STATISTICAL ANALYSIS PLAN

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

A Phase III Randomized, Double Blind, Placebo-controlled, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Fixed-dose Combination RHB-104 in Subjects with Moderately to Severely Active Crohn's Disease

Protocol No. RHB-104-01

[redacted]

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SIGNATURE PAGE*

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*Statistical Analysis Plan including TLFs

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REVISION HISTORY

Statistical Analysis Plan Text FINAL 3.0 based on 29 September 2017 Final Protocol (Protocol Amendment 11.0)

Summary of Changes from version 2.0

1. Section 5: updated definition for per protocol population.
2. Section 2.2.1, added a paragraph to indicate that use of rescue medication is considered as treatment failure.
3. Section 6.1.5: clarified the rule for AE end date imputation when day is missing.
4. Sections 2.2.3.4, 6.3.3.6: removed SF-36 total scores and indicated that the derived scores are from QualityMetric.
5. Section 6.3.3.7: for IBDQ added some clarifications on handling missing data.
6. Sections 2.2.3.3, 6.3.3.10: CDEIS and SES-CD, removed all week 52 related summaries and outputs as week 52 is not collected.
7. Section 8.1: Remove ECG tables as they are listings only and removed DSMB TLF from list as they are not applicable for final analysis. Some outputs are renumbered for continuity.
8. Sections 6.3 and 8.1: added reference for addendum under section 6.3 and related output in section 8.1.
9. Section 6.3.4.1: added clarifications for planned MAP analysis as the first paragraph.
10. Throughout: Fixed a few typos and grammar correction.
11. Added Shuhong Zhao as one co-author and Jed Henke as sr. review.
12. Updated protocol version on cover page.

Statistical Analysis Plan Text FINAL 2.0 based on 29 March 2017 Final Protocol (Protocol Amendment 10.0)

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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
ANCOVA	Analysis of Covariance
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
CABG	Coronary Artery Bypass Graft
C. difficile	*Clostridium difficile*
CCFA	Crohn's and Colitis Foundation of America
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CE	Covered Entity
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

Abbreviation	Term
DHHS	Department of Health and Human Service
DO	Doctor of Osteopathy
DSMB	Data And Safety Monitoring Board
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
°F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GMP	Good Manufacturing Practices
HDPE	High-density Polyethylene
HE	Health Economic(s)
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-Related Quality-of-life
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IWRS	Interactive Web Response System
ITT	Intent-To-Treat
kg	Kilogram
L	Liter

Abbreviation	Term
lb	Pound
LDH	Lactate Dehydrogenase
MAP	*Mycobacterium avium subsp. paratuberculosis*
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MCS	Mental Component Summary
MI	Myocardial Infarction
mITT	Modified intent-to-treat
mg	Milligram
n	Number of Subjects
Min	Minimum
NCR	No Carbon Required
PA	Physician's Assistant
PIPEDA	Personal Information Protection and Electronic Documents Act
PCR	Polymerase Chain Reaction
PCS	Physical Component Summary
PHI	Personal Health Information
PI	Principal Investigator
PK	Pharmacokinetics
popPK	Population Pharmacokinetics
popPKAP	Population PK Analysis Plan
QD	Once-Daily
QTc	Corrected Q-T Interval
QTcF	Corrected Q-T Interval using Fridericia's Formula
REB	Research Ethics Board
RHB	RedHill Biopharma Ltd.
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAF	Safety Population

Abbreviation	Term
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36	Short Form-36 Health Survey
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 require 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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Efficacy Objective

The primary objective is to assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of remission (CDAI score <150) at week 26 assessment as compared to subjects randomized to receive placebo.

2.1.2 Key Secondary Efficacy Objectives

1. Assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of response at the 26 week assessment as compared to subjects randomized to receive placebo.
2. Assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of remission at the 52 week assessment as compared to subjects randomized to receive placebo.
3. Assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of durable (long-term) remission in assessments from week 26 through week 52 as compared to subjects randomized to receive placebo.
4. Assess whether subjects randomized to receive RHB-104 have a higher probability of being in state of early remission at the 16 week assessment as compared to subjects randomized to receive placebo.
5. Assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of steroid free remission at the 52 week assessment as compared to subjects randomized to receive placebo. Subjects must be maintained off steroids for 3 weeks in order to be determined to be in steroid free remission, e.g., by week 49.

2.1.3 Other Supportive Secondary Efficacy Objectives

1. To compare the arm-specific time to remission and time to response.
2. To compare the arm-specific duration of remission and duration of response.
3. To compare the proportion of subjects who have maintained remission from week 16 through week 52.
4. To assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of response at the 16 week assessment as compared to subjects randomized to receive placebo.
5. To assess the difference between the treatment groups in health-related quality-of-life using the IBDQ and SF-36 questionnaire instruments.
6. To compare arm-specific endoscopic 26-week changes using the CDEIS and SES-CD score in those subjects who consent to undergo colonoscopy.
7. To assess the effect of RHB-104 on markers of inflammation.
8. To assess the proportion of subjects in steroid free remission in each treatment arm at week 26. Subjects must be maintained off steroids for 3 weeks in order to be determined to be in steroid free remission e.g. by week 23.

2.1.4 Other Exploratory Efficacy Objectives

1. To characterize the pharmacokinetic profiles of each of the active agents (and active metabolites for clarithromycin and rifabutin) using a population PK approach.
2. To assess the efficacy outcome measures for interaction with the baseline assay results for MAP infection (positive versus negative) to use in development of MAP blood PCR testing.
3. To compare the arm-specific changes in MAP PCR status (positive to negative) from pre- to post-treatment at week 26 and week 52.
4. To compare arm-specific 26-week change from baseline in the endoscopic index (ΔCDEIS and ΔSES-CD) and the clinical index (ΔCDAI)
5. To compare the arm-specific changes in MAP culture status (positive to negative) from pre- to post-treatment at week 26 and week 52.
6. To assess the tissue levels of the active agents of RHB-104 in colon biopsy samples if possible.

2.1.5 Safety Objective

Assess the safety impact of treatment with RHB-104.

2.2 Outcomes/Endpoints

The efficacy endpoints for statistical comparison between the RH-104 treatment and Placebo are grouped into 4 families for statistical analysis: (i) Primary efficacy endpoint; (ii) Key Secondary efficacy endpoints; (iii) Other Supportive Secondary efficacy endpoints; and (iv) Other Exploratory efficacy endpoints. The endpoints in families (i) and (ii) that are for potential treatment efficacy labeling claim will have multiplicity adjustment to control type 1 error rate.

2.2.1 Primary Efficacy Endpoint/Variable: Remission

In general use of rescue medication is considered as treatment failure (not achieve 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 6.1.8 for more details.

The primary efficacy variable is the proportion of subjects experienced remission at Week 26, where remission is defined as a subject having a Crohn's Disease Activity Index (CDAI) score of <150. Subjects who have a Week 26 CDAI measurement ≥ 150 or who do not have a CDAI measurement at Week 26 will be classified as not achieved remission.

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

2.2.2 Key Secondary Efficacy Endpoints/Variables

Key Secondary efficacy endpoints include the following:

- Proportion of subjects experienced response at week 26, where response is defined as reduction from baseline of ≥100 in CDAI score. Subjects who have a change from baseline to week 26 in CDAI score which is not a reduction of ≥ 100 or who do not have a change from baseline to week 26 in CDAI score will be classified as not experienced response.
- Proportion of subjects in remission Week 52, where remission is defined as a subject having a CDAI score of <150. Subjects who have a week 52 CDAI measurement ≥ 150 or who do not have a CDAI measurement week 52 will be classified as not achieved remission.
- Proportion of subjects experienced Durable Remission (CDAI score < 150) from week 26 through week 52. Subjects experiencing a CDAI score ≥ 150 at any visit time point assessment between week 26 and week 52 or have no CDAI measurement week 26 or week 52 will be considered not achieved Durable Remission.
- Proportion of subjects in Early Remission week 16, where remission is defined as a subject having a CDAI score of <150. Subjects who have a week 16 CDAI score ≥ 150 or who do not have a CDAI measurement week 16 will be classified as not achieved early remission.
- Proportion of subjects in steroid free remission week 52, where remission is defined as a subject having a CDAI score of <150. Subjects must be maintained off steroids for 3 weeks in order to be determined to be in steroid free remission, e.g., by week 49.

