Statistical Analysis Plan

Protocol Title: A Randomized Double Blind Active Comparator Controlled Phase III Study to Assess the Safety and Efficacy of RHB-105 in the Treatment of Confirmed *Helicobacter pylori* (*H. pylori*) Infection

NCT Number: NCT03198507

Protocol Number: RHB-105-02

Protocol Version, Date Protocol Amendment 3, 22 Mar 2018

SAP Document Version, Date:

Final 2.0, 20 Nov 2018

Addendum 1.0, 06 Feb 2019

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RedHill Biopharma Ltd.

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ICON ID:	3101/0005
Document Version, Date:	Final 2.0, 20 Nov 2018

Prepared by:

ICON Clinical Research Services

On behalf of:

RedHill Biopharma Ltd.

REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
Version Draft 1.0/ 24 Apr 2017	Initial version	N/A	N/A
Version Draft 2.0/ 12 Apr 2018	2nd Draft	N/A	Update after RedHill Review and release of Protocol Amendment 3
Version Draft 3.0/ 25 Jun 2018	3rd Draft	N/A	Update of compliance calculation Clarification of summary of concomitant medications Addition of pre-final analysis
Version Final 1.0/ 06 Sep 2018	Final 1.0	N/A	Minor updates regarding the handling of repeated test of cure visits Addition of subgroup analyses by pharmacokinetics Addition of subgroup analyses by SOC therapy categories for H. pylori eradication in the SOC phase Addition of summary of susceptibility by USA regions Update of secondary efficacy endpoint: eradication of *H.pylori* instead of failure of eradication
Version Final 2.0/ 20 Nov 2018	Final 2.0	N/A	Update of the analysis of patient disposition Addition of primary efficacy by site Addition of a listing for physical examination after screening

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence Interval
CLO	*Campylobacter*-like organism
CSR	Clinical Study Report
FAS	Full Analysis set
GCP	Good clinical practice
H. pylori	*Helicobacter pylori*
ICH	International Conference on Harmonisation
IRB/EC	Institutional Review Board/Independent Ethics Committee
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Affairs®
MIC	Minimum inhibitory concentration
mITT	Modified Intent-to-treat
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred term
RBC	Red blood cell
SAE	Serious Adverse Events
SAF	Safety Analysis population
SAP	Statistical Analysis Plan
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOC	System organ class (in context of adverse events or medical history)
SOC	Standard of care (in context of study phase)
TEAE	Treatment emergent adverse event
TFL	Table, Figure and Listings
UBT	Urea Breath Test
USA	United States of America
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol RHB-105-02 "A Randomized Double Blind Active Comparator Controlled Phase III Study to Assess the Safety and Efficacy of RHB-105 in the Treatment of Confirmed Helicobacter pylori (*H. pylori*) Infection", Amendment 3 dated 22 Mar 2018 for final analysis. The table of contents and templates for the Table, Figure, Listings (TFL)s will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR). The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E9 guidelines.

The SAP is finalized and signed prior to any of the following: study unblinding and database hard lock. For operational efficiency, an earlier time is usually targeted. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

All data analyses and generation of TFLs will be performed using SAS 9.3® or higher.

2 STUDY OBJECTIVES

2.1 Primary objective(s)

The primary objective of this study is to assess the effectiveness of RHB-105 to eradicate *H. pylori* as indicated by ^{13}C Urea Breath Test (UBT) for *H. pylori*.

2.2 Secondary objective(s)

The secondary objective of this study is the examination of the primary endpoint, the occurrence of *H. pylori* eradication, within subgroups of subjects formed by the occurrence of antibiotic resistance and susceptibility prior to therapy.

2.3 Safety objective(s)

The safety objective is to assess the safety profile of RHB-105.

3 STUDY DESIGN

3.1 General study design

This is a randomized, double-blind, active comparator controlled study of RHB-105 in adult subjects complaining of epigastric discomfort that have been screened and found to be positive for *H. pylori* infection via ^{13}C UBT and follow up upper endoscopy (culture, histology or urease test). All subjects who meet inclusion and exclusion criteria and have positive ^{13}C UBT will undergo upper endoscopy with three biopsies taken from each of the antrum and corpus of the stomach. One biopsy from both the corpus and antrum will be combined and tested for *H. pylori* via a rapid urease test at the point of care. One biopsy from both the corpus and antrum will be combined and sent for *H. pylori* testing at the central histology laboratory. One biopsy from both the corpus and antrum will be combined and sent to the central laboratory for *H. pylori* culture with susceptibility testing assessing amoxicillin, clarithromycin, metronidazole and rifabutin. Subject specific pretreatment culture susceptibility and resistance results will be provided to the investigator in those subjects who fail to eradicate *H. pylori* upon post treatment ^{13}C UBT analysis. All other susceptibility data will remain blinded until study completion. The active comparator arm is expected to demonstrate an approximate 70% efficacy rate and RHB-105 is being investigated for superiority with an expected approximate 83% efficacy rate.

The study will be conducted at up to 65 sites in the United States of America (USA). Once informed consent has been obtained and upon positive screening and enrollment into the study, eligible subjects will be randomized in a ratio of 1:1 between active comparator arm (n=222) and the active investigational arm (RHB-105) (n=222). Subjects will receive RHB-105 or active comparator (RHB-105-LT) for 14 days. Eradication of *H. pylori* infection will be determined based on ^{13}C UBT testing conducted between 43 and 71 days after initiation of therapy. In the event a female subject becomes pregnant during the course of the double-blind phase of the study and refuses to undergo the ^{13}C UBT assessment, then a fecal antigen test may be performed at the local lab. Results of the fecal antigen test will substitute for the ^{13}C UBT test of cure for this subject in all efficacy analyses.

Subjects who fail to eradicate *H. pylori* upon post treatment ^{13}C UBT analysis will receive investigator prescribed susceptibility directed therapy based on culture and sensitivity results from biopsy samples prior to therapy. The investigator may prescribe local standard of care therapy if susceptibility results are not contributory or are unavailable. These subjects will also undergo repeat endoscopy to assess changes in susceptibility and resistance. All information related to therapy including drugs, doses and duration administered will be collected, and subjects will be reassessed for eradication of *H. pylori* 28 - 60 days following completion of therapy, ideally between 43 and 71 days after initiation of therapy. Susceptibility data will only be provided for those subjects who fail to eradicate *H. pylori.*

3.2 Randomization and blinding

Subjects will be assigned to treatment using permuted block randomization without additional stratification.

