Statistical Analysis Plan: Gates MRI-TBD03-201

Study Title:	A phase 2a, dose escalation, controlled, randomized study to evaluate safety, early bactericidal activity (EBA) and pharmacokinetics of TBA-7371 in adult participants with rifampicin-sensitive pulmonary tuberculosis
Study Number:	Gates MRI-TBD03-201
Study Phase:	2a
Sponsor:	Bill & Melinda Gates Medical Research Institute (Gates MRI) 245 Main Street Cambridge, MA 02142
Version	Amendment 1
NCT#:	NCT04176250
Date:	4 October 2022

Confidentiality Statement

1 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

2 SIGNATURE PAGE

Study Title: A phase 2a, dose escalation, controlled, randomized study to evaluate safety, early bactericidal activity (EBA) and pharmacokinetics of TBA-7371 in adult participants with rifampicin-sensitive pulmonary tuberculosis

Study Number: Gates MRI-TBD03-201

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I am the author of this document
Signing Time: 10-Oct-2022 | 11:24:48 EDT
F60BA739EB864856A2326BB0C7ABC408

Prepared by: _____ Date: 10-Oct-2022 | 11:24:59 EDT
[redacted]
Biostatistician II
MMS Holdings, Inc.

[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10-Oct-2022 | 11:26:33 EDT
062F6857B8694CC8BBA87850CC5DEAE5

Reviewed by: _____ Date: 10-Oct-2022 | 11:26:36 EDT
[redacted]
Senior Manager, Biostatistics
MMS Holdings, Inc.

Approved by: _____ Date: _____
[redacted] Ph.D.
Portfolio Statistics Leader
Gates MRI

Approved by: _____ Date: _____
[redacted] MD, MSc
Clinical Development Leader
Gates MRI

Approved by: _____ Date: _____
[redacted]
Clinical Operations Leader
Gates MRI

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	Adverse Drug Reaction(s)
AE	adverse event(s)
AESI	adverse event of special interest
AIC	Akaike Information Criteria
ATC	Anatomical Therapeutic Chemical
AUC_{inf}	Area Under the Plasma Concentration-Time Curve Extrapolated to Infinity
AUC_{last}	Area Under the Plasma Concentration-Time Curve up to the Last Measurable Drug Concentration
AUC_{tau}	Area Under the Plasma Concentration-Time Curve to the End of the Dosing Period
BA_{CFU}	Bactericidal Activity as Assessed by CFU
BA_{LAM}	Bactericidal Activity as Assessed by Sputum LAM Assay
BA_{TTP}	Bactericidal Activity as Assessed by TTP
BCI	Bayesian Credi ility Interval
BID	Bis in Die (atin for twice a day)
BP	Blood Pressure
bpm	Beats Per Minute
BT	Body Temper ture
BW	Body Weight
CFU	Colony Forming Units
CI	Confidence Interval
C_{max}	Maximum Plasma Drug Concentration
C_{min}	Minimum Plasma Drug Concentration
CRO	Contract Research Organization
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
EBA	Early Bactericidal Activity
EWV	Early Withdrawal Visit

ECG	Electrocardiogram
eCRF	Electronic Case Report Form
HRZE	Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E)
Gates MRI	Gates Medical Research Institute
HR	Heart Rate
IDMC	Independent Data Monitoring Committee
LAM	Lipoarabinomannan
LLOQ	Lower Limit of Quantification
MAR	Minimum angle of resolution
MIC	Minimum Inhibitory Concentration
min	Minute
mL	Milliliter
MGIT	Mycobacteria Grow n Indicator Tube
mITT	Modified Intent-to-Treat
PD	Pharmacodynamics
PE	Physical Examination
PK	Pharmacokinetics
PP	Per Protocol
PT	Prothrombin Time
QD	Quaque Di ′Latin for once a day)
QTcF	QT Corrected for HR Using Fridericia's Method
RR	Respiratory Rate
SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class

TB	Tuberculosis
TID	Ter in Die (Latin for three times a day)
T_{max}	Time to Maximum Plasma Drug Concentration
TNTC	Too numerous to count
TTP	Time to sputum culture Positivity
λ_z	Elimination Rate Constant

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the framework of the statistical analyses, including the planned tables, listings and figures to assess the safety, early bactericidal activity (EBA) and pharmacokinetics (PK) of TBA-7371 in adult participants with rifampicin-sensitive pulmonary tuberculosis. The details in this SAP are based on Gates MRI-TBD03-201 protocol amendment 3 (Version 4) dated 07 July 2020 and Independent Data Monitoring Committee (IDMC) charter, version 1 dated 07 October 2019.

5 OBJECTIVES AND ENDPOINTS

5.1 Primary Objectives and Endpoints

The primary bactericidal activity objective of this study is to demonstrate the 14-day early bactericidal activity from screening ("0") to day 14 (EBA 0-14) of 5 dose regimens of TBA-7371 monotherapy and Isoniazid[H], Rifampicin[R], Pyrazinamide[Z], Ethambutol[E] (HRZE) fixed dose combination, as assessed by colony forming unit (CFU) counts on solid media culture. The primary endpoint associated with this objective is the average change per day, from screening ("0") to day 14 [BA_{CFU}(0-14)] of the log_{10}CFU/mL counts.

The primary safety objective of this study is to assess the severe/serious adverse event (AE) burden of 5 dose regimens of TBA-7371 monotherapy and HRZE over a 14-day treatment period. The primary endpoint associated with this objective is frequency of study participants who experienced one or more severe (≥ grade 3) and /or serious AEs from day 1 to through day 15.

Primary early bactericidal activity and safety objectives and associated endpoints are summarized in the Table 1.

Table 1. Primary Objective and Endpoint

Objectives	Endpoint
Early bactericidal activity	
Demonstrate the 14-day EBA from screening ("0") to day 14 of 5 dose regimens of TBA-7371 monotherapy and HRZE as assessed by CFU counts on solid media culture.	Slope, i.e. average change per day, from screening ("0") to day 14 [BA_{CFU}(0-14)] of the log_{10}CFU/mL counts.
Safety	
Assess the severe/serious AE burden of 5 dose regimens of TBA-7371 monotherapy and HRZE over a 14-day treatment period.	Frequency of study participants who experienced one or more severe (≥ grade 3) and /or serious AEs from Day 1 through Day 15.

5.2 Secondary Objectives and Endpoint

Secondary EBA, safety and pharmacokinetics/pharmacodynamics (PK/PD) objectives and associated endpoints are summarized in Table 2.

Table 2. Secondary Objectives and Endpoint

Objectives	Endpoint
Early bactericidal Activity	
Demonstrate the EBA of the first 2 days (screening ["0"] to day 2) and of the remaining 12 days (day 2 to day 14) of 5 dose regimens of TBA-7371 monotherapy and HRZE, as assessed by CFU counts on solid media culture	• Slope, i.e. average change per day, from Screening (Day 0) to Day 2 [BA_{CFU}(0-2)] of the log_{10}CFU/mL counts; • Slope from Day 2 to Day 14 [BA_{CFU}(2-14)] of the log_{10}CFU/mL counts.
Demonstrate the EBA of 5 dose regimens of TBA-7371 monotherapy and of HRZE, as assessed by alternative methods: • Time to sputum culture positivity (TTP) in Mycobacteria Growth Indicator Tube (MGIT) culture • Sputum lipoarabinomannan (LAM) assay	TTP: • Slope of the time to TTP in the MGIT system from Screening (Day 0) to Day 14 [BA_{TTP}(0-14)], • Slope of the TTP in the MGIT system from Screening (Day 0) to Day 2 [BA_{TTP}(0-2)]; • Slope of the TTP in the MGIT system from Day 2 to Day 14 [BA_{TTP}(2-14)]; LAM: • Slope of the log concentration of sputum LAM from Screening (Day 0) to Day 14 [BA_{LAM}(0-14)]; • Slope of the log concentration of sputum LAM from Screening (Day 0) to Day 2 [BA_{LAM}(0-2)]; • Slope of the log concentration of sputum LAM from Day 2 to Day 14 [BA_{LAM}(2-14)].
Safety	
Assess the adverse event (AE) profile of each dose regimen of TBA-7371 and HRZE over the 14-day treatment period.	Frequency from Day 1 through Day 15 of participants with AE and frequency of AEs: overall, by system organ class (SOC) and preferred term; by seriousness, intensity (severity), expectedness and relatedness to study drug.
Assess the impact on eye symptoms, visual acuity and color vision of each dose regimen of TBA-737 and HRZE over the 14-day treatment period.	From Day 1 through Day 15: • Frequency of participants with any new (vs. Screening) eye symptom in one or both eyes. • Mean and frequency distribution of duration of each eye symptom. • Mean and frequency distribution of percentage of days with any eye symptom and each of the eye symptoms.

