STATISTICAL ANALYSIS PLAN

NC-005-(J-M-PA-Z)

A PHASE 2 OPEN-LABEL PARTIALLY RANDOMIZED TRIAL TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF COMBINATIONS OF BEDAQUILINE, MOXIFLOXACIN, PA-824 AND PYRAZINAMIDE DURING 8 WEEKS OF TREATMENT IN ADULT SUBJECTS WITH NEWLY DIAGNOSED DRUG-SENSITIVE OR MULTI DRUG-RESISTANT, SMEAR-POSITIVE PULMONARY TUBERCULOSIS

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VERSION NUMBER AND DATE: VERSION 2.0, 14DEC2016

Statistical Analysis Plan (SAP) Signature Page

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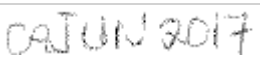
Author:	Divan Burger, PhD		
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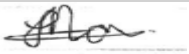
Author:	Lucia Mans, BSc (Hons)		
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The signatures below indicate review and approval of the proposed analysis and presentation of data as planned for protocol NC-005-(J-M-PA-Z) Version 1.0, dated 31 January 2014, including final protocol amendment 01, dated 19 September 2014 (incorporated into the working protocol Version 1.1, dated 19 September 2014).

This version of the statistical analysis plan (SAP) was approved by the undersigned.

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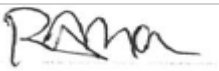
Approved By:	Robert Schall, PhD		
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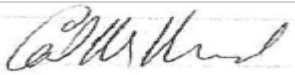
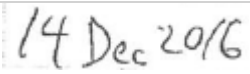
Approved By:	Carl Mendel		
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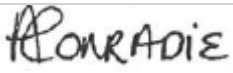
Approved By:	Almari Conradie, MPh		
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Modification History

Unique Identifier for this Version	Date of Document Version	Authors	Significant Changes from Previous Authorized Version
1.0	22FEB2016	Divan Burger & Lucia Mans	Not applicable.
2.0	14DEC2016	Divan Burger & Lucia Mans	• All wording related to "topline" updated to "snapshot". • Section 1 (Introduction) – Phrase added to state that the pharmacokinetic (PK) analysis will be described in a separate statistical analysis plan (SAP). • Section 4.3 (Final Analysis) – Paragraph added to state the minimum inhibitory concentration (MIC) data will form part of an appendix to the "final analysis". • Section 6.3 (End of Treatment) – Definition for end of treatment measurement added. • Section 6.4 (End of Study) – Definition for end of study measurement added. • Section 6.5 (Treatment-Emergent Incidences) – Definition of treatment-emergent updated to include measurement up to and including the Day 70 Follow-up visit. Also, definition of post-treatment incidences during the Day 70-140 Follow-up period updated to start after the Day 70 Follow-up measurement. • Section 6.10 (Software Version) – R Version 3.0.2 or higher added as software used. Removed software used for PK analysis as this is now part of the separate PK SAP. • Section 9 (Disposition and Withdrawals) – Removed the paragraph on the randomization and visit dates listings, as these will not be presented separately anymore. Also, paragraph on inclusion and exclusion criteria was removed as this will not be presented in a data listing anymore. Text was added to indicate that protocol deviations during study conduct will be displayed. Updated text for derivations for detail on day 140 follow-up. • Section 10 (Demographics and Other Baseline Characteristics) – Derivation for tuberculosis (TB) duration updated to be presented in days. • Section 11 (Medical and Treatment History [Excluding Human Immunodeficiency Virus {HIV}, Tuberculosis {TB} and Ophthalmology

Unique Identifier for this Version	Date of Document Version	Authors	Significant Changes from Previous Authorized Version
			History]) – Data listing will be presented for all patients screened, not just all patients randomized/assigned to study drug. • Section 12 (Concomitant Medications and Procedures) – Definition for concomitant medications added. • Section 15 (Efficacy Analyses) - Cultures collected 60 days after the first study drug administration will be excluded from the statistical analysis of efficacy data. • Section 15.1.3 (Primary Efficacy Analysis) - For the calculation of the precision matrix of the Wishart distribution, the linear mixed effects regression model (incorporating censoring) will be fitted using the "lmec" library of the R project. • Section 15.2 (Secondary Efficacy Variables) - Additional "proportions" analyses of liquid and solid media sputum culture conversion have been included for coached spot sputum samples. • Section 15.2 (Secondary Efficacy Variables) – Removed inferences on v_{50j}. • Section 15.1.3 (Primary Efficacy Analysis) - Minor typographical corrections to the specification of truncated normal prior distributions have been made. • Section 7.3 (Examination of Subgroups) - Additional subgroup analyses of bactericidal activity by laboratory have been included. • Section 15.2.3 (Secondary, Exploratory and Sensitivity Efficacy Analyses) - The analyses of log(TTP) and log(CFU) count collected from coached spot sputum samples will include the sensitvity analyses (specification of the Student t distribution). • Section 15.2.3 (Secondary, Exploratory and Sensitivity Efficacy Analyses) - Inferences on the differences of Kaplan-Meier estimates at the end of the treatment period (Day 56) have been included. • Section 15.2.3 (Secondary, Exploratory and Sensitivity Efficacy Analyses) - As a sensitivity analysis for time to sputum culture conversion of overnight sputum samples, the coached spot sputum samples will be used if results of the overnight sputum samples are not available. • Section 15.2.3 (Secondary, Exploratory and Sensitivity Efficacy Analyses) –

Unique Identifier for this Version	Date of Document Version	Authors	Significant Changes from Previous Authorized Version
			Kaplan-Meier analysis: Patients' time to sputum culture conversion or censoring on or after Day 53 will be considered as events which occurred on Day 56. • Section 15.2.3 (Secondary, Exploratory and Sensitivity Efficacy Analyses) - Patients' time to sputum culture conversion or censoring on or after Day 53 will be considered as events which occurred on Day 56. • Section 15.2.3 (Secondary, Exploratory and Sensitivity Efficacy Analyses) - Kappa coefficients applicable to the "agreement" analysis will no longer be "weighted". • Section 15.3 (Tuberculosis Symptoms and Weight) – Updated text to indicate that a shift table and stacked bar chart will be displayed for tuberculosis symptoms. Replaced box-and-whisker plot for weight with a mean weight over time line plot. • Section 17.2 (Adverse Events [AEs]) – Updated definitions of treatment-emergent adverse events and post-treatment adverse events during the Day 70-140/Follow-up period. All Standardized MedDRA query tables removed. • Section 17.3 (Deaths) – Section added to describe the analysis of deaths (table and listing). All further sections were renumbered to make place for the deaths section. • Section 17.4 (Laboratory Tests) – Text on worst case for laboratory classifications removed, as worst case tables will not be displayed. Text was added to indicate that a stacked bar chart for classifications according to laboratory reference ranges will be displayed. Liver enzyme profile plots for patients who died and patients with serious TEAEs removed. • Section 17.7 (Physical Examination) – Analysis text on physical examination removed. • Section 17.8 (Ophthalmological Examination) – Analysis text updated to indicate that decreases and increases from baseline will be displayed for the near and distance visual acuity test. A slit lamp grading of > 0.0 will be displayed in a data listing. • Updated signature page from Stephen Murray to Carl Mendel.

Table of Contents

Page:

1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and mycobacteriology characterization data for protocol NC-005-(J-M-Pa-Z). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on Working Protocol Version 1.1, dated 19 September 2014.

The pharmacokinetic (PK) analysis and analysis on MIC data of this study will be described in a separate SAP.

2 Study Objectives

The primary objective of this study is to evaluate the bactericidal activity, safety, and tolerability of bedaquiline, PA-824 and pyrazinamide in drug-sensitive (DS) tuberculosis (TB) and bedaquiline, moxifloxacin, PA-824 and pyrazinamide in multi-drug resistant (MDR) TB (MDR-TB).

Secondary objectives include evaluating the bactericidal activity, safety and tolerability of bedaquiline dosed using two different schemes (400 mg daily for two weeks followed by 200 mg three times a week [loading dose/t.i.w] and 200 mg daily [200 mg]). Additional key secondary objectives are to evaluate the population PK characteristics of bedaquiline, moxifloxacin, PA-824 and pyrazinamide when administered as a part of 3- and 4-drug regimens in adults with TB, and investigation of the methodology of sputum sampling by comparing colony forming unit (CFU) count and time to positivity (TTP) in liquid culture (MGIT), quantified from both overnight and coached spot sputum samples.

The study endpoints are listed in Section 4.2 of the protocol.

3 Study Design

3.1 General Description

This is a Phase 2, multi-center, open-label, partially randomized study conducted in four parallel treatment groups. The study will be performed at multiple sites globally.

Drug-Sensitive (DS) Tuberculosis (TB) (DS-TB):

A total of 180 eligible patients who meet all of the inclusion criteria and none of the exclusion criteria, aged between 18 and 75 years (inclusive), with newly diagnosed, smear-positive DS pulmonary TB will be randomized to one of three treatment groups:

- **J$_{(\text{loading dose/t.i.w.})}$PaZ:** Bedaquiline 400 mg once daily from Day 1 up to Day 14, 200 mg three times per week from Day 15 up to Day 56; plus PA-824 200 mg once daily from Day 1 up to Day 56; plus pyrazinamide 1500 mg once daily from Day 1 to Day 56.
- **J$_{(200\ \text{mg})}$PaZ:** Bedaquiline 200 mg once daily from Day 1 up to Day 56; plus PA-824 200 mg once daily from Day 1 up to Day 56; plus pyrazinamide 1500 mg once daily from Day 1 to Day 56.
- **HRZE:** Isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg and ethambutol 275 mg from Day 1 up to Day 56.

The HRZE treatment group is included as a control for the DS treatment groups. Additionally, it is included as a control for the quantitative mycobateriology.

Multi-Drug Resistant (MDR) Tuberculosis (TB) (MDR-TB):

Up to 60 eligible patients who meet all of the inclusion criteria and none of the exclusion criteria, aged between 18 and 75 years (inclusive), with newly diagnosed, smear-positive MDR pulmonary TB will be assigned to the following treatment group: **$J_{(200\ mg)}MPaZ_{MDR}$:** Bedaquiline 200 mg once daily from Day 1 up to Day 56; plus moxifloxacin 400 mg once daily from Day 1 up to Day 56; plus PA-824 200 mg once daily from Day 1 up to Day 56; plus pyrazinamide 1500 mg once daily from Day 1 to Day 56.

The number of patients to be randomized/assigned to each treatment group is presented below.

Treatment Groups

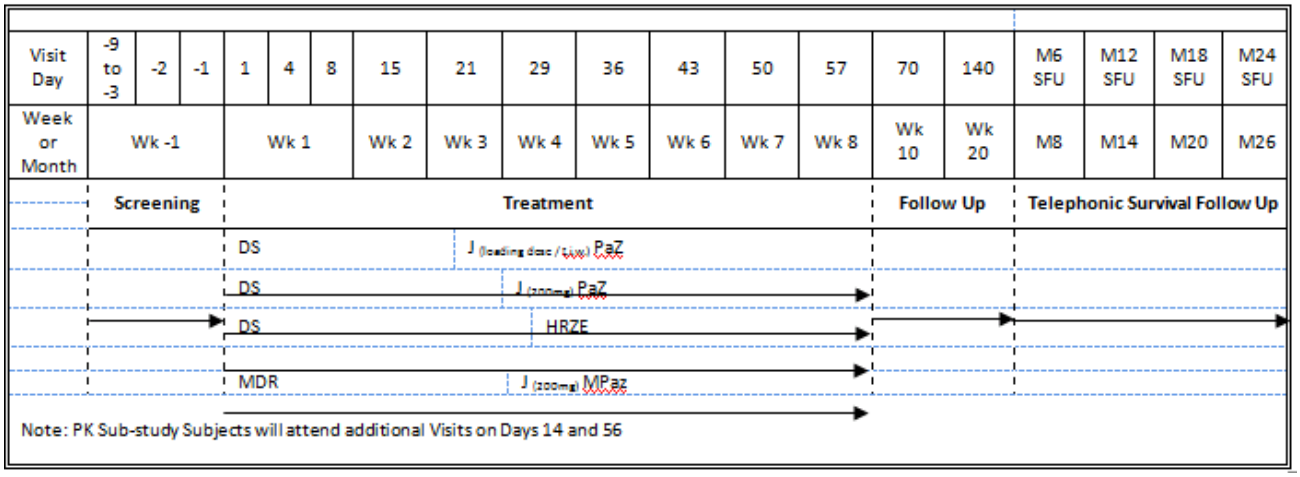
	Treatment Group	Patient Population	Number of Patients
1.	$J_{(loading\ dose/t.i.w.)}PaZ$	DS-TB	60
2.	$J_{(200\ mg)}PaZ$	DS-TB	60
3.	HRZE	DS-TB	60
4.	$J_{(200\ mg)}MPaZ_{MDR}$	MDR-TB	Up to 60

DS: Drug-sensitive. MDR: Multi-drug resistant. TB: Tuberculosis.

A schematic of study design is presented below.

Fifteen (15) patients from each of the treatment groups will be included in a PK sub-study, for whom intense-sampling will be performed on Day 14 and Day 56.

Study Schematic



3.2 Schedule of Events

The schedule of events can be found in Section 1.2 of the protocol.

3.3 Changes to Analysis from Protocol

There are no changes to analyses from the protocol.

4 Planned Analyses

The following analyses will be performed for this study:

- Data Safety and Monitoring Committee (DSMC) analysis.
- Snapshot analysis.
- Final analysis.
- Survival follow-up analysis.

4.1 Data Safety and Monitoring Committee (DSMC) Analysis

A DSMC analysis will be performed by Quintiles Biostatistics after 10 MDR patients have completed 2 weeks of treatment.

A DSMC analysis will be performed by Quintiles Biostatistics once 33% of the patients have completed the 8-week treatment period.

The DSMC analyses will be described in the DSMC charter and separate output templates.

4.2 Snapshot Analysis

A snapshot analysis, based on the analysis of a subset of efficacy, safety (including electrocardiogram [ECG]), pncA sequencing and mycobacteriology characterization endpoints, will be performed after the last DS-TB patient has completed the 8-week treatment period and Day 70/Follow-up, and the safety (including ECG), TTP and CFU are available. Adverse events (AEs) and serious adverse events (SAE) will also be analyzed for the snapshot analysis.

The database snapshot will occur after the last DS-TB patient has completed the 8-week treatment period and Day 70/Follow-up. The aforementioned data (excluding ophthalmology, drug susceptibility, minimum inhibitory concentration [MIC] data, and final analysis AEs, SAEs) will be soft locked for the database snapshot. The ophthalmology, drug susceptibility data and final analysis AEs, SAEs and concomitant medications, will only be available at the time of final analysis database lock, and will therefore not form part for the snapshot analysis.

The snapshot analysis as described in this SAP, using table, data listing and figure (TLF) shells (to be outlined in a separate output templates document), will be performed by Quintiles Biostatistics following database snapshot.