3.3 Study treatments and assessments

A list of subjects screened but deemed ineligible will be maintained indicating reason(s) for exclusion.

Treatment assignments will be based on a centralized computer-generated randomization scheme using permuted block randomization without additional stratification.

Each subject will have a randomization code assigned that corresponds to treatment assignment and a unique identifier for drug packaging purposes. Once a subject number and treatment have been assigned to a subject, the subject identification number cannot be reused even if the subject discontinues the study early or withdraws prior to receiving any study medication. Subjects who discontinue from the study or who have previously participated in the study will not be permitted to re-enroll. Subjects may be rescreened if endoscopic results for *H. pylori* are unavailable during the screening window. Subjects will be randomized to one of the following groups:

Treatment Arms:

444 Subjects Randomized	Arm 1	222 Subjects	RHB-105
	Arm 2	222 Subjects	Active Comparator

3.4 Post-treatment Standard of Care

Subjects who fail to eradicate *H. pylori* will receive susceptibility directed standard of care therapy as prescribed by the treating investigator based on initial pretreatment results, and will undergo upper endoscopy with culture to assess changes in susceptibility and resistance. The investigator may prescribe local standard of care therapy if susceptibility results are not contributory or are unavailable. Susceptibility data will only be provided for those subjects who fail to eradicate *H. pylori.*

A detailed description of procedures and assessments to be conducted during this study is summarized in the Scheduled of Study Assessments in **Table 1** below.

Table 1: Schedule of Study Assessments - Double-Blind Phase of Study

Assessments and Recordings	Visit 0 Screening Day -42 to -2	Visit 1 Baseline Day 1	Visit 2 Phone follow-up Day 8 (±1 day)	Visit 3 Safety Visit Day 13 (±2 days)	Visit 4 Phone follow-up Day 28-60 (±2 days)	Visit 5 Test of Cure Day 43-71 (+7 days)
Subject Information and Demographics	X					
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Urine Pregnancy Test on Females of Child Bearing Potential	X	X		X		X
Medical History	X	X				
Physical Examination with Vital Signs	X	X		X		X
Concomitant Medications	X	X		X		X
Laboratory Studies						
• Hematology, Chemistry, Urinalysis	X			X		X[b]
• ^{13}C UBT[a]	X[a]					X[a]
• HBs Ag, HCV Ab, HIV$_1$ /HIV$_2$ Abs	X					
Upper Endoscopy to determine *H pylori* status) • Biopsy for CLO • Biopsy for histology • Biopsy for culture and susceptibility	 X X X					
• CYP2C19 Genotyping		X				
Blood Sample for PK Assessment of amoxicillin, omeprazole, rifabutin, and 25-O-desacetyl-rifabutin – TO BE PERFORMED ON SUBJECTS WHO EARLY TERMINATE DURING 14 DAY COURSE OF TREATMENT IF POSSIBLE		X[c]		X[c]		
Electrocardiogram	X					
Diary Dispensed		X				
Randomization		X				
Study Drug Dispensed		X				
Critical Review of Diary for: • Missed Doses • Concomitant Medications				 X X		
Drug Accountability/Compliance				X		X
Adverse Event Assessment (SAEs through Visit 5/43-71 days post initiation of study drug). (Reminder at Visits 2 and 4)		X	X	X	X	X
Stress Compliance and Follow-up			X			
Stress ^{13}C UBT Testing and Reminder of Upcoming Appointment					X	

[a] Subject is to fast from solid food for at least one hour for ^{13}C UBT prior to blood draw.

[b] For subjects with abnormal results at Visit 3.

[c] Blood samples taken prior to first dose at visit 1, and prior to AM dose at visit 3 to assess plasma levels of amoxicillin, omeprazole, rifabutin, and 25-O-desacetyl-rifabutin.

Table 1: Schedule of Study Assessments - Standard of Care (SOC) Phase of Study

Assessments and Recordings	Visit 5A ^{13}C UBT Follow-up Day 44-72 (+7 days)	Visit 6 SOC Baseline and Endoscopy After Day 44-72 (+ 14 days)	Visit 7 Phone follow-up Day 50 - 79 (±2 days)	Visit 8 SOC Test of Cure Day 85 – 140 (+14 days)
Urine Pregnancy Test on Females of Child Bearing Potential		X		
Vital Signs		X		
Concomitant Medications		X		
Unblinded ^{13}C UBT Results: • Subjects with positive result – schedule upper endoscopy • Subjects with negative result – Visit 5 is their end-of-study visit	X			
Susceptibility Directed (initial endoscopy samples) or Standard of Care Therapy to Eradication Failure Subjects with Positive ^{13}C UBT		X		
Endoscopy with Biopsy (x2) for Culture and Susceptibility in Subjects with Positive ^{13}C UBT		X		
Stress Compliance Follow-up and Schedule ^{13}C UBT			X	
^{13}C UBT[a]				X

[a] Subject is to fast from solid food for at least one hour for ^{13}C UBT prior to blood draw.

4 STUDY ENDPOINTS

4.1 Primary efficacy endpoint(s)

The primary efficacy endpoint of this study is:

- The occurrence of *H. pylori* eradication as confirmed via ^{13}C UBT testing 43-71 days after initiation of treatment. In the event a female subject becomes pregnant during the course of the double-blind phase of the study and refuses to undergo the ^{13}C UBT assessment, results of a fecal antigen test may be performed at the local lab as a substitute.

4.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints of this study are:

- Antibiotic Resistance and Susceptibility Subgroup Analyses -
  The primary endpoint will be summarized within subgroups formed by the presence of *H. pylori* susceptibility and resistance to amoxicillin, clarithromycin, metronidazole and rifabutin determined based upon samples obtained prior to initiating study treatment. The proportion of subjects with eradication of *H. pylori* and the treatment effect (difference in the proportions) will be estimated within each subgroup along with 95% 2-sided confidence intervals where there are an adequate number of subjects in the subgroup (e.g., at least 20 subjects per subgroup).
- Assess the difference in antibiotic resistance and susceptibility of *H. pylori* after treatment with study drug in treatment failure subjects.

4.3 Safety endpoint(s)

The safety endpoints of this study are:

- The occurrence and severity of treatment emergent adverse events during the study.
- Changes from baseline in hematology and chemistry laboratory values.