2.2.3 Supportive Efficacy Endpoints/Variables

2.2.3.1 Other Remission and Response Endpoints/Variables

- Proportion of subjects in remission from week 16 through week 52, where remission is defined as maintaining 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 at week 16 or week 52 will be considered not achieved Remission for this endpoint analysis.
- Proportion of subjects experienced early response week 16, where early 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 experienced early response.
- Proportion of subjects experienced response week 52, where response is defined as reduction from baseline of ≥100 in CDAI score. Subjects who have a change from baseline to week 52 in CDAI score which is not a reduction of ≥ 100 or who do not have a change from baseline to week 52 in CDAI score will be classified as not experienced response.

2.2.3.2 Time to Event Endpoints/Variables

- Time to remission – Number of weeks after randomization 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 baseline visit (Visit 1), 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 – Duration of remission defined as 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 baseline 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 baseline visit (Visit 1), plus 1 day, divided by 7. For those subjects not experienced response, time to response will be censored at the date of the last assessment of CDAI score.

- Duration of response – Defined as 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.

2.2.3.3 Endoscopic Change Variables

- Change from baseline to week 26 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.

- Correlations between the change from baseline to week 26 in CDEIS and SES-CD and the change from baseline to week 26 in CDAI.

- Proportion of subjects in remission by visit time post-baseline based on CDEIS and SES-CD measurements. Remission is defined as 0-3 score based on CDEIS measurement and defined as 0-2 score based on SES-CD measurement.

- Proportion responders based on CDEIS and SEC-CD at week 26. Responders based on CDEIS and SES-CD scores are defined and classified into two categories as 50% reduction from baseline score; and 25% reduction from baseline score to week 26.

2.2.3.4 Health Related Quality of Life Variables

- Change from baseline in the Short Form-36 Health Survey (SF-36) domain and component scores at each follow-up visit time point.

- Change from baseline in the IBDQ score at each follow-up visit time point. 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.

2.2.3.5 Markers of Inflammation Variables

Inflammation parameters include the following:

- Change from baseline in C-reactive protein
- Change from baseline in Fecal calprotectin

2.2.4 Other Exploratory Efficacy Endpoints/Variable(s)

2.2.4.1 Map Detection Endpoints/Variable

As specified in the objectives, the variables/endpoints in this section are intended to be for exploratory analysis. Depending on the availability of data, specific details of additional exploratory analyses to be conducted will be determined at the time of analyses.

Mycobacterium avium subsp. paratuberculosis (MAP) detection parameters include the following:

- Proportion of subjects with a MAP positive PCR blood assay at baseline.
- Proportion of subjects with a change in MAP blood PCR assay status after week 26 and after week 52 of treatment compared to baseline.
- Proportion of subjects with a MAP positive blood culture at baseline.
- Proportion of subjects with a change in MAP blood culture status after 26 weeks of treatment compared to baseline.
- Proportion of subjects with a change in MAP blood culture status after 52 weeks of treatment compared to baseline.
- Proportion of subjects with MAP positive colon biopsy PCR assay at baseline.
- Proportion of subjects with a change in MAP positive colon biopsy PCR assay status after 26 weeks of treatment compared to baseline.
- Proportion of subjects with a change in MAP positive colon biopsy PCR assay status after 52 weeks

2.2.4.2 Other Endpoints

- Proportion of subjects tapered off steroids in each treatment arm.
- Assess tissue levels of the active agents of RHB-104 in colon biopsy samples if possible.

2.2.5 Safety Endpoints/Variables

Safety parameters include the following.

- Adverse events
- Incidence of uveitis
- Laboratory parameters (hematology, chemistry, urinalysis)
- Vital signs
- ECG
- Physical examination
- Concomitant medications

3. STUDY DESIGN

This study is a multicenter, Phase III, randomized, placebo-controlled, parallel group, double-blind study designed to evaluate the efficacy and safety of RHB-104 compared to placebo to treat subjects with moderate to severe CD. RHB-104 consists of 3 antibiotics with activity against *Mycobacterium avium subsp. paratuberculosis* (MAP), a potential cause of CD. Subjects with active CD will be randomized at baseline in a 1:1 fashion to receive up to 52 weeks of RHB-104 or placebo. Subjects will remain on stable doses of their baseline CD treatment although steroids may be tapered after Week 8 at the discretion of the investigator.

The study is designed to assess remission at Week 26 as the primary endpoint. However, as MAP are slow growing mycobacteria without a proven antibiotic treatment, the duration of antibiotic treatment needed to achieve remission in subjects with CD caused by MAP may be longer than 26 weeks. Subjects with response at week 26 may ultimately achieve remission at a later time point with continued treatment for MAP. Also, subjects with CD treated for underlying MAP infection may experience benefits with a longer period of time in response or remission with RHB-104 treatment compared to placebo. Thus, the study is also designed to assess response, remission, and maintenance of remission in subjects on randomized treatment through week 52.

Blood samples will be collected at baseline and at every visit after the initial 4 weeks of treatment to test for MAP in the serum using a polymerase chain reaction (PCR) assay. MAP cultures will be prepared from whole blood at the baseline visit and after 26 and 52 weeks of treatment in subjects enrolled at North American study sites.

Safety and pharmacokinetics of the fixed-dose combination product, RHB-104, will also be assessed. Colonoscopy will be done in consenting subjects prior to initiation of study drug and after26 weeks of study drug to assess for mucosal healing as well as MAP status via PCR and culture. Optional biopsies will also be collected for possible measurement of tissue drug levels and archived for future MAP determinations.

4. SCHEDULE OF ASSESSMENTS AND TREATMENT ASSIGNMENT

4.1 Schedule of Assessments

The study schedule is summarized in the study visit schedule table below.

4.1.1 Study Visit Schedule

	Screening (Day -42 to screening Day -7)	Baseline Day 1 / Week 0[6]	Week 2	Week 4	Week 6	Weeks 8, 12, 16 and 20	Week 26	Weeks 35 and 44	Week 52	Week 56
Study Visit Window			± 3 days	± 3 days	± 3 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Informed Consent	X									
Inclusion/ Exclusion Criteria Demography and Medical History	X	X								
Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X	X
Vital Signs and Physical Examination	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessments			X	X	X	X	X	X	X	X
CDAI collection[1]		X		X		X	X	X	X	
Subject Assessments: IBDQ and SF-36		X					X		X	
Uveitis Assessment	X	X	X	X	X	X	X	X	X	X
ECG[2]	X	X	X	X		Weeks 8 and12	X		X	
Hematology and Biochemistry	X	X	X	X	X	X	X	X	X	X
Urinalysis[3]	X	X	X	X	X	X	X	X	X	X
Plasma Levels of RHB-104[4]							X			
Hep B S Ag, Hep C Ab, HIV and QuantiFERON®-TB	X									
C-Reactive Protein (CRP)	X	X				X	X	X	X	
MAP Testing Blood with Additional Sample for Future Use		X		X		X	X	X	X	
MAP culture from blood		X					X		X	
Fecal calprotectin	X	X				Week 12	X		X	
Stool Testing other[5]	X						X		X	
Pregnancy Test Urine	X	X	X	X	X	X	X	X	X	X
Colonoscopy[6] and CDEIS, storage of images, MAP testing , archive samples and possible analysis of drug levels	X						X			
Population PK Blood Sampling[4]			X	X	X	Week 8, 12 and 20		X	X	X[8]
Randomization (after meeting inclusion/exclusion criteria)[7]		X								

Study Drug and Diary Dispensing (with instructions for drug administration & diary completion[1])	Diary only	X	X	X	X	X	X	X		
Drug Return & Accountability			X	X	X	X	X	X	X	
Telephone reminder of dose escalation		Day 7	Day 21							

[1] **CDAI**: Subjects will complete a CDAI diary for the 7 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. At the screening visit the 7-Day CDAI diary will be distributed to the subject for completion before the Baseline visit and if applicable, before the colonoscopy preparation/procedure takes place.