Table 2. Secondary Objectives and Endpoint

	• Mean/median changes in visual acuity score from Screening to lowest score during Days 1-15. • Frequency of participants with any new color vision abnormalities (tritan, protan, deutan) in one or both eyes and degree of severity (mild, moderate, severe).
Assess the impact on heart rate (HR), blood pressure (BP) and electrocardiogram (ECG) profile of each dose regimen of TBA-7371 and of HRZE over the 14-day treatment period.	From Day 1 through Day 15: • Mean and frequency distribution of changes in heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) as measured by the following 2 (BP) or 3 (HR) methods: ▪ Manual HR, SBP and DBP from vital signs, after at least minutes in supine position ("manual, supine"); ▪ Manual HR, SBP and DBP from vital signs, after 2 (±0.5) minutes in standing position ("manual, 2-minute standing"); ▪ HR from ECG, supine position ("ECG, supine") • Frequency of participants with ≥ 25% increase in HR, decrea in SBP, decrease in DBP vs. baseline as measured with any of the methods described above. • Mean and frequency distribution of percentage of days with ≥ 25% increase in HR, decrease in SBP, decrease in DBP vs. baseline. Mean/median change from Screening through Day 15 in PR, RR, QRS, QT, and QTcF interval values from baseline ECG.
Assess whether there is tachyphylaxis over the -day treatment period for HR, SBP, DBP and eye symptoms	• Mean change in HR, SBP, and DBP from Day 1 to Days 4, 7, 10, 14, and 15 for each of 2 BP and 3 HR measurement methods described above. • Change in frequency of participants with eye symptoms (all, severe, serious) and change in worst visual acuity score and frequency of color vision abnormalities (tritan, protan, deutan) in one or both eyes and degree of severity (mild, moderate, and severe) from Day 1 to Days 4, 7, 10, 14, and 15.
Assess whether cardiovascular and/or ophthalmic adverse events persist or recur up to 4 weeks after discontinuation of treatment with TBA-7371.	• Mean change in HR, SBP, and DBP from Baseline to Days 28 and 42 and from Day 14 to Days 28 and 42 as measured by the following 2 (BP) or 3 (HR) methods: ▪ Manual HR, SBP and DBP from vital signs, after at least 10 minutes in supine position ("manual, supine");

Table 2. Secondary Objectives and Endpoint

	▪ Manual HR, SBP and DBP from vital signs, after 2 (±0.5) minutes in standing position ("manual, 2-minute standing"); ▪ HR from ECG, supine position ("ECG, supine") • Change in frequency of participants with eye symptoms (all, severe, serious) and change in mean visual acuity score and frequency of color vision abnormalities (tritan, protan, deutan) in one or both eyes and degree of severity (mild, moderate, and severe) from Screening to Days 28 and 42 and from Days 1-15 (combined) to Days 28-42 (combined).
Assess whether there are meaningful changes in safety laboratory measurement	For each blood/serum and urine parameter: • Mean, median, highest and lowest value. • Shift tables from Screening to Day 3, Day 7, Day 14, and Day 42.
Secondary, PK and PK/PD	
Evaluate the pharmacokinetics of TBA-7371 monotherapy over the 14-day treatment period.	TBA-7371 concentration profiles and PK parameters over the 14-day treatment interval: C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, $AUC_{1\ st}$, AUC_{tau}, C_{min}, half-life, accumulation ratios.
Identify the lowest exposure to of TBA-7371 associated with maximal EBA effect.	Expected concentration associated with 90% of the maximal TBA-7371 EBA effect (EC_{90}).

5.3 Exploratory Objectives

Details of exploratory objectives will be included in separate operational and/or analysis plans. Results of exploratory objectives may be reported separately from the main clinical study report.

Exploratory objectives may include but are not limited to:

- Exploration of the correlation between EBA and biomarkers such as mycobacterial cell-free DNA, ribosomal RNA ratio assay, sputum and/or peripheral blood gene expression profiles and serum cytokines or other proteins, urine LAM, and bacterial genotypic evaluations for emergence of resistance;
- Testing of susceptibility to TBA-7371 [minimum inhibitory concentration (MIC)];
- Population PK modeling.

6 STUDY DESIGN CONSIDERATIONS

6.1 Study Design

This is an interventional, 5-cohort, 3-step dose escalation clinical trial in adult participants between 18 to 60 years of age with rifampicin-sensitive pulmonary tuberculosis (TB). The escalation will occur sequentially in 3 steps: from Cohort I to Cohorts II and III, from Cohorts II and III to Cohort IV and from Cohort IV to Cohort V (see Figure 1). Within the 1st escalation step, participants will be randomized equally (1:1) to Cohort II or Cohort III, which have the same total daily dose (200 mg, see below). Within each cohort, participants will be randomized unequally (5:1) to TBA-7371 or HRZE (isoniazid [H] / rifampicin [R] / pyrazinamide [Z] / ethambutol [E]) fixed dose combination tablets. Rifafour® e-275 (Sanofi) tablets, a commercial presentation of HRZE approved and available in South Africa, will be used in the study. The study is open-label with masked laboratory assessments (except PK).

Each participant will undergo 3 study phases: Screening Phase, lasting up to 7 days, with no TB treatment; a 14-day Study Treatment Phase on TBA-7371 or HRZE; and a 28-day Follow-up Phase on standard of care TB treatment.

An IDMC will make dose escalation recommendations to the Sponsor. After the last Cohort I participant completing the Study Treatment Phase (day 14), the IDMC will recommend whether Cohort II and Cohort III can start enrollment (1st escalation step). The same approach will be taken for the 2nd escalation step from Cohorts II & III to Cohort IV and for the 3rd escalation step from Cohort IV to Cohort V. For each escalation step, the "go / no-go" recommendation will be based on accumulating safety data provided in an un-masked fashion to the IDMC. Additional data (e.g. PK) may be provided if available as supporting evidence.

Authorized study site personnel will dispense each dose of study drug.

This study will be open label for study participants, study site personnel, IDMC members, laboratory personnel involved in PK measurements and all sponsor and contract research organization (CRO) personnel. The study will be masked (blinded) for personnel involved in the conduct of all other laboratory procedures (including those for the primary end-point).

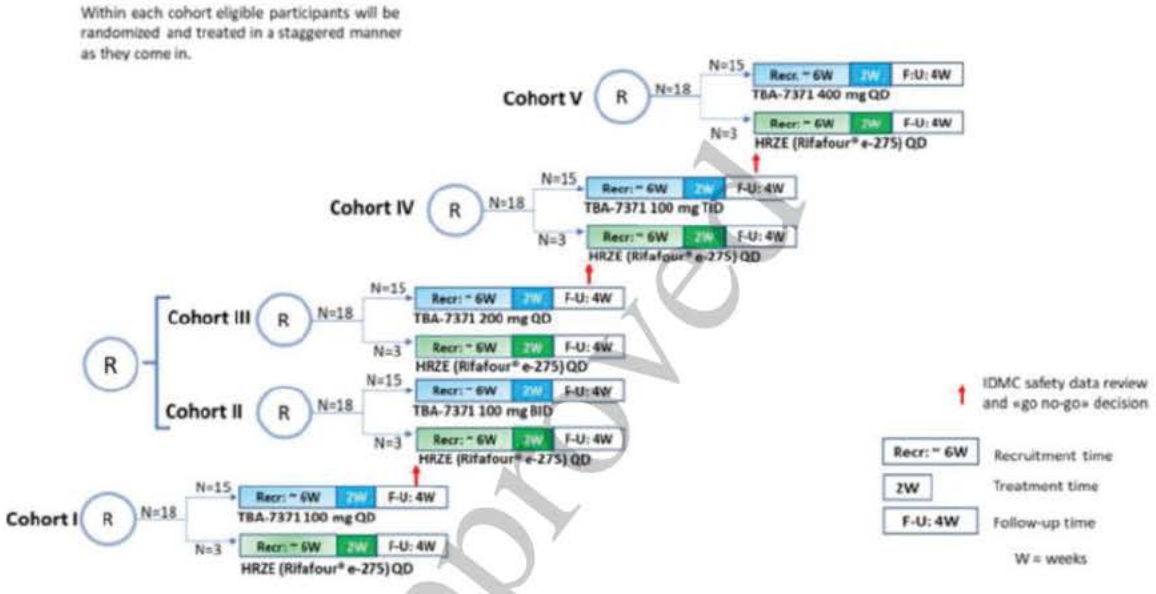
Study participants will be hospitalized for up to 7 days for the Screening Phase and will remain in hospital until the day after the last dose of study drug is dispensed (day 15). Written informed consent must be given before any screening procedure is started. Participants will leave the hospital on day 15 after all procedures scheduled for that day have been completed. Thereafter, participants will undergo scheduled visits on days 28 and 42 (±3 days) as outpatients during the Follow-up Phase.

Candidates will be screened to achieve 90 randomized study participants. Within each dose escalation cohort, 18 participants will be randomly assigned in a 5:1 ratio to TBA-7371 (N=15) or HRZE (N=3). The total sample size of the HRZE group (all cohorts combined) will be 15, assuming all cohorts will be allowed to undergo treatment.

Within each cohort, there will be no replacement for the first 2 early withdrawals (drop-outs) occurring in the Treatment Phase. Drop-outs from the 3rd onwards will be replaced to ensure that the total number of participants completing study treatment in each cohort is at least 16. Participants who withdraw prematurely during the Follow-up Phase will not be replaced.

6.1.1 Study Schema

Figure 1. Study Schema



Schedule of activities is presented in Appendix 1.

6.2 Sample Size Determination

Anticipating all cohorts are to be assessed in the study, approximately 90 participants will be randomized in a 5:1 ratio to either TBA-7371 or control group, totaling N = 15 participants for each TBA-7371 treatment and control groups (receiving treatment with HRZE).

Bactericidal effect

Based on Diacon et al. (Diacon, 2013) standard deviations associated with $BA_{CFU}(0\text{-}14)$ were relatively consistent across 5 treatment groups, ranging from 0.05 to 0.08. If we assume conservatively that the true standard deviation of the $BA_{CFU}(0\text{-}14)$ measures for the TBA-7371 treatment groups is equal to 0.1, then with N = 15 per group we have 80% (90%) power to detect a true group mean $BA_{CFU}(0\text{-}14)$ reduction of 0.067 (0.079), using a 1-sided alpha = 5%. For reference, the observed $BA_{CFU}(0\text{-}14)$ reduction in Diacon et al, 2013 were 0.040, 0.056, 0.077, 0.104, and 0.122 for Bedaquiline 100 mg, 200 mg, 300 mg, 400 mg and standard HRZE, respectively.