4.3 Final Analysis

The final analysis as described in this SAP, using TLF shells (to be outlined in a separate output templates document), will be performed by Quintiles Biostatistics following final analysis database lock of data for all patients (DS-TB and MDR-TB). The ophthalmology, drug susceptibility data and final analysis AEs, SAEs and concomitant medications, will be completed by the time of final analysis database lock, and will therefore only be included in the final analysis.

Final analysis database lock will occur after completion of the Day 140 follow-up visit, or 12 weeks following last study drug administration (and the CFU and TTP data are available), and after the ophthalmology, drug susceptibility data and final analysis AEs, SAEs and concomitant medications are available.

PK and MIC data will only be available after final analysis database lock and will therefore form part of an appendix to the final analysis.

Data associated with the survival follow-up analysis (survival follow-up data, AEs, SAEs and concomitant medications) will not be included in the final analysis.

4.4 Survival Follow-Up Analysis

The survival follow-up analysis (which will include survival follow-up data, AEs, drug-related SAEs and concomitant medications [associated with drug-related SAEs only]) will be included as an addendum to the clinical study report (CSR) of the final analysis. Relevant sections of the database will accordingly be reopened to include survival follow-up data, AEs, SAEs and concomitant medications. The database will accordingly be relocked afterwards.

5 Analysis Populations

Agreement and authorization of patients included/excluded from each analysis population (for both the snapshot and final analysis) will be reached (data review meeting) prior to the database snapshot and final analysis database lock, respectively. The criteria defining the various analysis populations will be outlined in a separate data review plan.

Pyrazinamide resistant patients will be excluded from the general efficacy analyses (applicable to both DS-TB and MDR-TB patients), except from the exploratory analyses associated with the comparison according to pyrazinamide resistant versus sensitive status in MDR-TB patients.

Note: Patients' pyrazinamide susceptibility status at baseline, applicable to the snapshot analysis, will be determined using pncA sequencing data only. For the final analysis, both pncA sequencing and MGIT data will be used to determine the latter. That is, pncA sequencing will be used as the primary determinant, but, should the pncA sequencing data be missing at the time of the final analysis, the MGIT data will be used to determine the latter instead.

For the purpose of analyses based on each of the analysis populations, patients will be classified according to actual study drug received, regardless of randomized/assigned study drug.

Note: Statistical analyses will not necessarily be performed for all of the below analysis populations. Analyses populations applicable to a certain analysis will be mentioned explicitly within the particular analysis sections of this document.

5.1 All Patients Screened

This analysis population will include all patients who provided written informed consent for this study.

Screening failures (i.e. patients not randomized/assigned to study drug) will be included in this analysis population.

The main purpose of this analysis population is to list disposition data of all patients enrolled in the study.

5.2 All Patients Randomized/Assigned to Study Drug

This analysis population will include all patients screened that were randomized to study drug (for the DS patient population) or assigned to study drug (for the MDR patient population).

The main purpose of this analysis population is to limit data listings to all patients randomized/assigned to study drug (thus excluding those patients who are [1] either screening failures or [2] "passed" screening but were not randomized/assigned to study drug).

5.3 Safety Analysis Population

This analysis population will include all patients who were randomized to study drug (for the DS patient population) or assigned to study drug (for the MDR patient population) and received at least one administration of study drug.

If there is any doubt whether a patient was treated or not, the patient will be assumed treated for the purposes of this analysis.

The main purpose of this analysis population is to summarize safety data for patients who were, during the course of the study, exposed to study drug.

5.4 Modified Intention-to-Treat (mITT) Analysis Population

This analysis population will contain all patients included in the Safety analysis population for whom valid corresponding efficacy data are available. Pyrazinamide resistant patients will be excluded from this analysis population (applicable to both DS-TB and MDR-TB patients).

The main purpose of this analysis population is to summarize efficacy data for patients based on the intention-to-treat principle, however modified by excluding those patients for whom no valid corresponding data are available, and also excluding those patients who are resistant to pyrazinamide.

5.5 Multi-Drug Resistant Tuberculosis (MDR-TB) Exploratory Analysis Population

This analysis population will contain all MDR-TB patients included in the Safety analysis population for whom valid corresponding efficacy data are available. Pyrazinamide resistant patients will be considered for this analysis population (provided that their pyrazinamide susceptibility status at baseline is available).

The main purpose of this analysis population is to compare efficacy data between pyrazinamide sensitive versus pyrazinamide resistant MDR-TB patients.

6 General Considerations

6.1 Reference Start Date and Study Day

Study day will be calculated from the reference start date which will be used to present start/stop day of assessments and events.

The reference start date is defined as the date of first study drug administration:

- If the date of assessment/event is on or after the reference date then:
  - Study day = (Date of assessment/event – Reference date) + 1.
- If the date of assessment/event is prior to the reference date then:
  - Study day = (Date of assessment/event – Reference date).

In the case where the assessment/event date is partial or missing, for which no imputation rules apply, study day, and any corresponding durations will be presented as missing in the data listings.

6.2 Baseline

Baseline is defined as the last available observation (scheduled or unscheduled) before the first study drug administration.

For analysis purposes, a separate baseline visit will be presented for each patient, where applicable.

6.3 End of Treatment Period

For the purpose of defining treatment-emergent events the end of treatment visit is defined as the last available observation (scheduled or unscheduled) made after the first study drug administration up to and including the Day 70 Follow-up visit (or up to and including 14 days after last study drug administration for patients not having the Day 70 Follow-up visit).

6.4 End of Study

The end of study visit is defined as the last available observation (scheduled or unscheduled) made after the first study drug administration.

6.5 Treatment-Emergent Incidences

A treatment-emergent incidence is defined as any event (scheduled or unscheduled) which started after the first study drug administration up to and including the Day 70 Follow-up visit (or up to and including 14 days after last study drug administration for patients not having the Day 70 Follow-up visit).

A post-treatment incidence during the Day 70-140/Follow-up period is defined as any event (scheduled or unscheduled) which started after the Day 70 follow-up visit up to the last visit, early study withdrawal or last contact associated with the Day 140/Follow-up period, as indicated on the 'Disposition' eCRF page, whichever occurs last.

Events recorded during the survival follow-up period will be reported separately.

6.6 Retests, Unscheduled Visits and Early Termination Data

In general, data recorded at the scheduled visit will be presented for by-visit summaries. Unscheduled measurements will not be included in by-visit summaries. Exception: The last available unscheduled laboratory assessment corresponding to screening assessments will be used for the Day -9 to Day -3 visit of all analyses. Unscheduled visits will be sorted in a chronological order, and the associated scheduled visit number will accordingly be provided in the data listings (e.g. Visit number X.Y for the Y^{th} unscheduled visit number associated with the X^{th} scheduled visit number).

In the case of a retest, the last available laboratory assessment will be used for all analyses, including identification of markedly abnormal laboratory assessments, regardless of whether the laboratory assessment for that particular scheduled visit is available or not.

In the case of a retest, the last available assessment will be used for all analyses.

Data listings will include scheduled, unscheduled and retest data.

6.7 Windowing Conventions

No visit windowing (i.e. remapping of visits based on visit windows, except for unscheduled visits associated with the Day -9 to Day -3 visit) will be performed for this study. The assigned scheduled visit will be used for by-visit summaries.

6.8 Statistical Tests

The default significance level is set at 5%. All confidence intervals (CIs) (95%) and statistical tests will be two-sided, unless otherwise specified.

No multiplicity adjustments will be done for this study.

6.9 Common Calculations

For quantitative measurements, change from baseline will be calculated as: (Value at Visit X – Baseline value).

For numerical values > 0 where the logarithmic transformation is required, the logarithm value will be calculated as: $\log_{10}$(Value).

6.10 Software Version

All analyses will be conducted using SAS® Version 9.4, OpenBUGS Version 3.1.2 (or higher) and R Version 3.0.2 (or higher).

7 Statistical Considerations

7.1 Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. Randomization to treatment groups is not stratified by country/site, and therefore, all analyses will be unstratified. However, subgroup analyses will be included by site (see Section 7.3).

7.2 Missing Data

Missing data will not be imputed for this study, unless otherwise specified.

7.3 Examination of Subgroups

A subset of patients from each treatment group will be included in a PK sub-study.

Subgroup analyses by site, laboratory, human immunodeficiency virus (HIV) status and absence or presence of cavities, will be performed for key efficacy analyses (see Section 15.1.5).

The CFU and TTP data will be analyzed for patients assigned to $J_{(200\ mg)}MPaZ_{MDR}$ according to their pyrazinamide susceptibility status at baseline (sensitive versus resistant). In addition, the analysis will be repeated for patients assigned to HRZE who are mono-resistant to isoniazid according to their susceptibility status at baseline.

8 Output Presentations

Appendix 2 contains conventions for presentation of data in TLFs.

Summary tables will be presented by treatment group, unless otherwise specified.

The shells to be provided in the separate output templates document will describe the format and content for presentation of TLFs, for the snapshot, final and survival follow-up analyses. The TLFs not to be provided for the snapshot analysis will be marked with an asterisk (*).

All percentages (%) calculated for a specific summary are calculated using the total number of patients included in the relevant analysis population with data, as the denominator, unless otherwise specified.

By default, descriptive statistics will include the number of patients (n), mean, standard deviation (SD), minimum, median and maximum for quantitative measurements.

9 Disposition and Withdrawals

9.1 Derivations

Disposition events of the Day 140 Follow-up period will take into account the last status of the patient up until Day 140. This will include the status of patients who withdrew consent before Day 140, patients who were not required to attend the Day 140 visit (received less than 15 days of treatment), patients who withdrew from treatment but continued into follow up, or patients that died before the Day 140 visit.

9.2 Analysis

Patient disposition and withdrawals up to Day 140 (obtained from the electronic case report form [eCRF] “Subject Disposition Up to D140” panel) will be summarized and presented in data listings for all patients screened.

Patient disposition and withdrawals for the Survival Follow-Up period (obtained from the electronic case report form [eCRF] "Subject Disposition Survival FU" panel) will be summarized and presented in data listings for all patients screened for the survival follow-up analysis.

The number of patients included in the relevant analysis populations, as well as the number of patients excluded with reasons for exclusion from the relevant analysis populations and protocol violations/deviations, will be summarized for patients randomized/assigned to study drug. Major protocol deviations during study conduct will be presented in data listings for all patients randomized/assigned to study drug.

10 Demographic and Other Baseline Characteristics

10.1 Derivations

Age (Years) and body mass index (BMI) (kg/m^2) will be calculated as follows:

Age (Years) = Floor of ([Date of informed consent – Date of birth]/365.25).
BMI (kg/m^2) = Weight (kg)/([Height {cm}/100]^2).

Human immunodeficiency virus (HIV) duration (Years) will be calculated as follows:

HIV duration (Years) = Floor of ([Date of first administration of study drug – Date of HIV diagnosis]/365.25).

Tuberculosis (TB) duration (Days) will be calculated as follows:

TB duration (Days) = Floor of (Date of first administration of study drug – Date of TB diagnosis).

If the date of birth, HIV or TB diagnosis is partial, then the date of birth, HIV or TB diagnosis will be imputed as follows:

- If the day of birth, HIV or TB diagnosis is missing, then the 15th day of the month will be used as the day of birth, HIV or TB diagnosis.
- If the month of birth, HIV or TB diagnosis is missing, then 02JUL will be used as the day and month of birth, HIV or TB diagnosis (i.e. the 183rd day of the year).

The imputed date of birth, HIV or TB diagnosis will not be presented in the data listings and will only be used for the calculation of age (Years), HIV duration (Years) and TB duration (Days).

10.2 Analysis

Demographic data and other baseline characteristics will be summarized for the Safety and mITT analysis populations, and presented in data listings for all patients screened. Summary tables will only be displayed if at least 10 percent of patients fall within the specific analysis population.

The following demographic and other baseline characteristics will be summarized and presented in data listings:

- Age (Years).
- Gender.
- Race.
- Site.
- HIV status:
  - Negative.
  - Positive.
- HIV duration (Years).

- Antiretrovirals (ARVs).
- TB type.
- TB duration (Days).
- Karnofsky performance score (%).
- Ophthalmology history:
  - Personal history of vision or eye disorders.
  - Immediate family history of cataracts.
  - Personal history of prior eye surgery.
  - Eye trauma (right and left eye).
- Height (cm).
- Weight (kg).
- BMI (kg/m^2).
- Chest X-ray:
  - Normal.
  - Abnormal.
  - Cavities:
    - No cavities.
    - Unilateral.
    - Bilateral.

Tuberculosis (TB) and HIV history, and TB symptoms, will be presented in data listings.

11 Medical and Treatment History (Excluding Human Immunodeficiency Virus [HIV], Tuberculosis [TB] and Ophthalmology History)

11.1 Derivations

Medical history (excluding HIV, TB and ophthalmology history) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 17.1.

Uncoded medical history events will be presented as “uncoded”.

11.2 Analysis

Medical history (excluding HIV, TB and ophthalmology history) will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT) for the Safety analysis population and presented in data listings for all patients screened.

12 Concomitant Medications and Procedures

12.1 Derivations

Concomitant medications will be coded using World Health Organization-Drug Dictionary (WHO-DD) 01JUN2014_CLASSIC, whereas procedures will be coded using MedDRA central coding dictionary, Version 17.1. Preferred Anatomical Therapeutic Chemical (ATC) coding will be applied to medications for this study.

Uncoded concomitant medications and procedures will be presented as “uncoded”.

12.2 Analysis

Concomitant medications will be summarized by WHO-DD ATC Level 4, whereas procedures will be summarized by MedDRA SOC and PT for the Safety analysis population, and presented in data listings for all patients screened. Concomitant medications are defined as medications which started 30 days prior to the first study drug administration or during the study up to the Day 70 Follow-up visit.

Concomitant medications which started during the survival follow-up period will be listed separately.

13 Study Drug Exposure

13.1 Derivations

The date of first study drug administration will be derived as the first dosing date from the investigational medicinal product (IMP) administration eCRF page. The date of last study drug administration will be obtained from "Date of Last Dose of IMP" from the patient disposition eCRF page.

Interruptions, compliance, and dose changes will not be taken into account for the purpose of calculating the duration of exposure.

Duration of exposure (days) = (Date of last study drug administration – Date of first study drug administration) + 1.

13.2 Analysis

Exposure to study drug will be summarized for the Safety and mITT analysis populations, and presented in data listings for all patients randomized/assigned to study drug.

14 Study Drug Compliance

14.1 Derivations

The number of doses missed will be obtained from the missed doses eCRF page.

The expected number of doses taken will be calculated as the duration of exposure, as a patient is dosed daily.

The actual number of doses taken will be calculated as the difference between the expected number of doses taken and the number of doses missed.

Overall compliance to study drug will be calculated as follows: Compliance to study drug (%) = 100 × (Actual number of doses taken/Expected number of doses taken).

Compliance to study drug will be categorized as follows:

- < 80%.
- ≥ 80%.

