2 SYNOPSIS

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF ACTIVE INGREDIENT(S): Clarithromycin, rifabutin, and clofazimine	**Volume:** **Page:**	

Title of Study: 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 (RHB-104-01).

Investigators: A total of 93 sites received Independent Ethics Committee or Institutional Review Board approval to participate in this study and enrolled at least 1 subject. The complete list of investigators and their addresses is provided in Appendix 16.1.4.

Study Sites: The study was conducted at 93 study sites across Australia, Bulgaria, Canada, Czech Republic, Israel, New Zealand, Poland, Serbia, Slovakia, and the United States.

Publication (Reference): None.

Studied Period: 04 Oct 2013 - 30 Nov 2018	Phase of Development: III

Objectives:

Primary Objective: To assess whether subjects randomized to receive RHB-104 had a higher probability of being in a state of remission at the 26-week assessment as compared to subjects randomized to receive placebo.

Key Secondary Objectives:

- To assess whether subjects randomized to receive RHB-104 had a higher probability of being in a state of response at the 26-week assessment as compared to subjects randomized to receive placebo.
- To assess whether subjects randomized to RHB-104 had a higher probability of being in a state of remission at the 52-week assessment as compared to subjects randomized to receive placebo.
- To assess whether subjects randomized to RHB-104 had a higher probability of being in a state of remission in assessments from Week 26 through Week 52 as compared to subjects randomized to receive placebo.
- To assess whether subjects randomized to receive RHB-104 had a higher probability of being in a state of remission at the 16-week assessment as compared to subjects randomized to receive placebo.
- To assess whether subjects randomized to receive RHB-104 had 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 have been maintained off steroids for 3 weeks in order to be determined to be in steroid free remission, e.g., by Week 49.

Selected Other Supportive Objectives:

- To compare the arm-specific time to remission and response
- To compare the arm-specific duration of remission and response
- To compare the proportion of subjects who had maintained remission from Week 16 through Week 52
- To assess whether subjects randomized to receive RHB-104 had a higher probability of being in a state of response at the 16-week assessment as compared to subjects randomized to receive placebo
- To assess the difference between arms in health-related quality of life using the Inflammatory Bowel Disease Questionnaire (IBDQ) and Short Form-36 Health Survey (SF-36) questionnaires

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 **NAME OF ACTIVE INGREDIENT(S):** Clarithromycin, rifabutin, and clofazimine	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(FOR NATIONAL AUTHORITY USE ONLY)

- To compare arm-specific endoscopic 26-week changes using the Crohn's disease (CD) Endoscopic Index of Severity (CDEIS) and Simple Endoscopic Score for Crohn's Disease (SES-CD) score in those subjects who consented to undergo colonoscopy
- To assess the effect of RHB-104 on markers of inflammation
- To assess the proportion of subjects in steroid free remission in each treatment arm at Week 26. Subjects had to be maintained off steroids for 3 weeks in order to be determined to be in steroid free remission, e.g., by Week 23.

Other Exploratory Objectives:

- To characterize the pharmacokinetic (PK) profiles of each of the active agents (and active metabolites for clarithromycin and rifabutin) using a population PK approach
- To assess the efficacy outcome measures for interaction with the baseline assay results for *Mycobacterium avium subsp. paratuberculosis* (MAP) infection (positive versus negative) for use in development of MAP diagnostic
- To compare the arm-specific changes in MAP buffy coat and biopsy culture status from pre to post-treatment at Week 26 and Week 52 (buffy coat only at Week 52) and their relationship to the state of remission
- To compare arm-specific 26-week changes from baseline in the endoscopic index (ΔCDEIS and ΔSES-CD) and the clinical index (ΔCDAI [Crohn's Disease Activity Index])
- To assess the tissue levels of the active agents of RHB-104 in colon biopsy samples if possible.

Safety Objective: To assess the safety impact of treatment with RHB-104.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel group, Phase 3 study to evaluate the safety, efficacy, and PK of the fixed-dose combination product RHB 104 in the treatment of CD. Approximately 324 subjects were to be randomized in 1:1 ratio to active therapy or placebo towards assessing the Week 26 primary endpoint. Subjects were stratified by whether they used protocol-permitted anti-tumor necrosis factor (TNF) agents (yes or no), and then randomized into 1 of the 2 arms, designated as the control arm and the experimental arm, where the intended intervention in the control arm was placebo, and the intended intervention in the experimental arm was RHB-104. The design of the study was treat-through, meaning that subjects were not re-randomized at Week 26 but treated in blinded manner according to their original treatment assignments through Week 52. Subjects were administered blinded study medication starting at 1 capsule twice daily (BID), increasing at Weeks 2, 3, 4, and 5 via dose escalation (forced titration) to reach 5 capsules BID at Week 5. A placebo-control group was used as the comparator since there was currently no approved antimicrobial therapy for subjects with active CD.