Safety

With N = 15 per group, we have approximately 80% (90%) probability to observe at least one AE if the true AE rate is 10% (15%). We have only 54% probability to observe at least one AE if the true AE rate is 5%. Across the five TBA-7371 treatment groups (N=75), we have 90% probability to observe at least one AE if the true AE rate is 3.0%.

6.3 Efficacy Measures

Table 3. Efficacy Endpoint

	Endpoint
Primary EBA	Slope, i.e. average change per day, from Screening (Day 0) to Day 14 [BA_{CFU}(0-14)] of the log CFU counts.
Secondary EBA	• Slope, i.e. average change per day from Screening (Day 0) to Day 2 [BA_{CFU}(0-2)] of the log CFU counts. • Slope, i.e. average change per day from Day 2 to Day 14 [BA_{CFU}(2-14)] of the log CFU counts. • Slope of the time to sputum culture positivity (TPP) in the MGIT system from Screening ("0") to Day 14 [BA_{TTP}(0-14)]. • Slope of the TPP in the MGIT system from Screening (Day 0) to Day 2 [BA_{TTP}(0-2)]. • Slope of the TPP in the MGIT system from Day 2 to Day 14 [BA_{TTP}(2-14)]. • Slope of the log concentration of sputum LAM from Screening (Day 0) to Day 14 [BA_{LAM}(0-14)] • Slope of the log concentration of sputum LAM from Screening (Day 0) to Day 2 [BA_{LAM}(0-2)] • Slope of the log concentration of sputum LAM from Day 2 to Day 14 [BA_{LAM}(2-14)].

6.4 Safety Measures

Table 4. Safety Endpoint

	Endpoint
Primary safety	Frequency of study participants who experienced one or more severe (≥ grade 3) and/or serious AEs from Day 1 through Day 15.
Secondary safety	Adverse events from Day 1 through Day 15: • Frequency from Day 1 through Day 15 of participants with AEs and frequency of AEs: overall, by system organ class and preferred term; by seriousness, severity, expectedness and relatedness to study drug. Eye symptoms from Day 1 through Day 15:

Table 4. Safety Endpoint

	• Frequency of participants with any new (vs. Screening) eye symptom in one or both eyes. • Mean and frequency distribution of duration (hours) of each eye symptom. • Mean and frequency distribution of percentage of days with any eye symptom and each of the eye symptoms. • Mean/median change in visual acuity score from Screening to lowest score during Days 1-15. • Frequency of participants with any new color vision abnormalities (tritan, protan, deutan) in one or both eyes and degree of severity (mild, moderate, severe). Heart rate (HR) and blood pressure (BP) from Day 1 through Day 15: • Mean and frequency d ،tribution of changes in HR, SBP and DBP as measured by the following 2 (BP) or 3 (HR) methods: o Manual H ،، SBP and DBP from vital signs, after at least 10 minutes in supine position (“manual, supine”); o Manua، HR, SBP and DBP from vital signs, after 2 (±0.5) minutes in standing position (“manual, 2-min standing”); o HR from ECG, supine position (“ECG, supine”) • Frequency of participants with ≥ 25% increase in HR, decrease in SBP, decrease in DBP s. baseline as measured with any of the methods described above. • Mean and freque٣ y distribution of percentage of days with ≥ 25% increase in HR, decrease in SBP, decrease in DBP vs. baseline. • Mean/median change from screening through day 15 in RR, PR, QRS, QT, QTcF values from baseline ECG. Tachyphylaxis over the 14-day treatment period for HR, SBP, DBP and eye symptoms: • Mean change in HR, SBP and DBP from Baseline (Day 1, pre-dose) to Days 4, 7, 10, 14, and 15 for each of the 2 BP and 3 HR measurement methods described above. • Change in frequency of participants with eye symptoms (all, severe, serious) and change in worst visual acuity score and frequency of color vision changes from Day 1 to Days 4, 7, 10, 14 and 15. Cardiovascular and/or ophthalmic AEs persistence or recurrence up to 4 weeks after discontinuation of treatment with TBA-7371: • Mean change in HR, SBP and DBP from Baseline (Day 1, pre-dose) to Days 28 and 42 and from Day 14 to Days 28 and 42 for each of the following measurement methods:

Table 4. Safety Endpoint

	○ Manual HR, SBP and DBP from vital signs, after at least 10 minutes in supine position ("manual, supine"); ○ Manual HR, SBP and DBP from vital signs, after 2 (±0.5) minutes in standing position ("manual, 2-min standing"); ○ HR from ECG, supine position ("ECG, supine") • Change in frequency of participants with eye symptoms (all, severe, serious) and change in worst visual acuity score and frequency of color vision changes from Screening (Day 0) to Days 28 and 42 and from Days 1-15 (combined) to Days 28-42 (combined). Safety laboratory measurements: • Mean, median and range of each blood/serum and urine safety parameter at screening, Days 3, 7, 14, and 42. • Shift tables of blood/serum and urine safety parameter from screening to Days 3, 7, 14 and 42.

6.5 Pharmacokinetic Measures

Table 5. PK and PK/PD Endpoint

	Endpoint
Secondary PK and PK/PD	• TBA-7371 concentration profiles and PK parameters over the 14-day treatment interval: C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{tau}, C_{min}, half-life, accumulation ratios. • Correlation between TBA-7371 AUC, C_{max}, T>MIC and CFU counts on solid media culture. • Expected concentration associated with 90% of the maximal TBA-7371 EBA effect (EC_{90}).

7 STUDY POPULATIONS

7.1 Populations for Analyses

Analysis populations are show in Table 6.

Table 6. Populations for Analyses

Population	Description
Randomized population	All participants randomly assigned to study intervention, who either have randomized date or randomization number.
Modified intention to treat (mITT) efficacy population	All participants randomly assigned to study intervention, who received at least one dose of the study intervention. Participants will be analyzed according to the intervention they actually received.
Per Protocol (PP) efficacy population	All participants randomly assigned to study intervention, who received the study intervention, and did not substantially deviate from the protocol procedures. Participants who substantially deviated will be identified prior to database lock. Participants will be analyzed according to the intervention they actually received.
Safety population	All participants randomly assigned to study intervention and who received at least one dose of the study intervention. Participants will be analyzed according to the intervention they actually received.
PK population	All participants who received at least one dose of TBA-7371 and have at least one pair of pre- and post-dose blood samples with measurable concentrations.

8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

No changes have been made to the planned analyses.

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 General Conventions

Treatment groups consist of the following study interventions:

1. TBA-7371 100 mg QD
2. TBA-7371 100 mg BID
3. TBA-7371 200 mg QD
4. TBA-7371 100 mg TID
5. TBA-7371 400 mg QD
6. HRZE QD

The nomenclatures of study interventions will be used to display in tables, figures, and listings.

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated using descriptive statistics. For categorical variables, summary tables will be provided giving sample size, absolute and relative frequency. For continuous variables, summary tables will be provided giving sample size, arithmetic mean, geometric mean (if appropriate), standard deviation, coefficient of variation (if appropriate), median, minimum and maximum. For variables with non-normal distribution, medians and interquartile range will be calculated, and the appropriate non-parametric tests will be applied. Unless specified otherwise, all confidence intervals will be two-sided 95% confidence intervals. Given the primary endpoint is tested using a one-sided test at 0.05, the corresponding 90% confidence interval will be provided. One-sided p-value will be displayed with 4 decimal places; if the p-value is less than 0.0001, display as "<0.0001".

Change from baseline or screening for a measured variable at a particular post-baseline time point will be computed as the value at the post-baseline time point minus the baseline or screening value, as appropriate.

Percentages will be displayed with one decimal place and percentages for zero counts will be omitted from the presented results. If the percentage is greater than 0 but rounds to 0.0% (e.g. 0.04%), display as "(<0.1)".

SAS code of SAS procedures that will be used to perform efficacy and safety analyses is provided in Appendix 4.

9.2 Definitions

Screening EBA Measure: Average of the EBA measurements (i.e., log CFU, TTP in MGIT, and log concentration of sputum LAM) from the day -2 and day -1 overnight sputum samples of the screening phase will be used to determine the screening EBA measurement. If one of the overnight sputum samples is missing, the single non-missing sample will be directly used as the screening EBA measurement.

Baseline definition for other efficacy and safety variables: The last assessment made prior to the first administered dose of study intervention will be considered baseline for analysis purposes. Baseline values of ECG and vital signs are measured on Day 1 before the first dose of study medication is administered.

Day 1: Study day 1 is the day of first administration of TBA-7371 or HRZE. Positive study days will be counted forward from Day 1. Day -1 will be the date immediately preceding Day 1, and negative study days will be counted backward from Day 1.

9.3 Interim Analysis

No formal interim analysis is planned in this trial.

Unmasked safety and (if available) PK data on each cohort will be provide to the Independent Data Monitoring Committee (IDMC) to aid in recommendations related to dose escalation.

9.4 Handling of Missing Data

9.4.1 Missing or Partial Dates for Adverse Events

Missing or partial AE start dates will be imputed for the purpose of determining whether the AEs are treatment emergent. Data handling rules for missing or partial start/stop date for AEs are detailed in Appendix 2. The missing or partial dates will be displayed in the data listings as reported on the electronic case report form (eCRF) rather than the imputed dates.