4.4 Exploratory endpoint(s)

The exploratory endpoints of this study are:

- Upon study completion and unblinding of all subjects, CYP2C19 status will also be summarized and subgroup analyses of efficacy based on CYP2C19 status and pharmacokinetics will be performed using descriptive methods.
- Eradication rates in failure to eradicate subjects who receive susceptibility directed standard of care will be analyzed descriptively.

4.5 Pharmacokinetic endpoint(s)

The pharmacokinetic endpoint of this study is:

- The plasma concentrations of amoxicillin, omeprazole, rifabutin, and the rifabutin metabolite 25-O-desacetyl-rifabutin on Day 13 will be summarized by time following most recent dose.

5 SAMPLE SIZE AND POWER

Sample size for this study has been calculated based on a superiority comparison assuming 83% effectiveness for the new treatment, and 70% effectiveness for the control, with 90% power and a 2-sided alpha of 5%. Using these specifications, 222 subjects per arm will be required.

6 ANALYSIS POPULATIONS

6.1 Full Analysis Set (FAS) / Safety population

The FAS (based upon the intention-to-treat principle as described in ICH-E9) will consist of all subjects who received at least one dose of randomized study treatment and will be identical with the safety population (SAF). In the FAS subjects will be analyzed as randomized, in the SAF subjects will be analyzed as treated. If after unblinding it is detected that at least one subject did not receive the randomized study treatment summaries specified for the FAS may also be repeated for the SAF.

6.2 Modified Intent-to-treat (mITT) population

The mITT population is a subset of the FAS and will consist of all subjects who received at least one dose of randomized study treatment and undergo a ^{13}C UBT test at Visit 5 (with the allowed exception for female women becoming pregnant outlined in Section 4.1). In the mITT population subjects will be analyzed as randomized.

6.3 Per-Protocol population (PP)

The PP population is a subset of the mITT and will consist of all subjects who consume at least 75% of planned study treatment received, have no major protocol violations leading to exclusion from the PP population as determined during the Population Classification meeting (see Section 6.5) and undergo a ^{13}C UBT test at Visit 5 (with the allowed exception for females becoming pregnant as outlined in Section 4.1). In the PP population subjects will be analyzed as randomized.

6.4 PK Population (PKP)

The PKP will include those subjects in the FAS that have demonstrable presence of any component of investigational drug at Visit 3.

6.5 Protocol deviations/violations and exclusions from analysis sets

All violations and exclusions of subjects from analysis sets will be identified at the Classification Meeting just prior to study unblinding, through clinical review input provided by RedHill.

Protocol deviations will be classified as major (key) or minor (non-key) as outlined in Protocol Deviation Criteria Form Version 2.0, 08 December 2017. According to the definition in this document a major (key) protocol deviation is any change, divergence or departure from the study design or procedures defined in the protocol that might significantly affect a subject's rights, safety or welfare or the completeness, accuracy and/or reliability of the study data. A major protocol deviation in this sense does not necessarily lead to exclusion from the PP population. Examples of major protocol deviations that might be exclusive are:

- Subject or caregiver did not provide informed consent prior to participation in any study procedures as required and in compliance with ICH/Good Clinical Practice (GCP)

- Subject randomized in the study and does not meet inclusion/exclusion criteria
- Subject did not complete the final study visit of the double-blind phase (Visit 5)
- Subject is not fasting from food and drink 1 hour before ^{13}C UBT test at Visit 5
- Subject is assigned or provided wrong study medication kit/ Errors in treatment assignment
- Compliance less than 75% with double-blind study drug per pill count
- Subject taking a prohibited medication
- Subject/investigator were unblinded to treatment
- Visit 5 performed earlier than 42 days from Visit l

Major protocol deviations leading to exclusion from the PP population will be defined at the Classification Meeting.

Major protocol deviations leading to exclusion from the PP population will be summarized with descriptive statistics by category. A listing of all deviations (minor and major, also including major deviations not leading to exclusion from PP) with date of deviation and specifics of events will also be included.

7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived variables

The below table provides the list of derived variables for Demographic and baseline characteristics, various duration derivations, drug compliance, baseline derivations and other important derivations applicable for this study.

Variables	Formula
Demographic and Baseline characteristics	
Body mass index (BMI) (kg/m^2)	weight (kg)/[height (m)]^2
Derivation of Duration	
Study day at any visit	Date of interest – date of first dose of study drug. One day is added if this difference is ≥ 0
Extent of Exposure (Days)	Date of last randomized study medication intake – Date of first randomized study medication intake + 1
Baseline Derivations	
Baseline	Visit 1 Day 1
Laboratory or vital signs baseline	The baseline value is defined as the last observation prior to the first dose of study drug.
Change from baseline	Post baseline value – Baseline value

7.2 Handling of missing or incomplete data

Imputation rules for missing or partial Adverse Event (AE) start date for the purpose of identifying treatment-emergent AEs (TEAE) are defined below. These imputed dates are only created for the purpose of identifying TEAE programmatically; they will not be used in any data displays

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with treatment exposure period to determine whether the AE is pre-treatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start Month as January and the Day as 1.

Compare the imputed AE start date with treatment exposure period to determine whether the AE is pre-treatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

Imputation rules for missing or partial medication start/stop dates are defined below:

Missing or partial medication start date:

- If only Day is missing, use the first day of the month.
- If Day and Month are both missing and Year is not missing, use the first day of the year.
- If Day, Month and Year are all missing, use a date before the first dose date.

Missing or partial medication stop date:

- If only Day is missing, use the last day of the month.
- If Day and Month are both missing, use the last day of the year.
- If Day, Month and year are all missing, assign ‘continuing’ status to stop date

Date imputation will only be used for computational purposes, e.g., determination of treatment-emergent status. Actual date values as they appear in the original CRFs will be shown in the data listings.

Non-date Values:

There will be no imputation for missing data for non-date values.

8 STATISTICAL METHODS

8.1 General statistical conventions

All statistical procedures will be completed using SAS version 9.3® or higher. Specifications for table, figure, and data listing formats can be found in the TFLs specifications for this study.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. Two-sided 95% confidence intervals (CI) will be provided when relevant. P-values will be presented with 4 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.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), minimum and maximum.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

For summary purposes, baseline will be defined as the last available pre-dose value; all summaries will be presented by treatment group, unless otherwise specified.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings only. All listings will be sorted by investigational site, subject number, date/time and visit. The treatment group (Investigation Arm, Active comparator) as well as subject's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on All Subjects Randomized.

