STATISTICAL ANALYSIS PLAN

RedHill Biopharma Ltd.
21 Ha'arba'a St.,
Tel-Aviv 64739, Israel

An Open Label Study to Assess the Efficacy and Safety of Fixed-Dose Combination RHB-104 in Subjects with Active Crohn's Disease Despite 26 Weeks of Participation in the MAP US RHB-104-01 Study

Protocol No. RHB-104-04

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE*

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REVISION HISTORY

This is first version

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Term
5-ASA	5-acetyl salicylic acid
6-MP	6-mercaptopurine
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase
AST (SGOT)	Aspartate Aminotransferase
ATC	Anatomical–Therapeutic–Chemical
bid	Twice-daily
BPM	Beats per Minute
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
°C	Celsius
C. difficile	*Clostridium difficile*
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
cm	Centimeter
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
°F	Fahrenheit

Abbreviation	Term
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ITT	Intent-to-Treat
kg	Kilogram
L	Liter
lb	Pound
LDH	Lactate Dehydrogenase
MAP	*Mycobacterium avium subsp. paratuberculosis*
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
n	Number of Subjects
Min	Minimum
PCR	Polymerase Chain Reaction
PCS	Physical Component Summary
QD	Once-Daily
QTc	Corrected Q-T Interval
QTcF	Corrected Q-T Interval using Fridericia's Formula
RHB	RedHill Biopharma Ltd.
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SES-CD	Simple Endoscopic Score for Crohn’s Disease
SF-36	Short Form-36 Health Survey

Abbreviation	Term
SOC	System Organ Class
SOP	Standard Operating Procedure
TB	*Mycobacterium Tuberculosis*
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings, Figures
TNF	Tumor Necrosis Factor
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VF	Ventricular Fibrillation
WBC	White Blood Cell
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary coding system

1. INTRODUCTION

Crohn's Disease (CD) is an inflammatory bowel disease (IBD) that is serious, debilitating, and potentially life-threatening. The disease is termed a “disease of the young” because it usually strikes children, teens, and young adults. Typically onset is between the ages of 15 to 25 years. Its inflammation can cause severe pain, diarrhea, and other intestinal problems. CD affects men and women equally and appears to show a familial predisposition. Approximately 20-30% of people with CD have a direct blood relative with some form of IBD. World-wide, an estimated 1.4 million people suffer from CD (700,000 US) and the number of sufferers is growing at a rate of at least 1% each year. The disease is now considered to be the second most common chronic inflammatory disorder after rheumatoid arthritis.

One of the potential causes of CD is thought to be gastrointestinal infection with *Mycobacterium avium subspecies paratuberculosis* (MAP) and mycobacterial molecules have been shown to dysregulate immune signaling pathways as part of the organism’s evolved survival strategy. MAP has been difficult to isolate from CD patients and it is postulated that it asserts its pathological effect either as an infectious agent or by modifying local cytokine responses.

One of the hindrances to testing for MAP infection in CD patients is that MAP is a very slow growing mycobacterium. MAP shed their cell walls when they infect humans, a tactic that enables them to escape identification and attack by human immune system defenses.

Studies conducted to demonstrate the presence of MAP noted it in 55.4% (range 16-92%) of CD subjects vs. 8.2% (range of 0-49%) of control groups across multiple diagnostic specimens e.g. blood, tissue and culture. Recent work in Israel, Japan, and Ireland has shown that human tissue and white cells can be infected with MAP and this infection results in cytokine production, especially TNF-α and therefore indicates that MAP plays a role in CD.

Current therapies for the treatment of CD aim towards alleviation of the disease symptoms and offer limited efficacy while often causing significant side effects. In addition, the cost of a number of these available therapies is prohibitive, thereby providing limited access to some patients. As a result, there continues to be a significant unmet need for more effective disease management of CD.

Several studies evaluating antimicrobial treatment directed at MAP to treat patients with CD have been reported. Given their slow growth and periods of latency, treatment of mycobacterial diseases requires multiple antibiotics including triple therapy to avoid the development of resistance.

RHB-104 consists of three antimicrobial agents with known activity against mycobacteria, i.e., clarithromycin, rifabutin, and clofazimine. The rationale for the development of RHB-104 is to demonstrate the efficacy of an antimicrobial therapy consisting of clarithromycin: 95mg, rifabutin: 45mg, and clofazimine: 10mg in the treatment of CD patients. These active ingredients and doses were selected to maximize therapeutic effectiveness against MAP. The dosing rationale of each active ingredient is supported by the following:

- prescriber information for each active ingredient
- the study by Selby et al. utilizing a sub-optimal treatment regimen
- a long-term, retrospective Australian study where 52 subjects were treated for up to nine years on this therapy

Subjects who have completed 26 weeks of blinded study drug administration in the RHB-104-01 study (MAP US) and remain out of remission with CDAI ≥150 will be eligible for participation in this study designed to offer open label therapy with active RHB-104.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to estimate the remission rate, defined as a CDAI score of less than 150, at 16 weeks after the initiation of the open-label phase.

2.1.2 Secondary Objective

The secondary objective is to estimate the response rate of patients, defined by a reduction of CDAI score of ≥100 points at week 16 after the initiation of the open-label phase.

2.1.3 Selected Other Secondary Objectives

1. To estimate the average duration of remission among participants.
2. To estimate the average time to first response among participants.
3. To estimate the average duration of response among participants.
4. To estimate the proportion of participants who maintain a state of remission from week 16 through week 52.

2.1.4 Selected Other Objectives

MAP Detection:

1. To estimate the proportion of subjects with a MAP positive blood PCR assay at baseline (week 0 of the open label phase).
2. To estimate the proportion of subjects with a change in MAP blood PCR assay status after 16 weeks of treatment compared to baseline (week 0 of the open label phase).
3. To estimate the proportion of subjects with a change in MAP blood PCR assay status after 52 weeks of treatment compared to baseline (week 0 of the open label phase).
4. To make sequential comparisons of MAP blood PCR assay results per subject.
5. To estimate the proportion of enrolled subjects with a MAP positive blood culture at baseline (week 0 of the open label phase).
6. To estimate the proportion of subjects with a change in MAP blood culture status after 26 weeks of treatment compared to baseline (week 0 of the open label phase).
7. To estimate the proportion of subjects with a change in MAP blood culture status after 52 weeks of treatment compared to baseline (week 0 of the open label phase).

Because the buffy coat is the actual component of blood that is cultured, MAP blood culture should be considered equivalent to MAP buffy coat culture. Because the development of a MAP

blood PCR assay is still in progress, MAP detection objectives 1-4 will comprise the contents of a later report and will not be addressed in tables, listings, or figures of this clinical study report.

Endoscopic Changes in Those Subjects Who Undergo Colonoscopy:

8. To estimate the change from baseline in the mean Crohn's Disease Endoscopic Index of Severity (CDEIS) after 16 and 52 weeks of treatment).
9. To estimate the change from baseline in the total Simple Endoscopic Activity Score weeks (SES-CD) after 16 and 52 weeks of treatment.
10. To make a comparison of success rates of (ΔCDEIS and SES-CD) defined by 25% and 50% improvements.
11. To estimate the correlation between the change from baseline in the endoscopic index (ΔCDEIS) and the clinical index (ΔCDAI) after 16 and 52 weeks of treatment.
12. To make a comparison of success rates of (ΔCDEIS) defined by 25% and 50% improvements and CDAI defined remission.
13. To make a comparison of success rates of (ΔCDEIS) defined by 25% and 50% improvements and CDAI defined response.
14. To make a comparison of success rates of (ΔSES-CD) defined by 25% and 50% improvements and CDAI defined remission.
15. To make a comparison of success rates of (ΔSES-CD) defined by 25% and 50% improvements and CDAI defined response.

