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

(MAP US2)

Protocol Number:	**RHB-104-04**
US IND Number:	**73,479**
[redacted]	[redacted]
[redacted]	[redacted]
Version and Date:	**Final Version 1.0 / 16 December 2016**

STATEMENT OF COMPLIANCE

This study will be carried out in accordance with Good Clinical Practices (GCP) as identified and/or required by the following regulations and guidance:

- Declaration of Helsinki (Tokyo, 2004)
- US Code of Federal Regulations: 45 CFR Part 46, 21 CFR Parts 50, 56, and 312
- Canadian Food and Drug Regulations F-27 – C.R.C., c. 870: Division 5 (C.05.)
- EU Directive 2001/20/EC and 2005/28/EC
- ICH E6; Consolidated Guidelines on Good Clinical Practices (1997)
- Appropriately identified sponsor/CRO and local clinical SOPs

Title:	**An Open Label Study to Assess the Efficacy and Safety of Fixed-Dose Combination RHB-104 in Subjects with Active Crohn's Disease Despite 26 Weeks of Participation in the MAP US RHB-104-01 Study (MAP US2)**
Phase:	Phase III
Study Population:	Active subjects in the RHB-104-01 **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** (MAPUS) study with CDAI of greater than or equal to 150 despite 26 weeks of treatment with investigational drug. The following inclusion criteria apply: • Participation in RHB-104-01 for: o 26 weeks, and a Crohn's Disease Activity Index (CDAI) score of ≥ 150 at Visit Week 26 OR o More than 26 weeks, with a CDAI ≥150 at Visit Week 26 and all subsequent visits, and subject is between Week 26 and 52 within 4 weeks (28 days) of site activation • White blood cell count ≥ $3.5x10^9$ at screening. • Subject agrees to use the following effective contraceptive methods o diaphragm, cervical cap, contraceptive sponge or condom with spermicidal foam/gel/cream/suppository o IUD/IUS o progestogen injection (Depo-Provera®) throughout the study and for at least 6 weeks after last study drug administration, unless subject or partner of subject is post-menopausal or otherwise incapable of becoming pregnant by reason of surgery or tubal ligation, or has had a vasectomy. In regions where local regulatory contraceptive requirements differ, the ICF will reflect local policies The following key exclusion criteria apply: • Treatment with any medication that causes QT prolongation or Torsades de Pointes, including but not limited to: amiodarone, amitriptyline, astemizole, cisapride, citalopram dose greater than 20 mg/day, dihydroergotamine, disopyramide, dofetilide, dronedarone, ergotamine, ibutilde, ondansetron or other 5-HT_3 receptor antagonists, pimozide, procainamide, quinidine, quinine, quinolones, ranolazine, risperidone, sotalol, terfenadine and tolteridine. QT prolonging drugs may be referenced at the CredibleMeds® web site: https://crediblemeds.org/index.php/drugsearch • Treatment with the following CYP3A4 interactive medications: alfentanyl, alprazolam, amlodipine, anti-retroviral agents, apixabin, aprepitant, aripiprazole, atorvastatin, boceprevir, buspirone, carbamazepine, carvedilol, colchicine, cyclosporine, digoxin, diltiazem, estrogens, felodipine, fluconazole, fluvoxamine, grapefruit juice, haloperidol, ketoconazole, lovastatin, lurasidone, metoprolol, nefazodone, nifedipine, nisoldipine, nitrendipine, propranol, roflumilast, simvastatin, St. John's wort, and voriconazole. • Positive stool results for *C. difficile*. • Currently diagnosed or history of uveitis confirmed by either an ophthalmologist or