[2] **ECG**: Five minute continuous digital 12-lead ECG after resting 10 minutes in a supine position

[3] **Urine Testing**: Dipstick test only, unless results are abnormal

[4] **Frozen plasma sample**: For Week 26 clarithromycin, rifabutin, clofazimine, 14-hydroxy-clarithromycin, and 25-O-desacetyl-rifabutin plasma concentration measurement.

[5] **Stool testing***: E, coli* 0157 toxin, culture (includes *salmonella, campylobacter, yersinia*), ova, and parasites testing done at Screening only. *C. difficile* toxin and stored sample for potential analysis of fecal microbiome done at Screening, Weeks 26 and 52

[6] **Colonoscopy**: to be performed at least 8 days before or at the Week 0 visit. If performed at the Week 0 visit, then the 7 days prior to the start of the colonoscopy preparation will be used to calculate the baseline CDAI score. At visit week 26: the colonoscopy must be performed 3-4 days post visit week 26. Only CDEIS compatible colonoscopies will have biopsies and CDEIS performed, although biopsies are optional.

[7] **Randomization**: At screening, IWRS will be accessed to record the subject's screening information. Randomization and study drug kit assignment will be confirmed in the IWRS at the baseline visit, after subject eligibility is confirmed.

[8] **PK Blood Sampling:** single time point.

4.2 Dosage and Administration of Study Drug

Study treatment will be taken twice-daily (bid) with food. Subjects will self-administer study drug orally, as per the following dosage schedule:

		Weeks				
		1	**2**	**3**	**4**	**5-52**
		(1 bid) 2 capsules	**(2 bid) 4 capsules**	**(3 bid) 6 capsules**	**(4 bid) 8 capsules**	**(5 bid) 10 capsules**
		Active Daily Dose (mg)				
Active Treatment Arm	**RHB-104** **Clarithromycin** **Rifabutin** **Clofazimine**	**190mg** **90mg** **20mg**	**380mg** **180mg** **40mg**	**570mg** **270mg** **60mg**	**760mg** **360mg** **80mg**	**950mg** **450mg** **100mg**
Placebo Arm	**Placebo**	**placebo**	**placebo**	**placebo**	**placebo**	**placebo**

4.3 Randomization and Treatment Assignment Procedures

A total of 410 subjects that meet study eligibility requirements will be randomly assigned in permuted blocks to receive active (RHB-104) or placebo treatment in a 1:1 ratio using an Interactive Web Randomization System (IWRS). Randomization will be performed within strata defined by whether subjects use protocol permitted anti-TNF agents (yes/no). The randomization

code will only be available to personnel responsible for the randomization of subjects or labeling of the study drug. The sponsor and all personnel involved in the conduct of the study will be blinded to the treatment assigned to each subject.

5. ANALYSIS POPULATIONS

All screened 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 primary efficacy analyses will be based on the ITT population, which is defined as all subjects randomized. Subjects will be analyzed according to the treatment group to which they were randomized.

The Modified Intent-to-Treat (mITT) Population: The Modified Intent-to-treat population is defined as patients who fulfill all inclusion/exclusion criteria. The sensitivity analyses will be performed using the mITT population. Subjects will be analyzed according to the treatment group to which they were randomized.

The Safety Population (SAF): The safety population includes subjects who are randomized and receive at least one dose of study medication. The primary safety analyses will be based on the SAF population. Subjects will be analyzed according to the treatment which they actually received.

Per-Protocol Population (PP): The PP Population includes all randomized subjects who receive at least one dose of RHB-104 or placebo and complete dose escalation to target dose of 5 capsules bid, as well as all subjects without major protocol deviations that would have a significant impact on clinical outcome. Relevant protocol deviations may include errors in treatment assignment, the use of excluded medication that might affect study drug bioavailability, poor compliance (< 80% compliant over study duration), and subjects lost to follow-up. Protocol deviations will be reviewed and the list of major deviations warranting exclusion from the PP Population will be finalized prior to study unblinding. Subjects will be analyzed according to the treatment group to which they were randomized.

The primary and key secondary efficacy sensitivity analyses may be repeated on the PP Population.

6. STATISTICAL METHODOLOGY

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

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, efficacy, 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.

The primary hypothesis testing will be two-sided statistical significance testing (alpha level = 0.05) comparing active treatment to placebo and mainly dedicated to assessing the primary endpoint and the key secondary endpoints. Point and interval estimates (95% confidence intervals) will be calculated and presented by treatment group for each parameter. Computed p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as '< 0.0001' and p-values greater than 0.9999 will be presented as '> 0.9999' in the tables.

All statistical analyses will be performed using SAS statistical software (Version 9.3 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 and the version used will be footnoted in the respective summary tables. Concomitant medications will be coded using the most recent version of World Health Organization (WHO) Drug dictionary.

6.1.2 Multiplicity and Testing Strategy

Multiplicity issues in statistical inference in this study may arise from repeated tests on several multiple endpoints specified in the protocol. Additionally, the impact of the Type I error probability (α) because of the formal planned interim analysis to be conducted needs to be understood.

The protocol specified α-spending for the planned interim analysis is 0.003. Hypotheses tests at the final analysis will be conducted at significance level of $\alpha = 0.049$. The multiple efficacy tests for the study final analysis will employ a serial sequential gatekeeper strategy to maintain the Type 1 error rate at $\alpha = 0.049$ across two families of analyses that support the primary, and key secondary objectives. The protocol pre-specified strategy is to use a hierarchy of significance tests where each test acts as a gatekeeper to tests below it. The endpoints will be tested in a sequential manner and will follow the sequential order given below starting with Remission ranked 1. Any inferential and hypothesis testing of a subsequent endpoint will be performed only if the test for the preceding endpoint is significant. In other words, the endpoint hypothesis examined earlier serves as gatekeeper. For this study as listed below in sequence of clinical importance, Remission week 26 is first rank (1) and will be tested first followed by Response week 26 (rank 2), followed by Remission week 52 (rank 3), Durable Remission week 26 through week 52 (rank 4), followed by Remission week 16 (rank 5), and followed by Steroid free Remission week 52 (rank 6). Again it is important to note that once one hypothesis is tested and found not to be significant at $\alpha = 0.049$, all subsequent tests will not be performed. The multiplicity adjustment following hierarchal testing procedure comparing RHB-104 with Placebo will only be performed on the following key clinical efficacy endpoints listed in order of clinical importance:

1. Remission (CDAI score < 150) week 26 - Primary Efficacy Endpoint.
Key Secondary Efficacy Endpoints:
2. Response (reduction from baseline of ≥100 in CDAI score) week 26.
3. Remission (CDAI score < 150) week 52
4. Durable Remission (CDAI score < 150) from week 26 through week 52 in remission.

5. Remission (CDAI score < 150) week 16
6. Proportion of subjects in steroid free remission week 52 (CDAI score < 150 and no steroids use by week 49).

For the endpoints not included in the above pre-specified multiple testing, the P-values and confidence intervals will be presented with NO adjustment for multiplicity. Nominal P-values and confidence intervals are consequently supplementary/supportive to the primary efficacy analyses.

6.1.3 Subgroups

To further assess consistence of the study outcome data, the primary efficacy, key secondary efficacy, and select safety data may be further broken down and summarized by the following baseline subgroups characteristics with potential differing influence on outcome:

- Sex: male, female
- Race: White, Black, Other
- Region: Countries will be grouped into geographical regions, e.g., US, Canada, Europe, etc.
- Alcohol consumption: (Yes/No)
- Smoking: (previous smoker, currently smoking, Nonsmoker)
- Prior CD treatments (e.g., surgery/no surgery)
- Years of CD (Categories to be determined at the time of analysis)
- Prior use of anti-TNF agents (yes or no)
- Prior use of immunomodulators (yes or no)
- Prior use of Corticosteroids (yes/no)
- CRP level at baseline
- Fecal Calprotectin level at baseline

The final subgroups to be assessed will be completed at the time of analysis depending on the available data by each subgroup.