2.1.5 Safety Objective

Assess the safety impact of treatment with RHB-104.

2.2 Outcomes/Endpoints

The outcome endpoints for summaries by treatment from the parent study (RHB-104 treatment and Placebo) and overall are grouped into 4 families based on level of objectives: (i) primary endpoint; (ii) key secondary endpoint; (iii) selected other secondary endpoints; and (iv) selected other endpoints.

2.2.1 Primary Endpoint/Variable: Remission

In general use of rescue medication is considered as treatment failure (not achieving remission or response) if there are any new use of rescue medication to treat CD or increased rescue medication dose from baseline prior to any remission or response assessment. Please refer to section 6.1.6 for more details.

The primary variable is the proportion of subjects who experienced remission at Week 16 after the initiation of open-label phase, where remission is defined as a subject having a Crohn's Disease Activity Index (CDAI) score of <150. Subjects who have a Week 16 CDAI measurement ≥ 150 or who do not have a CDAI measurement at Week 16 will be classified as not having achieved remission at that time point. Initiation of open-label phase is the first dosing time of open-label phase and from here and after it would be reference as initiation.

The CDAI is used to assess the activity of CD; higher scores indicate more active disease.

2.2.2 Key Secondary Endpoint/Variable

The key secondary variable is the proportion of subjects who experienced response at week 16 after initiation, where response is defined as reduction from baseline of ≥100 in CDAI score. Subjects who have a change from baseline to week 16 in CDAI score which is not a reduction of ≥ 100 or who do not have a change from baseline to week 16 in CDAI score will be classified as not having experienced response at that time point.

2.2.3 Selected Other Secondary Endpoints/Variables

- Time to remission – Number of weeks after initiation that a subject first records a state of remission (CDAI score < 150). It will be calculated as the date on which remission is first observed minus the date of the first dosing date plus 1 day, divided by 7. For subjects still on study and not achieved remission at the time of assessment, time to remission will be censored at the date of the last assessment of CDAI score.
- Duration of remission – The number of weeks the subject is in remission (CDAI score < 150). It will be calculated as the first date following remission at which CDAI is ≥150 minus the date of remission, plus 1 day, divided by 7. Those subjects who experienced remission and continue to be in remission at the time of their last CDAI assessment will be censored at the date of their last CDAI assessment. Duration of remission will be calculated only for patients achieving remission.
- Time to response – Number of weeks after initiation that a subject first achieves a state of response (a reduction from baseline of ≥100 in CDAI score). It will be calculated as the date on which response is first observed minus the date of the first dose, plus 1 day, divided by 7. For those subjects who have not experienced response, time to response will be censored at the date of the last assessment of CDAI score.
- Duration of response – Time in weeks that a subject is in a state of response (a reduction from baseline of ≥ 100 in CDAI score). It will be calculated as the first date following response at which the reduction from baseline in CDAI is <100 minus the date of response, plus 1 day, divided by 7. Those subjects who experienced response and continue to be in response at the time of their last CDAI assessment will be censored at the date of their last CDAI assessment. Duration of response will be calculated only for patients achieved response.
- Proportion of subjects experienced maintenance of remission (CDAI score < 150) from week 16 through week 52. Subjects experiencing a CDAI score ≥ 150 at any visit time point assessment between week 16 and week 52 or have no CDAI measurement week 16 or week 52 will be considered as having not achieved maintenance of remission.

2.2.4 Selected Other Endpoints/Variables

2.2.4.1 Map Detection Endpoints/Variable

Mycobacterium avium subsp. paratuberculosis (MAP) detection parameters include the following with baseline defined as week 0 of the open label phase:

- Proportion of subjects with positive MAP buffy coat culture at baseline, weeks 26 and 52.

- Proportion of subjects with a change in MAP buffy coat culture after 26 and 52 weeks of treatment compared to baseline.

2.2.4.2 Endoscopic Change Endpoint/Variables

- Change from baseline to week 16 and 52 in Crohn's Disease Endoscopic Index of Severity (CDEIS) and Simple Endoscopic Score for Crohn's Disease (SES-CD). The CDEIS and SES-CD are endoscopic scoring systems for the assessment of CD.

- Success rate by 25% improved in CDEIS from baseline to week 16 and 52. Success is achieved if the CDEIS score is decreased by 25%.

- Success rate by 50% improved in CDEIS from baseline to week 16 and 52. Success is achieved if the CDEIS score is decreased by 50%.

- Success rate by 25% improved in SES-CD from baseline to week 16 and 52. Success is achieved if the SES-CD score is decreased by 25%.

- Success rate by 50% improved in SES-CD from baseline to week 16 and 52. Success is achieved if the SES-CD score is decreased by 50%.

- Comparison of success rate of by 25% and 50% improved in CDEIS from baseline to week 16 and 52 vs CDAI defined remission.

- Comparison of success rate of by 25% and 50% improved in CDEIS from baseline to week 16 and 52 vs CDAI defined response.

- Comparison of success rate of by 25% and 50% improved in SES-CD from baseline to week 16 and 52 vs CDAI defined remission.

- Comparison of success rate of by 25% and 50% improved in SES-CD from baseline to week 16 and 52 vs CDAI defined response.

2.2.4.3 Health Related Quality of Life Endpoint/Variables

- The Short Form-36 Health Survey (SF-36) domain and component scores at week 16 and 52.

- Change from baseline in the total IBDQ score to week 16 and 52. Inflammatory Bowel Disease Questionnaire (IBDQ) score is designed to measure effects of subject's inflammatory bowel disease on their daily functions and quality of life during last 2 weeks.

2.2.4.4 Markers of Inflammation Endpoint/Variables

Inflammation parameters include the following:

- Change from baseline in C-reactive protein (CRP)
- Change from baseline in fecal calprotectin

2.2.5 Safety Endpoints/Variables

Safety parameters include the following:

- Incidence of adverse events
- Laboratory parameters (hematology, chemistry, urinalysis)
- Clostridium difficile toxin
- Vital signs
- ECG
- Physical examination
- Concomitant medications

3. STUDY DESIGN

This is an open label, multicenter, Phase III, study designed to evaluate the efficacy and safety of RHB-104 to treat subjects with active CD as defined by CDAI ≥ 150 despite 26 weeks of treatment with study drug in RedHill Biopharma Study RHB-104-01. RHB-104 consists of 3 antibiotics with activity against *Mycobacterium avium subsp. Paratuberculosi*s (MAP), a potential cause of CD. Eligible subjects with active CD who have completed 26 weeks of study drug as part of the RHB-104-01 study will receive up to 52 weeks of open label RHB-104. Subjects enrolled in the open label study may have current CD therapies adjusted or withdrawn as clinically indicated by their local investigator after 8 weeks of open label RHB-104 treatment. Sites should begin tapering steroids upon completion of 4 weeks of RHB-104 treatment with the goal of being steroid free by week 14 – Refer to Appendix 13 of protocol.

MAP are slow growing mycobacteria without a proven antibiotic treatment, and the duration of antibiotic treatment required to achieve remission in subjects with CD caused by MAP is believed to be approximately 16-26 weeks. Subjects with response at week 26 may ultimately achieve remission at a later time point with continued treatment for MAP. Similarly, some subjects may achieve response or achieve remission prior to week 26. This study is designed to assess response, remission, and maintenance of remission in subjects on open label RHB-104 through week 52, as well as corticosteroid free remission at week 16.