All analyses and summary tables will be displayed by treatment group. Primary and few key secondary endpoints will be analyzed by sub-groups. For the definition of subgroups of interest please refer to Section 8.9.

8.1.1 Model structure or SAS codes

Chi-Square test without continuity correction

The following SAS statements will be used for the primary and secondary endpoint analyses:

```
PROC  FREQ data=<dataset name>;
        TABLES response variable*treatment group /CHISQ OUT=< output dataset name>
        OUTPUT OUT=stats;
RUN;
```

8.2 Subject disposition

Subject disposition information will be presented for all subjects and summarized by treatment group and overall. The number and percent of subjects who are randomized, who received at least one dose of randomized study treatment, who were randomized and not treated, and who were treated and not randomized will be presented. Further, the number and percent of subjects who had a test of cure at the end of the double-blind phase, who had a test of cure and a (calculated) compliance ≥ 75%, who had a test of cure and a (calculated) compliance < 75%, who had no test-of cure after the double-blind phase, who were eligible for the standard of care (SOC) phase, who were eligible for and entered the SOC phase, and who were eligible for but did not enter the SOC phase will be presented. For the calculation of compliance see Section 8.5.2. In addition the number of subjects who discontinued their double-blind treatment but who completed the double-blind phase and vice versa will be shown. For the subjects who had a test of cure at the end of the double blind phase but with (calculated) compliance less than 75%, the reason for treatment discontinuation will be summarized by treatment group and overall with the following categories:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Withdrawal by subject
- Protocol deviation
- Randomized in error
- Other.

The number of subjects randomized will be used as the denominator for the percentage calculation.

For the subjects who entered the SOC phase of the trial the number and percentage of subjects who completed the SOC treatment, who discontinued SOC treatment, who completed the SOC phase at Visit 8 and who discontinued the SOC phase prematurely will be presented. Primary reason for discontinuation of the SOC phase and for discontinuation of SOC treatment will be summarized with the following categories:

- Adverse event

- Death
- Lost to follow-up
- Non-compliance with standard of care
- Physician decision
- Withdrawal by subject
- Protocol deviation
- Other.

The number of subjects who entered the SOC phase of the trial will be used as the denominator for the percentage calculation.

Subject disposition will be listed.

The number and percent of subjects in each analysis set will also be tabulated.

The number and percentage of subjects excluded from the mITT and PP population by reason for exclusion will be summarized by treatment group for the FAS.

8.3 Protocol deviations

The number of subjects with major protocol deviations leading to exclusion from the PP population will be summarized by treatment group and overall. Subjects deviating from a major criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one major protocol deviation will be counted once in the overall summary.

A data listing will be provided by site and subject for all the major and minor protocol deviations.

The protocol deviations criteria will be uniquely identified in the summary table and listing. The unique identifiers will include but are not limited to the following:

- < 75% of planned study treatment received
- Developed withdrawal criteria during the trial and was not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant medications
- Other

8.4 Demographics and baseline characteristics

Demographic and baseline characteristics, including upper endoscopy to determine *H. pylori* status, will be summarized with descriptive statistics by treatment group.

8.4.1 Demographics

Age (in years), baseline weight (in kg), BMI (kg/m^2) and height (in cm) and other continuous demographic variables at baseline will be summarized descriptively for the FAS. Age category (< 65, ≥ 65 years), sex, primary race, ethnicity and other categorical variables will be summarized using frequency counts for the FAS.

8.4.2 Baseline and disease characteristics

The categorical baseline characteristics such as baseline ECG overall assessment, Biopsy for Campylobacter-Like Organism (CLO), CYP2C19 status, Biopsy for histology and Biopsy for culture and susceptibility (categorized) will be summarized using frequency counts for the FAS. Categorized susceptibility will also be summarized by region (sub-regions of the United States), where a classification of the study sites to region will be done according to the following table.

Region	States
West	California, Nevada, Utah, Colorado, Arizona
South	Texas, Oklahoma, Arkansas, Louisiana, Tennessee
Southeast	Florida, Alabama, Georgia, South Carolina, North Carolina, Virginia
Northeast	Maryland, Connecticut, New York
Central	South Dakota, Wisconsin, Michigan

Categorized susceptibility may also be summarized by state or study site as a post-hoc analysis.

Minimum inhibitory concentration (MIC) values at baseline will be summarized together with the MIC values from Visit 6 for subjects entering the SOC phase. Continuous baseline variables such as vital signs: temperature (°C), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats/min) and respiratory rate (breaths/min) will be summarized by descriptive statistics in the same way as continuous demographic variables for the FAS.

Categorization for Susceptibility of Amoxicillin, Clarithromycin, Metronidazole and Rifabutin will be derived according to the following rules:

MIC Values (ug/mL)

Antibiotic	Susceptible	Intermediate	Resistant
Amoxicillin	≤ 0.125	-	> 0.125
Clarithromycin	≤ 0.25	0.5	> 0.5
Metronidazole	≤ 8	-	> 8
Rifabutin	≤ 1	-	> 1

Source (except for Clarithromycin): "The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.1, 2018. http://www.eucast.org.". For Clarithromycin: “CLSI (Clinical and Laboratory Standards Institute), Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria, M45, 3rd Edition, 2016.”

8.4.3 Medical history

A summary of medical history will be presented by treatment group, system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Affairs® (MedDRA) Version 19.0 or higher.

A comprehensive data listing will also be included.

8.4.4 Prior and concomitant medications

A prior medication is defined as medication that stopped before the date of the first dose of randomized treatment (i.e. last medication intake is prior to first dose of treatment date (exclusive)).

A concomitant medication is defined as a medication with either

- a recorded medication start date falling within the double-blind or SOC phase of the trial, or
- a recorded medication start date prior to the first day of study medication during the randomized treatment period without any recorded medication stop date prior to the start of the randomized treatment period.

Medications with incomplete start or stop dates will be considered concomitant medications if it is possible that they could have been concomitant medications.

Concomitant medications will be coded with the World Health Organization (WHO) drug dictionary (Enhanced – Format C, 03MAR2015 or later version). Concomitant medications will be summarized for each treatment group by Anatomical Therapeutic Chemical (ATC) 3rd level and preferred name for the following two categories (not exclusive):

- concomitant medications given during the double-blind phase (ie concomitant medications with a start date before or during the double blind phase of the study), and
- concomitant medications (excluding prescribed standard of care (SOC) medications) given during the SOC phase for subjects entering the SOC phase of the trial (ie concomitant medications either ongoing on the first day of SOC medication or with a start date on or after the first day of SOC medication).