6.1.4 Baseline Definition

Baseline period consists of 42 days (covering screening period) immediately preceding first administration of study treatment. Any assessment performed during these 42 days before first administration of study treatment will be considered baseline assessment. Study day 1 will be the first day of study drug administration. For all endpoints requiring baseline results, e.g., comparison with post-baseline, the baseline is the last non-missing result prior to first dose.

6.1.5 Missing Data and Handling of Dropouts

All available efficacy and safety data will be included in data listings and tabulations. All patients who prematurely discontinue for any reason will be considered failures for the different proportion based endpoints.

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 the protocol, subjects with missing week 26 assessment will be assumed to not be in a state of remission at week 26 (i.e., non-responders). Similarly, for subjects with missing week 52 assessments will be assumed not to be in state of remission at week 52. Sensitivity analyses may be performed on Observed Case (completer analysis) only.

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.

6.1.6 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

6.1.7 Pooling of Investigator Sites

The primary analysis will use data pooled across all investigative sites. The Regions (UK, US, Canada, New Zealand, Israel, Slovakia, etc.) and site differences may be explored in preliminary analyses depending on how many subjects randomized by each site/region. Preliminary exploratory analyses may be conducted to determine potential influence of treatment-by-investigative site/region interaction on the primary and key secondary efficacy endpoints by graphical visualization and tabulations of the data and where necessary, using statistical models incorporating treatment, site, and treatment-by-site interaction. A significance level of 0.10 will be used in any of the analyses in identifying potential treatment-by-site interactions. The exploratory results indicating non-significant interaction will be indicative that pooled data across sites/regions was free of the impact of any extreme investigative sites/regions. It is recognized that the power to detect an interaction will be limited due to some sites with limited enrollments.

6.1.8 Efficacy Data with High Doses of Steroids Use and Rescue Medications Use

Corticosteroids Use:
A subject may use corticosteroids or increased dose levels of corticosteroids for reasons other than CD, and may start corticosteroid tapering at 8 weeks. If the subject experiences a worsening of disease activity during the taper, and/or the oral corticosteroid dose temporarily increased, in these circumstances the subject will be considered a treatment failure in the steroid free remission analysis but will continue to remain on the study and complete all scheduled visits.

Use of Rescue Medications:

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
- Antibiotics as treatment of CD
- Total parenteral nutrition as treatment of CD
- Systemic or rectal corticosteroid therapy
- Anti-TNF or other biologic agent

In the ITT efficacy analyses, subjects who initiate or modify dose/regimens to treat CD symptoms will be considered as treatment failures.

6.1.9 Determination of Sample Size

The sample size justification is provided in the protocol and was based on the review of published literature in similar patient population (Sandborn et al., 2013). A total sample size of 410 subjects (205 per treatment arm) was computed to be sufficient with one stratification anti-TNF agent use (yes/no) to detect a minimum difference of 15 percentage points between RHB-104 treatment (36% Remission) and Placebo (21% Remission) with 90% Power at two-sided significance level, α=0.05. The test statistic used for this analysis was a two-sided Cochran-Mantel-Haenszel (CMH) test controlling for the stratification variable (anti-TNF agents (yes/no) under the ITT principle. These calculations were made to allow for two sequential tests to be made using the O'Brien-Fleming spending function to determine the test boundaries. The interim analysis (first sequential test) will occur when 50% of the patients have their outcome data measured (i.e., reach 26 weeks of follow-up). The 2-sided alpha level for stopping the trial for efficacy at the interim analysis is 0.003. If this criterion is not met the trial will be continued and the final analysis (second sequential test) will be performed using a 2-sided alpha level of 0.049 for testing the primary outcome (Elashoff, 2007). In all analyses, subjects with missing 26 week assessments will be assumed to not be in a state of remission at 26 weeks.

It should be noted that the intervention effect used in the sample size derivation for the study is 15% improvement in 26 week remission success, however a clinically meaningful difference in this measure (26 week remission success proportion) is 9% (in absolute percent) based on clinical expert opinion. Therefore, any statistically significant difference between groups that has an observed percent difference of 9% or larger would indicate that treatment is effective.

Protocol Version 11.0 curtails the number of expected enrolled patients to 324 (162 per group). Final analysis of the data is to be carried out when approximately 324 patients have completed the Week 26 primary endpoint assessment. This sample size curtailment reflects the study's current accrual trends. The anticipated power will be at least 80% given the study design stage assumptions regarding the treatment groups primary efficacy endpoint (36% RHB-104 vs. 21% Placebo).

6.2 Subject Characteristics

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

6.2.1 Subject Disposition

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

All screened subjects will be summarized in subject disposition summary tables. The number and percent of screened subjects in each of the following categories will be presented.

- Subjects screened
- Screen failures and by criteria
- Subjects randomized
- Subjects completing weeks 26 and 52
- Subjects discontinued from the study and by reason of discontinuation.

The number and percentage of randomized patients who are ITT evaluable, mITT evaluable, safety evaluable (SAF), and PP evaluable will be summarized by treatment group and overall.

The number and percentage of randomized subjects, who complete the study through weeks 26, and 52, and who discontinue the study by reason will be summarized by treatment group and overall.

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 treatment group and overall based on the safety population and ITT population. The summary will be grouped into different categories of violations such as:

- Errors in treatment assignment
- Violation of inclusion/exclusion criteria
- 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. Demographics variables will be summarized descriptively for the ITT and SAF population by treatment group and will include the following variables:

- Age at enrollment continuous variable [Years]
- Sex
- Race
- Ethnicity
- Height
- Weight
- BMI

6.2.3.2 Background/Baseline Characteristics

The following list of variables will be summarized to further characterize the patient population at baseline by treatment group:

- Crohn's disease (CD) characteristics: CD Surgical history; duration of CD since first diagnosis, baseline CDAI score; baseline CDEIS and SES-CD scores
- Age at first diagnosis
- Stratification anti-TNF agents (yes or no)
- Smoking
- Alcohol consumption
- MAP Test status: PCR Blood Assay: (Positive/Negative) Baseline
- Map Test status: Blood Culture (Positive/Negative) Baseline
- Baseline serum inflammation marker: C-reactive protein (CRP)
- Baseline stool inflammation marker: Fecal calprotectin
- Baseline IBDQ
- Prior use of steroids (yes/no)
- Prior use of immunomodulators (yes/no)

The final analysis list of baseline characteristics will be completed at the time of analysis depending on the available data. The baseline characteristics will be summarized descriptively for the ITT population by treatment group. 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.

6.2.4 Treatment Exposure and Drug Accountability

6.2.4.1 Treatment Exposure

Exposure will be summarized for the ITT population and 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 treatment group and also presented as subject data listing for the ITT population and Safety population.

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

Physical examination of 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) at baseline and post-baseline visits will be tabulated for each body system with the number and percentage of subjects.

All physical examination results will be presented in a subject data listing, including the description of abnormalities.

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 and at baseline on the medical history eCRF. 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 and baseline on the history eCRF. Data will be presented descriptively by treatment group and also presented as data listing for the ITT population.

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 prior medications and concomitant medications by treatment group.

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 tem, and date.

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

6.3 Efficacy Analysis

The efficacy primary analyses will be based on the ITT population as the primary population. Any Supportive/sensitivity analyses may be assessed on subgroup populations of subjects that will be defined for each endpoint as needed for implementing specific sensitivity analysis. Additional analyses as defined in SAP addendum will be performed accordingly as specified.

6.3.1 Primary Efficacy Analysis

The primary efficacy analysis will be performed on ITT population. Sensitivity analyses may be performed on Observed Case (completers only), on subjects with no violation of key inclusion/exclusion criteria (mITT population), and on PP population.

The primary efficacy variable is the proportion of subjects experienced remission week 26, where remission is defined as a subject having a Crohn's Disease Activity Index (CDAI) score of < 150. Subjects who have a week 26 CDAI measurement ≥ 150 or who do not have a CDAI measurement week 26 will be classified as not achieved remission. The primary analysis will compare the RHB-104 treated group to Placebo treated group on ITT population using Cochran-Mantel-Haenszel (CMH) chi-square test controlling for the stratification variable anti-TNF agents use (yes/no). The null and alternative hypotheses are as follows, where π_R and π_P are the proportion of subjects with remission in the RHB-104 and placebo treated groups, respectively.