Safety data were reviewed by medical monitors, and summary information was reviewed by an external Data Safety Monitoring Board (DSMB) approximately one-third (21 November 2016) and two-thirds (25 July 2017) of the way through the study. On 25 July 2017, the DSMB reviewed the unblinded interim safety and efficacy data and recommended continuing the study through enrolment with no changes to the protocol, investigator's brochure, study conduct, or informed consent form (ICF).

While the study was powered for 410 subjects, clinical study protocol, Version 11.0, curtailed the number of expected enrolled subjects to be 324 (162 per group). This sample size curtailment reflected the study's actual accrual trends. The anticipated power was at least 80% given the study design stage assumptions regarding the treatment groups' primary efficacy endpoint (36% RHB-104 versus 21% placebo).

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 **NAME OF ACTIVE INGREDIENT(S):** Clarithromycin, rifabutin, and clofazimine	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(FOR NATIONAL AUTHORITY USE ONLY)

Number of Subjects: Approximately 324 subjects were planned to be randomized in 1:1 ratio to active therapy or placebo. A total of 331 subjects (166 subjects to RHB-104 and 165 to placebo.) were randomized and treated, of which 225 subjects completed the study through Week 26 with CDAI assessment. A total of 128 subjects completed the study through Week 52 with CDAI assessment.

Diagnosis and Criteria for Inclusion:

Subjects meeting all of the following criteria were eligible to be enrolled in the study:

1. Males and females of 18 to 75 years of age
2. Signed full informed consent provided as per the protocol
3. CD diagnosed by endoscopy or radiography and/or histology at least 6 months prior to randomization into the study. Colonoscopies performed within 5 weeks of screening could have been used to confirm active CD A colonoscopy could have been performed to confirm the presence of active CD, if C-reactive protein (CRP) and fecal calprotectin were normal at screening. The method used to confirm the presence of active CD was to be documented in the source document and electronic case report form (eCRF). This colonoscopy could have been performed as a CDEIS/SES-CD compatible (digital video equipment) or non-compatible procedure. Subjects who underwent colonoscopy and failed to meet inclusion criteria were ineligible, and were not biopsied and not randomized.
4. Crohn's Disease involving the ileum and/or colon
5. Current CDAI score of ≥220 and ≤450
6. Current treatment with at least 1 of the following therapies:
    - Oral 5-aminosalicylic acid (5-ASA) compounds: Dose had to be stable for at least 4 weeks before baseline
    - Corticosteroid therapy: Dose had to be stable for at least 2 weeks before baseline
    - Azathioprine or 6-mercaptopurine (6-MP) or methotrexate: Dose had to be stable for at least 8 weeks before baseline
    - Infliximab or adalimumab: Dose had to be stable for at least 14 weeks before baseline
7. White blood cell count ≥3.5×10^9 at screening
8. Active CD, defined by at least 1 of the following: C-reactive protein (CRP) > Upper Limit of Normal (ULN) at screening, fecal calprotectin > ULN at screening, or radiographic (magnetic resonance enterography or computed tomography enterography), or endoscopic confirmation of the presence of active CD within 5 weeks of screening visit
9. Subjects agreed to use the following effective contraceptive methods only throughout the study and for at least 6 weeks after last study drug administration, unless subject or partner of subject was post-menopausal or otherwise incapable of becoming pregnant by reason of surgery or tubal ligation or had a vasectomy:
    - Diaphragm, cervical cap, contraceptive sponge, or condom with additional spermicidal foam/gel/cream/suppository

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 **NAME OF ACTIVE INGREDIENT(S):** Clarithromycin, rifabutin, and clofazimine	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(FOR NATIONAL AUTHORITY USE ONLY)

- Intrauterine device/intrauterine system
- Progestogen injection (Depo-Provera®)

In regions where local regulatory contraceptive requirements differed, the ICF reflected local policies.