9.4.2 Missing Incomplete Dates for Prior or Concomitant Medications

Missing or partial medication start or stop dates will be imputed for the purpose of determining whether the medication are taken concomitantly. Data handling rules for missing or partial start/stop date medications are detailed in Appendix 3. The missing or partial dates will be displayed in the data listings as reported on the eCRF rather than the imputed dates.

9.4.3 Missing Efficacy Data

Unless specified otherwise, no imputation for missing efficacy data will be performed for the planned efficacy analyses.

9.5 Independent Data Monitoring Committee (IDMC)

The IDMC is established to oversee the safety of this study and to make a go/no-go recommendation at each dose escalation step.

The IDMC will operate according to the most current version of the IDMC charter, outlined in the introduction section of this document. The IDMC structure, participants and other details are provided in the charter and are not repeated in this document. The charter describes the scope of responsibilities of the IDMC and identifies its members. Additionally, it outlines the meeting schedule and format, provides procedures for ensuring confidentiality, and explains the administrative procedures that will be followed. The IDMC charter provides meeting information and other details.

The IDMC will review patient profiles containing unmasked safety and, if available, PK data during regularly scheduled safety review meetings. The IDMC may request additional information, or a pause in recruitment and study treatment, while safety data are being evaluated.

9.6 Masking (Blinding)

This study will be open label for study participants, study site personnel, IDMC members, laboratory personnel involved in PK measurements and all sponsor and CRO personnel. The study will be masked (blinded) for personnel involved in the conduct of all other laboratory procedures (including those for the primary end-point).

9.7 Pooling Strategy for Study Sites

Data will be pooled across all study sites.

9.8 Visit Windows/Unscheduled Visits

Efficacy and safety analyses will use the nominal visits as collected in the study database, thereby, visit windows will not be applied.

Unscheduled visits will not be included in by-visit summaries or analysis, but may contribute to the baseline value and worst post-baseline assessments.

10 STATISTICAL ANALYSIS METHODS

10.1 Participant Disposition

The number and percentages of participants for each population (mITT, PP, Safety, and PK) will be summarized. For computing percentages, the denominator will be the number of participants in the mITT population.

Participants' disposition will be summarized for the following study phases:

Screening Phase:

The numbers and percentages of participants who were screened, screen failures, and reasons for screen failure. For computing percentages, the denominator will be the number of participants screened.

Study Treatment Phase:

The number and percentages of participants who were randomized, completed treatment, discontinued treatment and reasons for discontinuation of treatment, completed study, discontinued study and reasons for discontinuation of study will be tabulated by treatment group and will be summarized for mITT, PP, Safety and PK populations. For computing percentages, the denominator will be the number of participants for the given population and treatment group.

10.2 Demographics and Baseline Characteristics

Demographic parameters (age, sex, race, and ethnicity) and other baseline characteristics (body weight, body mass index (BMI), HIV status, CD4+ T-cell count (if HIV-positive), HR, DBP, SBP, current eye symptom, visual acuity impairment in one or both eyes, color vision deficiency in one or both eyes, log CFU on solid culture, TTP in liquid MGIT culture, and log concentration of sputum LAM, drug susceptibility testing for isoniazid and rifampicin, and minimum inhibitory concentrations (MIC) of TBA-7371) will be summarized by treatment group for all participants in the mITT and safety populations.

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, and median, minimum, maximum). Categorical variables will be summarized using counts and percentages.

A data listing of demographics and baseline characteristics will be provided.

10.3 Treatment Exposure

For each participant in the safety population, duration of exposure to study drug will be calculated as (last dose date – first dose date + 1). Duration of exposure will be summarized as both continuous and categorical variables by treatment group. For categorical presentation, the frequency and percentage of participants in each of the following categories will be presented: ≤3 days, 4 to 6 days, 7 to 9 days, 10 to 13 and 14 days by treatment group.

A data listing of treatment exposure will be provided.

10.4 Protocol Deviations

A summary of the frequency and percentage of participants in the safety population with major protocol deviations for each deviation category will be provided by treatment group. A participant with multiple occurrences of a major protocol deviation in the same deviation category will only be counted once. A listing of protocol deviations by treatment group and participant will be provided.

11 EFFICACY PARAMETERS

11.1 Log CFU/mL Counts

11.1.1 Primary Analysis

CFU/mL counts are derived from CFU count per mL collected from the Middlebrook 7H11S plates of overnight sputum samples, where sputum is collected twice during the screening phase (Days -2 and -1) and daily on 14 consecutive days during the study treatment phase (Days 1 to 14). CFU/mL will be calculated as follows:

$$CFU/mL = \frac{mean\ of\ two\ CFU\ plate\ counts}{dilution\ factor \times\ 0.909\ \times\ 0.2}$$

where 0.909 is a 10:1 dilution of sputum in sputasol and 0.2 mL is the volume on the plate.

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

- Contaminated or no result: The CFU/mL counts associated with contaminated or no result samples will be set to missing.
- Too numerous to count (TNTC ≥401 colonies): The CFU/mL counts associated with TNTC samples will be set to 401.
- CFU/mL counts <5: The CFU/mL counts will be set to 5.

The primary end-point will be the slope of the $\log_{10}$CFU/mL counts from Screening to Day 14 [BA_{CFU}(0-14)], i.e., average change in $\log_{10}$CFU/mL count per day over 14 days. The $\log_{10}$CFU/mL counts vs. time profiles over 14 days of treatment may be biphasic, i.e. the rate of change in log CFU changes over time. A simple solution (Diacon et al., 2013) is to characterize the participant-specific log CFU count vs. time profiles using a bilinear regression model, which has been proved to fit the data of many TB bactericidal agents quite well, especially over the time interval of 14 days.

The form of the bilinear regression model is given by:

$$\log_{10} CFU/mL = \alpha - \beta_1 \cdot t + \varepsilon; \qquad t \le \kappa;$$

$$\log_{10} CFU/mL = \alpha + (\beta_2 - \beta_1) \cdot \kappa - \beta_2 \cdot t + \varepsilon; \qquad t > \kappa$$

where the parameters α and κ are the intercept and node parameter of the regression curve, respectively, the slopes β_1 and β_2 characterize the line ،r decline on or before the node ($t \le \kappa$) and after the node ($t > \kappa$), respectively, and ε is the error term assumed to be independently distributed normally with mean zero and variance σ^2. The parameters are constrained to aid in convergence as such: $\alpha > 0,\ 1 < \kappa < 14,\ \sigma^2$ ⁄ 0, all ∈ ℝ. The SAS PROC NLMIXED procedure will be used to fit the bilinear regression model for individual participants in each treatment group. Suggested starting values for the parameters are $(\alpha, \beta_1, \beta_2, \kappa) = (6,0,0,2)$ however a grid search approach can be followed to obtain sensible starting values. See SAS code in the Appendix which uses a grid search and picks the best fitting model.

If the bilinear regression model is selected, the average change in $\log_{10}$ CFU/mL per day over 14 days will be estimated for each ،articipant i by:

$$BA_{CFU}(0-14)_i = \lceil \hat{\kappa}_i \hat{\beta}_{1i} + (14 - \hat{\kappa}_i)\hat{\beta}_{2i}) \rceil / 14$$

where $\hat{\beta}_{1i}$ is the estimated slope prior to the estimated inflection point $\hat{\kappa}_i$, and $\hat{\beta}_{2i}$ is the estimated slope after the estimate ' inflection point $\hat{\kappa}_i$. The parameters of main interest include the slopes $\hat{\beta}_{1i}$ and $\hat{\beta}_{2i}$, and the inflection points, $\hat{\kappa}_i$, and can be readily estimated using least squares. BA_{CFU}(0-14) can be estimated i ⌉ROC NLMIXED directly.

In the case where a subject does not have a non-missing measurement at Day 14, we have that

$$BA_{CFU}(0-t_{last})_i = [\hat{\beta}_{1i} + (t_{last} - \hat{\kappa}_i)\hat{\beta}_{2i})] / t_{last}$$

where t_{last} is the last time point at which CFU was observed.

However, it is also likely that some of the participant specific $\log_{10}$CFU/mL count vs. time profiles will be better characterized using a simple linear regression model.

The form of the simple regression linear model is given by:

$$log_{10} CFU/mL = \alpha - \beta_1 \cdot t + \varepsilon$$

where the parameters α and slope β_1 are the intercept and the slope that characterize the linear decline, and ε is the error term assumed to be independently distributed normally with mean zero and variance σ^2. The SAS PROC NLMIXED procedure will also be used to fit a simple linear

regression model for individual participants in each treatment group in order to ensure the Akaike information criteria (AIC) values for the linear and bilinear models are based on the same form of the likelihood function. Suggested starting values for the parameters are $(\alpha, \beta_1) = (6,0)$ however a grid search approach can be followed to obtain sensible starting values.

If the linear regression model is selected, the average change in $\log_{10}$CFU/mL count per day over 14 days will be estimated by the constant linear regression slope estimate, $\hat{\beta}_{1i}$, i.e.

$$BA_{CFU}(0-14)_i = \hat{\beta}_{1i}.$$

Therefore, for each participant, slopes will be estimated using both bilinear and simple linear regression models, and the better fit model based on lower AIC will be selected for that participant and used to estimate BA_{CFU}(0-14). The $\log_{10}$CFU/mL screening measurement used in the model will be the average of the two individual screening measurements. BA_{CFU}(0-14) will be calculated for each participant within a treatment group individually, and then used as the response variable in an ANCOVA model, with a fixed effect for treatment group and screening $\log_{10}$CFU/mL count as a covariate. Treatment group means from the ANCOVA model will be used to quantify the evidence that each of the treatment group mean BA_{CFU}(0-14) is less than 0 (i.e., that the treatment group mean has a negative slope on average). The mITT population will be used for the primary efficacy analysis with analyses using the per-protocol population performed to assess the robustness of results. The SAS PROC MIXED procedure will be used to fit an ANCOVA model.