The following example is given for illustrative purposes:

Example: A patient in the HRZE treatment group for 7 days on treatment is expected to have 7 doses. From the eCRF it is noted that he missed 2 doses in total (which may have been at different visits). Compliance to study drug for this patient is then calculated as 71.43% ([5/7] × 100).

14.2 Analysis

Compliance to study drug (i.e. not by visit interval, but over the whole of the treatment period) will be summarized for the Safety and mITT analysis populations, and presented in data listings for all patients randomized/assigned to study drug.

15 Efficacy Analysis

Three types of media, namely liquid media and **7H11S** and **7H11S+C** solid media, will be used to grow cultures collected from overnight and coached spot sputum samples. Cultures collected after Day 60 (relative to first study drug administration) will be excluded from the statistical analysis of efficacy data.

15.1 Primary Efficacy Variable

15.1.1 Derivations

TTP in Liquid Media: Overnight Sputum Samples

The primary efficacy variable is log(TTP) over time (derived from TTP results in liquid media) collected from overnight sputum samples. The logarithm of the TTP result per timepoint will be calculated as follows:

$$\log(\text{TTP}) = \log(\text{TTP/hours}) = \log_{10}(\text{TTP result}).$$

log(TTP) collected before the first study drug administration (Day -2 and Day -1) will be used as log(TTP) at Day 0.

In addition, the TTP result can be categorized as follows:

Terminology: TTP Results

Terminology for TB Culture	Description
Contaminated: "MTC present with contamination" or "positive for Mycobacterium tuberculosis complex and contaminated" or "contaminated" or "positive for AFB growth and contaminated"	Sputum culture reported as positive; a positive result from a blood agar test suggests that contamination is present. A Ziehl-Neelsen smear is subsequently performed to determine whether AFB is present, showing that the culture was positive for TB, regardless of the sample's contamination status. The numeric TTP result associated with this terminology is indicated as "no result" or "-".
"No result" or NA"	No processing done, or other problems associated with the calculation of TTP. The numeric TTP result associated with this terminology is indicated as "no result" or "-".
Negative: "MTC negative" or "negative for Mycobacterium tuberculosis complex"	After 42 days incubation, no growth is reported in the tube. The numeric TTP result associated with this terminology is indicated as "no result" or "-".
Unable to produce	If indicated that "patient was unable to produce sputum". The numeric TTP result associated with this terminology is indicated as "no result" or "-".

Terminology for TB Culture	Description
Positive: "MTC present" or "positive for Mycobacterium tuberculosis" or "positive for AFB growth"	Positive MGIT culture and negative blood agar suggest that a true positive culture, with no influence from contaminants, is present. The numeric TTP result associated with this terminology is indicated in days or hours.

AFB: Acid-fast bacilli; MGIT: Mycobacterial growth indicator tube; NA: Not applicable; TB: Tuberculosis; TTP: Time to positivity.

Numeric TTP results (associated with "positive" results) reported as "> 1008 hours" will be considered as "negative" results.

The following rules and conventions will apply for the handling of the aforementioned categories:

- **Contaminated/Unable to produce:** The TTP results associated with "contaminated" or "unable to produce" samples will be set to missing.
- **No result or not applicable (NA):** The TTP results will be set to missing in the case of "no result" or NA. Specifically, log(TTP) of patients who withdrew early from the study will not be imputed, and will therefore be treated as missing.
- **Negative:** The TTP results associated with "negative" sample results will be right-censored at 600 hours or the maximum observed TTP in the study, whichever is greatest.

15.1.2 Efficacy Endpoints

Rate of Change in TTP: Overnight Sputum Samples

The primary efficacy endpoint is the rate of change in log(TTP) collected from overnight sputum samples, over 8 weeks of treatment, i.e. the bactericidal activity of log(TTP) over Day 0 to Day 56 (or $BA_{TTP}[0\text{-}56]$).

For a given patient, $\mathrm{BA_{TTP}}(t_1 - t_2)$ from Day t_1 to Day t_2 is expressed as follows:

$$\mathrm{BA_{TTP}}(t_1 - t_2) = 100 \cdot \left(10^{\left[\frac{\hat{f}(t_2)-\hat{f}(t_1)}{t_2-t_1}\right]} - 1\right) \tag{15.1}$$

where $\hat{f}(t_1)$ and $\hat{f}(t_2)$ represent the model-fitted log(TTP) at Day t_1 and Day t_2, respectively, as calculated by the regression of observed log(TTP) over time. Here, $\mathrm{BA_{TTP}}(\mathrm{t_1 - t_2})$ represents the daily percentage change in TTP from Day t_1 to Day t_2.

Secondary efficacy endpoints (based on the primary efficacy variable) include $\mathrm{BA_{TTP}}$(0-2) and $\mathrm{BA_{TTP}}$(14-56) collected from overnight sputum samples over 8 weeks of treatment.

15.1.3 Primary Efficacy Analysis

Regression Analyses:

The following Bayesian non-linear mixed effects (NLME) regression model (Burger, D.A. and Schall, R., 2015) will be fitted to log(TTP) collected from overnight sputum samples, observed from Day 0 to Day 56, of all patients jointly included in the mITT analysis population:

$$y_{ijk} = \alpha_{ij} + \beta_{1ij} t_{ijk} + \beta_{2ij}\gamma_j \log\left(\frac{\exp\left[\frac{t_{ijk}-\kappa_j}{\gamma_j}\right]+\exp\left[-\frac{t_{ijk}-\kappa_j}{\gamma_j}\right]}{\exp\left[\frac{\kappa_j}{\gamma_j}\right]+\exp\left[-\frac{\kappa_j}{\gamma_j}\right]}\right) + e_{ijk} \tag{15.2}$$

where $\alpha_{ij} = \alpha_j + u_{0ij}$, $\beta_{1ij} = \beta_{1j} + u_{1ij}$ and $\beta_{2ij} = \beta_{2j} + u_{2ij}$, y_{ijk} represents log(TTP) for patient $i = 1, \ldots, N_j$ in treatment group $j = 1, \ldots, J$ at timepoint $k = 1, \ldots, K_{ij}$ and t_{ijk} is the corresponding time. u_{0ij}, u_{1ij} and u_{2ij} denote random coefficients for patient i assigned to treatment j and e_{ijk} is the random error term at time t_{ijk} of patient i assigned to treatment group j.

The random coefficients α_{ij}, $\lambda_{1ij} = (\beta_{1ij} - \beta_{2ij})$ and $\lambda_{2ij} = (\beta_{1ij} + \beta_{2ij})$ can be interpreted as the intercept and rate (or slope) parameters during the initial and terminal phase of the treatment period, respectively.

For the prevention of numerical overflow, the regression model will be fitted with the times (sample days) t_{ijk} expressed in weeks.

Let $\boldsymbol{\mu_{ij}}$ denote the vector of random coefficients $(\alpha_{ij}, \beta_{1ij}, \beta_{2ij})'$, which is assumed to be independent and identically distributed (*i.i.d.*) as follows:

$$\boldsymbol{\mu_{ij}} \sim N_3(\boldsymbol{\mu_j}, \boldsymbol{\Omega_{\mu j}}) \tag{15.3}$$

where $\boldsymbol{\mu_j} = (\alpha_j, \beta_{1j}, \beta_{2j})'$ and $\boldsymbol{\Omega_{\mu j}} = \begin{bmatrix} \sigma^2_{\alpha_j} & Cov_j(\alpha_{ij}, \beta_{1ij}) & Cov_j(\alpha_{ij}, \beta_{2ij}) \\ Cov_j(\alpha_{ij}, \beta_{1ij}) & \sigma^2_{\beta_{1j}} & Cov_j(\beta_{1ij}, \beta_{2ij}) \\ Cov_j(\alpha_{ij}, \beta_{2ij}) & Cov_j(\beta_{1ij}, \beta_{2ij}) & \sigma^2_{\beta_{2j}} \end{bmatrix}$.

In order to complete the Bayesian specification of the regression model, proper prior distributions will be assigned to all unknown parameters. The values of the hyper parameters will be chosen in such a way to assure vagueness with regard to prior belief on the parameters.

The prior distributions for $\boldsymbol{\mu_j}$ and $\boldsymbol{\Omega_{\mu j}}$ will be assumed to follow a multivariate normal and Wishart distribution, respectively, namely:

$$\boldsymbol{\mu_j} \sim N(\mathbf{0}, 10^4 \times \boldsymbol{I_3}) \tag{15.4}$$

$$\boldsymbol{\Omega_{\mu j}^{-1}} \sim W(3, 3 \times \boldsymbol{R_j}) \tag{15.5}$$

where $\mathbf{0} = (0, 0, 0)'$ and $\boldsymbol{I_3}$ denotes a 3×3 identity matrix, and $\boldsymbol{R_j}$ represent 3×3 inverse scale matrices.

Here, $\boldsymbol{R_j}$ will be derived by fitting the model as a linear mixed effects regression model under the assumption that the node and smoothness parameters are fixed at $\kappa_p = \frac{(11+3)}{2\times7} = 1$ and $\gamma_p = \frac{(2+0.05)}{2} = 1.025$, respectively. Accordingly, the estimates for $\boldsymbol{\Omega_{\mu j}}$ will be calculated using the methodology by Vaida and Liu (2009), to serve as $\boldsymbol{R_j}$. The linear mixed effects regression model (incorporating censoring) will be fitted using the "lmec" library of the R project.

The parameters κ_j, γ_j and $\sigma^2_{\kappa j}$ are assumed to follow uniform distributions, namely:

$$\kappa_j \sim U\left(\frac{3}{7}, \frac{11}{7}\right) \tag{15.6}$$

$$\gamma_j \sim U(0.05, 2) \tag{15.7}$$

Here, γ_j govern the "smoothness" or "speed" of the transition from one rate (or slope) to another, whereas κ_j can be viewed as the nodes at which the regression functions transition from one rate (or slope) to another.

Finally, the parameters σ^2_{ej} are assumed to follow an inverse gamma distribution, namely:

$$\sigma^2_{ej} \sim IG(10^{-4}, 10^{-4}) \tag{15.8}$$

With the regression model described above, the node parameters κ_j are restricted to the range $\frac{3}{7}$ to $\frac{11}{7}$ weeks. The "smoothness" parameters γ_j are restricted to the range 0.05 to 2. The level at which a given log(TTP) is censored will be taken into account (therefore treating the log[TTP] result as censored). Adjustment to the regression model will be made should the data not be optimally fitted using the specified bounds of the node parameter.

The Markov Chain Monte Carlo (MCMC) Gibbs sampling algorithm will be used to draw samples from the joint posterior distribution of the preceding regression model parameters. The MCMC Gibbs sampler is an algorithm based on drawing from the full conditional posterior distributions of each regression model parameter, conditional on the latest values of the remaining parameters in the regression model. Samples drawn from the full conditional posterior distributions have been shown to approximate samples from that of each regression model parameter's unconditional joint posterior distribution once convergence has been reached. The OpenBUGS software will be used to carry out the MCMC Gibbs sampling procedure.

Given that the regression model is quite complex (as it incorporates a large number of regression parameters) good starting values should be used to expedite convergence of the MCMC algorithm. The corresponding regression model's individual (per patient) parameter estimates, obtained from the SAS® procedure PROC NLMIXED, can be used as starting values for the regression model's random coefficients. The first Q observations need to be omitted from the T simulated observations, as the first Q observations may be invalid due to poor convergence during the initial stage (simulation "burn-in"). Graphical convergence diagnostics, such as iteration and autocorrelation plots, will be used to monitor convergence of the regression model's posterior samples. The posterior samples may be thinned to reduce the autocorrelation amongst posterior samples. For additional validation of the convergence of posterior samples, multiple chains of posterior samples, each with different sets of starting values, may be simulated.

Posterior estimates and corresponding 95% Bayesian credibility intervals (BCIs) for the mean $BA_{TTP}(0\text{-}56)$, including pairwise comparisons, will be presented accordingly in summary tables and figures for the mITT analysis population.

15.1.4 Secondary Efficacy Analyses

Regression Analyses:

log(TTP) over time will be summarized descriptively for each collection visit for the mITT analysis population. Here, censored log(TTP) will be imputed with the level at which they are censored. The actual TTP results will be presented in data listings for all patients randomized/assigned to study drug.

From the analysis described in Section 15.1.3, posterior estimates and corresponding 95% BCIs for the mean BA_{TTP}(0-2) and BA_{TTP}(14-56), including pairwise comparisons, will be presented accordingly in summary tables and figures for the mITT analysis population. Similarly, the aforementioned will be presented for the mean regression parameters and future regression slopes $\beta_{2fj} = \beta_{2j} + u_{2fj}$ (where the subscript f stands for "future") in summary tables for the mITT analysis population. The individual (per patient) BA_{TTP}(0-56), BA_{TTP}(0-2) and BA_{TTP}(14-56) estimates will be summarized by descriptive statistics and presented in figures and data listings (including individual regression model parameters) for the mITT analysis population. Data listings and plots of the observed and model-fitted log(TTP) over time will be presented accordingly for all patients randomized/assigned to study drug, and the mITT analysis population, respectively. These data of patients who are resistant to pyrazinamide and mono-resistant to isoniazid (according to their susceptibility status at baseline) will be flagged in data listings. The level at which log(TTP) is censored will be indicated in the relevant data listings and figures. The posterior estimate and corresponding 95% BCI of the mean log(TTP) for each sample day will be presented by treatment group on an individual (per patient) basis (summary tables; separate graphs per treatment group) for the mITT analysis population. The posterior estimate of the mean log(TTP) for each sample day will be presented by treatment group on an overall basis (combined graph for all treatment groups) for the mITT analysis population.