	optometrist. • Evidence of any significant hematological, hepatic, renal, cardiac, pulmonary, metabolic, neurological, psychiatric or other disease (e.g. porphyria) that might interfere with subject's ability to safely enter and or complete the study requirements. • Clinically significant abnormalities of hematology or biochemistry as confirmed by repeat testing based on investigator's discretion, including but not limited to, elevations greater than 2 times the upper limit of normal of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), or creatinine clearance less than 60 ml/min at screening via estimated Cockcroft-Gault formula: Creatinine Clearance = [140 - age in years] * weight (kg) / 72 * Serum Creatinine (mg/dl) [multiply estimated rate by 0.85 for women], using actual body weight. • QTcF>450ms in males and QTcF>460ms in females, bundle branch block, or major ST or T wave abnormalities that make the assessment of the QT impossible. • Females who have a positive pregnancy test or are lactating.
Number of Subjects:	Estimated total: Approximately 100 subjects
Number of Sites:	The study will be conducted at up to 150 sites in the USA, Canada, Israel, Australia, New Zealand, Poland, Bulgaria, Czech Republic, Romania, Slovakia and Serbia
Study Design:	This is an open label, multicenter, Phase III, study designed to evaluate the efficacy and safety of RHB-104 to treat subjects with active CD as defined by CDAI ≥ 150 despite 26 weeks of treatment with study drug in RedHill Biopharma Study RHB-104-01. RHB-104 consists of 3 antibiotics with activity against *Mycobacterium avium subsp. paratuberculosi*s (MAP), a potential cause of CD. Eligible subjects with active CD who have completed 26 weeks of study drug as part of the RHB-104-01 study will receive up to 52 weeks of open label RHB-104. Subjects enrolled in the open label study may have current CD therapies adjusted or withdrawn as clinically indicated by their local investigator after 8 weeks of open label RHB-104 treatment. Sites should begin tapering steroids upon completion of 4 weeks of RHB-104 treatment with the goal of being steroid free by week 14 – Refer to Appendix 13. MAP are slow growing mycobacteria without a proven antibiotic treatment, and the duration of antibiotic treatment required to achieve remission in subjects with CD caused by MAP is believed to be approximately 16-26 weeks. Subjects with response at week 26 may ultimately achieve remission at a later time point with continued treatment for MAP. Similarly, some subjects may achieve response or achieve remission prior to week 26. This study is designed to assess response, remission, and maintenance of remission in subjects on open label RHB-104 through week 52, as well as corticosteroid free remission at week 16. Blood samples will be collected at Screening and at every visit after the initial 8 weeks of treatment to test for MAP in the serum using a polymerase chain reaction (PCR) assay. Similarly, MAP cultures will be prepared from whole blood collected at Screening and at weeks 16, 26 and 52. Safety of the fixed-dose combination product, RHB-104, will also be assessed. Colonoscopy will be done in consenting subjects at baseline (prior to initiation of open label RHB-104) and after 16 and 52 weeks of open label RHB-104 to assess for mucosal healing as well as MAP status via PCR and culture. **Study Visit Schedule:** Screening, Baseline, and follow-up visits at weeks 2, 4, 8, 16, 26, 39, 52, and 56. Subjects undergoing colonoscopy will have a procedural visit after week 16 and 52 assessment so as to not interfere with data collection.

<table>
<tr><td>Subject Participation Duration:</td><td>Subjects will receive RHB-104 for up to 52 weeks</td></tr>
<tr><td>Treatment:</td><td>RHB-104; a fixed-dose combination of 95 mg clarithromycin, 45 mg rifabutin, and 10 mg clofazimine.</td></tr>
<tr><td>Route of Administration:</td><td>Oral capsule.</td></tr>
<tr><td>Dosage Regimen for Investigational Product:</td><td>The target dose of RHB-104 is 5 capsules administered bid.