A data listing will be included that shows all medications by preferred name and verbatim name. Prior medications will be excluded from the summaries but will be included in the listing.

Prescribed SOC medications will be summarized by ATC 3rd level and preferred name for those subjects who entered the SOC phase of the study. The summary will be done by treatment group of the double-blind phase and overall.

8.5 Extent of exposure

The following information on drug exposure will be presented for each treatment group for the SAF:

- Descriptive statistics for number of days treatment was received and number of capsules taken will be presented by treatment group

8.5.1 Treatment duration

Duration of double-blinded study drug (in days) will be calculated as: last dose date – first dose

date + 1 day, regardless of study drug interruption.

Treatment duration will be summarized by treatment group on the SAF using descriptive statistics.

Duration of SOC treatment for subjects entering the SOC phase of the trial will be calculated as last dose date of SOC treatment – first dose date of SOC treatment + 1 day and summarized in the pertaining group of subjects. The summary will be done by treatment group of the double-blind phase and overall.

8.5.2 Treatment compliance

Subjects will be instructed to bring their study medication and all empty packaging to each clinic visit. Compliance with double-blinded study drug will be assessed by capsule counts, and details will be recorded and reconciled against expected medication use. Compliance will be calculated as a percentage of expected usage at each study visit as follows:

For all subjects (including those who do not complete the treatment with study medication) compliance (%) will be calculated as

$$100 \text{ x } \frac{[(\text{total number of capsules dispensed}) - (\text{total number of capsules returned})]}{168}$$

Subjects taking too many capsules will have a resulting compliance of over 100%.

Study drug compliance will be summarized by treatment group with descriptive statistics. They will also be summarized in categories "<=75% compliant", ">75% – 90% compliant", ">90% – 100% compliant", and "> 100% compliant" using frequency tables.

Compliance with SOC treatment will not be considered.

All exposure and compliance data will be provided in data listings.

8.6 Efficacy analyses

All efficacy analyses will be conducted on the FAS as primary analyses and repeated on the mITT and PP populations as sensitivity analyses.

8.6.1 Analysis of primary efficacy endpoint(s)

The primary endpoint is this study is eradication of *H. pylori* as confirmed via ^{13}C UBT test results at the test of cure Visit 5 (Day 43-71) or fecal antigen test. Subjects with negative test results will be considered treatment successes. Subjects who test positive for *H. pylori* infection will be considered treatment failures, those subjects with indeterminate, not assessable, or missing results from actual test of cure visits will undergo a repeat ^{13}C UBT testing. Persistent indeterminate results and subjects without any ^{13}C UBT test after baseline will be considered as treatment failures and will be included as additional (sub-)category in the pertaining summary tables.

Subjects who have their test of cure visit prior to 28 days after their last dose of study medication will

have a re-test within the protocol defined visit window of Visit 5. In this case the result of the re-test will be used in the primary analysis. In case this happens in more than 5 cases, a sensitivity analysis will be done in the FAS where the results from the first ^{13}C UBT test will be used instead of the results from the re-test.

Hypotheses:

Let p_O denote the response rate under RHB-105 and p_P denote the response rate under the active comparator then the primary two-sided hypothesis to be tested is

H_0: $p_O - p_P = 0$

vs the alternative

H_1: $p_O - p_P \neq 0$

This hypothesis will be evaluated using the FAS as the primary analysis population.

Proportion of subjects with eradication of *H. pylori* will be tested between two treatment groups using the chi-square test at the 5% level of significance; in addition the estimated treatment difference along with the corresponding 95% CI will be presented.

As sensitivity analyses the analysis of the primary endpoint will be repeated in the mITT and PP populations (where those subjects lost to follow-up or not completing Visit 5 will be excluded from the analysis). Further, the following sensitivity analyses to investigate the impact of imputation rules for subjects who did not provide a result of the ^{13}C UBT test at Visit 5 will be added in the FAS:

1. Eradication rates by treatment will be calculated in subjects with observed data (mITT population), and the same eradication rates will be assumed for subjects with unobserved (missing) data. For this purpose, multiple imputations will be used where for a subject with missing data the event of eradication/non-eradication will be randomly assigned according to a Bernoulli-distribution with rate as estimated from the subjects with observed data. The results of this multiple imputation will be combined over the iterations according to the method of Rubin (1987) to generate an estimator for the treatment difference with corresponding 95% CI and a p-value for the associated chi-square test.
2. All active-controlled subjects with missing data will be assumed as treatment successes while all subjects treated with the investigational regimen will be assumed as treatment failures. This method is used only to give a lower bound on the upper limit of the confidence interval for the difference in eradication rates because such a scenario would be unlikely to actually occur.
3. All subjects with missing data will be assumed as treatment successes.

Sensitivity analyses 2. and 3. will be conducted in a similar manner to the primary analysis.

A further analysis of the primary efficacy parameter will be performed by study site. For this analysis, sites which have randomized less than 5 subjects will be pooled by region of the United States (see table in Section 8.4.2) to form clusters of sites by region. If after this step there is still a (pooled) site with less than 5 subjects, this site will be pooled with the smallest pooled site from the other regions.

8.6.2 Analysis of secondary efficacy endpoint(s)

Antibiotic Resistance and Susceptibility Subgroup Analyses -

The primary endpoint will be summarized within subgroups formed by the presence of *H. pylori* susceptibility and resistance to amoxicillin, clarithromycin, metronidazole and rifabutin determined based upon samples obtained prior to initiating study treatment.

Proportion of subjects with eradication of *H. pylori* will be tested between two treatment groups using the chi-square test at the 5% level of significance; in addition estimated differences within each subgroup along with 95% CIs will be presented.

Assess the difference in antibiotic resistance:

The difference in antibiotic resistance and susceptibility of *H. pylori* after treatment with study drug in treatment failure subjects will be summarized by treatment group. No formal statistical tests will be performed for group comparison.

8.6.3 Analysis of exploratory endpoint(s)

Upon study completion and unblinding of all subjects, CYP2C19 status (performed at baseline) will be summarized by treatment arm. CYP2C19 status is classified as ultra rapid metabolizers, extensive metabolizers, intermediate metabolizers and poor metabolizers. A summary table of CYP2C19 status and *H. pylori* infection eradication success will be presented, and a chi-square test will be performed to test if CYP2C19 status is associated with treatment success.