In order to establish whether patients with higher bacterial load at Day 0 (i.e. α_{ij}) are associated with higher initial and terminal rates of decline in log(TTP) (i.e. λ_{1ij} and λ_{2ij}, respectively) and similarly, to establish whether higher rates of decline during the initial phase (i.e. λ_{1ij}) are associated with higher terminal rates of decline (i.e. λ_{2ij}), or *vice versa*. That is, posterior samples of correlation coefficients between random intercepts and slopes, i.e. $\rho_{\alpha_j\lambda_{1j}}$, $\rho_{\alpha_j\lambda_{2j}}$and $\rho_{\lambda_{1j}\lambda_{2j}}$, can be obtained, and will be presented in summary tables for the mITT analysis population, e.g.:

$$\rho_{\alpha_j\lambda_{1j}} = \frac{Cov_j(\alpha_{ij}, \lambda_{1ij})}{\sqrt{Var_j(\alpha_{ij})Var_j(\lambda_{1ij})}} = \frac{Cov_j(\alpha_{ij}, \beta_{1ij}) - Cov_j(\alpha_{ij}, \beta_{2ij})}{\sqrt{\sigma^2_{\alpha_j}\left(\sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} - 2Cov_j[\beta_{1ij}, \beta_{2ij}]\right)}} \quad (15.9)$$

$$\rho_{\alpha_j\lambda_{2j}} = \frac{Cov_j(\alpha_{ij}, \lambda_{2ij})}{\sqrt{Var_j(\alpha_{ij})Var_j(\lambda_{2ij})}} = \frac{Cov_j(\alpha_{ij}, \beta_{1ij}) + Cov_j(\alpha_{ij}, \beta_{2ij})}{\sqrt{\sigma^2_{\alpha_j}\left(\sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} + 2Cov_j[\beta_{1ij}, \beta_{2ij}]\right)}} \quad (15.10)$$

$$\rho_{\lambda_{1j}\lambda_{2j}} = \frac{Cov_j(\lambda_{1ij}, \lambda_{2ij})}{\sqrt{Var_j(\lambda_{1ij})Var_j(\lambda_{2ij})}} = \frac{\sigma^2_{\beta_{1j}} - \sigma^2_{\beta_{2j}}}{\sqrt{\left(\sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} - 2Cov_j[\beta_{1ij}, \beta_{2ij}]\right)\left(\sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} + 2Cov_j[\beta_{1ij}, \beta_{2ij}]\right)}} \quad (15.11)$$

15.1.5 Exploratory Efficacy Analyses

Regression Analyses:

The regression model in Section 15.1.3 will be fitted using interaction terms for site, laboratory, HIV status (see Section 10), presence or absence of cavities (see Section 10) and treatment group for the mITT analysis population. For each interaction term, separately for site and treatment group, and HIV status and treatment group, posterior estimates and corresponding 95% BCIs for the mean BA_{TTP}(0-56) will be presented accordingly in summary tables for the mITT analysis population.

The regression model in Section 15.1.3 and Section 15.1.4 will be fitted by comparing patients according to their pyrazinamide susceptibility status at baseline (sensitive versus resistant) for the MDR-TB exploratory analysis population. This analysis may be performed for DS-TB patients on an ad-hoc basis if sample size warrants.

The regression analyses described in Section 15.1.3 and Section 15.1.4 will be repeated for patients assigned to HRZE included in the mITT analysis population who are mono-resistant to isoniazid according to their susceptibility status at baseline if sample size warrants.

15.1.6 Sensitivity Efficacy Analyses

Regression Analyses:

The regression model in Section 15.1.3 can incorporate the assumption that the residual errors and random intercept and slope parameters follow *i.i.d.* (multivariate) Student t distributions, respectively, i.e.:

$$e_{ijk} \sim T\left(0, \sigma_{ej}^2, v_j\right) \tag{15.12}$$

$$\boldsymbol{\mu_{ij}} \sim T_3\left(\boldsymbol{\mu_j}, \boldsymbol{\Omega_{\mu j}}, w_j\right) \tag{15.13}$$

where $\sigma_{ej}^2 \sim IG(10^{-4}, 10^{-4})$ and $\boldsymbol{\Omega_{\mu j}^{-1}} \sim W\left(3, 3 \times \boldsymbol{R_j}\right)$ are scale parameters and matrices, respectively, and v_j and w_j represent the corresponding degrees of freedom.

The parameters v_j and w_j are assumed to follow uniform distributions, namely:

$$v_j \sim U(2{,}100) \tag{15.14}$$

$$w_j \sim U(2, 100) \tag{15.15}$$

The specification of the Student t distribution for both random coefficients (intercepts and slopes) and residual errors may provide a more robust modeling approach for outliers in any of the latter components of the given model. The analyses described in Section 15.1.3 and Section 15.1.4, excluding the correlation analysis between random coefficients, will be repeated for the mITT analysis population using the regression model which incorporates the specification of the Student t distribution.

15.2 Secondary Efficacy Variables

15.2.1 Derivations

15.2.1.1 CFU Count in Solid Media: "7H11S" Overnight Sputum Samples

Secondary efficacy variables include log(CFU) count over time, derived from CFU counts per mL collected from "**7H11S**" overnight sputum samples. log(CFU) counts will be calculated as follows:

$$\log(\text{CFU}) = \log(\text{CFU/mL}) = \log_{10}(\text{Mean of four CFU plate counts} \times \text{factor} \times 10^{\text{dilution}})$$

In the above formula, the "factor" compensates for the dilution of the specimens during the culture process, converting the result back to the actual CFU count per milliliter. The factor will respectively be set to 20 and 11 for samples associated with equal and 10% Sputasol volumes. The CFU calculations/determinations will be done for both types of media separately.

The four CFU plate counts associated with a given sputum sample will consist of two CFU counts from two different plates.

All log(CFU) counts collected before the first study drug administration (Day -2 and Day -1) will be used as the log(CFU) counts at Day 0.

Furthermore, results from the four CFU plate counts will be categorized as follows:

Terminology: CFU Counts

Terminology for TB Culture	Description
"Contaminated" or "CU" (contaminated and unreadable)	Plate overgrown with contaminants (CFU counts therefore not available).
"No result" or "NA"	No processing done, or other problems associated with the calculation of CFU counts.
"CR (contaminated but readable)/"n" or CR/"TNTC"	Plate overgrown with contaminants but CFU counts readable.
Zero ("0")	No growth on the plate.
TNTC (≥ 200 colonies)	Too numerous to count.
Unable to produce	If indicated that "patient was unable to produce sputum".
Numerical value	The CFU count equivalent to the number of colonies recorded as a numerical value. A numerical value will also be recorded for "CR/n" where "n" will be the number of colonies.

CFU: Colony forming unit; NA: Not applicable.

For a given sputum sample, if "0" is reported for one of the two plates, and a result other than "0" is reported for the other plate, then the average of zero ("0") and of the (non-zero) count for the second plate will be used for the calculation of log(CFU) count.

Similarly, for a given sputum sample, if "TNTC (≥ 200 colonies)" is reported for one of the two plates, and a result other than "TNTC" is reported for the other plate, then the average of a count of 200 ("TNTC [≥ 200 colonies]") and of the (non-zero) count for the second plate will be used for the calculation of log(CFU) count.

If the CFU counts for one of the two plates are reported as "contaminated" or "no result", and a result other than "contaminated" or "no result" is reported for the other plate, then the CFU counts of the second plate will be used for the calculation of log(CFU) count.

The following rules and conventions will apply for the handling of the aforementioned categories:

- **Contaminated or CU (contaminated and unreadable):** The CFU counts associated with contaminated or "contaminated and unreadable" samples will be set to missing.
- **No result (unable to produce/sample leaked/sample not collected) or NA:** The CFU counts will be set to missing in the case of "no result" or "NA". Specifically, all missing log(CFU) counts due to early withdrawal from the study (see Section 9) will not be imputed, and will therefore be treated as missing.
- **CR/"n" (Contaminated but readable) or CR/TNTC:** For CFU counts associated with "contaminated but readable" or "CR/TNTC", the CFU count recorded in the "n" value of the field will be considered for analysis. log(CFU) count associated with a result of "TNTC (≥ 200 colonies)" (only applicable when the four CFU plate counts are reported as "TNTC [≥ 200 colonies]") will be right-censored at a value of 200.
- **"0":** For the purpose of log-transformation, log(CFU) count associated with a result of "0" (only applicable when the four CFU plate counts are reported as "0") will be left-censored at a value of 1.

Rationale: The smallest possible CFU count above zero is 1 for counts from the one plate and zero for counts from the other plate with zero dilution, leading to a calculated log(CFU) count of:

log(CFU) count = $\log([0 + 0 + 1 + 1]/4 \times 20 \times 10^{0}) = \log(10) = 1$.

- **TNTC (≥ 200 colonies):** log(CFU) count associated with a result of "TNTC (≥ 200 colonies)" (only applicable when the four CFU plate counts are reported as "TNTC [≥ 200 colonies]") will be right-censored at a value of 200.

Other secondary efficacy variables include:

15.2.1.2 TTP in Liquid Media: Coached Spot Sputum Samples

log(TTP) over time, derived from TTP results collected from coached spot sputum samples.

15.2.1.3 CFU Count in Solid Media: "7H11S+C" Overnight Sputum Samples

log(CFU) counts over time, derived from CFU counts per mL collected from "**7H11S+C**" overnight sputum samples.

15.2.1.4 CFU Count in Solid Media: "7H11S" Coached Spot Sputum Samples

log(CFU) counts over time, derived from CFU counts per mL collected from "**7H11S**" coached spot sputum samples.

15.2.1.5 CFU Count in Solid Media: "7H11S+C" Coached Spot Sputum Samples

log(CFU) counts over time, derived from CFU counts per mL collected from "**7H11S+C**" coached spot sputum samples.

Note: log(TTP) and log(CFU) count collected from coached spot sputum samples will be calculated similarly to those collected from overnight sputum samples.

15.2.2 Efficacy Endpoints

15.2.2.1 Rate of Change in CFU Count: "7H11S" Overnight Sputum Samples

Secondary efficacy endpoints include the rate of change in log(CFU) count collected from "**7H11S**" overnight sputum samples, over 8 weeks of treatment, i.e. the bactericidal activity of log(CFU) count over Day 0 to Day 56 (or BA_{CFU}[0-56]).

For a given patient, $BA_{CFU}(t_1 - t_2)$ from Day t_1 to Day t_2 is expressed as follows:

$$BA_{CFU}(t_1 - t_2) = -\frac{\hat{f}(t_2) - \hat{f}(t_1)}{t_2 - t_1} \quad (15.16)$$

where $\hat{f}(t_1)$ and $\hat{f}(t_2)$ represent the model-fitted log(CFU) count at Day t_1 and Day t_2, respectively, as calculated by the regression of the observed log(CFU) count over time.

Other secondary efficacy endpoints (based on the secondary efficacy variables) include BA_{CFU}(0-2) and BA_{CFU}(14-56) collected from "**7H11S**" overnight sputum samples over 8 weeks of treatment.

15.2.2.2 Rate of Change in TTP: Coached Spot Sputum Samples

Endpoints associated with the rate of change in TTP over 56 days of treatment, collected from coached spot sputum samples, are analogous to those collected from overnight sputum samples.

15.2.2.3 Rate of Change in CFU Count: "7H11S+C" Overnight Sputum Samples

Endpoints associated with the rate of change in CFU count over 56 days of treatment, collected from "7H11S+C" overnight sputum samples, are analogous to those collected from "7H11S" overnight sputum samples.

15.2.2.4 Rate of Change in CFU Count: "7H11S" Coached Sputum Samples

Endpoints associated with the rate of change in CFU count over 56 days of treatment, collected from "7H11S" coached spot sputum samples, are analogous to those collected from "7H11S" overnight sputum samples..

15.2.2.5 Rate of Change in CFU Count: "7H11S+C" Coached Sputum Samples

Endpoints associated with the rate of change in CFU count over 56 days of treatment, collected from "7H11S+C" coached spot sputum samples, are analogous to those collected from "7H11S" overnight sputum samples.

15.2.2.6 Time to Liquid Media Sputum Culture Conversion

Other secondary efficacy endpoints include the time to sputum culture conversion, derived from results in liquid media, collected from sputum samples over 8 weeks of treatment. For sputum samples collected before Day 56, the time (study day) to liquid media sputum culture conversion is defined as the time (study day) of the first of two consecutive available sputum samples (thus excluding "contaminated", "no result", "unable to produce" or missing) reported as "negative". For sputum samples collected on Day 56, the time (study day) to liquid media sputum culture conversion is defined as the time (study day) of the last available (Day 56) sputum sample reported as "negative". The time to liquid media sputum culture conversion will be determined separately from overnight and coached spot sputum samples, and also based on both overnight and coached spot sputum samples combined.

15.2.2.7 Proportion of Patients with Liquid Media Sputum Culture Conversion

Other secondary efficacy endpoints include the proportion of patients with liquid media sputum culture conversion at Day 28, Day 42 and Day 56, collected from overnight and coached spot sputum samples over 8 weeks of treatment.

15.2.2.8 Time to Solid Media Sputum Culture Conversion

Other secondary efficacy endpoints include the time to sputum culture conversion, derived from results in solid media, collected from "**7H11S**" sputum samples over 8 weeks of treatment. The time to solid media sputum culture conversion will be determined separately from overnight and coached spot sputum samples, and also based on both overnight and coached spot sputum samples combined.

15.2.2.9 Proportion of Patients with Solid Media Sputum Culture Conversion

Other secondary efficacy endpoints include the proportion of patients with solid media sputum culture conversion at Day 28, Day 42 and Day 56, collected from "**7H11S**" overnight and coached spot sputum samples over 8 weeks of treatment.

15.2.2.10 Correlation and Agreement Between Overnight and Coached Spot Sputum Samples

Other secondary efficacy endpoints include the following:

- The correlation of log(TTP) between overnight and coached spot sputum samples.
- The correlation of log(CFU) count between overnight and coached spot sputum samples, separately for both types of media (**7H11S**" and "**7H11S+C**").
- The agreement of liquid media sputum culture conversion between overnight and coached spot sputum samples.
- The agreement of solid media sputum culture conversion between overnight and coached spot sputum samples, separately for both types of media (**7H11S**" and "**7H11S+C**").
- The agreement of solid media sputum culture conversion between "7H11S" overnight and "7H11S+C" overnight sputum samples.

15.2.3 Secondary, Exploratory and Sensitivity Efficacy Analyses

Regression Analyses

For the analysis of log(CFU) count collected from "**7H11S**" and "**7H11S+C**" overnight and "**7H11S**" and "**7H11S+C**" coached spot sputum samples, those described for the primary efficacy variable (see Section 15.1) will be repeated using the same regression model in Section 15.1, however incorporating a slight modification in the sign of the slope parameters β_1 and β_2:

$$y_{ijk} = \alpha_{ij} - \beta_{1ij} t_{ijk} - \beta_{2ij}\gamma_j \log\left(\frac{\exp\left[\frac{t_{ijk}-\kappa_j}{\gamma_j}\right]+\exp\left[-\frac{t_{ijk}-\kappa_j}{\gamma_j}\right]}{\exp\left[\frac{\kappa_j}{\gamma_j}\right]+\exp\left[-\frac{\kappa_j}{\gamma_j}\right]}\right) + e_{ijk} \quad (15.17)$$

where y_{ijk} represents the log(CFU) count for patient $i = 1, \ldots, N_j$ in treatment group $j = 1, \ldots, J$ at timepoint $k = 1, \ldots, K_{ij}$. The parameters of the regression model are analogous to those described in Section 15.1.

log(TTP) collected from coached spot sputum samples will be analyzed similarly to the analysis described in Section 15.1.

The analyses of log(TTP) and log(CFU) count collected from coached spot sputum samples, and those applicable to the "7H11S+C" media, will not include the exploratory analyses described in Section 15.1.

The analyses of log(TTP) and log(CFU) count collected from coached spot sputum samples will include the sensitvity analyses described in Section 15.1, and will be performed for the mITT analysis population.

Time to **Liquid** Media Sputum Culture Conversion

The time to liquid media sputum culture conversion will be analyzed using Kaplan-Meier "survival" analysis, and will be depicted in figures. The log-rank test will be used for the comparison of the median time to liquid media sputum culture conversion. In addition, the corresponding hazard ratios for time to liquid media sputum culture conversion will be reported. Patients will be censored at the last available valid sample day should no sample be collected at Day 56.