Blood samples will be collected at Screening and at every visit after the initial 8 weeks of treatment to test for MAP in the serum using a polymerase chain reaction (PCR) assay. Similarly, MAP cultures will be prepared from whole blood collected at Screening and at weeks 16, 26 and 52.

Safety of the fixed-dose combination product, RHB-104, will also be assessed.

Colonoscopy will be done in consenting subjects at baseline and after 16 and 52 weeks of open label RHB-104 to assess for mucosal healing as well as MAP status via PCR and culture.

4. SCHEDULE OF ASSESSMENTS AND TREATMENT ASSIGNMENT

4.1 Schedule of Assessments

Appendix 1 provides reference information from eCRF guidelines about subject data migration from the parent study.

The study schedule is summarized in the study visit schedule table on next page.

4.1.1 Study Visit Schedule

	Screening / Opt Screening / Visit Week 26 of RHB-104-01	Baseline Day 1 / Week 0[2]	Week 2	Week 4	Week 8	Week 16	Week 26	Week 39	Week 52	Week 56
Study Visit Window	(up to 21 days before BL if initial colonoscopy is performed)	Up to 21 days post SCR	± 3 days	± 3 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Informed Consent	X									
Inclusion/ Exclusion Criteria Demography, Medical History	X	X								
Concomitant Medications Assessment		X[3]	X	X	X	X	X	X	X	X
Vital Signs and Physical Exam.	X[1]	X	X	X	X	X	X	X	X	X
Adverse Event Assessments		X[3]	X	X	X	X	X	X	X	
Diary Dispensing (AE/ConMed)		X	X	X	X	X	X	X	X	X
Steroid Status		X				X	X	X	X	X
CDAI assessment	X[1]				X	X	X	X	X	X
CDAI Diary Dispensing[9]					X	X	X	X	X	
Subject Assessments: IBDQ and SF-36	X[1]					X	X		X	
Uveitis Assessment	X[1]		X	X	X	X	X	X	X	X
ECG[10]	X[1]			X		X			X	X
Hematology and Biochemistry	X[1]		X	X	X	X	X	X	X	X
Urinalysis[11]	X[1]		X	X	X	X	X	X	X	X
C-Reactive Protein (CRP)	X[1]					X	X	X	X	
MAP Testing Blood (PCR) with Add'l Sample for Future Use	X[1]				X	X	X	X	X	X
MAP culture from blood	X[1]					X	X		X	
Fecal calprotectin	X[1]					X	X		X	
***C. difficile* Testing**	X[1]						X		X	
Pregnancy Test Urine	X[1]	X	X	X	X	X	X	X	X	X
Optional Colonoscopy and CDEIS/SES-CD; store images	X[4]					X[5]			X[8]	
IWRS Entry		X[7]		X[8]			X[8]			
Study Drug Dispensing		X	X	X	X	X	X	X		
Dispensing of Drug Administration Instructions[12]		X	X							
Drug Return & Accountability		X[13]	X	X	X	X	X	X	X	
Review of stool sampling technique					X	X		X		
Telephone reminder of dose escalation		Day 7	Day 21							

[1] Procedure performed as part of RHB-104-01
[2] Baseline visit should be scheduled once the RHB-104-01 Wk26 / RHB-104-04 Screening CDAI score has been calculated (using RHB-104-01 Wk26 hematocrit value).
[3] Ongoing AEs/ConMeds from RHB-104-01 should be captured in RHB-104-04 eCRF (AEs & ConMeds for RHB-104-01 are captured in -01 eCRF up to day prior to -04 BL)
[4] The colonoscopy must be performed on or before the Baseline or Week 0 visit and must not interfere with CDAI data collection. If applicable, biopsies may be collected as part of the RHB-104-01 study.
[5] In consenting subjects, colonoscopy must be performed up to 14 days after visit Week 16.
[8] In consenting subjects, colonoscopy must be performed a minimum of 8 days and a maximum of 20 days prior to visit Week 52.
[7] IWRS must be accessed to register the assignment & dispensing of an Open-Label start-up kit, following confirmation of eligibility.
[8] IWRS must be accessed to register the dispensing of an Open-Label maintenance kit.
[9] CDAI: Subjects will complete a CDAI diary for the 7 full days preceding their next study visit. To ensure compliance, site personnel will contact subjects prior to initiation of the CDAI-recording period, to review the process for adequate CDAI data collection.
[10] ECG: Five minute continuous digital 12-lead ECG after resting 10 minutes in a supine position
[11] Urine Testing: Dipstick test only, unless results are abnormal.
[12] Site staff must discuss and review Drug Administration Instructions with subjects, both at drug dispensing and compliance evaluation, during dose escalation.
[13] Study drug return of maintenance kit #2 bottles (RHB-104-01) and accountability

4.2 Dosage and Administration of Study Drug

The target dose of RHB-104 is 5 capsules administered bid. In order to reach this target with minimal adverse effects, subjects who received placebo during the RHB-104-01 study will be titrated up over the first 4 weeks of treatment, and the dose will remain stable thereafter. Subjects who received RHB-104 will continue to receive RHB-104. In order to maintain blinding in the RHB-104-01 study all subjects will receive 5 blinded capsules bid for the duration of the RHB-104-04 study as detailed below. The study drug will be taken with food. Subjects who fail dose escalation to 5 capsules bid will be considered treatment failures and withdrawn from the study.

Blinded bid Dose Titration and Maintenance Dosing in RHB-104-04 is

		RHB-104-04 START-UP KIT (Weeks 1-4)				*MAINTENANCE KITS (Weeks 5-52)*
		Weeks				
		1	2	3	4	5-52
		Active Daily Dose (mg)				
BLINDED ACTIVE ARM (ACTIVE + ACTIVE)	RHB-104 Clarithromycin Rifabutin Clofazimine	950mg 450mg 100mg	950mg 450mg 100mg	950mg 450mg 100mg	950mg 450mg 100mg	950mg 450mg 100mg
		# Capsules Taken (daily)				
	Bottle 1	8 capsules RHB-104	6 capsules RHB-104	4 capsules RHB-104	2 capsules RHB-104	10 capsules RHB-104
	Bottle 2	2 capsules RHB-104	4 capsules RHB-104	6 capsules RHB-104	8 capsules RHB-104	
OR		**Active Daily Dose (mg)**				
BLINDED PLACEBO ARM (PBO + ACTIVE)	RHB-104 Clarithromycin Rifabutin Clofazimine	190mg 90mg 20mg	380mg 180mg 40mg	570mg 270mg 60mg	760mg 360mg 80mg	950mg 450mg 100mg
		# Capsules Taken (daily)				
	Bottle 1	8 capsules PLACEBO	6 capsules PLACEBO	4 capsules PLACEBO	2 capsules PLACEBO	10 capsules RHB-104
	Bottle 2	2 capsules RHB-104	4 capsules RHB-104	6 capsules RHB-104	8 capsules RHB-104	

4.3 Subject Number

Subjects will maintain the identification number that was assigned in RHB-104-01.

5. ANALYSIS POPULATIONS

All subjects who signed informed consent will be included in the disposition table counts. The following populations will be used for data analysis.

The Intent-to-Treat (ITT) Population: The ITT population is defined as all subjects who are enrolled in this open-label study and signed the consent form. Efficacy endpoint analyses will be based on ITT population or specified otherwise.