Test Product, Dose, Mode of Administration, and Batch Number(s):
Study treatment was taken BID with food. Subjects had to 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	 190 mg 90 mg 20 mg	 380 mg 180 mg 40 mg	 570 mg 270 mg 60 mg	 760 mg 360 mg 80 mg	 950 mg 450 mg 100 mg
Placebo Arm	Placebo	placebo	placebo	placebo	placebo	placebo
Abbreviation: BID = twice daily						

Duration of Treatment: The duration of the study participation for each subject was approximately 62 weeks

Reference Therapy, Dose, Mode of Administration, and Batch Number(s): Matching placebo self-administered BID by the subjects orally

Study Endpoints:

Primary Efficacy Endpoint: The primary efficacy variable was defined as the proportion of subjects experienced remission at Week 26, where remission was defined as a subject having a CDAI score of <150. Subjects who had a Week 26 CDAI measurement ≥150 or who did not have a CDAI measurement at Week 26 were classified as not having achieved remission. The CDAI was used to assess the activity of CD; higher scores indicated more active disease.

Secondary Efficacy Endpoints:

Key secondary efficacy endpoints included the following:

- Proportion of subjects who experienced response at Week 26, where response was defined as reduction from baseline of ≥100 in CDAI score. Subjects who did not have a reduction in CDAI of ≥100 or did not have a CDAI measurement at Week 26 were classified as not having achieved response.

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 NAME OF ACTIVE INGREDIENT(S): Clarithromycin, rifabutin, and clofazimine	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

- Proportion of subjects who were in remission Week 52, where remission was defined as a subject having a CDAI score of <150. Subjects who had a Week 52 CDAI measurement ≥150 or who did not have a CDAI measurement Week 52 were classified as not having achieved remission.
- Proportion of subjects who experienced durable remission (CDAI score <150) from Week 26 through Week 52. Subjects who experienced a CDAI score ≥150 at any visit time point assessment between Week 26 and Week 52 or had no CDAI measurement at Week 26 or Week 52 were considered not having achieved durable remission.
- Proportion of subjects in early remission Week 16, where remission was defined as a subject having a CDAI score of <150. Subjects who had a Week 16 CDAI score ≥150 or who did not have a CDAI measurement Week 16 were classified as not having achieved early remission.
- Proportion of subjects in steroid-free remission Week 52, where remission was defined as a subject having a CDAI score of <150. Subjects had to be maintained off steroids for 3 weeks in order to be determined to be in steroid free remission, e.g., by Week 49.
- Subset analyses were performed to assess the effects of baseline factors, such as concomitant medications and higher baseline activity, on these endpoints. Higher baseline activity measures included higher cutoffs for CRP or calprotectin or minimal requirements based on baseline SES-CD score.

Supportive Efficacy Endpoints:

Supportive efficacy endpoints included the following:

1. Remission and response endpoints/variables
   - Proportion of subjects in remission from Week 16 through Week 52.
   - Proportion of subjects who experienced early response at Week 16.
   - Proportion of subjects experienced response at Week 52.
2. Time to event endpoints/variables
   - Time to remission – Number of weeks after randomization that a subject first recorded a state of remission (CDAI score <150).
   - Duration of remission – Duration of remission defined as the number of weeks the subject was in remission (CDAI score <150).
   - Time to response – Number of weeks after baseline that a subject first achieved a state of response (a reduction from baseline of ≥100 in CDAI score).
   - Duration of response – Defined as time in weeks that a subject was in a state of response (a reduction from baseline of ≥100 in CDAI score).
3. Endoscopic change variables
   - Change from baseline to Week 26 in CDEIS and SES-CD.

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 NAME OF ACTIVE INGREDIENT(S): Clarithromycin, rifabutin, and clofazimine	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

- 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.
- Proportion of responders based on CDEIS and SEC-CD at Week 26.

4. Health-related quality of life variables
- Change from baseline in the 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.

5. Markers of inflammation variables
- Change from baseline in CRP.
- Change from baseline in fecal calprotectin.

Exploratory efficacy Endpoints/Variables:

1. MAP detection endpoints/variables

Depending on the availability of data, specific details of additional exploratory analyses were to be determined at the time of analyses.

MAP detection parameters included the following:
- Proportion of subjects with a MAP-positive polymerase chain reaction (PCR) blood assay at baseline.
- Proportion of subjects with a change in MAP PCR blood assay status at Week 26 and Week 52 of treatment compared to baseline.
- Proportion of subjects with 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
- Timeline of MAP PCR blood assay status from baseline and Week 4 though the end of the study.