As a sensitivity analysis, the coached spot sputum samples will be used if results of the overnight sputum samples are not available.

Patients' time to sputum culture conversion or censoring on or after Day 53 up to and including Day 60 will be considered as events which occurred on Day 56.

The identity transformation will be applied to obtain the 95% CIs for the "survival" function and quartiles of the "survival" times. The differences, including 95% CIs, of the probability of time to liquid media sputum culture conversion between treatment groups will be presented. The 95% CIs will be calculated as follows:

$$(\widehat{KM}_i - \widehat{KM}_j) \pm Z_{\left(1-\frac{\alpha}{2}\right)} \times \sqrt{\widehat{SE}_i^2 + \widehat{SE}_j^2}$$

where $\widehat{KM}_i$ and $\widehat{KM}_j$ are respectively the estimated probabilities of the i^{th} and j^{th} treatment group, and $\widehat{SE}_i$ and $\widehat{SE}_j$ are the associated estimates of the standard errors (SEs). $Z_{(x)}$ is the x^{th} quantile of the standard normal distribution. Here, $\alpha = 0.05$.

The "survival" analysis will be performed for the mITT and MDR-TB exploratory analysis populations.

Proportion of Patients with **Liquid** Media Sputum Culture Conversion

The proportion of patients with liquid media sputum culture conversion per visit will be compared pairwise between treatment groups using a Chi-Square test with treatment group as row variable and liquid media sputum culture conversion status (i.e. with versus without liquid media sputum culture conversion) as column variable. In addition, the corresponding odds ratios for patients with liquid media sputum culture conversion per visit will be reported. The analysis will be performed for the mITT analysis population.

Time to **Solid** Media Sputum Culture Conversion

The time to solid media sputum culture will be analyzed similarly to the analysis of time to liquid media sputum culture conversion. The analysis will be performed for the mITT and MDR-TB exploratory analysis populations.

Proportion of Patients with **Solid** Media Sputum Culture Conversion

The proportion of patients with solid media sputum culture conversion will be analyzed similarly to the analysis of the proportion of patients with liquid media sputum culture conversion. The analysis will be performed for the mITT analysis population.

Correlation Between Overnight and Coached Spot Sputum Samples:

Pearson correlation coefficients of the following will be calculated and presented in summary tables for the mITT analysis population:

- log(TTP) quantified from overnight sputum samples versus log(TTP) quantified from coached spot sputum samples.

- log(CFU) count quantified from overnight sputum samples versus log(CFU) count quantified from coached spot sputum samples (separately for both types of media).

The correlation analysis will be adjusted for patient. That is, patients will be "partialled out" of the analysis.

Agreement Between Overnight and Coached Spot Sputum Samples:

Kappa coefficients stratified by patient of the following will be calculated and presented in summary tables for the mITT analysis population:

- Liquid media sputum culture conversion readouts from overnight sputum samples versus those from coached spot sputum samples.
- Solid media sputum culture conversion readouts from overnight sputum samples versus those from coached spot sputum samples (separately for both types of media).

Agreement Between Charcoal Treated and Non-Charcoal Treated Overnight Sputum Samples:

Kappa coefficients stratified by patient of the following will be calculated and presented in summary tables for the mITT analysis population:

- Solid media sputum culture conversion readouts from "7H11S" overnight sputum samples versus those from "7H11S+C" overnight sputum samples.

15.3 Tuberculosis Symptoms and Weight

All summaries for TB symptoms and weight will be performed for the mITT analysis population, unless otherwise specified. Data listings for the aforementioned will be based on all patients randomized/assigned to study drug. Displays of TB symptoms will only occur for patients with TB symptoms available.

15.3.1 Derivations

Not applicable.

15.3.2 Analysis

A shift in TB symptoms from baseline to end of treatment will be displayed, where TB symptoms are classified “None”, “Mild”, “Moderate” or “Severe”.

TB symptoms will also be presented by means of a stacked bar chart over all scheduled visits.

Mean weight (kg) over time will be presented in a figure.

16 Mycobacteriologic Characteristics

16.1 Derivations

Mycobacteriologic assessments, beyond the scope of mycobacterial growth indicator tube (MGIT) and solid media data, include:

- Sputum smear results.
- Confirmation of Mycobacterium TB.
- Molecular drug susceptibility.
- Streptomycin, isoniazid, rifampicin and ethambutol (SIRE) drug susceptibility, also for fluoroquinolone and pyrazinamide.
- pncA.

16.2 Analysis

Summaries of mycobacteriologic characteristics will be performed for the Safety analysis population. Data listings for the aforementioned will be based on all patients randomized/assigned to study drug.

17 Safety Outcomes

All summaries for safety will be performed for the Safety analysis population, unless otherwise specified. Data listings for the aforementioned will be based on all patients randomized/assigned to study drug.

17.1 Survival Follow-Up

Survival follow-up data, including overall survival follow-up, will be summarized descriptively using frequencies and percentages (n and %) (qualitative) by visit.

17.2 Adverse Events (AEs)

17.2.1 Derivations

Adverse events (AEs) will be coded using MedDRA central coding dictionary, Version 17.1.

Uncoded AEs will be presented as “uncoded”.

A treatment-emergent adverse event (TEAE) is defined any AE which started or worsened on or after the first study drug administration up to and including the Day 70 Follow-up visit (or up to and including 14 days after last study drug administration for patients not having the Day 70 Follow-up visit).

A post-treatment AE is defined as any AE which started or worsened after the Day 70 Follow-up visit up to the last visit, early study withdrawal or last contact associated with the Day 140/Follow-up period, as indicated on the 'Disposition' eCRF page, whichever occurs last.

Partial dates for AEs will not be imputed. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case assigned, i.e. a TEAE.

Appendix 3 contains conventions for the calculation of TEAEs.

Treatment-Emergent Adverse Events (TEAEs) Leading to Death

Treatment-emergent adverse events (TEAEs) leading to death are defined as TEAEs for which outcome is indicated as "fatal".

Serious Treatment-Emergent Adverse Events (TEAEs)

Serious TEAEs are defined as TEAEs for which serious is indicated as "yes".

Treatment-Emergent Adverse Events (TEAEs) Leading to Early Withdrawal from Study

Treatment-emergent adverse events (TEAEs) leading to early withdrawal from the study are defined as TEAEs for which study discontinuation is indicated as "yes".

Treatment-Emergent Adverse Events (TEAEs) Leading to Discontinuation of Study Drug

Treatment-emergent adverse events (TEAEs) leading to discontinuation of study drug are defined as TEAEs for which action taken with study drug is indicated as "IMP stopped".

Drug-Related Treatment-Emergent Adverse Events (TEAEs)

Drug-related TEAEs are defined as TEAEs for which relationship to study drug is indicated as "possible", "probable", "certain" or missing.

Treatment-Emergent Adverse Events (TEAEs) by Severity

Severity is categorized as "grade I (mild)", "grade II (moderate)", "grade III (severe)", "grade IV (potentially life-threatening)".

Liver-Related Adverse Events

Liver-related adverse events are defined as any events with a high level group term of "HEPATIC AND BILIARY NEOPLASMS BENIGN", "HEPATIC AND HEPATOBILIARY DISORDERS", "HEPATOBILIARY DISORDERS CONGENITAL", "HEPATOBILIARY NEOPLASMS MALIGNANT AND UNSPECIFIED", "HEPATOBILIARY INVESTIGATIONS" or "HEPATOBILIARY THERAPEUTIC PROCEDURES".

17.2.2 Analysis

An overall summary, including the incidence of TEAEs (applicable to each observation period; only deaths and SAEs are applicable to "AEs during the survival follow-up period") by SOC and PT, will be presented for some of the categories described.

The incidence of drug-related TEAEs by SOC, PT and severity will be presented.

Post-treatment AEs will be presented overall. Incidences of post-treatment AEs will be presented for serious AEs and AEs leading to early withdrawal from the study.

A data listing with all AEs (including coding details), all AEs for patients who died and serious adverse events (SAEs) will be presented.

17.3 Deaths

17.3.1 Derivations

Deaths will be presented as captured on the Subject Disposition eCRF page.

17.3.2 Analysis

The number of deaths, as well as the causes of deaths will be summarized for all patients randomized/assigned to study drug and will be presented by treatment group. Deaths, date of death, cause of death, adverse events leading to death and the adverse event's relationship to study drug will be presented in data listings for patients randomized/assigned to study drug.

17.4 Laboratory Tests

17.4.1 Derivations

A list of laboratory tests (hematology, clinical chemistry, urinalysis, serum endocrinology and other laboratory tests) to be included in the analysis is presented in Section 6.3 of the protocol.

Quantitative laboratory measurements reported as "< X", i.e. BLQ, or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the data listings.

Quantitative laboratory measurements will be categorized in accordance with the relevant laboratory reference ranges as follows:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition, quantitative liver enzyme (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase and total bilirubin) laboratory measurements will be characterized in accordance with the predefined markedly abnormal criteria as presented below:

- Result > 3 × Upper limit of normal (ULN).
- Result > 10 × ULN.
- 1.1 × ULN ≤ Measurement < 2 × ULN (Grade 1).
- 2 × ULN ≤ Measurement < 3 × ULN (Grade 2).
- 3 × ULN ≤ Measurement ≤ 8 × ULN (Grade 3).
- Measurement > 8 × ULN (Grade 4).

17.4.2 Analysis

Summaries of hematology, clinical chemistry, urinalysis and serum endocrinology laboratory tests, by visit, will include the following:

- Actual and change from baseline in laboratory measurements (quantitative).

Quantitative ("low", "normal" and "high" classifications according to laboratory reference ranges) will be summarized in a shift table (from baseline) to end of treatment, and presented in a stacked bar chart.

Other laboratory results (apart from hematology, clinical chemistry, urinalysis and serum endocrinology laboratory tests) will be listed.

Treatment-emergent incidences and post-treatment incidences during the Day 70 or 140 Follow-up period for liver enzyme abnormalities, will be summarized.

Total bilirubin versus ALT (normalized values) will be presented in figures (eDISH plot). Here, 2 times the ULN for total bilirubin, and 3 times the ULN for ALT will be provided accordingly (using horizontal and vertical lines). The most extreme treatment-emergent measurement for the aforementioned laboratory tests will be presented. The figure will be displayed on the logarithmic scale and will be repeated for total bilirubin versus AST (normalized values).

Liver enzyme profile plots will be provided for the following:

- Patients with eDISH abnormalities. (Based on Possible Hy's Law criteria).
- Patients with treatment-emergent Grade 3 or Grade 4 AST or ALT measurements.

An abnormality possibly meeting Hy's Law criteria is defined as an event where a patient has an AST or ALT result ≥ 3 x ULN and a total bilirubin result ≥ 2 x ULN.

Patients with ALT or AST > 3, 5, 8 or × ULN will be provided in data listings.

17.5 Electrocardiogram (ECG) Parameters

17.5.1 Derivations

The mean of the three observed values obtained from triplicate readings per visit will be used for analysis purposes.

The actual QT, QTcB and QTcF intervals will be classified as follows:

- QT/QTcB/QTcF interval < 450 msec.
- 450 msec ≤ QT/QTcB/QTcF interval < 480 msec.
- 480 msec ≤ QT/QTcB/QTcF interval < 500 msec.
- QT/QTcB/QTcF interval ≥ 500 msec.

The change from baseline in QT, QTcB and QTcF intervals will be classified as follows:

- > 0 and < 30 msec increase from baseline.
- ≥ 30 msec and < 60 msec increase from baseline.
- ≥ 60 msec increase from baseline.

17.5.2 Analysis

Electrocardiogram (ECG) will be summarized for the Safety analysis population (tables and figures), and presented in data listings for all patients randomized/assigned to study drug.

Summaries of ECG measurements, by visit and timepoint (where applicable), will include the following:

- Actual and change from baseline in ECG measurements (quantitative).
- Frequencies and percentages (n and %) (qualitative).
- Tukey honestly significant difference (HSD) analysis of the change from baseline in QTcB and QTcF interval between treatment groups.

The mean QTcB and QTcF interval will be presented in summary tables and figures by visit and timepoint.

Quantitative ECG measurements will be summarized in shift tables (from baseline) by visit.

Treatment-emergent incidences of the aforementioned QT, QTcB and QTcF interval classifications will be summarized.

17.6 Vital Signs

17.6.1 Derivations

Vital signs will be characterized in accordance with the predefined markedly abnormal criteria as presented below:

Abnormality Code	Vital Sign			
	Heart Rate	**DBP**	**SBP**	**Respiratory Rate**
Abnormally low	≤ 50 bpm	≤ 50 mmHg	≤ 90 mmHg	< 12 bpm
Grade 1 or mild		> 90 mmHg to < 100 mmHg	> 140 mmHg to < 160 mmHg	≥ 17 bpm to ≤ 20 bpm
Grade 2 or moderate		≥ 100 mmHg to < 110 mmHg	≥ 160 mmHg to < 180 mmHg	≥ 21 bpm to ≤ 25 bpm
Grade 3 or severe		≥ 110 mmHg	≥ 180 mmHg	> 25 bpm
Abnormally high	≥ 120 bpm			

bpm: Beats per minute, DBP: Diastolic blood pressure, SBP: Systolic blood pressure.

17.6.2 Analysis

Summaries of vital signs, including BMI (kg/m^2), by visit, will include the actual and percent change from baseline in vital signs.

Treatment-emergent incidences of markedly abnormal vital signs will be summarized.

Vital signs will be presented in data listings.

17.7 Physical Examination

17.7.1 Derivations

Not applicable.

17.7.2 Analysis

Not applicable.

17.8 Ophthalmological Examination

17.8.1 Derivations

The following ophthalmological examination results will be reported for this study:

- Visual acuity.
- Slit lamp examination.

17.8.2 Analysis

Qualitative analysis will be performed on visual acuity test data (frequencies and percentages).

Decreases (and increases) of 1, 2 and more than 2 lines from baseline to Day 140 Follow-up will be presented per eye for the visual acuity near test.

Decreases (and increases) of 1, 2 and more than 2 categories from baseline to Day 140 Follow-up will be presented per eye for the visual acuity distance test.

For lens opacities, an Age Related Eye Disease Study 2 (AREDS2) grading of > 0.0 will be listed for all patients randomized/assigned to study drug.

17.9 Other Assessments

The following assessments will only be presented in data listings for all patients randomized/assigned to study drug:

- Sample collection information.
-

18 List of References

Burger, D.A. and Schall, R. (2015). A Bayesian nonlinear mixed-effects regression model for the characterization of early bactericidal activity of tuberculosis drugs. *Journal of Biopharmaceutical Statistics* 25(6), 1247–1271.

Hahn, G.J. and Meeker, W.Q. (1991). Statistical Intervals: A Guide for Practitioners, New York: John Wiley & Sons.