Null hypothesis $H_o: \pi_R = \pi_P$

"Proportion (%) of subjects in Remission in RHB-104 Treatment is equal to Proportion (%) of subjects in Remission in Placebo Treatment at week 26"

Alternative hypothesis $H_1: \pi_R \neq \pi_P$

"Proportion of subjects in Remission for RHB-104 Treatment is not equal to Proportion of subjects in Remission for Placebo treatment at week 26"

For each treatment group, descriptive statistics will be presented including the number of observations, proportion (%) of subjects in remission.

The primary analysis will compare RHB-104 group to the placebo group using a two-sided test at the $\alpha = 0.049$ level of significance.

The statistical criterion for primary objective success will be met if the CMH chi-square test p-value comparing the RHB-104 arm with the placebo arm (Higher proportion in RHB-104 than placebo) is less than 0.049 based on a 2-sided test taking into account the pre-specified protocol alpha spent at interim equal to 0.003.

For each treatment group, parameter estimates with 95% confidence interval will be presented including the number of observations and proportion (%) of subjects in remission.

To assess the robustness of the primary results, sensitivity analysis will be performed on mITT and on observed case (only completers with 26 weeks of data). The observed case population will include only subjects that have 26 weeks assessment.

Logistic regression modeling will be implemented as additional exploratory analysis to assess the modifying effect of prognostic baseline characteristics identified prospectively as clinically important baseline factors/variables on the remission outcome in both treatment groups at week 26. This will model a categorical response variable Remission (< 150 CDAI score) at week 26 (yes/no) as a function of treatment, stratification anti-TNF agents (yes/no) use, and treatment-by-baseline clinical factor interaction. The aim is to assess consistence/inconsistence of the treatment differences across each of the pre-defined clinically important baseline characteristics (one-variable-at-a-time). Each prognostic factor will be fitted separately (one-variable-at-a-time) in the model and output results including 95% confidence intervals presented in forest plots showing consistence/inconsistence by treatment group. The following baseline factors are considered prospectively to be potentially clinically important:

- Baseline serum inflammation marker: C-reactive protein (Normal/High)
- Baseline stool inflammation marker: Fecal calprotectin (Normal/High)
- Baseline CDEIS score (0-3; >3 score)
- Baseline SES-CD score (0-2; >2 score)
- Baseline IBDQ Score
- Duration of CD
- Prior surgical treatment for CD (yes/no)
- MAP-Test PCR Blood assay (Positive/Negative) Baseline
- MAP-Test Blood culture (Positive/Negative) Baseline
- Gender (male/female)
- Age at first Diagnosis of CD
- Smoking (yes/no)
- Alcohol consumption (yes/no)
- Use of Immunomodulators (yes/no)
- Use of steroids (yes/no)

The continuous variables may be categorized into different classification categories depending on the number of observations and final decisions on categories for each variable will be determined at the time of analysis.

6.3.2 Key Secondary Efficacy Endpoints Analyses

Five key secondary efficacy endpoints of clinical importance are considered for primary inferential claims. Since gate keeping hierarchical sequential testing strategy is required for multiplicity adjustment, any claim on these key secondary efficacy endpoints will be made only if the primary efficacy endpoint parameter meets the criterion for statistical success. The hierarchical sequence hypothesis testing for multiplicity adjustment is summarized in section 6.1.2 above. The hypothesis testing will be done in a sequential manner following the sequential order given in section 6.1.2 with the understanding that any hypothesis test of a subsequent endpoint will be performed only if the test for the preceding endpoint is significant. In other words, the endpoint hypothesis examined earlier serves as gatekeeper.

6.3.2.1 Response week 26

The Response week 26 is defined as the proportion (%) of subjects that experienced reduction from baseline of ≥ 100 in CDAI score. The same statistical analysis strategy as described for the primary endpoint including sensitivity and exploratory analyses will be repeated for the proportion responders (%) at 26 weeks comparing the two treatment groups. Summary parameter estimates generated from the statistical analyses will be presented by treatment group, and will include the number and proportion of subjects achieving response along with the model estimated odds ratio (including 95% confidence interval) and p-value comparing RHB-104 treatment to placebo. The same sensitivity and exploratory analyses as for primary endpoint analysis may be conducted and summarized.

6.3.2.2 Remission week 52

Remission at week 52 will be derived following similar strategy as for the primary endpoint. The subjects in remission will include subjects experienced remission (CDAI < 150 score) at week 26 and also at week 52, and subjects that were non-responders at week 26 but are responders at week 52 (Late responders).

The same statistical methods as used for the primary endpoint will be used for this analysis. The proportion of subjects experienced remission at 52 weeks will be summarized for each treatment group and compared between the two treatments using Cochran-Mantel-Haenszel (CMH) chi-square test. Summary parameter estimates generated from the statistical analyses will be presented by treatment group, and will include the number and proportion of subjects achieving response along with the model estimated odds ratio (including 95% confidence interval) and p-value comparing RHB-104 treatment to placebo. The same sensitivity and exploratory analyses as for primary endpoint analysis may be conducted and summarized.

6.3.2.3 Durable (or Sustained) Remission

This analysis is intended to compare the two treatment groups considering only the subjects that experienced remission (CDAI < 150 score) week 26 through week 52 (Sustained Remission). Subjects who are not in remission at any visit point assessment between 26 and 52 weeks will be considered as non-responders for this analysis. The same statistical method as used for the primary endpoint will be used for this analysis. The proportion (%) of subjects experienced sustained remission will be summarized for each treatment group and compared between the two treatments using Cochran-Mantel-Haenszel (CMH) chi-square test. Summary parameter estimates generated from the statistical analyses will be presented by treatment group, and will include the number and proportion of subjects achieving response along with the model estimated odds ratio (including 95% confidence interval) and p-value comparing RHB-104 treatment to placebo. The same sensitivity and exploratory analyses as for primary endpoint analysis will be conducted and summarized.

An additional complementary analysis and summary will be presented for the Proportion of subjects that maintained durable remission at least 3 out of the 4 visits assessed (i.e. ≥ 75% of the visits in remission) week 26 through week 52.

6.3.2.4 Early Remission week 16

Early Remission week 16 will be derived following similar strategy as for the primary endpoint. The summary results will show the number and proportion (%) of subjects experienced early remission (CDAI < 150 score) week 16.

The same statistical approach as for the primary analysis will be employed to compare proportion (%) of subjects experienced Early Remission for the RHB-104 treated group versus Placebo treated group on ITT population using Cochran-Mantel-Haenszel (CMH) chi-square test controlling for the stratification variable anti-TNF agents use (yes/no). Summary parameter estimates generated from the statistical analyses will be presented by treatment group, and will include the number and proportion of subjects in remission along with the model estimated odds ratio (including 95% confidence interval) and p-value comparing RHB-104 treatment to placebo. The same sensitivity and exploratory analyses as for primary endpoint analysis may be conducted and summarized.

6.3.2.5 Steroid free remission week 52

This analysis is to compare the proportion (%) of subjects that achieved steroid free remission week 52 in the two treatment groups. To be considered to be in steroid free remission, a subject has to be in remission (CDAI score < 150) week 52 and is off steroids use for at least 3 weeks. The 3 weeks steroid free period is by week 49.

The statistical analysis strategy, the statistical tests comparing the two treatment groups, summary and presentation of the results will be similar to the primary endpoint analysis based on CMH chi-square tests. Summary parameter estimates generated from the statistical analyses will be presented by treatment group, and will include the number and proportion of subjects in steroid free remission along with the model estimated odds ratio (including 95% confidence interval) and p-value comparing RHB-104 treatment to placebo. The same sensitivity and exploratory analyses as for primary endpoint analysis may be conducted and summarized.

6.3.3 Supportive Secondary Efficacy Endpoints

This group of secondary efficacy endpoints is considered to be supportive of the efficacy for the primary and the key secondary endpoints. Therefore, there will be no multiplicity adjustments for this group of endpoints. Summary statistics and tests of hypotheses will be considered descriptive/supportive.