The Safety Population (SAF): The safety population includes subjects who received any amount of study medication. The safety analyses will be based on the SAF population.

6. STATISTICAL METHODOLOGY

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

In general, if there is disagreement between this SAP and the statistical methods outlined in the protocol, the SAP would supersede the protocol.

Descriptive statistics summary results will be produced and presented for all the data collected on the different assessments that include demographics, baseline characteristics, concomitant medications, outcome, and safety endpoints. Continuous data summary descriptive statistics will include the number of observations, means, standard deviations, medians, and ranges. Categorical variables will be summarized with frequencies and percentages or specified otherwise.

In the parent study, there was one randomization stratification factor, use of protocol permitted anti-TNF agents (yes/no). In the current study, treatment comparisons will be performed without taking this stratification factor into consideration unless specified otherwise.

All statistical analyses will be performed using SAS statistical software (Version 9.4 or an updated latest higher version available at the time of analysis). Adverse events will be coded using the most recent MedDRA version available at the time of analysis. Concomitant medications will be coded using the most recent version of World Health Organization (WHO) Drug dictionary. The actual version of each dictionary will be footnoted in the respective outputs.

6.1.2 Baseline Definition

For subject who received any dose of study drug, baseline is the last non-missing result prior to first dose including the data collected during the parent study for SES-CD, CDEIS, Calprotectin, CRP and all lab assessment. For subjects who are enrolled into this open-label study but never received any study drug, baseline is either assessment collected at baseline visit if available or screening visit or as specified otherwise.

For fecal calprotectin, the baseline is the last available assessment up to day 3.

6.1.3 Missing Data and Handling of Dropouts

All available outcome and safety data will be included in data listings and tabulations.

CDAI Missing Data:

The computation of CDAI requires 7 days of consecutive diary daily data. For subjects with CDAI diary data reported that is less than 7 days of data, the reported data will be standardized to 7 days by dividing the sum of CDAI score over the number of days of data by total number of days of reported data multiplied by 7. If less than 4 days of diary data is available, the subject will be categorized as a non-responder and the CDAI score will be considered missing. As specified in section 2.2, subjects with missing assessment will be assumed to not be in a state of remission/success for each scheduled visit (week 16, 26, or 52).

Handling of missing date information for AEs:
The term *missing date* refers to a completely missing date or to partial date where month or/and day or/and year is/are missing, e.g. missing month/day/year. Missing start and end dates will be imputed conservatively, i.e. missing values will be imputed in such a way that the duration of the AE is considered with the longest possible duration. The missing start date and end date of AE will be imputed for the purpose of defining treatment emergent adverse events (TEAE) and for assigning events to treatment periods using the following definitions:

(i) Adverse Event Start Date:
Event Missing Day: If Adverse event day is missing but month and year present, then impute the 1st of the month unless month and year are the same as first dose of study drug then impute day first day of dose.
Event Missing day and month – If adverse event day and month both are missing but year is present then impute 1st January unless year is the same as first dose date then impute day and month first dose day and month.
Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

(ii) Adverse Event End Date:
Missing day – If AE day is missing but month and year is present then impute the last day of the month.
Missing day and month – If AE has missing day and month but year is present then impute 31st December.
Completely Missing – Required to look at whether the AE is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present (i.e. do not impute a date). If the AE has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is after the last dose date.

(iii) TEAE definition with missing start and stop dates: If the start date of an adverse event is incomplete or missing, the event will be assumed to be a treatment-emergent adverse event (TEAE), unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicates that the event started prior to dosing. Missing/incomplete information will be reported as missing/incomplete in the subject listings.

(iv) Adverse event relationship: If the relationship for an adverse event is not recorded, it will be assumed to be treatment related in the presentation of the statistical summary of incidence results. Missing information will be reported as missing in the subject listings.

(v) Adverse event severity: If the severity of an adverse event is missing, the severity will be assumed to be severe when summarizing data. Missing information will be reported as missing in the subject listings.

(vi) Non-study medication (concomitant medications, steroids) start and stop dates: If the start and/or stop dates of non-study medication use are incomplete or missing, the use will be assumed to be concomitant, unless the incomplete date information clearly indicates that the use stopped prior to study medication dosing. Missing/incomplete information will be reported as missing/incomplete in the subject listings.

6.1.4 Conversion of time interval

In case time interval was calculated in days and need to be converted into weeks, months or years the following conversion factors need to be used:

1 week = 7 days
1 month = 30.4 days
1 year = 365.25 days

6.1.5 Pooling of Investigator Sites

All summaries and analysis will use data pooled across all investigative sites.

6.1.6 Rescue Medications Use

Subjects rescued with the following treatments or whose baseline doses/regimens are increased to treat new or unresolved CD symptoms may remain on the study drug at the discretion of the investigator and continue to be assessed at all scheduled study visits:

- Oral or rectal 5-ASA compounds
- Azathioprine or 6-mercaptopurine (6-MP) or methotrexate
- Total parenteral nutrition as treatment of CD
- Systemic or rectal corticosteroid therapy
- Anti-TNF or other biologic agent

In analyses of remission or response, subjects who initiate new treatment or increase concomitant medication to treat CD symptoms will be considered as treatment failures.

6.1.7 Determination of Sample Size

This study is anticipated to enroll 100 patients. With that number of patients, a two-sided 95% confidence interval (using the exact Clopper-Pearson method) will have a maximum width of 0.203 (i.e., +/- 10.15%) conservatively assuming the measure of interest has proportion of successes of 50%. This confidence interval will be narrower for any other possible observed proportion.

6.2 Subject Characteristics

All subject characteristics data will be listed by subject, and summarized for the ITT population, except as noted otherwise.

6.2.1 Subject Disposition

Subject disposition will be presented for all subjects by parent study treatment group and overall for the ITT population. Disposition information that will be summarized will include number of subjects who completed the study, number who withdrew prematurely, and reasons for withdrawal.

The number and percent of subjects in each of the following categories will be presented.

- Safety population
- Subjects completing weeks 16 and 52
- Subjects discontinued from the study and by reason of discontinuation.

6.2.2 Protocol Deviations

Subjects with major protocol deviations will be identified by the medical or clinical data review prior to database lock. The deviations will be summarized by parent treatment group and overall based on the safety population. The summary will be grouped into different categories of violations such as below as example:

- Inclusion/Exclusion Criteria Deviations
- Non-compliance with study procedures
- Inappropriate intake of prohibited medications
- Poor compliance with study medications
- Lost to follow-up
- Administrative decision of investigator or sponsor

Multiple deviations can occur in the same subject and thus a subject may be counted in more than one deviation category.

A listing of subjects with major deviations will be presented.

All decisions regarding major deviations will be discussed and agreed upon with the sponsor prior to the database lock.

6.2.3 Demographics and Background Baseline Characteristics

6.2.3.1 Subject Demographics data.

Demographics data is collected at time of screening after informed consent is obtained and migrated from the parent study (please refer to Appendix for details). Demographics variables will be summarized descriptively for ITT subjects by parent study treatment group and overall and will at least include the following variables:

- Age at screening as continuous variable [Years]
- Sex
- Race
- Ethnicity
- Height
- Weight
- Smoking status and alcohol consumption
- BMI

6.2.4 Treatment Exposure and Drug Accountability

6.2.4.1 Treatment Exposure

Exposure will be summarized for the SAF population. Subjects are instructed to bring their study medication and all empty packaging to the clinic visit. Cumulative treatment exposure per subject will be calculated as sum of all dosage of treatment consumed. Time on treatment (in days) will be calculated per subject as the number of days of study medication intake during the trial. This will be calculated as:

Date of last study medication administration – Date of first study medication administration + 1.