Multiplicity will be handled by means of a step-down sequential approach. The five TBA-7371 treatment regimens will be divided into 3 testing groups: Group 1 = Cohort V (400 mg QD) and Cohort IV (100 TID); Group 2 = Cohort III (200 mg QD) and Cohort II (100 BID); and Group 3 = Cohort 1 (100 QD). Group 1, or the group with the highest cohort allowed by the IDMC will be tested first using a Hochberg multiplicity adjustment: if the maximum and minimum one-sided p-values are ≥0.05 and ≥0.025, respectively, formal testing will be stopped and all cohorts below will be declared a failure; if the maximum and minimum one-sided p-values are ≥0.05 and <0.025, formal testing will be stopped but the regimen with p-value <0.025 will be declared a success; if the maximum and minimum one-sided p-values are <0.05 and <0.025, both cohorts will be declared a success and testing will proceed to Group 2 regimens with the same step-down approach to continue until a failed cohort is observed.

The study will be declared a success if at least one of the TBA-7371 treatment groups achieves a statistically significant 1-sided p-value and demonstrates an acceptable safety profile.

Geometric mean and geometric mean ratio of post-baseline to baseline of CFU/mL counts with 95% confidence interval (CI) at each time point will be presented in line plots by treatment group. In addition, observed and fitted lines of bilinear and linear regression models of $\log_{10}$CFU/mL counts over time will be presented for each participant.

11.1.2 Secondary Analysis

EBA measures $BA_{CFU}(0\text{-}2)$ and $BA_{CFU}(2\text{-}14)$ will be calculated from the bilinear regression model and assessed similarly as described for $BA_{CFU}(0\text{-}14)$ in Section 11.1.1. There will be no adjustment for multiple comparisons and no formal success criteria for all secondary EBA measurements.

In order to estimate $BA_{CFU}(0\text{-}2)$ and $BA_{CFU}(2\text{-}14)$, the parameter κ is fixed at 2 so that the bilinear model used becomes

$$\log_{10} CFU/mL = \alpha - \beta_{1i} \cdot t + \varepsilon; \qquad t \leq 2;$$
$$\log_{10} CFU/mL = \alpha + (\beta_{2i} - \beta_{1i}) \cdot 2 - {}_{2i} \cdot t + \varepsilon; \qquad t > 2$$

and therefore we have for participant i that

$$BA_{CFU}(0-2)_i = \hat{\beta}_{1i}$$

and

$$BA_{CFU}(2-14)_i = \hat{\beta}_{2i}.$$

11.1.3 Sensitivity Analysis

Two approaches will be conduct ,d as sensitivity a- alysis of CFU efficacy analysis.

11.1.3.1 ANCOVA model using average change from baseline

Given that treatment ends on Day 14, $BA_{CFU}(0\text{-}14)$ of $\log_{10}$CFU/mL counts over 14 days of treatment will be estimated by calculating an average of the change from baseline to day 14 in log of CFU as follows:

$$BA_{CFU}(0-14)_i = \frac{\log_{10}(CFU/mL)_{14} - \log_{10}(CFU/mL)_{base}}{14}.$$

An ANCOVA model will be fitted as done in Section 11.1.1. If the CFU is missing at Day 14, then the latest time point with a measurement with the corresponding denominator will be used, e.g. if the latest day with a CFU measurement is Day 10, then the divisor in the formula above will be 10.

11.1.3.2 Random intercepts and slopes model across all data points

A mixed model with random intercepts and slopes will be fitted in order to estimate the average change from baseline to Day 14. It will use all log CFU data points for all participants and time points. The model is given by

$$\log_{10} CFU/mL = \alpha + u_i + (\beta_1 + b_i)t + \beta_{2j}X_{1j} + \beta_{3j}X_{1j}t + \beta_4 X_{2i} + \varepsilon_{ij}$$

where $t = 0,1, \ldots, 14$, X_{1j} is the dummy indicator for treatments $j = 1, \ldots, 5$ with HRZE as the reference group, X_{2i} the covariate for baseline $\log_{10}$CFU/mL, u_i the random intercepts with distribution $u_i \sim N(0, \sigma_u^2)$, b_i the random slopes with distribution $b_i \sim N(0, \sigma_b^2)$ and $\varepsilon_{ij} \sim N(0, \sigma^2)$. An unstructured covariance structured will be used for the variance-covariances of the random effects. It may be simplified to variance components (option "vc") if the former doesn't yield convergence or there is no gain in model fit as decided through the AIC. The fixed effects of the model are given by day t, treatment group X_j, baseline $\log_{10}$CFU/mL and the interaction between time and treatment group.

The average slope over time for each treatment group will be estimated and reported with 90% confidence intervals using the time and interaction effects, i.e.

$$(\hat{\beta}_1 + \hat{\beta}_{3j}).$$

11.2 Secondary Efficacy Endpoints

11.2.1 Time to Sputum Culture Positivity

When time to sputum culture positivity for a participant is not concluded by Day 42 (i.e., > 42 days), the value will be defined to be 43 days. For each participant, linear and bilinear regression models will be fit, and the better fit model based on lower AIC similarly as described for BA$_{CFU}$(0-14) in Section 11.1.1 will be used to estimate BA$_{TTP}$(0-14), BA$_{TTP}$(0-2) and BA$_{TTP}$(2-14) of TTP from Screening to Day 14, Screening to Day 2 and Day 2 to Day 14, respectively. BA$_{TTP}$(0-14), BA$_{TTP}$(0-2) and BA$_{TTP}$(2-14) will be analyzed using an ANCOVA model, with a fixed effect for treatment group and baseline TTP as a covariate. An ANCOVA model will be used to quantify the evidence that at the each of the treatment group mean BA$_{TTP}$(0-14), BA$_{TTP}$(0-2) and BA$_{TTP}$(2-14) is less than 0.

Mean and mean change from baseline of TTP with 95% CI at each time point will be presented in line plots by treatment group. In addition, observed and fitted lines of bilinear and linear regression models of TTP over time will be presented for each participant.

11.2.2 Sputum Lipoarabinomannan

When a value of concentration of sputum LAM is < lower limit of quantification (LLOQ), the value will be defined to be half of LLOQ. For each participant, linear and bilinear regression models will be fit, and the better fit model based on lower AIC similarly as described for BA$_{CFU}$(0-14) in Section 11.1.1 will be used to estimate BA$_{LAM}$(0-14), BA$_{LAM}$(0-2) and BA$_{LAM}$(2-14) of log concentration of sputum LAM from Screening to Day 14, Screening to Day 2 and Day 2 to Day 14, respectively. BA$_{LAM}$0-14), BA$_{LAM}$(0-2) and BA$_{LAM}$(2-14) will be analyzed using an ANCOVA model, with a fixed effect for treatment group and baseline log value of concentration of sputum LAM as a covariate. An ANCOVA model will be used to quantify the evidence that each of treatment group mean BA$_{LAM}$(0-14), BA$_{LAM}$(0-2) and BA$_{LAM}$(2-14) is less than 0.

Geometric mean and geometric mean ratio of post-baseline to baseline of concentration of sputum LAM with 95% CI at each time point will be presented in line plots by treatment group. In addition, observed and fitted lines of bilinear and linear regression models of log concentration of sputum LAM over time will be presented for each participant.

11.3 Subgroup Analyses

Subgroup analyses will be performed with respect to the primary efficacy variable. The subgroups will include the following:

- Sex: female and male
- Age group: <45 and ≥45 years old
- HIV: positive and negative (using the Baseline assessment)

11.4 Interim Analysis

No formal interim analysis is planned in this trial.
Unmasked safety and (if available) PK data on each cohort will be provided to the IDMC for dose escalation recommendations.

11.5 Sensitivity Analysis

All sensitivity efficacy analyses will be performed in the per-protocol population to assess the robustness of results.

If the study identifies participants who are randomized to the HRZE treatment group with confirmed isoniazid-resistant and rifampicin susceptible tuberculosis based on the Hain test, a sensitivity analyses of efficacy endpoints will be performed in the HRZE treatment group after excluding these participants from the mITT population.

12 SAFETY ANALYSIS

All safety analyses will be performed in the Safety population.

12.1 Adverse Events

Adverse events (AEs) will be recorded from the time a participant has signed the informed consent until end of study. Each verbatim AE term will be coded to a SOC and preferred term using the most recent version of the Medical Dictionary for Regulatory Activities dictionary version 22.0 or higher. Intensity for each AE will be graded as Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially Life-threatening), or Grade 5 (Death) according to the Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [DAIDS 2017].

If the start date of an AE is incomplete or missing, the event will be assumed to be started after day 1, unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicates that the event started before study day 1.

Summaries of system organ class (SOC) and preferred term will be sorted alphabetically by SOC and by decreasing frequency of preferred term in the all TBA-7371 group (then alphabetically for ties). If a participant has more than one AE at a given level (e.g. SOC and preferred term), the participant will only be counted once within that level.

An AE listing by participant will display all reported AEs up to end of Follow-up visit (Day 42) or the Early Withdrawal visit, and will include the verbatim term in addition to the SOC and preferred term. This listing will also include all relevant data associated with the event: e.g. date of onset, date resolved, date of first dose, date of last dose, severity, frequency, outcome, relationship to study drug, action taken with study drug, and required therapy. When a date is presented, the study day associated with the date will also be displayed. Separate listings will be presented for participants with serious adverse events (SAEs), participants with AEs leading to discontinuation and participants who died, if any.