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

The four endpoints will require time to event modeling approach. Cox Proportional Hazard modeling will be used to compare the time to event in both treatments while simultaneously adjusting for stratification variable anti-TNF agents use (yes/no). The explanatory variables in the model will include treatment, and the stratification variable anti-TNF agents use (yes/no). Patients who do not achieve the outcome event at the end of the study will be censored on the last visit date recorded. Patients who discontinued early will be censored on the last date of contact. Censored observations and confidence intervals for the estimated median times will be presented.

The null hypothesis that is tested is that of equal time to event distribution between the two treatments. Equality of the distributions of event times implies that there are similar response event rates between the two treatments not only for the entire treatment period, but also for any visit time point assessed post-baseline during the study. Rejection of the null hypothesis indicates that the event rates significantly differ between the two treatments at one or more visit time points assessed post-baseline. Kaplan Meier survival curves and parameters showing time-to-first observed response outcome will be summarized by treatment. 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. The log-rank test will be used to test for differences between RHB-104 treatment and placebo, and p-values from the tests will be presented. Kaplan-Meier plots with descriptive summary statistics will be presented.

6.3.3.2 Sustained Remission week 16 though week 52

This analysis is intended to compare the two treatment groups based on the proportion (%) of subjects achieved Sustained Remission defied as maintaining CDAI score < 150 from week 16 through week 52. Subjects who are not in remission at any visit point assessment between week 16 and week 52 will be considered as non-responders for this analysis. The same statistical method as used for the primary endpoint will be used for this analysis. The proportion (%) of subjects experienced sustained remission will be summarized for each treatment group and compared between the two treatments using Cochran-Mantel-Haenszel (CMH) chi-square test. Summary parameter estimates generated from the statistical analyses will be presented by treatment group, and will include the number and proportion of subjects achieving sustained remission along with the model estimated odds ratio (including 95% confidence interval) and p-value comparing RHB-104 treatment to placebo.

An additional complementary analysis and summary will be presented for the Proportion of subjects that maintained durable remission at least 5 out of the 6 visits assessed (i.e. ≥ 83% of the visits in remission) week 16 through week 52.

6.3.3.3 Response at Week 52

The Response is defined as reduction from baseline of ≥100 in CDAI score week 52. The responders will include subjects who were responders week 26 through week 52 and the subjects that were non-responders at week 26 but were responders week 52 (Late Responders).

The same statistical methods as used for the primary endpoint will be used for this analysis. The proportion of subjects experienced response at 52 weeks will be summarized for each treatment

group and compared between the two treatment groups using Cochran-Mantel-Haenszel (CMH) chi-square test.

6.3.3.4 Early Response week 16

The Early Response week 16 is defined as the proportion (%) of subjects that experienced reduction from baseline of ≥ 100 in CDAI score. The same statistical methods as used for the primary endpoint will be used for this analysis. The proportion of subjects (%) experienced early response week 16 will be summarized for each treatment group and compared between the two treatments using Cochran-Mantel-Haenszel (CMH) chi-square test. Summary parameter estimates generated from the statistical analyses will be presented by treatment group, and will include the number and proportion of subjects achieving response along with the model estimated odds ratio (including 95% confidence interval) and p-value comparing RHB-104 treatment to placebo.

6.3.3.5 Steroid free remission week 26

This analysis is to compare the proportion (%) of subjects that achieved steroid free remission week 26 comparing the two treatment groups. To be considered to be in steroid free remission subject has to be in remission (CDAI score < 150) week 26 and maintained off steroids for at least 3 weeks. The 3 weeks steroid free period is by week 23.

The statistical analysis strategy, the statistical tests comparing the two treatment groups, summary and presentation of the results will be similar to the primary endpoint analysis based on CMH chi-square tests. Summary parameter estimates generated from the statistical analyses will be presented by treatment group, and will include the number and proportion of subjects achieving response along with the model estimated odds ratio (including 95% confidence interval) and p-value comparing RHB-104 treatment to placebo.

6.3.3.6 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 to inVentiv for data summary and analysis.

Summary descriptive statistics including mean, standard deviation, median and range (including 95% confidence intervals) will be presented in tables and bar graphs for the actual and change from baseline scores for each domain and component summary score by treatment and by visit. The change from baseline for each domain and component summary score will be analyzed using an analysis of covariance (ANCOVA) model with treatment group, stratification variable anti-TNF agents use (yes/no) as classification factors, and baseline score as covariate. The treatment parameter estimates from the analysis models including means, 95% confidence intervals and associated 2-sided p-values will be presented.

6.3.3.7 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 mean, standard deviation, median and range (including 95% confidence intervals) will be presented in tables and bar graphs for the actual observed and change from baseline scores for each domain and overall by treatment and by visit.

The change from baseline IBDQ score will be analyzed using an analysis of covariance (ANCOVA) model with treatment group, stratification variable anti-TNF agents use (yes/no) as classification factors, and baseline IBDQ score as a covariate. The treatment parameter estimates from the analysis model including means, 95% confidence intervals and associated 2-sided p-values will be presented.

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

The CRP is used as marker of inflammation. The C-reactive Protein (CRP) level data collected at different visits 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, standard deviation, median and range for each treatment by visit. The change from baseline CRP comparing the two treatment groups will be analyzed using an analysis of covariance (ANCOVA) model with treatment group, stratification variable anti-TNF agents use (yes/no) as classification factors, and baseline CRP as a covariate. The treatment parameter estimates from the analysis model including means, 95% confidence intervals and associated 2-sided p-values will be presented including bar graphs.

In addition, the CRP level will be classified into two categories: "Normal (≤ 0.999 mg/dL)" and "High (> 10 mg/dL)". Summary results will show number of patients and proportion (%) with "Normal level" and with "High Level" by treatment group at baseline and at different visit time-points with data collected post-baseline. The same statistical method and modeling as used for the primary endpoint will be used for this analysis. The proportion of subjects "Normal" at baseline and at each visit with data post-baseline will be compared between the two treatments using Cochran-Mantel-Haenszel (CMH) chi-square test controlling for the stratification variable anti-TNF agents use (yes/no).

Supplementary shift tables will be presented showing proportion of subjects at baseline that were in each category and shifted from one category to another or remained in the same category at the different post-baseline visits.

6.3.3.9 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. Summary descriptive statistics for the actual observed and change from baseline will include mean, standard deviation, median and range for each treatment by visit. The change from baseline Fecal calprotectin comparing the two treatment groups will be analyzed using an analysis of covariance (ANCOVA) model with treatment group, stratification variable anti-TNF agents use (yes/no) as classification factors, and baseline Fecal calprotectin as a covariate. The treatment parameter estimates from the analysis model including means, 95% confidence intervals and associated 2-sided p-values will be presented including bar graphs.

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 (%) with "Normal level" and with "High Level" by treatment group at baseline and at different visit time-points with data collected post-baseline. The same statistical method and modeling as used for the primary endpoint will be used for this analysis. The proportion of subjects "Normal" at baseline and each visit with data post-baseline will be compared between the two treatments using Cochran-Mantel-Haenszel (CMH) chi-square test controlling for the stratification variable anti-TNF agents use (yes/no).

Supplementary shift tables will be presented showing proportion of subjects at baseline that were in each category and shifted from one category to another or remained in the same category at the different post-baseline visits.

6.3.3.10 Endoscopic Assessment Based on CDEIS and SES-CD at Week 26

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 drop 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, proportion of surface covered by ulcers, proportion of surface affected by disease, and presence and severity of stenosis). 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, except for the presence and extent of stenosis, which ranges from 0 to 11 (Total SES-CD score range 0–56).

The CDEIS and SES-CD mean scores at baseline and week 26, and change from baseline scores to week 26 will be summarized by treatment group for subjects who consent to undergo colonoscopy. The change from baseline CDEIS and SES-CD scores comparing the two treatment groups based on each of the two scoring systems will be analyzed using analysis of covariance (ANCOVA) models with treatment group, stratification variable anti-TNF agents use (yes/no) as classification factors, and baseline CDEIS score or SES-CD as covariate. The treatment parameter estimates from the analysis models including means, 95% confidence intervals and associated 2-sided p-values will be presented.