Dosing data will be presented descriptively by parent study treatment group and overall and also presented as subject data listing for the Safety population.

In addition, treatment duration (RHB-104 or Placebo) of combined parent study and current study will be descriptively summarized by parent study treatment group. Combined treatment duration in weeks will also be categorically summarized displaying the number and percentage of patients with treatment duration by every 10 weeks and by parent study treatment group.

6.2.4.2 Accountability/Compliance

Drug compliance will depend upon capsule counts at each visit. Subjects are instructed to bring their study medication and all empty packages to each clinic visit. Compliance will be assessed by capsule counts recorded by each site for each subject. The details of medication used will be recorded and reconciled against expected medication use. Compliance will be calculated as the reported medication used by subject as percentage (%) of expected usage. Summary descriptive statistics will be presented for the number and proportion of subjects non-compliant (< 80% compliant) for safety population.

Extent of compliance of each subject data will be presented in subject listing for the SAF population.

6.2.5 Physical Examination

Complete physical examination is performed at screening and includes each subject's major body systems: general appearance, head/eyes/ears/nose/throat, neck, lungs, heart, abdomen, genitourinary, extremities, neurological, skin, and lymphatics and other. Results (normal, abnormal and clinically significant abnormal and not clinically significant) will be tabulated for each body system with the number and percentage of subjects.

Number of percent of subjects with significant change in physical examination from previous visit at baseline and subsequent post baseline visits will be summarized.

6.2.6 Medical History (excluding Crohn's disease)

6.2.6.1 Medical History (excluding Crohn's disease)

Pre-existing medical conditions are recorded at screening on the medical history eCRF per subject data migration from the parent study (please refer to Appendix for details). For each subject, medical history data will be presented in a data listing.

6.2.6.2 Crohn's Disease History

Crohn's disease history is recorded at screening on the history eCRF per subject data migration from the parent study (please refer to Appendix for details). Data including steroid status (steroid-refractory disease or steroid-dependent disease) will be presented descriptively by parent study treatment group and overall and also presented as data listing. Duration of each condition is based on the first dose of study medications administration for the current extension study.

6.2.7 Prior and Concomitant Medications and Steroids

Prior medications will be defined as medications stopped prior to Day 1 of study medication. Concomitant medications include medications taken on or after the first dose of study medication as well as medications that started prior to the first dose of study medication and continued after the first dose of study medication. The following algorithm will be used to define prior and concomitant:

The medication will be assumed to be prior medication if it cannot be definitively shown that the medication did not start or continue during the treatment period.

If the start date or stop date of a medication is partially missing, the date will be compared as far as possible with the date of the start of administration of study drug. The following approach will be taken:

- If the start date of medication is complete and occurs on or after the day of the first dose, the medication will be assumed concomitant. If the start date occurs prior to the first

dose date but the end date is on or after the first dose date or the medication is recorded as ongoing, the medication will be considered concomitant.

- If the start day is missing but the start month and year are complete, a medication will only be excluded as being concomitant if the start month/year is before the month/year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration.
- If the start day and month are missing but the start year is complete, a medication will only be excluded as concomitant if the start year is before the year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration.
- If the start date is completely missing and the stop date is prior to first dose or completely missing, the medication will be assumed to be a prior medication.

All prior and concomitant medications recorded on CRF will be mapped to standardized terms using the World Health Organization Drug Dictionary coding system (WHO DD). The Anatomical–Therapeutic–Chemical (ATC) Classification level 2 and preferred term will be used to summarize the data by treatment group. A subject having the same medication more than once will be counted only once in the incidence table for that medication. For each ATC classification and Preferred Term the number and percentage of subjects will be displayed. Summary tables will be presented on SAF population separately for the following:

- Prior Medications Use for Crohn's Disease
- Prior Medications Use
- Concomitant Medications Use
- Prior Biological Agents Use
- Concomitant Medications Use for Crohn's Disease
- Prior Steroids Use
- Concomitant Steroids Use
- Concomitant Steroids Use for Crohn's Disease
- Prior Antineoplastic, Immumosupressive and Biologic Use
- Concomitant Antineoplastic, Immumosupressive and Biologic Use

All prior and concomitant medications/treatments will be presented in a data listing with dose, units, frequency, route of administration, indication, start and end dates for the safety population. A separate Steroids use subject listing may be presented providing the steroid coded ATC classification, preferred term, and date.

Any concomitant procedures recorded on CRF will be presented in a data listing with procedure name, date and reason.

6.3 Outcome Analysis

The outcome analyses will be based on all ITT subjects.

6.3.1 Primary Outcome Analysis

The primary outcome variable is the proportion of subjects experienced remission at week 16. 95% exact Clopper-Pearson confidence interval (CI) of the proportion of remission will be provided within each parent study treatment group and overall, as well as subgroup by anti-TNF agent use. Parent study treatment comparison will be performed using Fisher's exact test.

For the above primary analysis, subjects with a missing week 16 CDAI will be treated as not achieving remission. As a sensitivity analyses, the same analyses will be performed without imputation, i.e. subjects with missing week 16 CDAI will not be imputed, therefore it will be missing and excluded from analysis.

Logistic regression modeling will be implemented as additional exploratory analysis to assess relationships between the primary outcomes and putative effect modifiers. The putative effect modifiers include the following patient level biomarker assessment:

- Baseline serum inflammation marker: C-reactive protein (CRP ≥ 2.87 vs. < 2.87 mg/dL)
- Baseline stool inflammation marker: Fecal calprotectin (≥ 250 vs. < 250 mcg/g)
- Baseline SES-CD≥6, Fecal calprotectin ≥ 250 mcg/g or CRP≥ 2.87 mg/dL: Yes vs. No

The logistic regression model includes remission at week 16 (yes/no) as a function of parent study treatment by baseline biomarker factor. The aim is to identify if the effect of each baseline biomarker factor has significant effect on remission outcome. The analysis will be performed to compare parent study treatment groups. Odds ratio of remission rate (parent study treatment RHB-104 vs. placebo) and 95% CI will be presented using a Forest plot for each baseline biomarker level. Similar plots will be provided for week 16 response and week 52 remissions.

6.3.2 Key Secondary Outcome Analysis

The key secondary outcome variable is the proportion of subjects experienced response at week 16. 95% exact Clopper-Pearson confidence interval (CI) of the proportion of responders will be provided within each parent study treatment group and overall, as well as subgroup by anti-TNF agent use. Parent study treatment comparison will be performed using Fisher's exact test.

The same logistic regression analysis as the primary output variable will also be performed.

6.3.3 Selected Other Secondary Endpoints/Variables

6.3.3.1 Time to Event Endpoints/Variables Analysis

The Time to event endpoints that will be analyzed includes:
- Time to remission
- Duration of remission
- Time to response
- Duration of response

Kaplan Meier survival curves and parameters showing time-to-first observed response outcome will be summarized by parent study treatment, by anti-TNF use and overall. Summary statistics that will be presented will include minimum, maximum, the 25th and 75th percentiles, 95%

confidence intervals on the median (using the method of Brookmeyer and Crowley), and proportion of the events and censored data. Parent study treatment comparison will be performed using log-rank test.

Kaplan-Meier plots with descriptive summary statistics will be presented.