Food & Drug Administration (February 27, 1987). Supplementary suggestions for preparing an integrated summary of safety information in an original NDA submission and for organizing information in Periodic Safety Updates.

Vaida, F. and Liu, L. (2009). Fast implementation for normal mixed effects models with censored response. *Journal of Computational and Graphical Statistics* 18(4), 797–817.

Appendix 1: Rationale for Correction Factors

Most modern drugs are low-clearance drugs, since low clearance often (although not always) equates to long half-life and therefore once daily dosing. For low-clearance drugs, the biological activity in vivo is driven by the unbound (free) drug concentration.

In static in vitro systems, the setting by definition is low clearance and the free drug concentration will determine the biological response. If the free drug concentration in the in vitro system is different from that in vivo, a correction factor needs to be applied to extrapolate the in vitro results to the in vivo situation.

In the case of measuring MICs for *Mycobacterium* TB, protein in the medium is required. The most common protein used is bovine serum albumin (BSA) at a final concentration of 5 g/L, which is approximately one-eighth the concentration found in plasma. For a drug which is highly albumin-bound in plasma, 5 g/L BSA can still result in a very high degree of protein binding. In such a case, the measured MIC is not the intrinsic MIC of free drug. Therefore, extrapolating from the in vitro MIC to the MIC in plasma cannot be done just by multiplying the measured MIC by a correction factor based on the free fraction of drug in plasma. The correction factor needs to be adjusted for the free fraction in the in vitro assay as well.

Measuring MICs in whole serum is not done due to technical limitations. So, how do we decide on the appropriate correction factor to extrapolate in vitro findings to the in vivo situation?

This is easiest in the case of highly (> 99%) protein bound drugs where the free fraction is approximately linearly related to the amount of protein. That is, an in vitro system with one-eighth the amount of relevant protein as in plasma has an 8-fold higher free fraction of that drug than does plasma. In such a case, a measured in vitro MIC needs to be multiplied by a factor of 8 to obtain the predicted MIC in plasma.

For other drugs the calculation can be performed as follows. For an "unsaturable" drug, or a drug far from saturation like albumin, the mass action equation reduces to $B = nKF$, where B is the concentration of bound drug, n is the number of binding sites, K is the equilibrium association constant, and F is the concentration of free drug. The ratio $B/F = nK$ and is directly proportional to the number of binding sites. Let us set $B + F = 1$ (or 100%).

Thus, for the case of PA-824, which is a low clearance drug that is 85% bound to albumin in human plasma (which contains 40 g/L albumin), B/F in plasma = 85/15 = 5.67. B/F in the medium in which the MIC data are generated, containing 5 g/L albumin, is 8-fold lower, or 0.71. If $B/F = 0.71$ and $B + F = 1$ (setting the total $B + F$ to 100%), then solving algebraically $F = 0.58$. That is, in the medium in which the MIC data are generated, PA-824 is 58% free, or approximately 4-fold its free fraction in plasma. Therefore, a factor of 4 should be applied to the MIC in plasma, that is, an MIC measured in the usual assay should be multiplied by four to ascertain the MIC in plasma. This in fact was confirmed experimentally, with a 4.2-fold shift in MIC observed as the albumin concentration in the MIC assay medium was increased from 5 g/L to 40 g/L.

For the case of bedaquiline, which is greater than 99% protein bound in plasma, we use our (above) factor of 8. That is, the MIC in plasma is considered 8 times the MIC measured in the in vitro assay.

For the case of moxifloxacin, which is 30-50% bound in human plasma, correcting for protein binding is not considered necessary, as the correction factor would be within the error of the MIC assay.

Appendix 2: Programming Conventions for Tables, Data Listings and Figures (TLFs)

Paper Size, Orientation and Margins

The margin, page size and line size specifications as stipulated below will be used for the presentation of all TLFs:

	Landscape	Portrait
Margins (Inches):		
Top	1.25	1
Bottom	1	1
Left	1	1.25
Right	1	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® specifications:		
PAGESIZE	46	67
LINE SIZE	134	93

Fonts

The font type 'Courier New' should be used as default for tables and data listings, with a font size of 8. The font color should be black. No bolding, underlining and italics are permitted.

Header Information

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page).
- The sponsor name should appear in row 1, left-aligned.
- The word "J-M-Pa-Z" should appear in row 1, right-aligned.
- The protocol number should appear in row 2, left-aligned.
- The page identification in the format Page X of Y (where Y is the total number of pages for the TLF) should appear in row 2, right-aligned.
- The TLF identification number should appear in row 3, centered.
- The TLF title should start in row 4, centered.
- The TLF population should appear in row 5, centered. The population should be spelled out in full, e.g. Safety Analysis Population in preference to Safety analysis population.
- Row 6 should be a continuous row of underscores ('_') (the number of underscores should equal the line size).
- Row 7 should be a blank line.
- Mixed case should be used for titles.
- The column headings should be underlined with a row of underscores ('_').
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings should be in mixed case.
- In general, the analysis population count should appear in the column header in the form "(N=XXX)".

Table, Listing and Figure (TLF) Conventions

General:

- The first row in the body of the table or data listing should be blank.
- The left hand column should start in Column 1. No indenting or centering of the TLF should occur.
- Rounding should be done with the SAS® function ROUND.
- Numerical values in tables should be rounded, not truncated.
- Numerical values should be decimal point aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The study drug should appear first in tables with treatment group as columns.
- All variables contained on the eCRF (which have data present) should appear in the data listings, along with all derived data appearing in the corresponding tables.
- The width of the TLF should match the line size.

Univariate statistics:

- Statistics should be presented in the same order across tables (i.e., n, mean, SD, minimum, median and maximum).
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum, maximum and CV (%): N.
  - Mean and median: N + 1.
  - SD: N + 2.

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
  - 77 (100.0)
  - 50 (64.9)
  - 1 (2.7)

CIs:

- CIs should be presented with one additional decimal place as that of the raw data, and SDs and SEs with two additional decimal places as that of the raw data.
- CIs should be justified so that parentheses displayed on consecutive lines of a table "line up".

P-values:

P-values should be reported to four decimal places.

Ratios:

Ratios should be reported with one additional decimal place as that of the raw data.

Missing values:

A "0" should be used to indicate a zero frequency.

A blank will be used to indicate missing data in data listings.

Figure Output Conventions

Figures should be provided in RTF files using the SAS® Output Delivery System (ODS).

Dates and Times

Depending on data available, dates and times will take the form ddMMMyyyy and hh:mm.

Spelling Format

The spelling format to be used is English US.

Presentation of Treatment Groups

For TLFs, treatment groups will be represented in the following order:

Treatment Group	TLF Abbreviation
See Section 3.1	$J_{(loading\ dose/t.i.w.)}PaZ$
See Section 3.1	$J_{(200\ mg)}PaZ$
See Section 3.1	HRZE
See Section 3.1	$J_{(200\ mg)}MPaZ_{MDR}$
Screening Failure	Screening Failure

Presentation of Visits

For outputs, visits will be represented in the following order:

Visit Name
Day -9 to Day -3
Day -2

Visit Name
Day -1
Day 1
Baseline
Day 4
Day 8
Day 14
Day 15
Day 22
Day 29
Day 36
Day 43
Day 50
Day 56
Day 57
Day 70/Follow-up
Day 140/Follow-up
Unscheduled (chronologically)
Early Withdrawal
Month 8 Follow-Up
Month 14 Follow-Up
Month 20 Follow-Up
Month 26 Follow-Up

Note: Overnight sputum sample collection started one day prior to the visit.

Appendix 3: Partial Adverse Event (AE) Date Conventions

No AE date imputations will be done for this study.

Algorithm for Treatment-Emergent Adverse Events (TEAEs)

START DATE	STOP DATE	ACTION
Known	Known, partial or missing	If Start date < Study drug start date, then not TEAE. If Start date ≥ Study drug start date, then TEAE. If Start date = Study drug start date and the variable "...prior to first dose of study medication" is equal to "no", then TEAE. If Start date = Study drug start date and the variable "...prior to first dose of study medication" is equal to "yes", then not TEAE.
Partial, but known components show that it cannot be on or after study drug start date	Known, partial or missing	Not TEAE.
Partial, could be on or after study drug start date	Known	If Stop date < Study drug start date, then not TEAE. If Stop date ≥ Study drug start date, then TEAE. Else assumed TEAE.
	Partial	Assume stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and

START DATE	STOP DATE	ACTION
		month are unknown), then: If Stop date < Study drug start date, then not TEAE. If Stop date ≥ Study drug start date, then TEAE. Else assumed TEAE.
	Missing	Assumed TEAE.
Missing	Known	If Stop date < Study drug start date, then not TEAE. If Stop date ≥ Study drug start date, then TEAE. Else assumed TEAE.
	Partial	Assume stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If Stop date < Study drug start date, then not TEAE. If Stop date ≥ Study drug start date, then TEAE. Else assumed TEAE.
	Missing	Assumed TEAE.

PK, PD AND PK/PD STATISTICAL ANALYSIS PLAN

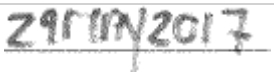
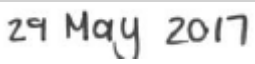
NC-005-(J-M-PA-Z)

A PHASE 2 OPEN-LABEL PARTIALLY RANDOMIZED TRIAL TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF COMBINATIONS OF BEDAQUILINE, MOXIFLOXACIN, PA-824 AND PYRAZINAMIDE DURING 8 WEEKS OF TREATMENT IN ADULT SUBJECTS WITH NEWLY DIAGNOSED DRUG-SENSITIVE OR MULTI DRUG-RESISTANT, SMEAR-POSITIVE PULMONARY TUBERCULOSIS

AUTHOR: DIVAN BURGER AND LUCIA MANS

VERSION NUMBER AND DATE: VERSION 2.0, 25MAY2017

PK, PD and PK/PD Statistical Analysis Plan (SAP) Signature Page

	Name	Signature	Date
Author:	Divan Burger, PhD		
Position:	Senior Biostatistician		
Company:	QuintilesIMS, South Africa		
	Name	**Signature**	**Date**
Author:	Lucia Mans, BSc (Hons)		
Position:	Biostatistician 1		
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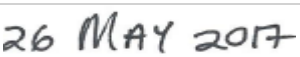
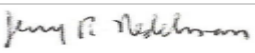
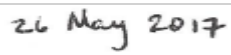
The signatures below indicate review and approval of the proposed PK analysis and presentation of data as planned for protocol NC-005-(J-M-PA-Z) Version 1.0, dated 31 January 2014, including final protocol amendment 01, dated 19 September 2014 (incorporated into the working protocol Version 1.1, dated 19 September 2014).

This version of the PK, PD and PK/PD statistical analysis plan (SAP) was approved by the undersigned.

	Name	Signature	Date
Approved By:	Robert Schall, PhD		
Position:	Senior Director, Biostatistics		
Company:	QuintilesIMS, South Africa		
Approved By:	Almari Conradie, MPh		
Position:	Global Clinical Project Manager		
Company:	Global Alliance for TB Drug Development		
Approved By:	Jerry Nedelman		
Position:	Senior Director, Pharmacometrics		
Company:	Global Alliance for TB Drug Development		

Modification History

Unique Identifier for this Version	Date of Document Version	Author	Significant Changes from Previous Authorized Version
1.0	08JUN2016	Divan Burger & Lucia Mans	Not applicable – First authorized version

Unique Identifier for this Version	Date of Document Version	Author	Significant Changes from Previous Authorized Version
2.0	25MAY2017	Divan Burger & Lucia Mans	• Updated the Quintiles logo to the QuintilesIMS logo. Also, updated "Quintiles" to "QuintilesIMS" throughout the document. • Removed Stephen Murray from the Signature Page, as he is no longer working at GATB. Replaced with Jerry Nedelman for Signature Page. • Section 5: Removed text referring to a data review plan, as the analysis populations were not outlined in such documentation, but rather discussed directly with GATB. Also, reference to a topline analysis removed as PK and PK-PD analyses are performed as a final analysis only. • Section 5.6: Reference link removed from text, as this is not applicable any longer.

Unique Identifier for this Version	Date of Document Version	Author	Significant Changes from Previous Authorized Version
2.0	25MAY2017	Divan Burger & Lucia Mans	• Section 9.1: Indicated that between-treatment comparisons will also be performed of TMIC. • Section 9.1.1: Added clarification for trailing BLQ values set to zero. • Section 9.1.1: Added text to explain $AUC_{(0-24)}$ will not be calculated if both concentrations at predose and 24 h are missing. • Section 9.1.2: Updated geometric mean CV% to CV%, and added formula for this. • Section 9.1.2: Updated that 95% CIs of the geometric mean will be constructed using natural log transformation and then anti-logged.

Unique Identifier for this Version	Date of Document Version	Author	Significant Changes from Previous Authorized Version
2.0	25MAY2017	Divan Burger & Lucia Mans	• Section 9.2.1: Updated formula for log-linear interpolation when PK concentrations are decreasing. Also, used "MIC" instead of "C_i" in formulae, as MIC is a constant over time.

Table of Contents

Page:

1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of pharmacokinetic (PK), pharmacodynamic (PD) and PK-PD data for protocol NC-005-(J-M-Pa-Z). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This PK statistical analysis plan (SAP) is based on Working Protocol Version 1.1, dated 19 September 2014.

2 Study Objectives

The primary objective of this study is to evaluate the bactericidal activity, safety, and tolerability of bedaquiline, PA-824 and pyrazinamide in drug-sensitive (DS) tuberculosis (TB) and bedaquiline, moxifloxacin, PA-824 and pyrazinamide in multi-drug resistant (MDR) TB (MDR-TB).

Secondary objectives include evaluating the bactericidal activity, safety and tolerability of bedaquiline dosed using two different schemes (400 mg daily for 2 weeks followed by 200 mg three times a week [loading dose/t.i.w] and 200 mg daily [200 mg]). Additional key secondary objectives are to evaluate the population PK characteristics of bedaquiline, moxifloxacin, PA-824 and pyrazinamide when administered as a part of 3- and 4-drug regimens in adults with TB, and investigation of the methodology of sputum sampling by comparing colony forming unit (CFU) count and time to positivity (TTP) in liquid culture (MGIT), quantified from both overnight and coached spot sputum samples.

The study endpoints are listed in Section 4.2 of the protocol.

3 Study Design

3.1 General Description

This is a Phase 2, multi-center, open-label, partially randomized study conducted in four parallel treatment groups. The study will be performed at multiple sites globally.

Drug-Sensitive (DS) Tuberculosis (TB) (DS-TB):

A total of 180 eligible patients who meet all of the inclusion criteria and none of the exclusion criteria, aged between 18 and 75 years (inclusive), with newly diagnosed, smear-positive DS pulmonary TB will be randomized to one of three treatment groups:

- **J$_{(\text{loading dose/t.i.w.})}$PaZ:** Bedaquiline 400 mg once daily from Day 1 up to Day 14, 200 mg three times per week from Day 15 up to Day 56; plus PA-824 200 mg once daily from Day 1 up to Day 56; plus pyrazinamide 1500 mg once daily from Day 1 to Day 56.
- **J$_{(200\ \text{mg})}$PaZ:** Bedaquiline 200 mg once daily from Day 1 up to Day 56; plus PA-824 200 mg once daily from Day 1 up to Day 56; plus pyrazinamide 1500 mg once daily from Day 1 to Day 56.
- **HRZE:** Isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg and ethambutol 275 mg from Day 1 up to Day 56.