Note: MAP buffy coat culture status and MAP biopsy culture status were confirmed by IS900 sequencing and were included in the final analyses. MAP blood PCR assay status and MAP colon biopsy PCR assay status were not performed due to the absence of a validated assay of uncultured MAP buffy coat or biopsy DNA.

2. Other Endpoints

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 **NAME OF ACTIVE INGREDIENT(S):** Clarithromycin, rifabutin, and clofazimine	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(FOR NATIONAL AUTHORITY USE ONLY)

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

Safety Endpoints/Variables:

The incidence of adverse events (AEs) during the study and changes from baseline in vital signs, *Clostridium difficile* (*C. difficile*) infection, uveitis, electrocardiogram, hematology, and chemistry laboratory parameters.

Statistical Methods:

The following populations were used for data analysis:

The Intent-to-Treat (ITT) population: The primary efficacy analyses were based on the ITT population, which included all randomized subjects. Subjects were analyzed according to the treatment group to which they were randomized.

The Modified ITT (mITT) population: The mITT population included all subjects who fulfilled all the inclusion/exclusion criteria. The sensitivity analyses were performed using the mITT population. Subjects were analyzed according to the treatment group to which they were randomized.

The Safety population: The safety population included subjects who were randomized and received at least 1 dose of study medication. The primary safety analyses were based on the safety population. Subjects were analyzed according to the treatment which they actually received.

Per-Protocol (PP) population: The PP population included all randomized subjects who received at least 1 dose of RHB-104 or placebo and completed dose escalation to target dose of 5 capsules BID, as well as all subjects without major protocol deviations that had a significant impact on clinical outcome.

The primary efficacy analysis compared 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 use of anti-TNF agents (yes/no); and a 2-sided test at the $\alpha = 0.049$ level of significance.

Completers: It is defined as subjects with no missing CDAI score at the corresponding visit.

SUMMARY OF RESULTS

Efficacy:

- The primary endpoint was achieved; more subjects in the RHB-104 group (61 [36.7%] subjects) experienced remission at Week 26 than the placebo group (37 [22.4%] subjects) and this difference achieved statistical significance (P = 0.0048). These findings were also observed in the mITT and PP population, and the completers analysis.
- More subjects in the RHB-104 group (73 [44.0%] subjects) experienced a response at Week 26 than the placebo group (50 [30.3%] subjects) and this difference achieved statistical significance (P = 0.0116). These findings were also observed in the mITT and PP population, and the completers analysis.
- Significantly more subjects experienced early remission at Week 16 in the RHB-104 group (70 [42.2%] subjects) than placebo (48 [29.1%] subjects; P = 0.0147) and likewise early response (79 [47.6%] subjects vs 60 [36.4%] subjects; P = 0.0422). At Week 52, more subjects in the RHB-104 group (47 [28.3%] subjects)

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 NAME OF ACTIVE INGREDIENT(S): Clarithromycin, rifabutin, and clofazimine	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

experienced remission than placebo (32 [19.4%] subjects); this difference did not achieve statistical significance (P = 0.0616). Significantly more subjects experienced a response at Week 52 for RHB 104 than placebo (59 [35.5%] subjects vs 35 [21.2%] subjects; P = 0.0042). Sustained remission at Week 16 through Week 52 was significantly more frequent in the RHB-104 group than placebo (difference: 10.2%, P = 0.0077).