6.3.3.2 Remission from Week 16 through week 52

Number and proportion of subjects experiencing maintenance of remission (CDAI score < 150) from week 16 through week 52 and the number and proportion of subjects experiencing remission at week 16 and week 52 will be provided within each parent study treatment group and overall, as well as subgroup by anti-TNF agent use. 95% exact Clopper-Pearson confidence interval (CI) for the proportion will also be presented. Parent study treatment comparison will be performed using Fisher's exact test.

In addition, similar summaries will be provided for remission at week 52 overall and for subjects who achieved remission at week 16

Proportion of subjects who achieved the following response will be provided overall and by parent study treatment:

Remission at week 16 plus 50% reduction in CRP or calprotectin from baseline
Remission at week 52 plus 50% reduction in CRP or calprotectin from baseline

6.3.4 Selected Other Endpoints/Variables

6.3.4.1 MAP Buffy Coat culture

All summaries will be done by parent study treatment and overall.

Number and percent of subjects will be summarized for MAP buffy coat culture (positive/negative) by scheduled visit (baseline, weeks 16, 26 and 52), 95% exact Clopper-Pearson confidence interval (CI) will be provided for the proportion of positive MAP buffy coat culture.

Shift table from baseline to each post baseline visit (weeks 16, 26 and 52) will be summarized.

6.3.4.2 Endoscopic Assessment Based on CDEIS and SES-CD

The Crohn's Disease Endoscopic Index of Severity (CDEIS) is a validated quantitative measure of disease severity upon endoscopy. The score ranges from 0-44 based upon the extent and severity of inflammation and ulcers seen during endoscopy of the colony. A response is a decrease in score from baseline.

The Simple Endoscopic Score for Crohn's Disease (SES-CD) is a validated quantitative measure of disease severity upon endoscopy that is based on four endoscopic variables (presence and size of ulcers, extent of ulcerated surface, extent of affected surface, and presence of narrowing). Each

variable is assessed in each of the five ileocolic segments: rectum, sigmoid and left colon, transverse colon, right colon, and ileum. Each of the four SES-CD variables is scored from 0 to 3, with the sum of the scores for each variable ranging from 0 to 15 (Total SES-CD score range 0–60).

CDEIS data are presented in data listing only.

The SES-CD total scores by visit (baseline and weeks 16 and 52) and change from baseline scores to week 16 and 52 will be summarized descriptively for subjects who consent to undergo colonoscopy by parent study treatment and overall. The summary statistics include number of observations, mean with 95% CI, standard deviation, median, inter-quartile ranges, minimum, and maximum.

Number and proportion of subjects who achieved success defined below and corresponding 95% exact Clopper-Pearson CI for the proportion will be provided.

- by 25% improved in SES-CD from baseline to week 16 and 52. Success is achieved if the SES-CD score is decreased by 25%.

- by 50% improved in SES-CD from baseline to week 16 and 52. Success is achieved if the SES-CD score is decreased by 50%.

Paired response between each of above defined improvement and corresponding CDAI remission (<150) at each visit will be compared using exact McNemar's test. Similarly, paired response between each of above defined improvement and corresponding CDAI response (>=100% decrease from baseline) at each visit will be compared using exact McNemar's test.

6.3.4.3 Quality of Life Assessment: SF-36 Questionnaire Total Score

The SF-36 Health Survey is a self-administered, 36-item questionnaire designed to measure 8 domains of functional health status and well-being. For this study, the questionnaire data is collected at baseline, week 26 and week 52. The SF-36 instrument guidelines will be used to assess and summarize the overall health status. The SF-36 consists of 8 scaled scores with range 0-100 with higher score indicating better health. The 8 sections or domains are:

- Vitality
- Physical functioning
- Bodily Pain
- General Health Perceptions
- Physical Role Functioning
- Emotional Role Functioning
- Social Role Functioning
- Mental Health

There are also two component scores. The Physical Component Summary Score is a composite of the Physical Functioning, Role Functioning, Bodily Pain and General Health scales. The Mental

Health Component Summary Score is a composite of the Vitality, Social Functioning, Role-Emotional and Mental Health scales.

All above-mentioned domain and component scores will be provided by QualityMetric and will be presented for data listings.

6.3.4.4 Inflammatory Bowel Disease Questionnaire (IBDQ) Score

IBDQ is used to assess IBD status. IBDQ is a valid and reliable quality of life instrument that incorporates social, systemic and emotional symptoms together with bowel-related symptoms into activity index. The IBDQ includes 32 questions on 4 areas of health-related quality of life:

Bowel Systems (10 questions: 1, 5, 9, 13, 17, 20, 22, 24, 26, 29),
Emotional Health Function (12 questions: 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32),
Social Function (5 questions: 4, 8, 12, 16, 28), and
System Function (5 questions: 2, 6, 10, 14, 18). Each item is rated on 7-point Likert scale (higher scores equate to higher quality of life).

A total IBDQ score is calculated as sum of all 32 scores and the total ranges from 32 to 224. If more than 4 questions are missing, then total scores will not be calculated. If 4 or fewer questions are missing, then missing questions will be imputed by the mean of the rest of available question scores.

Summary descriptive statistics including number of observations, mean with 95% CI, standard deviation, median, inter-quartile ranges, minimum, and maximum will be presented in tables and bar graph for the actual and change from baseline scores for IBDQ total score by scheduled visits (week 16 and week 52). The summaries will be done by parent study treatment and overall.

6.3.4.5 Serum Marker of Inflammation: C-reactive Protein (CRP)

The CRP is used as marker of inflammation. The CRP level data collected at baseline, week 16, 26, 39 and 52 will be used to assess inflammation at baseline and at different visits post-baseline. Summary descriptive statistics for the actual observed and change from baseline will include mean with 95% CI, standard deviation, median, inter-quartile ranges and range for each parent study treatment and overall by visit.

In addition, the CRP level will be classified into two categories: “Normal (≤ 0.999 mg/dL)” and “High (> 0.999 mg/dL)”. Summary results will show number of patients and proportion (%) along with 95% exact Clopper-Pearson CI with “Normal level” and with “High Level” by parent study treatment group and overall by visit. Shift tables from baseline to each post baseline visit will also be presented.

6.3.4.6 Stool Marker of Inflammation: Fecal calprotectin

The fecal calprotectin is used as marker of inflammation. The level of fecal calprotectin data collected at different visits will be used to assess inflammation at baseline and at different visits post-baseline (weeks 16, 26 and 52). Summary descriptive statistics for the actual observed and

change from baseline will include mean with 95% CI, standard deviation, median, inter-quartile ranges and range for each parent study treatment group and overall by visit.

In addition, fecal calprotectin will be classified into two categories: "Normal (≤ 162.9 mcg/g)" and "High (> 162.9 mcg/g)". Summary results will show number of patients and proportion (%) along with 95% exact Clopper-Pearson CI with "Normal level" and with "High Level" by treatment group by visit. In addition, shift tables from baseline to each post baseline visit will also be presented.

6.3.4.7 Additional Endpoints: CDAI score and PRO-2

PRO-2 is defined as 7 x (mean daily number of liquid or very soft stools) + 7 x (mean daily abdominal pain score) based on CDAI assessment. CDAI and PRO-2 scores will be summarized descriptively by visit.

6.4 Safety Analysis

All summarization of safety data will be based on the safety population by parent study treatment group and overall.

6.4.1 Adverse Events

Each verbatim adverse event (AE) term recorded during the study will be mapped to a system organ class and preferred term using the current MedDRA Dictionary.