Further subgroup analyses of efficacy will be done by subgroups based on pharmacokinetic measures. Definition of these measures will be provided after finalization of the double-blind study phase.

Subjects who have a positive ^{13}C UBT test at Visit 5 will receive SOC therapy for a certain time and then have a further test-of cure visit (Visit 8). Eradication rates for *H. pylori* at V8 will be summarized overall and by treatment group in the double-blind study phase**.**

8.7 Safety analyses

Safety analyses will be conducted on the SAF and will be performed for all safety variables specified below.

All safety data will be summarized by treatment group.

No statistical tests will be performed.

8.7.1 Adverse events

A treatment emergent adverse event (TEAE) is defined as any unfavorable and unintended sign, symptom, physical finding or disease, whether or not believed to be related to the investigational product that arises after the first dose of study drug was administered and not later than 28 days following the last dose of study drug. This includes any occurrence that was new in onset or aggravated in severity or frequency from the time the first dose of study drug was administered. Abnormal results of diagnostic procedures, or laboratory test abnormalities, should also be considered as TEAEs, ONLY if they result in any of the following:

- Discontinuation of study drug
- Require treatment or any other therapeutic intervention and/or
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)

All events, TEAEs and Serious adverse events (SAE)s, regardless of severity or causality, that occur between the time of first study drug administration and within 28 days following the last dose of blinded study drug are to be documented on the adverse event case report form with indications of onset, duration, severity (mild, moderate, and severe), seriousness, relationship to study drug (unrelated, unlikely, possible, probable, definite), remedial actions taken, and outcome.

All SAEs occurring during the administration of standard of care (SOC) drug are to be documented as SAEs on serious adverse event case report form (for SOC) with indications of onset, duration, severity (mild, moderate, and severe), relationship to SOC drug (unrelated, unlikely, possible, probably, definite), remedial actions taken, and outcome. If the SAE is deemed to be related to any of the standard of care drugs, it is the responsibility of the investigator to report the event to the manufacturer of the related drug, through the manufacturer's post-marketing surveillance system. Determination of eradication of *H. Pylori* infection will be based on ^{13}C UBT testing done between 43 and 71 days after initiation of blinded therapy. Due to this delay in time of 28-60 days, any SAEs that occur during the SOC dosing period will NOT be considered related to the study treatment regimen of RHB-105 or active comparator.

All Adverse events (AEs) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 or higher.

In summaries by SOC and PT, adverse events will be sorted by decreasing frequency in the overall total of SOC and of PT within each SOC. Events of the same frequency within classification level are sorted alphabetically.

AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- Related TEAEs (AE will be defined as related if causality is definite or probable or possible)

- TEAE's by closest related
- TEAEs by action taken
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation

All TEAEs will be summarized by SOC, PT and treatment group using frequency counts and percentages (i.e., number and percentage of subjects with an event). In addition an overall summary for the categories above will be prepared by treatment group and overall.

Where a subject has multiple adverse events within the same system organ class/with the same preferred term in the treatment period, the subject will only be counted once at the system organ class level/for this preferred term in adverse event frequency tables.

Events without recorded intensity/causality taken are summarized as severe /related.

All AEs will be included in comprehensive data listings. A separate listing will be included for AEs leading to discontinuation from study.

8.7.2 Serious adverse events

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is considered medically significant.

Separate data listings and summaries will be presented for all SAEs and deaths.

- Serious TEAEs
- Serious related TEAEs

Individual subject data listings will be provided for all deaths and discontinuation of study medication due to TEAEs.

8.7.3 Clinical laboratory evaluations

Key laboratory data (Chemistry and hematology, see **Table 2Table 2**) will be subjected to both a quantitative analysis and qualitative analysis where frequencies of normal, abnormal low, and abnormal high values will be computed. Additionally, abnormal results will be summarized with frequencies and percentages by clinical significance, panel, test, treatment group, and time point.

Urinalysis results and viral serology results at baseline will not be summarized but only presented in data listings. Pregnancy test results will also be summarized.

Shift tables demonstrating the changes (low/normal/abnormal) from baseline to worst post-baseline value will be displayed in cross-tabulations by panel, test and treatment group.

Other laboratory assessments and change from baseline, where applicable, will be summarized with descriptive statistics by panel, test, treatment group, and time point. For these quantitative analyses US conventional units will be used for all summaries.

Data listings will display all laboratory test results along with findings.

Table 2: Laboratory assessments in the RHB-105-20 study

Hematology	Clinical Chemistry	Special Testing	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood urea nitrogen (BUN) Creatinine Creatinine Clearance Total bilirubin (Direct and indirect fractionated) Lactate Dehydrogenase (LDH) Serum glutamic-pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) Serum glutamic-oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST) Creatine phosphokinase Alkaline phosphatase Sodium Potassium Chloride Gamma-glutamyltransferase (GGT) Bicarbonate Calcium Magnesium Inorganic phosphorus Amylase Uric acid Total cholesterol Total protein Glucose Albumin	CYP 2C19 genotyping HBs Ag HCV Ab HIV1 antibody HIV2 antibody Pharmacokinetic testing for: amoxicillin, omeprazole, rifabutin, and 25-O-desacetylrifabutin Urine pregnancy ^{13}C Urea Breath Test Culture and Resistance/ Susceptibility for *H. pylori* CLO – Campylobacter Like Organism (Rapid Urease Test) Histology for *H. pylori*	Leucocytes Nitrite Protein pH Blood Specific gravity Ketones Glucose Sediment microscopy, If indicated by the dipstick

8.7.4 Vital signs

The results and changes from baseline of vital signs (pulse, respiratory rate, supine systolic and supine diastolic blood pressure, oral temperature, and weight) will be summarized with descriptive statistics by treatment group and time point. A data listing of all vital signs data (including height at screening) will also be included.

8.7.5 Physical examinations

The physical examination listing will include date of exam, result (normal, abnormal, not examined), and description of abnormality for each major body system (general appearance, head/eyes/ears/nose/throat, neck, lungs, heart, abdomen, genitourinary, extremities, neurological, skin, and lymphatics). Detailed results of the general physical examination are only provided for the screening visit, otherwise it will only be denoted whether any clinically significant changes since the last study visit have been observed.

The results of physical examinations at screening will be summarized with frequencies and percentages by body system and treatment group.

All physical examination data will be displayed in data listings, one for the screening results and one for the subsequent changes.