- Proportions of subjects experiencing durable (or sustained) remission over Week 26 through Week 52 and steroid-free remission at Week 52 were higher for RHB-104 (33 [19.9%] and 11 [19.3%] subjects, respectively) than placebo (21 [12.7%] and 5 [9.1%] subjects, respectively), but these differences did not achieve statistical significance (P values 0.0851 and 0.1510, respectively).
- Median time to remission was significantly shorter for the RHB-104 group (12.1 weeks) than placebo (19.9 weeks; P = 0.0031) as was the time of response (8.3 weeks vs 12.1 weeks; P = 0.0164). The median duration of remission (27.1 weeks vs 16.7 weeks) and the median duration of response (40.1 weeks vs. 22.1 weeks) were longer for RHB 104 and achieved statistical significance for duration of response.
- Number of subjects providing CDEIS and SES-CD data at Week 26 were low. Generally, there were no significant differences between groups, although more subjects in the RHB-104 group showed a 25% reduction in SES-CD score at Week 26 than placebo (difference: 26.2%; P = 0.0478).
- C-reactive protein levels were generally similar for RHB-104 (1.338 mg/dL) and placebo (1.378 mg/dL) at baseline. Least squares mean changes from baseline up to Week 52 for the RHB-104 group were generally within the same range as those for placebo. No differences between RHB-104 and placebo achieved statistical significance.
- Mean fecal calprotectin levels at baseline were 542.710 µg/g for the RHB 104 group and 668.305 µg/g for the placebo group. Least squares mean changes from baseline up to Week 52 were negative for the RHB-104 group and positive for placebo. At Week 52, least squares mean change from baseline was -63.98 µg/g for RHB-104 and 116.50 mcg/g for placebo. No differences between RHB-104 and placebo achieved statistical significance.
- Sensitivity analyses of observed CDAI score from Weeks 1 through 26 (P = 0.0095) and from Weeks 1 through 52 (P = 0.0033) showed least squares mean CDAI scores were lower for RHB-104 than placebo; treatment difference achieved statistical significance in both analyses.
- Sensitivity analyses of patient reported outcomes (PRO)-2 scores over Weeks 1 through 26 (P <0.05) and Weeks 1 through 52 (P <0.05) showed greater reductions in PRO-2 scores for the RHB-104 group than placebo; in both analyses, differences achieved statistical significance from Week 16 onwards.
- Mean SF-36 and IBDQ scores increased in both groups during the course of the study, but no statistically significant differences were observed between groups.
- There were no statistically significant differences between groups in MAP buffy coat culture or colonic biopsy culture results. Subjects tapered off steroids more rapidly in the RHB-104 group than placebo.

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 **NAME OF ACTIVE INGREDIENT(S):** Clarithromycin, rifabutin, and clofazimine	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(FOR NATIONAL AUTHORITY USE ONLY)

- Inclusion of prior use of immunomodulators and baseline IBDQ in a logistic regression analysis led to a statistically significant odds ratio for adjusted early remission at Week 16 for RHB-104 vs. placebo. A higher percentage of subjects (12.7%) who received RHB-104 with no current use of anti-TNF agents achieved remission at Week 16 than placebo. Similarly, 12.0% more subjects who received RHB 104 with no current use of Remicade or Humira achieved remission at Week 16 than placebo.
- At Week 26, 18.4% more subjects with current use of immunomodulators achieved remission in the RHB-104 group than placebo; a statistically significant difference. More subjects who received RHB-104 with current use of azathioprine (difference of 21.5%), those not using anti-TNF (difference of 13.8%), and those not currently using Remicade or Humira (difference of 13.0%) also achieved remission at Week 26. Similarly, 13.0% more subjects who received RHB-104 not currently using Remicade or Humira and 15.2% more subjects that did not use 5-ASA achieved remission at Week 26 than placebo.
- At Week 26, the treatment difference between RHB-104 and placebo was statistically significant for subjects with stratification according to no anti-TNF use (difference in treatment compared with placebo: 13.8%, P = 0.0182). A higher percentage of subjects with stratification according to anti-TNF use achieved remission at Week 26 in the RHB 104 (n = 37) compared with placebo (n = 41); however, the treatment difference between the 2 groups was not statistically significant (difference compared with placebo: 15.4%, P = 0.1169). Similarly, a higher percentage of subjects with current use of Remicade or Humira (difference compared with placebo: 18.8%, P = 0.0798) in the RHB-104 achieved remission at Week 26 than placebo, but this difference was not statistical significant because of the smaller number of subjects (31 subjects in RHB-104 and 36 in placebo group).
- At Week 26, higher number of subjects with baseline CRP category high who received RHB-104 achieved remission (difference compared to placebo: 13.7%, P = 0.0198) compared with placebo.
- At Week 26, higher percentage of subjects who received RHB-104 achieved remission grouped by the presence of one of the following baseline categories: SES CD category ≥6, or calprotectin category ≥250 µg/g, or CRP category ≥0.287 mg\dL (difference compared with placebo: 14.0%, P = 0.0108). Also, a higher number of subjects in the RHB-104 group achieved remission at Week 52 by the presence of one of the following baseline categories: SES CD category ≥6, or calprotectin category ≥250 µg/g, or CRP category ≥0.287 mg\dL (difference compared with placebo: 10.8%, P = 0.0365).
- Although not statistically significant, a higher percentage of subjects in the RHB 104 group (n = 21) who were steroid dependent achieved remission at Week 52 compared with placebo (n = 16; treatment difference compared to placebo: 17.6%, P = 0.1751).
- Statistically significant higher percentage of subjects with fecal calprotectin >250 mg/dL, CRP >0.287 mg/dL or SES-CD >6 at baseline treated with RHB-104 achieved remission with 50% reduction either in calprotectin or CRP at Weeks 26 compared with placebo. At Week 16, the treatment difference