A treatment-emergent AE (TEAE) is defined as an AE that based on start date information occurred after the first study drug administration or an AE that started before the first study drug administration but worsened in severity (i.e., became more severe) after administration of the study drug.

Treatment related adverse events will be defined as the adverse events for which the investigator indicates the relationship to study drug as possible, probable, or definite. If the relationship to study drug for an AE is not recorded, it will be assumed to be treatment related in the summary tables. Similarly, if severity of an AE is missing, the severity will be summarized as severe.

A by-subject listing of all AEs (including non-treatment-emergent AEs) will be provided and will include all AE data recorded on the eCRF. All summaries of AEs will present the number and percent of subjects reported events by system organ class and preferred term and by treatment group. If a subject has multiple occurrences of an AE, the subject will be counted only once in the respective AE.

For summaries of adverse events by maximum severity or maximum relationship, if a subject has multiple occurrences of an AE, the subject will be counted only once for the respective Preferred Term at the maximum severity or maximum relationship.

An overall summary table by treatment and overall of AEs, SAEs, TEAEs, Serious TEAEs, treatment-related TEAEs, treatment-related SAEs, TEAEs leading to study discontinuation and study deaths will be provided using number and % of subjects.

Summary tables by treatment and overall will be provided by SOC and preferred term for each of the following types of AEs:

- All Treatment emergent AEs
- Study Drug related treatment emergent AEs
- Treatment emergent AEs by maximum severity
- Treatment emergent AEs leading to study discontinuation
- Serious Treatment emergent AEs (SAEs)
- Treatment-related serious AEs
- Treatment emergent AEs leading to Death

The following listings will be provided:

- All AEs
- Treatment related AEs
- AEs leading to study discontinuation
- SAEs
- Deaths

All study deaths will be listed using date and cause of death along with autopsy results as entered on the Death CRF.

6.4.2 Laboratory Parameters

Laboratory assessments will include:

Biochemistry: total protein, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), sodium, potassium, chloride, magnesium, glucose, total bilirubin, AST(SGOT), ALT(SGPT), alkaline phosphatase, amylase, albumin, BUN, calcium, creatinine, uric acid, HCO_3, total cholesterol, creatinine phosphokinase, and inorganic phosphorous.

Hematology: RBC count, hemoglobin, hematocrit, platelet count, WBC count, WBC differential.

Urinalysis: Pregnancy, pH (dipstick), specific gravity (dipstick), glucose (dipstick), protein (dipstick), ketones (dipstick), blood (dipstick), Nitrites, Leucocytes and sediment microscopy if indicated by the dipstick.

Laboratory results will be presented in listings in measured units and summaries in conventional units.

Continuous laboratory values will be summarized descriptively by treatment group over time for each visit and as change from baseline to each visit. Categorical laboratory values will be summarized as the number and percentages of subjects in each category by treatment group over time for visit.

Laboratory parameters will also be summarized in shift tables by treatment, to determine the number and percentage of subjects with measurements classified in a particular category at each post-baseline visit with reference to the same classification at baseline. Biochemistry and hematology parameters (which are continuous in nature) will use the classifications of low, normal, and high relative to normal ranges, whereas appropriate categories will be selected for urinalysis parameters (which are categorical in nature), for example, normal and abnormal.

Subjects missing a value at any time point will be excluded from the summary statistics for that time point. If a subject has more than one value at any time point, then the latest non missing value will be used for summarization. All values will be presented in the data listings.

Listings of all individual laboratory data, indicating any values out of the normal range will be produced. A listing of lab parameter values flagged as abnormal will also be provided.

6.4.3 Vital Signs

Vital signs include the following:

- Supine systolic blood pressure (SBP)
- Supine diastolic blood pressure (DBP)
- Supine pulse rate
- Respiratory rate
- Temperature
- Height
- Weight
- BMI

Vital signs are recorded at baseline and at different visits post-baseline. Actual and change from baseline values will be summarized using descriptive statistics by visit and treatment group. The mean, standard deviation, median, and range will be used to summarize the data. For each subject, vital signs data will be presented in a data listing.

6.4.4 12-Lead ECG

Study investigators will record each subject ECG data. The significance and interpretation of each ECG finding and assessments of the QTc and other ECG intervals will be made by the ECG specialized Lab. All ECG data will be presented in the subject data listings with annotations indicating any abnormal values. For analysis details and presentation of the ECG findings, a specialized independent technical report will be produced by different specialized expert.

6.4.5 Uveitis Assessment

Results from Uveitis assessments will be listed and summarized as the number and percentage of subjects with Uveitis suspected (yes or no), and if suspected, with Uveitis confirmed (yes or no).

6.5 Changes to Statistical Analysis Methods Planned in the Protocol

Because the buffy coat is the actual component of blood that is cultured, MAP blood culture should be considered equivalent to MAP buffy coat culture. Because the development of a MAP blood PCR assay is still in progress, MAP detection objectives 1-4 will comprise the contents of a later report and will not be addressed in tables, listings, or figures of this clinical study report.

Change from baseline in the Short Form-36 Health Survey (SF-36) total score have been removed to be consistent with parent study. Summary of domains are removed in SAP.

Correlations between the change from baseline in SES-CD and the change from baseline in CDAI to week 16 and 52 are not included in SAP.

7. ADDITIONAL OTHER EXPLOATORY ANALYSES

Other exploratory subgroup analyses to characterize safety and efficacy activities of HRB-104 may be conducted. These additional exploratory analyses will be decided at the time of final data analysis if deemed necessary.

8. TABLES, LISTINGS, AND FIGURES

The intended layouts for unique summary tables, listings, and figures (TLFs) are presented in a separate document. However, it may be necessary to change the table layouts, as appropriate, upon review of the data available without modifying the SAP text.

8.1 Tables, Listings and Graphs (TLFs) for Study Report

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Table 14.2.1.2.4	Remission at Week 16 by Baseline MAP Buffy Coat Culture Status : Intent-to-Treat Population
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Table 14.2.2	Key Secondary Endpoint - Response at Week 16: Intent-to-Treat Population
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Table 14.2.3.3.4	Remission at Week 52 and at least 50% Reduction in CRP or Calprotectin from Baseline for Subjects with Baseline SES-CD ≥ 6 or Calprotectin(mcg/g)≥ 250 or CRP(mg/dL) ≥ 2.87: Intent-to-Treat Population
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Table 14.2.3.3.6	Remission at Week 52 by Week 52 MAP Buffy Coat Culture Status: Intent-to-Treat Population
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Table 14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: Safety Population
Table 14.3.1.2.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Anti-TNF Use: Safety Population
Table 14.3.1.2.3	Summary of Treatment-emergent Adverse Events Occurring in at Least 5% of Subjects by System Organ Class and Preferred Term in Descending Frequency
Table 14.3.1.2.4	Summary of Treatment Related Treatment-emergent Adverse Events Occurring in at Least 5% of Subjects by System Organ Class and Preferred Term in Descending Frequency
Table 14.3.1.3	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Medication: Safety Population
Table 14.3.1.4	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity: Safety Population