12.1.1 Primary Safety Analysis

AEs with grade 3 intensity or greater are classified as severe AEs. The frequency distribution of participants who experienced 1, 2, or ≥3 severe AEs occurring from Day 1 through Day 15 will be summarized by treatment group. The frequency and proportion (expressed in percent) of participants and 95% CI for proportions in each category will be provided. For computing proportions, the denominator is the number of participants in the Safety population for the given treatment group.

Serious AEs will be summarized similarly as described for severe AEs.

12.1.2 Secondary Safety Analyses

12.1.2.1 Adverse Events

An AE overview table containing frequency and proportion (expressed in percent) of participants with AEs from Day 1 through Day 15 will be summarized by treatment group for the following:

- Any AE
- AEs with highest intensity [Grade 1, 2, and ≥3 (severe)]
- AEs related to study drug
- AEs leading to study drug discontinuation
- Serious AEs
- Serious adverse drug reactions
- AEs of special interest (AESI)

  In this trial the following AEs will be reported as AESI:

  - Anaphylactic reaction

- ≥ Grade 2 intensity and/or serious AE related to increase of HR;
- ≥ Grade 2 intensity and/or serious AE related to decrease of SBP;
- ≥ Grade 2 intensity and/or serious AE related to decrease of DBP;
- ≥ Grade 2 intensity and/or serious eye symptom-related AE;
- Per clinical discretion, the Investigator has clinical discretion to call an AE as an AESI even if these specific grading criteria are not specifically met.

Additionally, the frequency of AEs and frequency and proportion (expressed in percent) of participants with AE will be provided by SOC and PT and by treatment group for the following:

- Any AE
- AEs with highest intensity [Grade 1, 2, and ≥3 (severe)]
- AEs related to study drug
- AEs leading to study drug discontinuation
- Serious AEs

The frequency of AEs and frequency and proportion (expressed in percent) of participants with AE will be provided by PT and by treatment group for the following:

- Serious adverse drug reactions
- AEs of special interest

12.2 Eye Symptoms

Analysis of eye symptom-related AEs for all eye symptoms, severe eye symptoms, and serious eye symptoms will be based on new events that occurred after Screening. Severe eye symptoms are events that are assigned with grade 3 intensity or greater.

The frequency distribution of participants who experienced 1, 2, or ≥3 eye symptom-related AEs in one or both eyes during Day 1 to Day 15 will be summarized by treatment group for all eye symptoms, severe eye symptoms, and serious eye symptoms. The frequency and proportion (expressed in percent) of participants and 95% CI for proportions will be provided for the summary. For computing proportions, the denominator is the number of participants in the Safety population for the given treatment group.

Additionally, the frequency of symptom-related AEs and frequency and proportion (expressed in percent) of participants with eye symptom-related AEs in one or both eyes will be provided by PT and by treatment group for the following:

- All eye symptoms
- Severe eye symptoms
- Serious eye symptoms
- The frequency and proportion of participants with eye symptom-related AEs in one or both eyes that observed at Days 1, 4, 7, 10, 14, 15, Days 1-15 combined (i.e. any eye symptom-related AE observed on any Days 1-15), 28, 42, and Days 28-42 combined (i.e.

any eye symptom-related AE observed on any Days 28-42) will be provided by treatment group for the following: All eye symptoms

- Severe eye symptoms
- Serious eye symptoms

For the by-time point summary, the denominator for the proportion is the number of participants with eye symptom assessment at the given time point.

Any day that a participant reported an eye symptom-related AE in one or both eyes after screening will be counted toward the number of days of having eye symptoms in the study for that individual. Number of days of having eye symptoms will be summarized by treatment group using descriptive statistics for the following:

- All eye symptoms
- Severe eye symptoms
- Serious eye symptoms

Additionally, categorical number of days of having eye symptoms for participants with these events will be summarized by treatment group as follows:

- 1-3 days
- 4-6 days
- 7-9 days
- 10-12 days
- 13-15 days
- ≥16 days

The summary will include the frequency and proportion (expressed in percent) of participants for each category. For computing proportion, the denominator will be the number of participants with eye symptom-related AEs in the treatment group.

Average duration, expressed in hours, of eye symptom-related AEs in one or both eyes that were observed after screening for an individual participant will be computed as the average of duration of these events. Average duration, will be summarized by treatment group using descriptive statistics for the following:

- All eye symptoms
- Severe eye symptoms
- Serious eye symptoms

Additionally, categorical average duration of eye symptoms for participants with these events will be summarized by treatment group as follows:

- ≤1 hour
- >1-3 hours
- >3-5 hours
- >5-24 hours

- >24 hours

The summary will include the frequency and proportion (expressed in percent) of participants for each category. For computing proportions, the denominator will be the number of participants with eye symptoms in the treatment group.

Exploratory safety analysis may be performed to further assess eye symptoms (all, severe, serious) reported from Day 1 through Day 15 if deemed to add value. The data may be fit in the same spirit as the efficacy model using hierarchical Bayesian nonlinear mixed-effects logistics regression model, or other simpler model-based assessments.

12.3 Visual Acuity

The visual acuity scores will be converted to logMAR scale for analyzing change from baseline. LogMar scale is computed as logMAR = -log(visual acuity score in decimal scale).

Visual Acuity Score	Decimal Scale	LogMAR Scale
20/20	1.00	0.00
20/25	0.80	0.10
20/30	[illegible]	0.18
20/40	0.50	0.30
20/50	0.40	0.40
20/70	0.29	0.54
20/100	0.20	0.70
20/200	0.10	1.00
20/400	0.05	1.30
20/800	0.03	1.60

In logMAR scale, lower scores correspond to better vision, and as acuity becomes worse, the value of the logMAR increases.

Worst logMAR score is defined to be the highest value of logMAR scores measured on left and right eyes at a given time point. The changes in worst logMAR score from baseline to Days 1, 4, 7 10, 14, 15, Days 1-15 combined (i.e. most worst logMAR score on any Days 1-15), 28, 42, and Days 28-42 combined (i.e. most worst logMAR score on any Days 28-42) will be summarized by treatment group using descriptive statistics.

Additionally, the changes in worst logMAR score from Days 1-15 combined to Days 28-42 combined will be summarized similarly as described above.

The International Classification of Diseases 11 [ICD-11, 2018] classifies for distance vision impairment is as follows:

Classification of Vision Impairment	Distance Visual Acuity
Normal	Equal to or better than 20/40
Mild	Worse than 20/40 and equal to or better than 20/70

Moderate	Worse than 20/70 and equal to or better than 20/200
Severe	Worse than 20/200 and equal to or better than 20/400
Blindness	Worse than 20/400

The highest classification of vision impairment of left and right eyes at the given time point will be selected for the analysis. The frequency and proportion of participants for each level of the classification of vision impairment at baseline, Days 1, 4, 7, 10, 14, 15, Days 1-15 combined (i.e. worst vision impairment at any Days 1-15), 28, 42, and Days 28-42 combined (i.e. worst vision impairment at any Days 28-42) will be summarized by treatment group. For the by-time point summary, the denominator for the proportion is the number of participants with visual acuity assessment at the given time point.

The frequency and proportion of participants for each level of the classification of vision impairment at baseline that transitioned to a level of the classification of vision impairment at Days 1, 4, 7, 10, 14, 15, Days 1-15 combined (i.e. worst vision impairment at any Days 1-15), 28, 42, and Days 28-42 combined (i.e. worst vision impairment at any Days 28-42) will be provided by treatment group. For the by-time point summary, the denominator for the proportion is the number of participants with non-missing values at baseline and the given post-baseline time point.

Additionally, the transition of levels of classification of vision impairment from Days 1-15 combined to Days 28-42 combined will be summarized similarly as described above.

12.4 Color Vision

The three color vision deficits are deutan, protan, and tritan. The degree of severity of color vision deficit is graded as normal, mild, moderate, or severe. The severity of color vision abnormality will be assigned to the highest degree of severity of the 3 color vision deficits. For example, the severities of deutan, protan, and tritan are mild, moderate, normal, respectively, for one of the eyes. For this case, moderate will be assigned as the highest level of severity for color vision abnormality.

The highest level of severity of color vision abnormality of left and right eyes at the given time point will be selected for the analysis. The frequency and proportion of participants for each level of the severity of color vision abnormality at baseline, Days 1, 4, 7, 10, 14, 15, Days 1-15 combined (i.e. worst color vision abnormality at any Days 1-15), 28, 42, and Days 28-42 combined (i.e. worst color vision abnormality at any Days 28-42) will be summarized by treatment group. For the by-time point summary, the denominator for the proportion is the number of participants with visual acuity assessment at the given time point.

The frequency and proportion of participants for each level of the severity of color vision abnormality at baseline that transitioned to a level of the severity of color vision abnormality at Days 1, 4, 7, 10, 14, 15, Days 1-15 combined (i.e. worst color vision abnormality at any Days

1-15), 28, 42, and Days 28-42 combined (i.e. worst color vision abnormality at any Days 28-42) will be provided by treatment group. For the by-time point summary, the denominator for the proportion is the number of participants with non-missing values at baseline and the given post-baseline time point.

Additionally, the transition of levels of severity of color vision abnormality from Days 1-15 combined to Days 28-42 combined will be summarized similarly as described above.