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

Blinded bid Dose Titration and Maintenance Dosing in RHB-104-04
<table>
<tr><th>RHB-104-01 Study Drug</th><th>WK 1</th><th>WK 2</th><th>WK 3</th><th>WK 4</th><th>WK 5-36</th></tr>
<tr><td>Placebo</td><td>1 capsule RHB-104 + 4 capsules PBO Bid</td><td>2 capsules RHB-104 + 3 capsules PBO bid</td><td>3 capsules RHB-104 + 2 capsules PBO bid</td><td>4 capsules RHB-104 + 1 capsules PBO bid</td><td>5 capsules RHB-104 bid</td></tr>
<tr><td>RHB-104</td><td>5 capsules RHB-104 Bid</td><td>5 capsules RHB-104 bid</td><td>5 capsules RHB-104 bid</td><td>5 capsules RHB-104 bid</td><td>5 capsules RHB-104 bid</td></tr>
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<tr><td>Outcome Measures</td><td>Remission (primary outcome measure) – Remission in a subject is defined as a CDAI score of <150 at 16 weeks.

Response – A response in the individual subject is defined as reduction in CDAI score of ≥100 from baseline where baseline is the measure taken at Screening of this trial (Visit Week 26 of RHB-104-01).

Time to remission – The time (weeks after initiation) that a subject first records a state of remission.

Duration of remission – The time that a subject is in a state of remission.

Time to response – The time (weeks after initiation) that a subject first achieves a state of response.

Duration of response – The time that a subject is in a state of response.

Maintenance of Remission – Remission in a subject from week 16 through week 52.

Other Outcome Measures

MAP Detection:
Proportion of subjects with a MAP positive blood PCR assay at baseline (week 0 of the open label phase).
Proportion of subjects with a change in MAP blood PCR assay status after 16 weeks of treatment compared to baseline (week 0 of the open label phase).
Proportion of subjects with a change in MAP blood PCR assay status after 52 weeks of treatment compared to baseline (week 0 of the open label phase).</td></tr>
</table>

	• Sequential comparison of MAP blood PCR assay results per subject • Proportion of enrolled subjects with a MAP positive blood culture at baseline (week 0 of the open label phase). • Proportion of subjects with a change in MAP blood culture status after 26 weeks of treatment compared to baseline (week 0 of the open label phase). • Proportion of subjects with a change in MAP blood culture status after 52 weeks of treatment compared to baseline (week 0 of the open label phase). **Endoscopic Changes in Those Subjects Who Undergo Colonoscopy:** • Change from baseline in the mean Crohn's Disease Endoscopic Index of Severity (CDEIS) after 16 and 52 weeks of treatment • Change from baseline in the mean Simple Endoscopic Activity Score (SES-CD) after 16 and 52 weeks of treatment • Success rates of (∆CDEIS and SES-CD) defined by 25% and 50% improvements • Correlation between the change from baseline in the endoscopic index (∆CDEIS) and the clinical index (∆CDAI) after 16 and 52 weeks of treatment • Comparison of success rates of (∆CDEIS) defined by 25% and by 50% improvements in CDEIS vs CDAI defined remission • Comparison of success rates of (∆CDEIS) defined by 25% and by 50% improvements in CDEIS vs CDAI defined response • Correlation between the change from baseline in the endoscopic index (∆SES-CD) and the clinical index (∆CDAI) after 16 and 52 weeks of treatment • Comparison of success rates of (∆CDEIS) defined by 25% and by 50% improvements in SES-CD vs CDAI defined remission • Comparison of success rates of (∆CDEIS) defined by 25% and by 50% improvements in SES-CD vs CDAI defined response **Health-Related Quality-of-life (HRQoL):** • Change from baseline (initiation of open label phase) in the SF-36 questionnaire total score and domain scores to 16, 26 and 52 weeks. • Change from baseline (initiation of open label phase) in the mean Inflammatory Bowel Disease Questionnaire (IBDQ) score to 16, 26, and 52 weeks. **Inflammation:** • Changes from baseline in a serum marker of inflammation: C-reactive Protein (CRP) • Changes from baseline in a stool marker of inflammation: fecal calprotectin **Safety:** The incidence of adverse events during the study and changes from baseline in vital signs*, Clostridium difficile* toxin, ECG, hematology and chemistry laboratory parameters
Objectives:	**Primary Objective** The primary objective is to estimate the remission rate, defined as a CDAI score of less than 150, at 16 weeks after the initiation of the open-label phase. **Secondary Objective** To estimate the response rate of patients, defined by a reduction of CDAI score of ≥100 points at week 16 after the initiation of the open-label phase. **Selected Other Secondary Objectives** • To estimate the average duration of remission among participants. • To estimate the average time to first response among participants.