Table 14.3.1.5	Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term: Safety Population
Table 14.3.1.6	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term: Safety Population
Table 14.3.1.7	Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Maximum Relationship to Study Drug: Safety Population
Table 14.3.2.1	Listing of Subjects with Adverse Events that Led to Death: Safety Population
Table 14.3.2.2	Listing Subjects with Treatment-Emergent Serious Adverse Events: Safety Population
Table 14.3.2.3	Listing Subjects with Adverse Events that Led to Study Discontinuation or Study Drug Interruption: Safety Population
Table 14.3.2.4	Listing of Subjects with Treatment-Emergent Adverse Events Related to Study Drug: Safety Population
Table 14.3.2.5	Listing of Deaths: Safety Population
Labs Assessments	
Table 14.3.4.1	Biochemistry Laboratory Data – Observed and Change from Baseline: Safety Population
Table 14.3.4.2	Biochemistry Laboratory Data – Shift from Baseline: Safety Population
Table 14.3.4.3	Hematology Laboratory Data – Observed and Change from Baseline: Safety Population
Table 14.3.4.4	Hematology Laboratory Data – Shift from Baseline: Safety Population
Table 14.3.4.5	Urinalysis Laboratory Data – Observed and Change from Baseline: Safety Population
Table 14.3.4.6.1	Urinalysis Laboratory Data – Shift from Baseline – Numerical Tests: Safety Population
Table 14.3.4.6.2	Urinalysis Laboratory Data – Shift from Baseline – Categorical Tests: Safety Population
Other Safety Assessments	
Table 14.4.1	Vital Signs – Observed and Change from Baseline by Visit: Safety Population
Table 14.4.2	Summary of Uveitis Assessment by Visit: Safety Population

Listings:

Listing Number	**Title**
Listing 16.2.1.1	Subject Disposition and End of Participation in the Trial: Intent-to-Treat Population
Listing 16.2.1.2	Inclusion and Exclusion Criteria: Intent-to-Treat Population
Listing 16.2.2	Major Protocol Deviations: Intent-to-Treat Population
Listing 16.2.3	Analysis Populations: Intent-to-Treat Population
Listing 16.2.4.1	Demographics and Baseline Disease Characteristics: Intent-to-Treat Population
Listing 16.2.4.2	Crohn's Disease History: Intent-to-Treat Population
Listing 16.2.4.3	Medical History (excluding Crohn's disease): Intent-to-Treat Population

Listing 16.2.4.4	Surgical History of Crohn's disease: Intent-to-Treat Population
Listing 16.2.4.5	Prior Biological Agents Use: Intent-to-Treat Population
Listing 16.2.4.6	Prior Alcohol Consumption and Tobacco Use: Intent-to-Treat Population
Listing 16.2.4.7	Prior and Concomitant Medications Use: Intent-to-Treat Population
Listing 16.2.4.8	Prior and Concomitant Steroids Use: Intent-to-Treat Population
Listing 16.2.4.9	Crohn's Disease Prior and Concomitant Medications: Intent-to-Treat Population
Listing 16.2.4.10	Concomitant Procedures: Intent-to-Treat Population
Listing 16.2.5.1	Drug Exposure and Compliance: Intent-to-Treat Population
Listing 16.2.5.2	Drug Administration: Intent-to-Treat Population
Listing 16.2.6.1	Crohn's Disease Activity Index (CDAI) Score: Intent-to-Treat Population
Listing 16.2.6.2	Remission and Response Parameters: Intent-to-Treat Population
Listing 16.2.6.3	SF-36 Questionnaire Domain and Component Scores: Intent-to-Treat Population
Listing 16.2.6.4	Inflammatory Bowel Disease Questionnaire (IBDQ) Score: Intent-to-Treat Population
Listing 16.2.6.5	Inflammation Assessment – CRP marker
Listing 16.2.6.6	Inflammation Assessment – Fecal calprotectin
Listing 16.2.6.7	Endoscopic Assessment – CDEIS: Intent-to-Treat Population
Listing 16.2.6.8	Endoscopic Assessment – SES-CD: Intent-to-Treat Population
Listing 16.2.6.9	MAP Detection: Intent-to-Treat Population
Listing 16.2.7.1	Adverse Events: Safety Population
Listing 16.2.8.1	Laboratory Assessments -: Biochemistry: Safety Population
Listing 16.2.8.2	Laboratory Assessments – Hematology: Safety Population
Listing 16.2.8.3	Laboratory Assessments - Urinalysis: Safety Population
Listing 16.2.9.1	Stool Samples - C. Difficile Toxin: Safety Population
Listing 16.2.9.2	Urine Pregnancy Test: Safety Population
Listing 16.2.9.3	Uveitis Assessment: Safety Population
Listing 16.2.9.4.1	12-Lead ECG (Part 1): Safety Population
Listing 16.2.9.4.2	12-Lead ECG (Part 2): Safety Population
Listing 16.2.9.4.3	12-Lead ECG (Part 3): Safety Population
Listing 16.2.9.5	Vital Signs: Safety Population
Listing 16.2.9.6.1	Physical Examination at Screening: Safety Population
Listing 16.2.9.6.2	Physical Examination Significant Change from Previous Visit: Safety Population
Excel Listing	List of Drug Exposure - combined 01 and 04

9. REFERENCES

1. International Conference of Harmonization (ICH) E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonized Tripartite Guideline. (1999) Statistics in Medicine; 18:1905–1942.
2. SAP for the parent study RHB-104-01.

10. Appendix I: Subject Data Migration from RHB-104-01 to RHB-104-04 (eCRF Completion Guidelines - Inform)

Subject Migration

There are two types of migration, Partial and Full. Subjects who complete the optional screening visit receive a Partial data migration. Subjects who did not complete the optional screening visit receive a full migration. Data migrated from RHB-104-01 to RHB-104-04 will be frozen upon migration. Fields that will not be frozen are fields that will need to be completed during the course of the study.

Partial Migration (subject *completes* optional screening visit)

The only visit folders that will receive migrated data are Screening and Log Pages.

The following is a list of folders/forms that will receive migrated data.

Visit	Form
Screening	Demographics
Screening	Crohn's Disease History
Screening	Medical History
Screening	Surgical History for Crohn's Disease
Log Pages	Adverse Events • Only adverse events that are ongoing at time of migration will be migrated from RHB-104-01 to RHB-104-04.
Log Pages	Concomitant Medications • Only concomitant medications that are ongoing at time of migration will be migrated from RHB-104-01 to RHB-104-04.

After subject/data migration is complete any forms in the Screening visit that are marked as not started or incomplete require data entry to be completed.

Full Migration (subject *does not complete* optional screening visit)

The only visit folders that will receive migrated data are Screening and Log Pages.

The following is a list of folders/forms that will receive migrated data.

Visit	**Form**
Screening	Date of Visit
Screening	Demographics
Screening	Crohn's Disease History
Screening	Medical History
Screening	Surgical History for Crohn's Disease
Screening	Vital Signs Screening
Screening	Uveitis Assessment
Screening	12-Lead ECG
Screening	Urine Pregnancy Test ***(Only for Female subjects)*
Screening	Urine Dipstick
Screening	Laboratory sample collection
Screening	MAP Testing
Screening	MAP Culture
Screening	Crohn's Disease Activity Index Diary
Screening	Crohn's Disease Activity Index (CDAI)
Screening	Inflammatory Bowel Disease Questionnaire
Screening	Short Form-36 Health Survey
Screening	Stool samples
Log Pages	Adverse Events •Only adverse events that are ongoing at time of migration will be migrated from RHB-104-01 to RHB-104-04.
Log Pages	Concomitant Medications •Only concomitant medications that are ongoing at time of migration will be migrated from RHB-104-01 to RHB-104-04.

After subject/data migration is complete any forms in the Screening visit that are marked as not started or incomplete require data entry to be completed.