In addition, the CDEIS and SES-CD scores will be classified into two categories: "Remission (CDEIS 0-3 score; SES-CD 0-2 score)" and "No Remission (CDEIS > 3; SES-CD > 2 score)". Summary results will show number of patients and proportion (%) in "Remission" based on CDEIS and also based on SES-CD by treatment group at baseline and at different visit time-points with data collected post-baseline. The same statistical method and modeling as used for the primary endpoint will be used for this analysis.

The proportion of subjects at baseline and each visit in "Remission post-baseline will be compared between the two treatments using Cochran-Mantel-Haenszel (CMH) chi-square test controlling for the stratification variable anti-TNF agents use (yes/no). The same statistical summary will be repeated comparing the two treatment groups on proportion of responders based on CDEIS and SES-CD scores defined as 50% reduction from baseline score and 25% reduction from baseline score to week 26.

Supplementary shift tables will be presented showing proportion of subjects at baseline that were in "No Remission" category and shifted to "Remission" category or vice versa or remained in the same category at the different post-baseline visits.

The following highlights the efficacy summaries in form of tables and/or figures that will be displayed by treatment group for both the CDEIS and SES-CD outcomes assessments:

- Endoscopic Remission based CDEIS and SES-CD week 26

- Shift Tables from "No Remission" to Remission and vice versa
- Endoscopic Response: 50% reduction in CDEIS and SES-CD scores from baseline
- Endoscopic Response: 25% reduction in CDEIS and SES-CD scores from baseline

Additional supportive analysis will be implemented to estimate the correlations between the change from baseline to week 26 in the SES-CD total score, CDEIS total score, and the change from baseline to week 26 in the CDAI total score. The results will be presented in graphs including Pearson and Spearman correlation coefficients estimates. Scatter plots of the change in SES-CD total score and CDEIS total score versus the change in CDAI total score will be presented.

Listing of all subjects indicating CDEIS and SES-CD scores by visit by treatment group will be presented.

6.3.4 Other Exploratory Endpoints

6.3.4.1 MAP Detection: Blood PCR Assay, Blood Culture Test and Colon Biopsy PCR Assay

Initial blood culture analyses will be performed upon unblinding of the study using data that is available at the time of the data lock. However, subsequent analyses will be performed to allow for further development of the MAP PCR Blood Assay as well as to allow for the 6 month period required to grow MAP in culture for participants whose samples did not had adequate culture growth duration at the time of the data lock. Subsequent analyses will occur when all baseline samples for participants have at least 6 months of duration to grow MAP in culture, next analyses will be repeated when participants with 26 and 52 week data have corresponding 6 and 12 month MAP culture measurements, and finally an analysis will be performed once all participants have their corresponding 6 month MAP culture measurements available. Since this outcome measure is among the exploratory measures and not considered a primary efficacy endpoint, performing analyses at several time points based on the availability of 6-month MAP culture measurements is justified and will not jeopardize the rigor of the statistical testing proposed for the primary and secondary endpoints.

MAP detection analysis is intended to be exploratory. More exploratory analyses may be done but the decision on additional types of analyses will depend on the available data and the final decisions will be made at the time of analysis. Data collected on MAP detection based on PCR Blood Assay, Blood Culture Test and Colon Biopsy PCR assay will be summarized and presented as follows:

- Proportion of subjects (positive/Negative) for MAP at baseline and weeks 26 and week 52 post-baseline will be summarized by treatment group.

- Shift tables summarizing shifts in status (positive to negative; negative to positive, no change) from baseline to week 26 and week 52 post-baseline will be presented by treatment.

The same statistical approach as for the primary analysis will be employed to compare proportion of subjects (positive/negative) for the RHB-104 treated group versus Placebo treated group on

ITT population week 26 and week 52 using Cochran-Mantel-Haenszel (CMH) chi-square test controlling for the stratification variable anti-TNF agents use (yes/no).

Additional analysis will be implemented to estimate the correlations between the change from baseline to week 26 and week 52 in PCR Blood Assay level, Blood Culture Test, Colon Biopsy PCR Assay level, and the change from baseline to week 26 and week 52 in the CDAI total score. The results will be presented in graphs including Pearson and Spearman correlation coefficients estimates. Scatter plots of the change in Blood PCR Assay, Blood Culture Test, and Colon Biopsy PCR Assay level versus the change in CDAI total score will be presented.

6.3.4.2 Drug Levels in Tissue Samples

This is an exploratory analysis and will depend on the samples available at the end of the study for analysis. The tissue samples being collected will be analyzed for drug levels if possible at the end of the study. The patient listings will be presented with correlation of drug levels with CDAI and the other efficacy parameters assessed.

6.4 Population PK Analysis

Population PK analysis will be detailed in a separate document.

6.5 Safety Analysis

All summarization of safety data will be based on the safety population.

6.5.1 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.

6.5.2 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.

6.5.3 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.

6.5.4 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.

6.5.5 Uveitis Assessment

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

6.6 Data and Safety Monitoring Board (DSMB)

In order to ensure the safety of study participants, a Data Safety Monitoring Board (DSMB) will be established to monitor data on an ongoing basis. The committee will meet periodically to review interim safety data. Following their review, the DSMB will recommend whether the study should continue as is or be modified to improve safety. The DSMB will consist of at least one clinician with experience in the care of patients with inflammatory bowel disease and at least one statistician. The DSMB charter will describe the membership, responsibilities, meeting procedures related to the DSMB, output to be reviewed, and interim analysis rules to be applied. The DSMB at regular intervals will review the following, at each of the safety analyses meetings:

- Demographic and baseline characteristics
- Physical exam, vital signs, clinical laboratory findings, ECG findings
- Summaries of SAE, AEs and deaths
- Summaries of subject withdrawals
- Summaries of subject accrual and retention
- Summaries of protocol violations

The DSMB will carefully consider safety results and then provide a recommendation for continuing or stopping the trial for safety to the Sponsor after each DSMB safety meeting. There are three planned DSMB meetings for the study. The first meeting is planned for when 25% of patients reach 26 weeks of treatment. The second and third meetings are to occur after 50% and 75% of patients have completed 26 weeks of treatment or terminated study participation early. Once the required numbers of patients have reached each of these thresholds, a database snapshot will occur. The DSMB will convene to review safety data within 3 months of the data base snapshot. The timing between each DSMB meeting will be at least 6 months.

In addition, it is anticipated that during the second DSMB meeting, an interim efficacy (or inefficacy) and futility analyses will be performed and the results of this analysis evaluated by the DSMB.

It is prospectively planned as specified in the protocol that the second DSMB meeting at 50% randomized subjects will comprise a formal interim of safety and efficacy (or inefficacy) and futility analyses will be performed and the results of this analysis evaluated by the DSMB.

6.7 Interim Analysis

One prospectively planned interim analysis for safety and futility is planned after 50% (205) patients have completed week 26 of treatment. The DSMB will evaluate the results from this analysis to assess RHB-104 safety, efficacy (or inefficacy), and the feasibility of continuing or stopping the study. The planned interim analysis is designed to have an alpha level of 0.003 as the criteria for stopping the trial early for efficacy or inefficacy based on using the O'Brein-Fleming spending function to determine the test boundaries. For the interim analysis, the Cochran-Mantel-Haenszel (CMH) test will be used to compare treatment groups controlling for the

stratification variable (anti-TNF agents (yes/no). The interim test is a 2-sided test (P=0.003), meaning that the trial can be stopped if there is overwhelming evidence of efficacy or overwhelming evidence of inefficacy. Further details are provided in the DSMB charter for this study.

The protocol specified α-spending for the prospectively plan interim analysis is 0.003. All tests at the final analysis will be conducted at significance level of $\alpha = 0.049$. The interim analyses will consider subjects with missing 26 week assessments to not be in a state of remission at 26 weeks.