12.5 Vital Signs

12.5.1 Intraday Vital Signs Results

Intraday values of vital signs (HR, SBP, and DBP) measured while in supine and while in standing at predose, and 2.5h, 10.5h, and 16.5h after the time of 1st daily dose of study drug on Days 1, 4, 7, 10, and 14 and changes from predose taken on the same day will be summarized using descriptive statistics by treatment group. Line plots of mean of intraday HR, SBP, and DBP measured while in supine and while in standing by treatment group will be provided.

Potentially clinically important criteria of intraday changes from presdose in HR, SBP, and DBP while measured in supine and while in standing are defined as follows:

- ≥25% increase in supine HR
- ≥25% increase in standing HR
- ≥25% decrease in supine SBP
- ≥25% decrease in standing SBP
- ≥25% decrease in supine DBP
- ≥25% decrease in standing DBP

For each of the criteria, the frequency and proportion (expressed in percent) of participants who met the criterion at each time point will be provided by treatment group. For the by-time point summary, the denominator for the proportion is the number of participants in the treatment group with non-missing values at predose and the given post-predose time point taken on the same day.

12.5.2 Daily Vital Signs Results

Daily values of vital signs (HR, SBP, and DBP) measured while in supine and while in standing at baseline (Day 1 predose), Days 2 (predose), 3, 4 (predose), 5, 6, 7 (predose), 8, 9, 10 (predose), 11, 12, 13, 14 (predose), 15, 28, and 42 and changes from baseline will be summarized by treatment group using descriptive statistics. Line plots of mean of daily HR, SBP, and DBP measured while in supine and while in standing by treatment group will be provided.

Potentially clinically important criteria for changes from baseline in HR, SBP, and DBP while measured in supine and while in standing are defined as follows:

- ≥25% increase in supine HR

- ≥25% increase in standing HR
- ≥25% decrease in supine SBP
- ≥25% decrease in standing SBP
- ≥25% decrease in supine DBP
- ≥25% decrease in standing DBP

For each of the criteria, the frequency and proportion (expressed in percent) of participants who met the criterion at each time point will be provided by treatment group. For the by-time point summary, the denominator for the proportion is the number of participants in the treatment group with non-missing values at baseline and the given post-baseline time point.

For each of the criteria, any day that a participant whose vital signs results met the criterion will be counted toward the number of days with the criterion ıe in the study for that individual. Number of days with the criterion met will be summarized by treatment group using descriptive statistics.

Additionally, categorical number of days with the criterion met will be summarized by treatment group as follows:

- 1-3 days
- 4-6 days
- 7-9 days
- 10-12 days
- 13-15 days
- ≥16 days

The summary will include the frequency and proportion (expressed in percent) of participants for each category. For com ıing proportions, the denominator will be the number of participants in the treatment group who met the respective criterion.

12.5.3 Orthostatic Vital Signs Results

Orthostatic change in HR, SBP, and DBP is calculated as vital signs measurement recorded in standing position minus vital signs measurement recorded in supine position at same time point. Percentage orthostatic change in HR, SBP, and DBP is calculated as vital signs measurement recorded in standing position minus vital signs measurement recorded in supine position at same time point divided by vital signs measurement recorded in supine position at same time point.

Orthostatic changes in HR, SBP, and DBP at predose, and 2.5h, 10.5h, and 16.5h after the time of 1st daily dose of study drug on Days 1, 4, 7, 10, and 14 and daily measurements at Baseline, Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 28, and 42 will be summarized by treatment group using descriptive statistics. Line plots of mean of orthostatic change in HR, SBP, and DBP measured while in supine and while in standing by treatment group will be provided.

Potentially clinically important criteria for orthostatic hypotension are defined as follows:

- ≥25% increase in orthostatic HR

- ≥25% decrease in orthostatic SBP
- ≥25% decrease in orthostatic DBP
- ≥20 mmHg decrease in orthostatic SBP
- ≥10 mmHg decrease in orthostatic DBP

For each of the criteria, the frequency and proportion (expressed in percent) of participants who met the criterion at each time point will be provided by treatment group. For the by-time point summary, the denominator for the proportion is the number of participants in the treatment group with non-missing values at the given time point.

Any day that a participant met a potentially clinically important criterion of orthostatic hypotension will be counted toward the number of days with orthostatic hypotension in the study for that individual. Number of days with orthostatic hypotension will be summarized by treatment group using descriptive statistics for each of the criteria.

Additionally, categorical number of days with orthostatic hypotension will be summarized by treatment group as follows:

- 1-3 days
- 4-6 days
- 7-9 days
- 10-12 days
- 13-15 days
- ≥16 days

The summary will include the frequency and proportion (expressed in percent) of participants for each category. For computing proportions, the denominator will be the number of participants in the treatment group who met the respective criterion.

12.6 Electrocardiogram

12.6.1 Intraday ECG Results

Intraday values of ECG variables (HR, QRS duration, RR, PR, QT, and QTcF intervals) measured at predose, and 2.5h, 10.5h, and 16.5h after the time of 1st daily dose of study drug on Days 1, 4, 7, 10, and 14 and changes from predose taken on the same day will be summarized using descriptive statistics by treatment group.

Potentially clinically important criteria for QTcF are defined as follows:

- Observed: 451 to 480, 481 to 500, and >500 msec
- Change from predose taken on the same day: 31 to 60, and >60 msec

For each of the criteria, the frequency and proportion (expressed in percent) of participants who met the criterion at each time point will be provided by treatment group. For the by-time point summary, the denominator for the proportion is the number of participants in the treatment group with non-missing values at predose and the given post-predose time point taken on the same day.

Additionally, intraday value of ECG variables for sex subgroup (female and male) will be summarized similarly as described above. Boxplots of intraday values of QTcF by treatment group and sex will be provided.

12.6.2 Daily ECG Results

Values of ECG variables (HR, QRS duration, RR, PR, QT, and QTcF intervals) measured at baseline (Day 1 predose), Days 4 (predose), 7 (predose), 10 (predose), 14 (predose), 15, 28, and 42 and changes from baseline will be summarized using descriptive statistics by treatment group.

Potentially clinically important criteria for QTcF are defined as follows:

- Observed: 451 to 480, 481 to 500, and >500 msec
- Change from baseline: 31 to 60, and >60 msec

For each of the criteria, the frequency and proportion (expressed in percent) of participants who met the criterion at each time point will be provided by treatment group. For the by-time point summary, the denominator for the proportion is the number of participants in the treatment group with non-missing values at baseline and the given post-baseline time point.

Additionally, values of ECG variables for sex subgroup (female and male) will be summarized similarly as described above. Boxplots of daily values of QTcF by treatment group and sex will be provided.

12.7 Clinical Safety Laboratory Measurement

Clinical safety laboratory parameters include:

Haematology	complete blood count [red blood cells (erythrocytes), haemoglobin, platelets and white blood cells (leukocytes)] and differential (absolute counts) including neutrophils, lymphocytes, monocytes, eosinophils and basophils.
Serum chemistry	alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium.
Serum coagulation	prothrombin time, partial prothrombin time, international normalized ratio.
Urinalysis	specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase.

Clinical laboratory values for haematology, serum chemistry, coagulation, and urinalysis safety at baseline (screening), Days 3, 7, 14 and 42 changes from baseline will be summarized by treatment group using descriptive statistics. Changes may be assessed on the raw (difference) or

log (fold change) scale, depending on the whether the distribution of the measure is more appropriately described by a normal or lognormal distribution, respectively.

For urinalysis with categorical results, the frequency and proportion (expressed in percent) of participants will be tabulated for each category at baseline, Days 3, 7, 14, and 42 by treatment group. For the categorical urinalysis by-visit summary, the denominator for the proportion is the number of participants with non-missing values in the treatment group for the given parameter and time point.

Shift tables will used to summarize haematology, serum chemistry, and coagulation laboratory values by treatment group. Shift tables will display transition of participants having lab values categorized as low, normal, or high with respect to their lab parameters reference ranges at baseline to normal, low or high at Days 3, 7, 14, and 42. For the by time point summary, the denominator for the proportion is the number of participants with non-missing values at baseline and the given time point in the treatment group for the given lab parameter.

All laboratory test results will be listed. The listings will include date and study day of collection. All units will be displayed in Système International units. Out of reference ranges values will be flagged in the data listings (e.g., 'L' or 'H').

12.8 COVID-19/SARS-CoV-2 Test

The frequency and proportion of participants having negative or positive COVID-19/SARS-CoV-2 test will be summarized by treatment group at Days 7 and 15. For computing proportions, the denominator is the number of participants in the Safety population for the given treatment group and visit.

12.9 Drug Susceptibilities and MIC of TBA-7371

Drug susceptibility testing for isoniazid and rifampicin and MICs of TBA-7371 will be performed at Screening and Day 14. The frequency and proportion of participants having isoniazid resistance and/or rifampicin resistance detected by line probe assay will be provided by treatment group at Screening and Day 14. Any participant found to have isoniazid or rifampicin resistance by line probe assay will have further resistance testing performed and descriptive summaries of those results will be compiled. For computing proportions, the denominator is the number of participants in the Safety population for the given treatment group and visit.

MIC of TBA-7371 will be summarized by treatment group using descriptive statistics at Screening and Day 14.

13 PHARMACOKINETIC ANALYSES

All PK and PK/PD analyses will be performed for the PK population.