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 **NAME OF ACTIVE INGREDIENT(S):** Clarithromycin, rifabutin, and clofazimine	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(FOR NATIONAL AUTHORITY USE ONLY)

compared with placebo was 10.8% (P <0.0075), at Week 26, the difference was 21.7% (P <0.00001), and at Week 52, the difference was 15.2% (P <0.0004).

Pharmacokinetic Results: The results of the analysis of PK data collected are reported in a separate population pharmacokinetics report.

Tissue Pharmacokinetics: The data showed that the majority of the tissue samples had no detectable levels (below the limit of quantitation) of clarithromycin, 14-R-clarithromycin, rifabutin, 25-O-Desacetyl-rifabutin, or clofazimine

Safety:

- RHB-104 prolonged the corrected Q-T interval using Fridericia's formula (QTcF) interval at the studied dose by a mean placebo-corrected mean change from baseline QTcF from 2.8 ms at Week 1 to 30.6 ms at Week 52 but did not have a clinically relevant effect on heart rate or the PR and QRS intervals.
- Other than the significant QTcF interval increase, treatment with RHB-104 was generally well tolerated. No subjects died, and the number of subjects who experienced serious AEs were similar in the RHB-104 group as the placebo group; numbers of subjects with treatment-emergent AEs (TEAE) leading to discontinuation were also similar. Most subjects experienced TEAEs with a maximum severity of mild (36.9%) or moderate (33.5%).
- The occurrence of TEAEs was similar for the RHB-104 (145 [87.3%] subjects) and placebo (135 [81.8%] subjects) groups; although TEAEs judged by the Investigator to be drug-related were more frequent in the RHB-104 group (91 [54.8%] vs 51 [30.9%] subjects).
- Skin and subcutaneous disorders (24.1% vs 13.9%) and renal and urinary disorders (25.9% vs 7.9%) were more frequent in the RHB-104 group. The most frequent TEAEs were CD, chromaturia, abdominal pain, nausea, and headache.
- The frequency of chromaturia was notably higher for RHB-104 than placebo (42 [25.3%]) subjects vs 2 [1.2%] subjects).
- *C. difficile* infection occurred at a higher frequency in the placebo group (14 [8.5%] subjects) than RHB-104 (4 [2.4%] subjects). For the purposes of this report, *C. difficile* infection included 2 preferred terms *Clostridium difficile* infection and *Clostridium* test positive.
- There was only 1 confirmed case of uveitis and that occurred in the placebo group.
- As might be expected, increases in liver enzymes appeared more frequent in subjects on RHB-104 than subjects on placebo; there were no notable differences between groups in hematology, urinalysis or other safety parameters.

Conclusions:

RHB-104 was found to provide higher remission percentage than placebo at the primary endpoint at 26 weeks as well as a secondary endpoint of early remission at 16 weeks. Median time to remission was shorter in the RHB-104 group than placebo. Subjects receiving RHB-104 in addition to immunomodulators, anti-TNF agents, or steroids at baseline had higher remission rates than those administered placebo as add on therapy. Sensitivity

NAME OF COMPANY: RedHill Biopharma Ltd.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: RHB-104 **NAME OF ACTIVE INGREDIENT(S):** Clarithromycin, rifabutin, and clofazimine	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(FOR NATIONAL AUTHORITY USE ONLY)

analyses including PRO-2 scores over Weeks 1 through 26 and Weeks 1 through 52 similarly favored RHB-104, as did analyses based on elevated inflammatory markers such as CRP and fecal calprotectin. Under laboratory conditions in the study, no significant differences were observed between the RHB-104 and placebo groups in MAP buffy coat culture or colonic biopsy culture results.

RHB-104 was safe and generally well tolerated with similar TEAEs between the active and placebo groups with the exception of QT prolongation, chromaturia, and skin discoloration in the RHB 104 group. *C. difficile* infection, however, was more common in the placebo group.

Date of Report:02 July 2020