The HRZE treatment group is included as a control for the DS treatment groups. Additionally, it is included as a control for the quantitative mycobateriology.

Multi-Drug Resistant (MDR) Tuberculosis (TB) (MDR-TB):

Up to 60 eligible patients who meet all of the inclusion criteria and none of the exclusion criteria, aged between 18 and 75 years (inclusive), with newly diagnosed, smear-positive MDR pulmonary TB will be assigned to the following treatment group: **$J_{(200\ mg)}MPaZ_{MDR}$: Bedaquiline 200 mg once daily from Day 1 up to Day 56; plus moxifloxacin 400 mg once daily from Day 1 up to Day 56; plus PA-824 200 mg once daily from Day 1 up to Day 56; plus pyrazinamide 1500 mg once daily from Day 1 to Day 56.

The number of patients to be randomized/assigned to each treatment group is presented below.

Treatment Groups

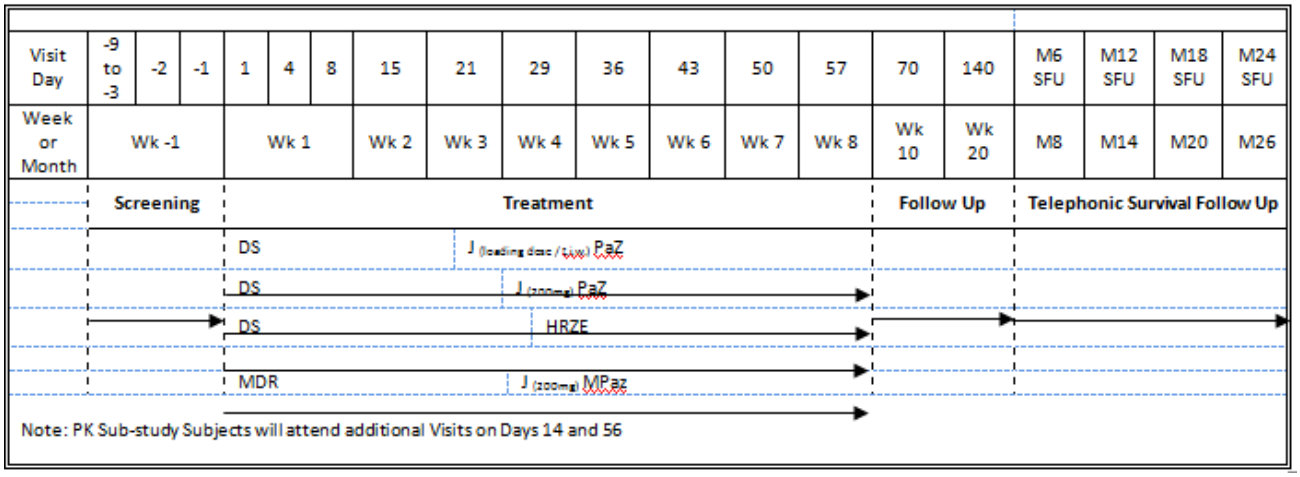
	Treatment Group	Patient Population	Number of Patients
1.	$J_{(loading\ dose/t.i.w.)}PaZ$	DS-TB	60
2.	$J_{(200\ mg)}PaZ$	DS-TB	60
3.	HRZE	DS-TB	60
4.	$J_{(200\ mg)}MPaZ_{MDR}$	MDR-TB	Up to 60

DS: Drug-sensitive. MDR: Multi-drug resistant. TB: Tuberculosis.

A schematic of study design is presented below.

Fifteen (15) patients from each of the treatment groups will be included in a PK sub-study, for whom intense-sampling will be performed on Day 14 and Day 56.

Study Schematic



3.2 Schedule of Events

The schedule of events can be found in Section 1.2 of the protocol.

3.3 Changes to Analysis from Protocol

In the multiple-dose Day 14 and Day 56 PK analyses, linear up/log down trapezoidal summation is the preferred method for calculating areas under the curve. This method will be used for deriving the total exposure parameters, instead of the linear trapezoidal rule described in the protocol.

4 Planned Analyses

The following PK analyses will be performed for this study:

- Final analysis.

4.1 Final Analysis

The final analysis as described in the main SAP handling safety and efficicy, using TLF shells (to be outlined in a separate output templates document), will be performed by QuintilesIMS Biostatistics following final analysis database lock of data for all patients (DS-TB and MDR-TB).

The final PK, PD and PK/PD analyses and associated figures will be the responsibility of the clinical pharmacokineticist at QuintilesIMS. The final PK, PD and PK/PD summaries and data listings as well as the statistical analyses of the PK, PD and PK/PD variables will be the responsibility of the study biostatistician at QuintilesIMS.

5 Analysis Populations

Agreement and authorization of patients included/excluded from each analysis population will be reached prior to the final analysis database lock.

For the purpose of analyses based on each of the analysis populations, patients will be classified according to actual study drug received, regardless of randomized/assigned study drug.

Note: Statistical analyses will not necessarily be performed for all of the below analysis populations. Analyses populations applicable to a certain analysis will be mentioned explicitly within the particular “analysis” sections of this document.

The number of patients included in the relevant analysis populations, as well as the number of patients excluded with reasons for exclusion from the relevant analysis populations, will be summarized for patients randomized/assigned to study drug.

5.1 All Patients Screened

A full description of the all patients screened analysis population can be found in the main SAP handling safety and efficacy.

5.2 All Patients Randomized/Assigned to Study Drug

A full description of the all patients randomized/assigned to study drug analysis population can be found in the main SAP handling safety and efficacy.

5.3 Safety Analysis Population

This analysis population will include all patients who were randomized to study drug (for the DS patient population) or assigned to study drug (for the MDR patient population) and received at least one administration of study drug.

If there is any doubt whether a patient was treated or not, the patient will be assumed treated for the purposes of this analysis.

The main purpose of this analysis population is to summarize safety data for patients who were, during the course of the study, exposed to study drug.

5.4 Modified Intention-to-Treat (mITT) Analysis Population

A full description of the mITT analysis population can be found in the main SAP handling safety and efficacy.

5.5 Multi-Drug Resistant Tuberculosis (MDR-TB) Exploratory Analysis Population

A full description of the MDR-TB analysis population can be found in the main SAP handling safety and efficacy.

5.6 Pharmacokinetic (PK) Analysis Population

The PK population will consist of all patients who receive the Test Product (J dosing regimens) or Control Product (HRZE regimen) and have at least 1 measured concentration for any corresponding analytes (J, J metabolite M2, Pa, Z, or M) at a scheduled PK time point after the start of dosing regimen of the respective drug and had no protocol violations/deviations or events with potential to significantly affect the PK of the investigational product (examples include, but may not be limited to, vomiting following oral dosing occurring within the time frame of 2 times the median time of maximum concentration (t_{max}), or sample processing errors that lead to inaccurate bioanalytical results). If any patients are found to be noncompliant with respect to dosing (eg, noncompliance on PK days or other study days, or have overall compliance <80% or have incomplete data), a decision will be made on a case-by-case basis as to their inclusion in the analysis, and subjected to the Sponsor's approval.

Patients in this population will be used for all applicable PK summaries.

Pharmacokinetic parameters will be derived for patients in the PK population from the sub-group of each treatment who had serial PK samples collected.

5.7 Pharmacokinetic (PK)-Pharmacodynamic (PD) Analysis Population

This analysis population will contain all patients included in the PK analysis population for whom valid PD data are available, and who had no major protocol violations/deviations (defined as violations/deviations affecting the integrity of the PD data) as confirmed by the sponsor and data review meeting.

The main purpose of this analysis population is to summarize PK-PD data for patients who have valid corresponding data available.

6 General Considerations

Further general considerations can be found in the main SAP handling safety and efficacy.

6.1 Software Version

All analyses will be conducted using SAS® Version 9.2 or higher and Phoenix® WinNonlin® 6.4 or higher (Certara L.P., Princeton, New Jersey), as applicable. Graphics for PK data presentation may also be prepared with SigmaPlot® 12.5 or higher (Systat Software, Inc., San Jose, California); or Phoenix® WinNonlin® 6.4 or higher, or SAS® Version 9.2 or higher.

7 Statistical Considerations

7.1 Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. Randomization to treatment groups is not stratified by country/site, and therefore, all analyses will be unstratified. However, subgroup analyses will be included by site (see Section 7.3).

7.2 Missing Data

Missing data will not be imputed for this study, unless otherwise specified.

7.3 Examination of Subgroups

A subset of patients from each treatment group will be included in a PK sub-study.

8 Output Presentations

Appendix 2 contains conventions for presentation of data in TLFs.

Summary tables will be presented by treatment group, unless otherwise specified.

The shells to be provided in the separate output templates document will describe the format and content for presentation of TLFs for the final analyses.

All percentages (%) calculated for a specific summary are calculated using the total number of patients included in the relevant analysis population with data, as the denominator, unless otherwise specified.

By default, descriptive statistics will include the number of patients (n), mean, standard deviation (SD), minimum, median and maximum for quantitative measurements.

9 Pharmacokinetics (PK) and Pharmacodynamics (PD)

9.1 Pharmacokinetics (PK)

Sparse samples (predose on Days 1, 4, 8, 15, 22, 29, 36, 43, 50, and during the site visits on Days 57 and 70) for all patients and serial samples up to 24 hours postdose on Day 14 and 56 for the PK sub-study patients were collected for the following analytes:

Pharmacokinetic Analyte(s) Per Treatment Group

Treatment Group	Analytes	Patient Population
$J_{(\text{loading dose/t.i.w.})}PaZ$	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200\ mg)}PaZ$	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200\ mg)}MPaZ$	J, J metabolite M2, Pa, Z, M	MDR-TB
HRZE	Z	DS-TB

DS: Drug-sensitive. J: Bedaquiline. M: Moxifloxacin. MDR: Multi-drug resistant. Pa: PA-824. TB: Tuberculosis. Z: Pyrazinamide.

The relevant PK summaries will be presented for all patients in the PK population. Multiple-dose PK parameters on Day 14 and Day 56 will be derived for bedaquiline, bedaquiline metabolite M2, moxifloxacin, PA-824, and pyrazinamide (depending on treatment group) for patients in the PK population from the sub-group of each treatment who had serial PK samples collected (Section 5.6).

9.1.1 Derivations

Pharmacokinetic (PK) Plasma Concentrations

Predose (or trough) PK plasma concentration samples of Day 15 and Day 57 collected from patients in the PK sub-study will also be used as the 24 hour post-dose PK plasma concentration sample of Day 14 and Day 56 in the respective concentration summaries and PK analyses.

For the purpose of summarizing concentration data, below the limit of quantitation (BLQ) concentrations will be treated as zero for the computation of descriptive statistics. Missing concentrations will be omitted from the calculation of descriptive statistics.

The following data handling conventions apply to the PK analyses for deriving the multiple-dose PK parameters on Day 14 and Day 56:

- Predose samples that are BLQ will be assigned a numerical value of zero.
- Postdose BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile.
- A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if reanalysis or exclusion of the data is warranted.
- Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing.
- Trailing BLQ values at the end of the collection interval (after the last quantifiable concentration) will be set to zero, and treated as missing when calculating $AUC_{(0-t)}$.
- If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantifiable values will be set to missing (blank data) and excluded from the PK analysis, unless otherwise warranted by the concentration-time profile.
- For $AUC_{(0-24)}$ calculations:
    - For PK analyses of bedaquiline and bedaquiline metabolite M2 on Day 56 of the $J_{(loading\ dose/t.i.w.)}$PaZ treatment, during the study timeframe of three times per week bedaquiline administration, missing predose and/or 24-h concentration will be kept as missing and $AUC_{(0-24)}$ will not be calculated.

- For all other analytes/study day/treatments, in which the respective drug is administered once daily, under the assumptions of linear PK and steady-state conditions, if predose concentration is missing, then the concentration shall be set to equal the concentration at 24 h (ie, end of the dosing interval). Likewise, if concentration at 24 h is missing, the concentration shall be set to the predose value. If both concentrations at predose and 24 h are missing, $AUC_{(0-24)}$ will not be calculated.

Pharmacokinetic (PK) Parameters

Pharmacokinetic parameters will be estimated by noncompartmental methods using actual elapsed time from dosing.

Areas under the curve will be calculated by linear up/log down trapezoidal summation, and at least 3 quantifiable postdose concentrations are required.

The following multiple-dose PK parameters will be calculated for all analytes and treatments on Day 14 and Day 56; unless otherwise indicated:

C_{max}	Observed maximum plasma concentration, obtained directly from the observed versus time concentration data
t_{max}	Time of C_{max}
$AUC_{(0-24)}$	Area under the PK plasma concentration time (t) curve from zero to 24 hours. As a general rule, AUC_{all} shall be used as an estimate of $AUC_{(0-24)}$ if concentrations fall to BLQ at or before reaching 24 hours unless otherwise warranted by the data. AUC_{all} is the area under the curve from zero (predose) to the time of the last observation (last quantifiable observation if no terminal BLQ values are present or first non-quantifiable observation if there are trailing BLQs).

$AUC_{(0-t)}$	Area under the PK plasma concentration time (t) curve from zero to time of last quantifiable analyte concentration.
C_{max}/D	Dose-normalized C_{max}
$AUC_{(0-24)}/D$	Dose-normalized $AUC_{(0-24)}$.
$AUC_{(0-t)}/D$	Dose-normalized $AUC_{(0-t)}$.
C_{min}	Observed minimum plasma concentration, obtained directly from the observed versus time concentration data
t_{min}	Time of C_{min}
C_{min}/D	Dose-normalized C_{min}

The dose normalized exposure parameters (C_{max}/D, C_{min}/D, $AUC_{(0-t)}/D$, and $AUC_{(0-24)}/D$) will be derived for analytes that have the corresponding study drug dose varied across regimens, and include: bedaquiline, bedaquiline metabolite M2, and pyrazinamide.

HRZE regimen (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg per combination tablet) is administered on a weight-based dosing scheme, as follows: 30-37 kg: 2 tablets; 38-54 kg: 3 tablets; 55-70 kg: 4 tablets; and 71 kg and over: 5 tablets. Pyrazinamide dose amount for calculating pyrazinamide dose-normalized PK parameters in the HRZE treatment on Day 14 and Day 56 will be derived as: 400 mg x number of combination tablets taken per administration specified in the protocol, based off weight measured on Day 1.

9.1.2 Analysis

In general, PK data listings and summaries will be presented by treatment, study day, and schedule time if applicable.

