In computing number of liquid or soft stools, abdominal pain, and general well-being, the date corresponding to Day 1 will be used as the baseline date. Dates for post-baseline visits will be obtained from the dates when CDAI components of extra-intestinal manifestations, opiate for diarrhea, abdominal mass findings, and weight were assessed at the site.

For computing the CDAI total, following steps are followed for combining the individual components:

- For Baseline visit, the components excluding hematocrit will be merged by patient, visit, and analysis date. For post-Baseline visits, components excluding hematocrit will be merged by patient, visit, analysis visit, analysis date, and imputation. Then the seven components are summed.
- Merge with hematocrit values by patient for the analysis visit at Baseline, and patient, visit, analysis visit, analysis date, and imputation, for post-Baseline visits.
- Add hematocrit value to the sum of the seven components from previous steps.

APPENDIX 4. GEBOES HISTOLOGY ACTIVITY INDEX AND ROBARTS HISTOPATHOLOGY INDEX

The following tables give details of the scoring for the Global Histologic Disease Activity Score (GHAS)[3,4] and a newly developed scoring system entitled the Robarts Histopathology Index (RHI)[5]. Higher numbers correspond to more inflammation and mucosal damage. For each CD segment, the GHAS score can be treated as a continuous measure on a 16 point scale. For each CD segment, the RHI score can be treated as a continuous measure on a 33 point scale. Scoring for both indices will be performed for each segment (i.e., ileum, right, transverse, left (descending and sigmoid), and rectum) that is visualized and for which biopsy samples are available. Similar to the SES-CD, sub-scores for each segment will be derived.

The eight components used to assess the per-CD segment GHAS score are noted in the table below. The maximum per-CD segment total score is 16.

Table 11. GHAS Grading System

GHAS Descriptors and Levels	
Epithelial damage	0: Normal 1: Focal Pathology 2: Extensive Pathology
Architectural changes	0: Normal 1: Moderately disturbed (<50%) 2: Severely disturbed (>50%)
Infiltration of mononuclear cells in the lamina propria	0: Normal 1: Moderately increase 2: Severe increase
Infiltration of polypmorphonuclear cells in the lamina propria	0: Normal 1: Moderately increase 2: Severe increase
Polypmorphonuclear cells in epithelium	0: Normal 1: In surface epithelium 2: Cryptitis 3: Crypt abscess
Presence of erosion and/or ulcers	0: No 1: Yes
Presence of granuloma	0: No 1: Yes
Number of biopsy specimens affected	0: None (0 of 6) 1: ≤3% (1 or 2 of 6) 2: 33-66% (3 or 4 of 6) 3:>66% (5 or 6 of 6)

[1] [redacted]

Exploratory GHAS Histologic Remission (no active inflammation in a measured segment) is defined in the following table, where the max overall GHAS score in a given segment must be less than or equal to 8, and each segment meets this standard:

Table 12. Per-CD Segment GHAS Scores Allowed for Histologic Remission

Epithelial damage	0
Architectural changes	0-2
Infiltration of mononuclear cells in the lamina propria	0-2
Infiltration of polypmorphonuclear cells in the lamina propria	0
Polypmorphonuclear cells in epithelium	0
Presence of erosion and/or ulcers	0
Presence of granuloma	0-1
Number of biopsy specimens affected	0-3

The four components used to assess the per-CD segment RHI score are noted in the table below. The maximum per-CD segment total score is 33.

Table 13. Robarts Histopathology Index (RHI) Grading System

Subcomponent Descriptors	Scores	Weighting factor
Chronic inflammatory infiltrate	0=No increase 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	1
Lamina propria neutrophils	0= None 1= Mild but unequivocal increase 2=Moderate increase 3=Marked increase	2
Neutrophils in epithelium	0=None 1 = <5% crypts involved 2= <50% crypts involved 3= >50% crypts involved	3
Erosion or ulceration	0=No erosion, ulceration or granulation tissue 1=Recovering epithelium + adjacent inflammation OR probable erosion-focally stripped 2=Unequivocal erosion 3=Ulcer or granulation tissue	5

An exploratory RHI Histologic Remission (no active inflammation in a measured segment) is defined in the following table. The maximum per-CD segment RHI score allowable for a segment to qualify for RHI Histologic Remission is 3. A patient not meeting at least one of the criteria 2, 3, or 4, below in a segment is defined as a non-RHI remitter for that segment. Note that criteria 1 is always met.

Table 14. Per-CD Segment RHI Scores Allowed for Histologic Remission

Subcomponent Descriptors	Scores	Weighting factor
Chronic inflammatory infiltrate	0-3	1
Lamina propria neutrophils	0	2
Neutrophils in epithelium	0	3
Erosion or ulceration	0	5

Global RHI Score

Global RHI Score is a weighted sum of the worst, i.e., the highest, of each of the four disease component scores across the four colonic segments, rectum, left colon, transverse colon, and right colon. Same weighting factors used in computing the RHI Score is used.

Global RHI Score =1x highest Chronic inflammatory infiltrate score + 2x highest Lamina propria neutrophils score + 3x highest Neutrophils in epithelium score + 5x highest Erosion or ulceration score.

APPENDIX 5. DOCUMENT REVISION HISTORY

Version	Date	Notes/Revisions
1.0	March 03 2016	Initial version.
1.1	November 23 2016	Updated with details and additional analyses.
1.2	January 26 2017	Updated with details on missing data and other details.
1.3	June 1, 2018	Updated to reflect the Week 12 and Week 52 summary tables generated for topline analyses, definition of treatment failure, as well as to reflect endpoint alterations and additional details regarding CDAI, SES-CD, GHAS, and RHI algorithms. Analysis of compliance rate categories has been excluded. Following endpoints have been removed from the SAP • PRO CD SF+AP response-25 • PRO CD SF+AP response-50 • PRO CD SF+AP response-30 + 2P • PRO2 CD response-25 • SF&AP clinical response-2 • SF&AP clinical response-1 • Endoscopic remission-2 • Histologic improvement • Histologic response Following endpoints have been added to the SAP • CRP-response-10 • FCP response-250 • Fistula Response • GHAS Improvement • GHAS Remission • RHI Improvement • RHI Response • RHI Remission • Global RHI Score • RHI Mucosal Healing
1.4	August 28, 2019	LOCF removed. Treatment Failure rule is used in NRI Efficacy graphs added
1.5	January 06, 2020	Changes from data review meeting • PFT abnormality has been revised • Missing segment imputation of SES-CD has been added

		• Lower bound of 0 for Hematocrit sub-score of CDAI has been added • Treatment failure criteria has been revised • RHI response analysis on all patients has been removed • RHI remission by segment for subset of segment score > 3 is replaced by RHI remission by segment for non-RHI remitters • CRP Change among patients having CRP ≥ 10 mg/L at Baseline has been added • Analysis window has been added to Safety follow-up visits • Unscheduled and early termination visits are included in all analysis windows • Patients requiring cardiac monitoring is determined programmatically • Listing of non-trial procedures added • Section on PK analysis is removed and combined with Section on PD • Description of SDTM data in Section 5 is removed