	• To estimate the average duration of response among participants. • To estimate the proportion of participants who maintain a state of remission from week 16 through week 52. **Selected Other Objectives** **MAP Detection:** • To estimate the proportion of subjects with a MAP positive blood PCR assay at baseline (week 0 of the open label phase). • To estimate the proportion of subjects with a change in MAP blood PCR assay status after 16 weeks of treatment compared to baseline (week 0 of the open label phase). • To estimate the proportion of subjects with a change in MAP blood PCR assay status after 52 weeks of treatment compared to baseline (week 0 of the open label phase). • To make sequential comparisons of MAP blood PCR assay results per subject • To estimate the proportion of enrolled subjects with a MAP positive blood culture at baseline (week 0 of the open label phase). • To estimate the proportion of subjects with a change in MAP blood culture status after 26 weeks of treatment compared to baseline (week 0 of the open label phase). • To estimate the proportion of subjects with a change in MAP blood culture status after 52 weeks of treatment compared to baseline (week 0 of the open label phase). **Endoscopic Changes in Those Subjects Who Undergo Colonoscopy:** • To estimate the change from baseline in the mean Crohn's Disease Endoscopic Index of Severity (CDEIS) after 16 and 52 weeks of treatment • To estimate the change from baseline in the mean Simple Endoscopic Activity Score (SES-CD) after 16 and 52 weeks of treatment • To make a comparison of success rates of (∆CDEIS and SES-CD) defined by 25% and 50% improvements • To estimate the correlation between the change from baseline in the endoscopic index (∆CDEIS) and the clinical index (∆CDAI) after 16 and 52 weeks of treatment • To make a comparison of success rates of (∆CDEIS) defined by 25% and 50% improvements and CDAI defined remission • To make a comparison of success rates of (∆CDEIS) defined by 25% and 50% improvements and CDAI defined response • To make a comparison of success rates of (∆SES-CD) defined by 25% and 50% improvements and CDAI defined remission • To make a comparison of success rates of (∆SES-CD) defined by 25% and 50% improvements and CDAI defined response **Safety Objective:** Assess the safety impact of treatment with RHB-104.
Study Completion:	Upon completion of clinical activities and safety follow-up.
Statistical Considerations	This study will provide numerous descriptive statistics with corresponding 95% confidence intervals for each of the outcomes described above. Since there is no randomization involved in this study, there will be no formal between group comparisons made. The primary outcome measure, remission rate defined as a CDAI score of less than 150 at week 16, is measured as a dichotomous variable (yes/no) for each participant. Thus, the overall rate

	and the corresponding 95% confidence interval will be estimated. This will be examined overall and then by anti-TNF agent use (yes/no). The secondary endpoint, response rate, will also be estimated with a corresponding 95% confidence interval. This too will be presented overall and then by anti-TNF agent use (yes/no). For each secondary endpoint measured on a dichotomous scale the overall proportion and corresponding 95% confidence interval will be estimated. For outcomes measured on a continuous scale descriptive statistics including means, standard deviations and 95% confidence intervals will be estimated. For variables that are not normally distributed medians and inter-quartile ranges will be estimated. For outcomes that are measured at multiple time points with short time intervals between measures (i.e., 4 weeks or less), time to event curves can be developed using Kaplan-Meier survival methods. A formal SAP will be developed prior to the completion of the study to describe in greater detail all statistical analyses to be performed. Safety will be assessed including routine laboratory work and adverse events.