8.7.6 Electrocardiograms

ECG measurements (heart rate, PR, QRS, QT, QTcF) as well as ECG results (normal, abnormal not clinically significant, abnormal clinically significant) are measured at screening only. ECG measurements will be summarized by descriptive statistics and ECG results with frequencies and percentages by treatment group. All ECG data will be displayed in a data listing.

8.8 Pharmacokinetic (PK) analyses

All PK analyses will be performed in the PK population.

Blood samples will be collected to assay the plasma concentrations of amoxicillin, omeprazole, rifabutin, and the rifabutin metabolite 25-O-desacetyl-rifabutin at baseline Visit 1 (Day 1) before the first dose of double-blinded study medication and Visit 3 (Day 13).

Plasma samples will be analyzed using validated methodology. Plasma concentration data for each analyte by time and treatment will be summarized through data tabulations and using descriptive statistics (n, mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum). Comprehensive data listings will also be included.

Plasma concentration data will also be summarized by the primary efficacy endpoint.

8.9 Subgroup analyses

The primary efficacy endpoint will be analyzed within subgroups formed by the presence of *H. pylori* susceptibility and resistance to amoxicillin, clarithromycin, metronidazole and rifabutin determined based upon samples obtained prior to initiating study treatment. Further subgroup analyses or the primary efficacy endpoint will be performed by CYP2C19 status and by subgroups based on pharmacokinetic measures.

8.10 Interim analysis

No interim analysis is planned for this study.

8.11 Analysis after the double-blind phase of the study

To allow for early availability of the primary efficacy and most important safety results there will be a primary lock of the databases after all patients have finalized the double-blind study phase and only the patients evaluable for the SOC phase continue their participation. Unblinding of the study and also the Population Classification meeting (see section 6.5) will be done at this stage.

The following analyses will be part of the primary study results:

- Subject disposition and location to analysis populations
- Demography
- Treatment exposure and compliance
- Responder analysis of eradication of *H. pylori*
- Responder analysis by resistance/susceptibility to antibiotics
- Eradication of *H. pylori* by CYP2C19 Status
- Treatment emergent AEs and SAEs.

9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

For the secondary endpoints the protocol states that "The proportion of subjects with failure to eradicate *H. pylori* and the treatment effect (difference in the proportions) will be estimated within each subgroup along with 95% 2-sided confidence intervals…" For the primary endpoint the proportion of subjects with treatment success (eradication of *H. pylori*) is evaluated, this proportion will now also be used for all secondary endpoints to ensure comparable results.

10 REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95- adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).
3. Rubin, D. B. (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons.

11 APPENDICES

Appendix A - Definitions for Clinical and Laboratory Adverse Events

All adverse events (clinical and laboratory) will be rated as follows:

Severity (Clinical Events Only)

Severity of clinical events are to be **graded** as follows:

1 = Mild:	Event Is noticeable to the subject, does not interfere with the subject's daily activities and usually does not require additional therapy or dose adjustment.
2 = Moderate:	Event may interfere with the subject's daily activities and may require additional therapy
3 = Severe:	Event may severely limit the subject's daily activities and typically requires therapy or intervention.

Causal Relationship

The investigators are to assess the **causal relationship** of all AEs using the following five categories:

Relationship	Causality	Description
Not related to investigational agent	Unrelated	The AE is clearly not related to the investigational agent.
	Unlikely	The AE is doubtfully related to the investigational agent.
Related to investigational agent	Possible	The AE may be related to the investigational agent.
	Probable	The AE is likely to be related to the investigational agent.
	Definite	The AE is clearly related to the investigational agent.

Appendix B - Visit Window

Day 1 for the treatment period is the start date of double-blinded study medication.

Table 3: Visit windows for treatment period (up to Visit 8)

Visit	Period	Day range
Visit 0	Screening	Day -42 to -2
Visit 1	Baseline	Day 1
Visit 2	Phone	Day 8 +/- 1
Visit 3	Safety	Day 13 +/- 2
Visit 4	Phone	Day 28 – 60 +/- 2
Visit 5	Test of Cure	Day 43 – 71 + 7
Visit 5a	^{13}C UBT Follow-up	Day 44 – 72 +7
Visit 6	SOC Baseline	After Day 44 – 72 +14
Visit 7	Phone	Day 50 – 79 +/- 2
Visit 8	Test of Cure	Day 85 – 140 + 14

Addendum to the Statistical Analysis Plan (SAP)

RedHill Biopharma Ltd.

Protocol Title:	A Randomized Double Blind Active Comparator Controlled Phase III Study to Assess the Safety and Efficacy of RHB-105 in the Treatment of Confirmed Helicobacter pylori (*H. pylori*) Infection
Protocol Number:	RHB-105-02
Protocol Version, Date	Protocol Amendment 3, 22 Mar 2018
ICON ID:	3101/0005
Document Version, Date:	Version 1.0, 06 Feb 2019

Prepared by:

ICON Clinical Research Services

On behalf of:

RedHill Biopharma Ltd.

REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
Version 1.0/ 06 Feb 2019	Initial version	N/A	N/A

TABLE OF CONTENTS

1 INTRODUCTION

The purpose of this Addendum to the Statistical Analysis Plan (SAP) is to provide a description of additional ad-hoc analyses performed after the final statistical analysis for study protocol RHB-105-02 "A Randomized Double Blind Active Comparator Controlled Phase III Study to Assess the Safety and Efficacy of RHB-105 in the Treatment of Confirmed Helicobacter pylori (*H. pylori*) Infection", Amendment 3 dated 22 Mar 2018.

2 SPECIFICATION OF ADDITIONAL ANALYSES

2.1 Additional Analyses of Efficacy

To investigate the primary efficacy outcome in relation to pharmacokinetic results three sensitivity analyses will be performed:

1. A sensitivity analyses performed in the Full Analysis Set (FAS) excluding patients from the active comparator group that have a measurable rifabutin concentration at Visit 3.
2. A sensitivity analysis performed in the Pharmacokinetic (PK) population, defined as subjects in the FAS that have demonstrable presence of any component of investigational drug at Visit 3 or for whom the PK assessment at Visit 3 was performed more than 250 hours after the last dose of randomized study drug before this assessment.
3. A sensitivity analysis performed in the PK population where in addition, as in the first sensitivity analysis, patients from the active comparator group that have a measurable rifabutin concentration at Visit 3 will be excluded from the analysis.