Pharmacokinetic data (concentrations and PK parameters) will be summarized using descriptive statistics, including n (for available data), mean, SD, median, minimum, maximum, geometric mean, and CV% calculated as: $100 \cdot \sqrt{(\exp(s^2)-1)}$, where s is the SD of the data on a log scale.

For discrete variables (eg, t_{max}, and t_{min}), only n, minimum, median, and maximum will be reported. In addition, for concentration data, the 95% CIs for the geometric mean will be calculated. CIs will be constructed on a log scale and anti-logged for presentation.

An n ≥3 will be required for calculations of descriptive statistics; except for minimum and maximum, where n ≥2 will be required. If n <2, no descriptive statistics will be calculated; only n will be presented.

All concentration data will be reported and analyzed with the same precision as the source data regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes both in the summary tables and by-subject listings. For the calculation of descriptive statistics and the statistical analysis, rounded values as presented in the data listings will be used. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (eg, C_{max} and C_{min}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual sample collection times (eg, t_{max} and t_{min}) will be reported with the same precision as the actual elapsed sampling time which is presented as 2 decimals.

For the reporting of descriptive statistics, the mean, standard deviation and confidence intervals will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place. Ratios of means for pharmacokinetic parameters will be presented with two decimal places (as a percentage). The p-values, if any, shall be reported to four decimal places or as <0.0001.

In addition, subgroup analyses of the aforementioned will be included by gender.

Pharmacokinetic (PK) Plasma Concentrations

Listings of PK blood sample collection times, derived sampling time deviations, and plasma concentrations of each analyte will be provided. For each analyte, trough (predose) plasma concentrations will be summarized by treatment and scheduled study day. Serial PK concentrations on Day 14 and Day 56 will be summarized by treatment, scheduled study day, and scheduled times.

For each analyte on Day 14 and Day 56, plots of the geometric mean (and corresponding 95% CIs) PK plasma concentrations over time (by study day) will be presented.

In addition, plots of the mean and individual PK plasma trough concentrations versus study day and plots of the geometric mean (and corresponding 95% CIs) PK plasma trough concentrations versus study day will be presented. Day 1 and Day 70 will be excluded from the trough graphical presentations.

Individual overlaid plasma concentration-time profiles on Day 14 and Day 56, presented by patient number, will also be generated for each analyte.

All concentration-time profile plots will be presented on linear and semi-logarithmic scales.

Pharmacokinetic (PK) Parameters

The multiple-dose PK parameters on Day 14 on Day 56 will be summarized by treatments for each analyte.

Scatter plots of individual and geometric mean Day 14 and Day 56 exposure parameters (C_{max}, C_{min}, $AUC_{(0-t)}$, and $AUC_{(0-24)}$) and dose normalized exposure parameters (C_{max}/D, C_{min}/D, $AUC_{(0-t)}/D$, and $AUC_{(0-24)}/D$) versus treatments will be presented as appropriate for bedaquiline and bedaquiline metabolite M2.

Additional graphical presentations of PK data may be added at the discretion of the PK scientist, if further illustration of the PK results is deemed appropriate.

In order to compare the effects of the two J dosing schemes on bedaquiline exposure, the time over MIC (TMIC), C_{max}, C_{min}, C_{trough}, and total exposures ($AUC_{(0-t)}$ and $AUC_{(0-24)}$) of bedaquiline and bedaquiline metabolite M2 will be compared using PK sub-study data from days 14 and 56. The primary comparisons will be performed for the $J_{(loading\ dose/t.i.w.)}$PaZ versus $J_{(200mg)}$PaZ DS-TB arms. Secondary comparisons of these PK parameters and TMIC between the $J_{(200mg)}$MPaZ MDR-TB and $J_{(200mg)}$PaZ DS-TB arms will also be evaluated. On the logarithmic scale, TMIC and PK parameters will be analyzed pairwise using an analysis of variance (ANOVA) with treatment group as main effect. Point estimates and corresponding 95% CIs for the geometric mean will be presented. Point estimates and corresponding 95% CIs for the geometric mean ratios (between treatment groups) will also be presented accordingly. Point estimates and corresponding 95% CI for geometric mean ratios will be estimated after back exponentiation.

9.2 Intense Sampling Pharmacokinetics (PK)-Pharmacodynamics (PD)

Intense sampling PK-PD will be summarized for all patients included in the PK sub-study.

9.2.1 Derivations

For each analyte (i.e. bedaquiline, bedaquiline metabolite M2, PA-824 and moxifloxacin, depending on treatment group), TMIC will be calculated as the percentage of time the PK plasma concentration is above MIC collected at Day -2. The PK and MIC data will be considered on an individual (per patient) basis.

The TMIC calculations will be performed using the MICs with and without accounting for protein-binding shift. The required adjustment is as follows:

Drug	Multiplication Factor
Bedaquiline	8
PA-824	4
Moxifloxacin	1
Pyrazinamide	Not applicable

For the TMIC calculations accounting for protein-binding shift, the MIC of the isolate from the individual study patient at Day -2 will be multiplied by these aforementioned multiplication factors.

The rationale for correction factors to be used to calculate TMIC with protein shift is explained in Appendix 1.

For the calculation of TMIC, the following will be taken into account:

- The number of hours that the individual patient's PK plasma concentration (separately for Day 14 and Day 56) was above the individual patient's predose MIC (Day -2) will be determined:
  - In situations where the PK plasma concentration crosses the threshold, interpolation will be used to determine the exact number of hours that the PK plasma concentration was above the threshold.

- Consequently the time above MIC will be expressed as a percentage (%) of the total hours over the relevant period.

The PK plasma concentration profiles per patient will be used to estimate the time over the threshold using the method described above.

An interpolated timepoint t_i will be calculated using linear or log-linear interpolation as follows:

- Linear interpolation is used when the PK plasma concentrations are increasing.

$$t_i = \left[t_{i-1} + \left| \frac{MIC - C_{i-1}}{C_{i+1} - C_{i-1}} \right| \times (t_{i+1} - t_{i-1}) \right]$$

- Log-linear interpolation is used when the PK plasma concentrations are decreasing.

$$t_i = \left[t_{i-1} + \left| \frac{\ln(MIC) - \ln(C_{i-1})}{\ln(C_{i+1}) - \ln(C_{i-1})} \right| \times (t_{i+1} - t_{i-1}) \right]$$

where C_{i-1} and C_{i+1} are the last available PK plasma concentrations before and after time t_i, i.e. t_{i-1} and t_{i+1}, respectively.

9.2.2 Analysis

Summary tables and data listings for TMIC will be provided for the PK analysis population.

Pearson correlation coefficients of the following will be calculated and presented in summary tables and figures for the PK analysis population with valid efficacy data available:

- The individual (per patient) estimates of BA_{TTP}(0-56), BA_{TTP}(14-56), BA_{CFU}(0-56) and BA_{CFU}(14-56) as calculated from the joint Bayesian NLME regression model versus the following PK parameters (per analyte):
  - C_{max} (Day 14 and Day 56).
  - $AUC_{(0-24)}$ (Day 14 and Day 56).
  - $TMIC_{(0-24)}$ (%) (Day 14 and Day 56).

The correlation analysis is only applicable to overnight sputum samples; "**7H11S**" only (CFU count).

10 Pharmacokinetic (PK) Plasma Concentration-QT Prolongation

10.1 Derivations

The relationship between predose PK plasma concentrations (for each analyte) versus the change from baseline in predose QT interval, QT interval corrected by Bazett's method (QTcB) and QT interval corrected by Fridericia's method (QTcF) (i.e. matched by timepoint) will be assessed.

10.2 Analysis

Pearson correlations between PK trough concentrations (for each analyte) and change from baseline in predose QT, QTcB and QTcF intervals (matched by timepoint and visit) will be presented in tables and figures for the PK-PD analysis population.

Appendix 1: Rationale for Correction Factors

Most modern drugs are low-clearance drugs, since low clearance often (although not always) equates to long half-life and therefore once daily dosing. For low-clearance drugs, the biological activity in vivo is driven by the unbound (free) drug concentration.

In static in vitro systems, the setting by definition is low clearance and the free drug concentration will determine the biological response. If the free drug concentration in the in vitro system is different from that in vivo, a correction factor needs to be applied to extrapolate the in vitro results to the in vivo situation.

In the case of measuring MICs for *Mycobacterium* TB, protein in the medium is required. The most common protein used is bovine serum albumin (BSA) at a final concentration of 5 g/L, which is approximately one-eighth the concentration found in plasma. For a drug which is highly albumin-bound in plasma, 5 g/L BSA can still result in a very high degree of protein binding. In such a case, the measured MIC is not the intrinsic MIC of free drug. Therefore, extrapolating from the in vitro MIC to the MIC in plasma cannot be done just by multiplying the measured MIC by a correction factor based on the free fraction of drug in plasma. The correction factor needs to be adjusted for the free fraction in the in vitro assay as well.

Measuring MICs in whole serum is not done due to technical limitations. So, how do we decide on the appropriate correction factor to extrapolate in vitro findings to the in vivo situation?

This is easiest in the case of highly (> 99%) protein bound drugs where the free fraction is approximately linearly related to the amount of protein. That is, an in vitro system with one-eighth the amount of relevant protein as in plasma has an 8-fold higher free fraction of that drug than does plasma. In such a case, a measured in vitro MIC needs to be multiplied by a factor of 8 to obtain the predicted MIC in plasma.

For other drugs the calculation can be performed as follows. For an "unsaturable" drug, or a drug far from saturation like albumin, the mass action equation reduces to $B = nKF$, where B is the concentration of bound drug, n is the number of binding sites, K is the equilibrium association constant, and F is the concentration of free drug. The ratio $B/F = nK$ and is directly proportional to the number of binding sites. Let us set $B + F = 1$ (or 100%).

Thus, for the case of PA-824, which is a low clearance drug that is 85% bound to albumin in human plasma (which contains 40 g/L albumin), B/F in plasma = 85/15 = 5.67. B/F in the medium in which the MIC data are generated, containing 5 g/L albumin, is 8-fold lower, or 0.71. If $B/F = 0.71$ and $B + F = 1$ (setting the total $B + F$ to 100%), then solving algebraically $F = 0.58$. That is, in the medium in which the MIC data are generated, PA-824 is 58% free, or approximately 4-fold its free fraction in plasma. Therefore, a factor of 4 should be applied to the MIC in plasma, that is, an MIC measured in the usual assay should be multiplied by four to ascertain the MIC in plasma. This in fact was confirmed experimentally, with a 4.2-fold shift in MIC observed as the albumin concentration in the MIC assay medium was increased from 5 g/L to 40 g/L.

For the case of bedaquiline, which is greater than 99% protein bound in plasma, we use our (above) factor of 8. That is, the MIC in plasma is considered 8 times the MIC measured in the in vitro assay.

For the case of moxifloxacin, which is 30-50% bound in human plasma, correcting for protein binding is not considered necessary, as the correction factor would be within the error of the MIC assay.

Appendix 2: Programming Conventions for Tables, Data Listings and Figures (TLFs)

Paper Size, Orientation and Margins

The margin, page size and line size specifications as stipulated below will be used for the presentation of all TLFs:

	Landscape	Portrait
Margins (Inches):		
Top	1.25	1
Bottom	1	1
Left	1	1.25
Right	1	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® specifications:		
PAGESIZE	46	67
LINE SIZE	134	93

Fonts

The font type 'Courier New' should be used as default for tables and data listings, with a font size of 8. The font color should be black. No bolding, underlining and italics are permitted.

Header Information

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page).
- The sponsor name should appear in row 1, left-aligned.
- The word "CONFIDENTIAL" should appear in row 1, right-aligned.
- The protocol number should appear in row 2, left-aligned.
- The page identification in the format Page X of Y (where Y is the total number of pages for the TLF) should appear in row 2, right-aligned.
- The TLF identification number should appear in row 3, centered.
- The TLF title should start in row 4, centered.
- The TLF population should appear in row 5, centered. The population should be spelled out in full, e.g. Safety Analysis Population in preference to Safety analysis population.
- Row 6 should be a continuous row of underscores ('_') (the number of underscores should equal the line size).
- Row 7 should be a blank line.
- Mixed case should be used for titles.
- The column headings should be underlined with a row of underscores ('_').
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings should be in mixed case.
- In general, the analysis population count should appear in the column header in the form "(N=XXX)".

Table and Data Listing Table, Listing and Figure (TLF) Conventions

General:

- The first row in the body of the table or data listing should be blank.
- The left hand column should start in Column 1. No indenting or centering of the TLF should occur.
- Rounding should be done with the SAS® function ROUND.
- Numerical values in tables should be rounded, not truncated.
- Numerical values should be decimal point aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The study drug should appear first in tables with treatment group as columns.
- All variables contained on the eCRF (which have data present) should appear in the data listings, along with all derived data appearing in the corresponding tables.
- The width of the TLF should match the line size.

Univariate statistics:

- Statistics should be presented in the same order across tables (i.e., n, mean, SD, minimum, median and maximum).
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum, maximum and CV (%): N.
  - Mean and median: N + 1.
  - SD: N + 2.

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
  - 77 (100.0)
  - 50 (64.9)
  - 0 (0.0)
- Where counts are zero, percentages of 0.0 should appear in the table.

CIs:

- CIs should be presented with one additional decimal place as that of the raw data, and SDs and standard errors (SEs) with two additional decimal places as that of the raw data.
- CIs should be justified so that parentheses displayed on consecutive lines of a table “line up”.

P-values:

P-values should be reported to four decimal places.

Ratios:

Ratios should be reported with one additional decimal place as that of the raw data.

Spacing:

Missing values:

A “0” should be used to indicate a zero frequency.

A blank will be used to indicate missing data in data listings.

Figure Output Conventions

Figures should be provided in RTF files using the SAS® Output Delivery System (ODS).

Dates and Times

Depending on data available, dates and times will take the form ddMMMyyyy and hh:mm.

Spelling Format

The spelling format to be used is English US.

Presentation of Treatment Groups

For TLFs, treatment groups will be represented in the following order:

Treatment Group	TLF Abbreviation
See Section 3.1 of main SAP handling safety and efficacy	$J_{(loading\ dose/t.i.w.)}PaZ$
See Section 3.1 of main SAP handling safety and efficacy	$J_{(200\ mg)}PaZ$
See Section 3.1 of main SAP handling safety and efficacy	HRZE
See Section 3.1 of main SAP handling safety and efficacy	$J_{(200\ mg)}MPaZ_{MDR}$
Screening Failure	Screening Failure

Presentation of Visits

For outputs, visits will be represented in the following order:

Visit Name
Day -9 to Day -3
Day -2
Day -1
Day 1
Baseline
Day 4
Day 8
Day 14
Day 15
Day 22
Day 29
Day 36
Day 43
Day 50
Day 56
Day 57
Day 70/Follow-up
Day 140/Follow-up
Unscheduled (chronologically)

Visit Name
Early Withdrawal
Month 8 Follow-Up
Month 14 Follow-Up
Month 20 Follow-Up
Month 26 Follow-Up

Note: Overnight sputum sample collection started one day prior to the visit.