Regarding the interim efficacy (or inefficacy) of the data, recommendations for early termination will be guided by the Lan-DeMets alpha-spending implementation of O'Brien-Fleming spending function to determine the test boundaries. The efficacy boundary preserves the overall 2-sided study alpha level of 0.05. The alpha level at first & second sequential test is 0.003 & 0.049, respectively.

The DSMB will carefully consider the safety and efficacy interim results and then provide a recommendation for continuing or stopping the study. The sponsor and all personnel involved in the conduct of the study will remain blinded to the treatment assigned to each subject. The DSMB will disseminate interim results in a manner that will protect the scientific and ethical aspects of the study. The responsibility of the DSMB, the scope of the data to be reviewed, the organization of the review process, dissemination requirements and procedures are described in DSMB charter.

6.8 Changes to Statistical Analysis Methods Planned in the Protocol

Changes to planned analyses from the protocol will be incorporated in the SAP, if they occur before the unblinding of the database.

7. ADDITIONAL OTHER EXPLOATORY ANALYSES

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

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

List of Tables and Graphs:

Table Number	*Title*
Analysis Populations and Disposition	
Table 14.1.1.1	Subject Disposition: All Enrolled Subjects
Table 14.1.1.2	Major Protocol Deviations: Intent-to-Treat Population
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Table 14.1.4.8	Prior Immunomodulators Use: Intent-to-Treat Population
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Treatment Exposure and Compliance	
Table 14.1.5.1	Study Drug Exposure: Intent-to-Treat Population
Table 14.1.5.2	Treatment Compliance: Intent-to-Treat Population
Primary Efficacy Endpoint	
Table 14.2.1.1	Primary Objective – Remission Week 26: Intent-to-Treat Population

Table 14.2.1.2	Sensitivity Analysis: Remission Week 26: Modified intent-to-Treat Population
Table 14.2.1.3	Sensitivity Analysis: Remission Week 26: Per-protocol Population
Table 14.2.1.4	Sensitivity Analysis: Remission Week 26: Completers Analysis (Observed Cases)
Table 14.2.1.5	Exploratory: Remission Week 26 by Treatment Group for Each Baseline Subgroup from Logistic Regression analysis: Intent-to-Treat Population
Figure 14.2.1.1	Exploratory: Remission Week 26 Forest Plots by Treatment Group for Each Baseline Subgroup Analysis: Intent-to-Treat Population
Key Secondary Efficacy Endpoints	
Table 14.2.2.1.1	Response Week 26: Intent-to-Treat Population
Table 14.2.2.1.2	Sensitivity Analysis - Response Week 26: Modified Intent-to-Treat Population
Table 14.2.2.1.3	Sensitivity Analysis - Response Week 26: Per-protocol Population
Table 14.2.2.1.4	Sensitivity Analysis - Response Week 26: Completers Analysis (Observed Cases)
Table 14.2.2.1.5	Exploratory: Response Week 26 by Treatment Group for Each Baseline Subgroup from Logistic Regression analysis: Intent-to-Treat Population
Figure 14.2.2.1.1	Exploratory: Response Week 26 Forest Plots by Treatment Group for Each Baseline Subgroup Analysis: Intent-to-Treat Population
Table 14.2.2.1.6	Sensitivity Analysis – Mixed Model Repeat Measures (MMRM) of CDAI Score: Intent-to-Treat Population
Table 14.2.2.1.7	Sensitivity Analysis – Mixed Model Repeat Measures (MMRM) of CDAI Score Change from Basleine: Intent-to-Treat Population
Table 14.2.2.1.8	Sensitivity Analysis – Negative Binomial Generalized Model Analysis of CDAI Remission: Intent-to-Treat Population
Table 14.2.2.1.9	Sensitivity Analysis – Poisson Generalized Model Analysis of CDAI Remission: Intent-to-Treat Population
Figure 14.2.2.1.6	Sensitivity Analysis – Mixed Model Repeat Measures (MMRM) of CDAI Score – Plot of Least Square Mean CDAI Score with 95% CI over time: Intent-to-Treat Population
Table 14.2.2.2.1	Remission Week 52: Intent-to-Treat Population
Table 14.2.2.2.2	Sensitivity Analysis - Remission Week 52: Modified Intent-to-Treat Population
Table 14.2.2.2.3	Sensitivity Analysis - Remission Week 52: Per-protocol Population
Table 14.2.2.2.4	Sensitivity Analysis - Remission Week 52: Completers Analysis (Observed Cases)
Table 14.2.2.2.5	Exploratory: Remission Week 52 by Treatment Group for Each Baseline Subgroup from Logistic Regression analysis: Intent-to-Treat Population
Figure 14.2.2.2.1	Exploratory: Remission Week 52 Forest Plots by Treatment Group for Each Baseline Subgroup Analysis: Intent-to-Treat Population
Table 14.2.2.3.1.1	Durable (Sustained) Remission Week 26 through Week 52: Intent-to-Treat Population
Table 14.2.2.3.1.2	Complementary Analysis: Proportion of subjects that maintained durable remission at least 3 out of the 4 visits assessed (i.e. ≥ 75% of the visits in

	remission) week 26 through week 52: Intent-to-Treat Population
Table 14.2.2.3.2	Sensitivity Analysis – Durable Remission Week 26 through Week 52: Modified Intent-to-Treat Population
Table 14.2.2.3.3	Sensitivity Analysis – Durable Remission Week 26 through Week 52: Per-protocol Population
Table 14.2.2.3.4	Sensitivity Analysis - Durable Remission Week 26 through Week 52: Completers Analysis (Observed Cases)
Table 14.2.2.3.5	Exploratory: Durable Remission Week 26 through Week 52 by Treatment Group for Each Baseline Subgroup from Logistic Regression analysis: Intent-to-Treat Population
Figure 14.2.2.3.1	Exploratory: Durable Remission Week 26 through Week 52 Forest Plots by Treatment Group for Each Baseline Subgroup Analysis: Intent-to-Treat Population
Table 14.2.2.4.1	Early Remission Week 16: Intent-to-Treat Population
Table 14.2.2.4.2	Sensitivity Analysis – Early Remission Week 16: Modified Intent-to-Treat Population
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Table 14.2.2.4.5	Exploratory: Early Remission Week 16 by Treatment Group for Each Baseline Subgroup from Logistic Regression analysis: Intent-to-Treat Population
Figure 14.2.2.4.1	Exploratory: Early Remission Week 16 Forest Plots by Treatment Group for Each Baseline Subgroup Analysis: Intent-to-Treat Population
Table 14.2.2.5.1	Steroid Free Remission Week 52: Intent-to-Treat
Table 14.2.2.5.2	Sensitivity Analysis – Steroid Free Remission Week 52: Modified Intent-to-Treat Population
Table 14.2.2.5.3	Sensitivity Analysis - Steroid Free Remission Week 52: Per-protocol Population
Table 14.2.2.5.4	Sensitivity Analysis - Steroid Free Remission Week 52: Completers Analysis
Table 14.2.2.5.5	Exploratory: Steroid Free Remission Week 52by Treatment Group for Each Baseline Subgroup from Logistic Regression analysis: Intent-to-Treat Population
Figure 14.2.2.5.1	Exploratory: Steroid Free Remission Week 52 Forest Plots by Treatment Group for Each Baseline Subgroup Analysis: Intent-to-Treat Population
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Table 14.2.3.1.1	Time to Remission: Intent-to-Treat Population
Table 14.2.3.1.2	Duration of Remission: Intent-to-Treat Population
Table 14.2.3.1.3	Time to Response: Intent-to-Treat Population
Table 14.2.3.1.4	Duration of Response: Intent-to-Treat Population
Figure 14.2.3.1.1	Time to Remission Kaplan Meir Survival Curve: Intent-to-Treat Population
Figure 14.2.3.1.2	Duration of Remission Kaplan Meir Survival Curve: Intent-to-Treat Population
Figure 14.2.3.1.3	Time to Response Kaplan Meir Survival Curve: Intent-to-Treat Population
Figure 14.2.3.1.4	Duration of Response Kaplan Meir Survival Curve: Intent-to-Treat Population
Supportive/Supplementary Endpoints: Remission and Response Endpoints	

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