2.2 Additional Analyses of Safety

To investigate the comparability of tolerance and safety of RHB-105 over the different phenotypes according to CYP2C19 genotyping results the number of treatment-emergent adverse events (TEAE)/number of subjects with any TEAE and the number of serious adverse events (SAE)/number of subjects with any SAE will be provided by phenotype.

3 TABLE MOCKS

Ad-hoc Table 1
Responder Analysis of Eradication of H. pylori: Sensitivity Analysis Excluding Subjects in the Active Comparator Group with Nonnegative Concentrations of Rifabutin at Visit 3
Full Analysis Set

Eradication of H. pylori	RHB-105 (N=xxx)	Active Comparator (N=xxx)	Treatment Difference
n	xx	xx	
Responder	xx (xx.x)	xx (xx.x)	
95% CI for proportion of responder	(xx.x, xx.x)	(xx.x, xx.x)	
Non-responder	xx (xx.x)	xx (xx.x)	
Positive test result	xx (xx.x)	xx (xx.x)	
Missing post-baseline test result	xx (xx.x)	xx (xx.x)	
Difference of Response rates (RHB-105 - Active Comparator)			xx.x
95% CI			(xx.x, xx.x)
p-value[a]			0.xxx

CI = Confidence Interval.
RHB-105 – all-in-one' combination oral capsule containing 12.5 mg rifabutin, 250 mg amoxicillin, and 10 mg omeprazole.
Active Comparator - all-in-one' combination oral capsule containing 250 mg amoxicillin, and 10 mg omeprazole.
n is the number of subjects in FAS population excluding subjects in the Active Comparator Group with nonnegative concentrations of Rifabutin at Visit 3.
Percentages are based on n.
Eradication of H. pylori as confirmed via ^{13}C UBT test results at the test of cure Visit 5 (Day 43-71) or fecal antigen test. Subjects with negative test results are considered as treatment successes (responder). Subjects who test positive for H. pylori infection are considered as treatment failures (non-responder). Subjects with indeterminate, not assessable, or missing results from actual test of cure visits should undergo a repeat ^{13}C UBT testing. Subjects with persistent indeterminate results and subjects without any ^{13}C UBT test after baseline will be considered as treatment failures.
95% CI for the proportion of responder are based on Wilson's method.
[a] P-value based on Chi-square test.

Source: Listing 16.2.6.1
Program Name: xxxxxx.SAS DB Snapshot/Lock Date: DDMMMYYYY Runtime: DDMMMYYYY HH:MM

Ad-hoc Table 2
Responder Analysis of Eradication of H. pylori
PK Analysis Set

Eradication of H. pylori	RHB-105 (N=xxx)	Active Comparator (N=xxx)	Treatment Difference
Responder	xx (xx.x)	xx (xx.x)	
95% CI for proportion of responder	(xx.x, xx.x)	(xx.x, xx.x)	
Non-responder	xx (xx.x)	xx (xx.x)	
Positive test result	xx (xx.x)	xx (xx.x)	
Missing post-baseline test result	xx (xx.x)	xx (xx.x)	
Difference of Response rates (RHB-105 - Active Comparator)			xx.x
95% CI			(xx.x, xx.x)
p-value[a]			0.xxx

CI = Confidence Interval.
RHB-105 - all-in-one' combination oral capsule containing 12.5 mg rifabutin, 250 mg amoxicillin, and 10 mg omeprazole.
Active Comparator - all-in-one' combination oral capsule containing 250 mg amoxicillin, and 10 mg omeprazole.
N is the number of subjects in PK analysis set. Percentages are based on N.
Eradication of H. pylori as confirmed via ^{13}C UBT test results at the test of cure Visit 5 (Day 43-71) or fecal antigen test. Subjects with negative test results are considered as treatment successes (responder). Subjects who test positive for H. pylori infection are considered as treatment failures (non-responder). Subjects with indeterminate, not assessable, or missing results from actual test of cure visits should undergo a repeat ^{13}C UBT testing. Subjects with persistent indeterminate results and subjects without any ^{13}C UBT test after baseline will be considered as treatment failures.
95% CI for the proportion of responder are based on Wilson's method.
[a] P-value based on Chi-square test.

Source: Listing 16.2.6.1
Program Name: xxxxxx.SAS DB Snapshot/Lock Date: DDMMMYYYY Runtime: DDMMMYYYY HH:MM

Repeat Ad-hoc table 1 for:

Ad-hoc Table 3
Responder Analysis of Eradication of H. pylori: Sensitivity Analysis Excluding Subjects in the Active Comparator Group with Nonnegative Concentrations of Rifabutin at Visit 3
PK Analysis Set

Ad-hoc Table 4
Overall Summary of Treatment Emergent Adverse Events (TEAEs) by CYP2C19 Status
Safety Analysis Set

CYP2C19 Status at Baseline Overall Incidence	RHB-105 (N=xxx) n (%)	Active Comparator (N=xxx) n (%)	Overall (N=xxx) n (%)
Ultrarapid metabolizers			
n	xx	xxx	xxx
Number of TEAEs in the double blind phase	xxx	xxx	xxx
Number of Subjects with any TEAE in the double blind phase	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Serious Adverse Events (SAEs) in the double blind phase	xxx	xxx	xxx
Number of Subjects with any SAE in the double blind phase	xx (xx.x)	xx (xx.x)	xx (xx.x)
Rapid metabolizers			
…			
Normal metabolizers			
…			
Intermediate metabolizers			
…			
Poor metabolizers			
…			

AE=Adverse Events; SAE=Serious Adverse Events; TEAE=Treatment Emergent Adverse Events
N=number of subjects in the treatment group analysis set.
RHB-105 – all-in-one' combination oral capsule containing 12.5 mg rifabutin, 250 mg amoxicillin, and 10 mg omeprazole.
Active Comparator - all-in-one' combination oral capsule containing 250 mg amoxicillin, and 10 mg omeprazole.
n is the number of subjects in the Safety Analysis Set in each treatment group by CYP2C19 status at baseline. Percentages are based on n.
Treatment emergent adverse event is defined as any event that occurs on or after the first dose of study drug administration and not later than 28 days following the last dose of study drug or any pre-existing event which worsened in severity after dosing.

Source: Listing 16.2.7.1.1

Program Name: xxxxxx.SAS DB Snapshot/Lock Date: DDMMMYYYY Runtime: DDMMMYYYY HH:MM