13.1 TBA-7371 Pharmacokinetics

Timing of TBA-7371 sampling for participants randomized to TBA-7371 will be as follows:

	QD Dosing	BID Dosing	TID Dosing
Screening Phase	Predose	Predose	Predose
Study Treatment Phase	1. Predose on Days 1, 2, 4, 7, and 14. 2. 30 min, 1h, 2.5h, 3h, 4h, 6h, 7h, 10.5h, 12h, and 16.5h on days 1, 7, and 14.	1. Predose on Days 1, 2, 4, 7, and 14. 2. 30 min, 1h, 2.5h, 3h, 4h, 6h, 7h, 10.5h, and 12h on days 1, 7, and 14.	1. Predose on Days 1, 2, 4, 7, and 14. 2. 30 min, 1h, 2.5h, 3h, 4h, 6h, and 7h on days 1, 7, and 14.

TBA-7371 concentrations below the limit of quantitation will be set to 0. TBA-7371 concentrations will be summarized by treatment group using nominal time points for all participants in the PK population. The following descriptive statistics will be provided: N, arithmetic mean, standard deviation, arithmetic percent coefficient of variation (CV), median, minimum, maximum, geometric mean, and geometric percent CV. Linear and semi-log plots of individual and mean concentrations versus nominal time will be presented by treatment group. Plasma concentration of TBA-7371 having value 0 will be excluded from semi-log plots.

The following PK parameters of Days 1, 7, and 14 will be derived using non-compartmental model.

Day 1	Day 7	Day 14
C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{tau}, C_{min}, half-life,	C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{tau}, C_{min}, half-life, accumulation ratio (C_{max} of day 1/C_{max} of day 7)	C_{max}, T_{max}, C_{last}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{tau}, C_{min}, half-life, accumulation ratio (C_{max} of day 1/C_{max} of day 14)

- C_{max} – maximum plasma concentration
- C_{min} – minimum plasma concentration
- T_{max} – time to maximum plasma concentration
- λ_z – elimination rate constant. The elimination rate constant will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The slope will be determined from a plot of the natural log of the terminal plasma concentrations against time; at least 3 terminal plasma concentration time points, beginning with the final concentration ≥ LLOQ and not including C_{max}, will be selected for the determination of λ_z; the regression will have a coefficient of determination $R^2 \geq 0.9000$.
- Half-life – terminal half-life = $\ln(2) / \lambda_z$.

- AUC_{last} – area under the plasma concentration-time curve from 0 up to the last measurable concentration ≥ LLOQ. AUC is calculated using the linear trapezoidal method.
- AUC_{inf} – AUC extrapolated to infinity. $AUC_{inf} = AUC_{last} + C_{last} / \lambda_z$, where C_{last} is the last measurable concentration ≥ LLOQ and λ_z is the terminal phase rate constant.
- AUC_{tau} – AUC to the end of the dosing period.

PK parameters of days 1, 4, 7, and 14 will be summarized using descriptive statistics number of participants, arithmetic mean, standard deviation, arithmetic percent CV, median, minimum, maximum, geometric mean, and geometric percent CV and will be provided by treatment group.

13.2 TBA-7371 Concentration-Effect Relationship

Spearman correlations, simple linear regressions and graphical visualizations will be used to summarize correlation between TBA-7371 AUC_{inf}, Cmax, T>MIC and CFU counts on solid media culture. The SAS PROC CORR and PROC REG will be used to compute Spearman correlations and fit simple linear regression models. The slope with 95% confidence interval, as well as the R-squared will be reported for the simple linear regression. This will be reported by treatment group as well as overall.

13.3 Exposure-Response Analysis

The exposure-response E_{max} model will be used to estimate EC_{90} as follows:

$$BA_{CFU}(0\text{-}14) = \frac{E_{max} \cdot C_{\max(ss)}}{EC_{50} + C_{\max(ss)}} + \varepsilon$$

where:

- $BA_{CFU}(0\text{-}14)$ is the average change in log(CFU) counts over each day from screening to day 14.
- E_{max} is the maximal TBA-7371 EBA effect.
- EC_{50} is the expected concentration of TBA-7371 associated with 50% of E_{max}.
- $C_{\max(ss)}$ is the steady state C_{max} of TBA-7371 measured at day 14.
- ε is a random error assumed to be normally distributed with mean zero and constant variance σ^2.

Exposure-response analysis will be performed in the PK population with participants having PK data measured on day 14. The SAS PROC NLMIXED procedure will be used to fit an E_{max} model. Maximum likelihood estimates and corresponding 95% CIs for E_{max} and EC_{50} will be provided. The prediction of EC_{90} to reach 90% of E_{max} is computed as

$$EC_{90} = 9 \cdot EC_{50}$$

95% CI for the estimate of EC90 will be provided. An exposure-response curve of E_{max} model will be produced and vertical reference lines for EC_{50} and EC_{90} will be provided for each treatment group as well as overall.

Alternative sigmoid exposure-response model may be explored if deemed appropriate.

14 PHYSICAL EXAMINATION

Clinically significant physical examination findings will be provided in a listing.

15 CONCOMITANT MEDICATIONS

All concomitant medications will be coded using the Wo d Health Organization Drug Dictionary, March 1, 2018 version or later. The Anatomical Therapeutic Chemical (ATC) Level 3 and preferred name will be used to list and summarize the data.

The frequency and percentage of participants taking concomitant medication will be summarized by drug class (ATC Level 3) and medication preferred term and b treatment group. Multiple concomitant medications usage by a participant in the same ATC category will be counted only once.

All concomitant medications will be provided in a listing.

16 REFERENCES

1. Diacon AH, et al. Randomized Dose-Ranging Study of the 14-Day Early Bactericidal Activity of Bedaquiline (TMC207) in Patients with Sputum Microscopy Smear-Positive Pulmonary Tuberculosis. Antimicrobial Agents and Chemotherapy 2013: 57(5): 2199-2203.

2. Burger DA and Schall R. A Bayesian Nonlinear Mixed-Effects Regression Model for the Characterization of Early Bactericidal Activity of Tuberculosis Drugs. Journal of Biopharmaceutical Statistics 2015; 25: 1247-1271.

3. Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health US Department of Health and Human Services (DAIDS) Regulatory Support Center. 2017. Table for grading the severity of adult and pediatric adverse events. Corrected version 2.1. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

4. World Health Organization. ICD-11 for mortality and morbidity statistics (ICD-11 MMS) 2018 version. https://icd.who.int/browse11/l-m/en.

17 APPENDICES

Appendix 1 Schedule of Activities

Assessments A ± 15-minute time window is allowed for all measurements	Screening Day [a]			Study Treatment Day													Follow-up Day [b]			EWV [c]
	-7 to -3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	28	42	
Written informed consent [1]	X																				
Hospital admission or discharge [2]	X																	X			
Demography and medical and treatment history	X																				
Physical examination [3]	X									X								X	X	X	X
Chest x-rays [4]	X																				
Blood/serum sample collection for HIV test and CD4 count	X																				
Serum sample collection for pregnancy status assessment	X																	X		X	X
Blood/serum sample collection for clin. safety lab assessment[5]	X					X				X								X		X	X
Urine sample collection for clinical safety lab assessment	X					X				X								X		X	X
Urine sample collection for isoniazid and drug screening [6]	X																				
Overnight sputum collection for eligibility asses. (volume, acid-fast bacilli Mtb pos. and rifampicin sensitivity) [7]	X																				
Vital signs and body weight recording [8]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG recording [9]	X			X			X			X			X				X	X	X	X	X
Eye assessment (visual acuity, color vision, symptoms) [10]	X			X			X			X			X				X	X	X	X	X

Assessments A ± 15-minute time window is allowed for all measurements	Screening Day [a]			Study Treatment Day													Follow-up Day [b]			EWV [c]
	-7 to -3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	28	42	
Study drug (IMP) administration [11]				X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Overnight sputum collection for EBA & exploratory measures. [12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Spot sputum collection for exploratory measurements [13]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Recording of AE, SAE (incl. serious ADR) and AESI [14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant treatments [14]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood/serum sample collection for PK measurements [15]				X	X		X			X							X				
[redacted]																					
COVID-19/SARS-CoV-2 Testing[17]	X									X								X			

a. **Screening (Days -7 to -1).** Screening procedures will be conducted during the up to 7-Day screening period. Screening assessments can be done at any time during this period, except for the written informed consent, which must be given before any screening is started, the overnight sputum collection for eligibility assessment, which must be completed on or before Day -3, and the overnight sputum collection for EBA, which must be done consecutively on Day -2 and Day -1. Subjects may be hospitalized for the entire screening period at the investigator's discretion, but must be hospitalized starting on Day -3.

b. **Follow-up (Days 15 to 42).** Allowed window for Day 28 and Day 42 visits: +/- 3 Days.

c. **Early Withdrawal Visit (EWV)** or **Unscheduled Visit**. Participants who withdraw before Day 14 will be asked to complete the EWV assessments within 2 Days of withdrawal. Participants who complete the Study Treatment Phase, but do not return for the Day 28 visit will be asked to return for the Day 42 visit. If access to sites is limited due to the local status of COVID-19 pandemic, the Day 28 and Day 42 visits could potentially be conducted by telephone. Procedures and assessments conducted during an unscheduled visit will be at the discretion of the investigator in consultation with the medical monitor.

1. **Written informed consent** will be given before any screening procedure is started.

2. **Hospital admission and discharge.** Study participants will be hospitalized by Day -3 of the Screening Phase and will remain in hospital until the Day after the last dose of study drug is dispensed (Day 15). Discharge from hospital will occur on Day 15 after all procedures planned for that Day are completed. Upon discharge, participants will be referred to the national TB treatment program for standard of care (SoC) treatment.
3. **Physical examination (PE).** Full PE will be conducted during the Screening Phase; focused PE (guided by medical history) will be conducted on Days 7, 15, 28, 42. Focused PE will be conducted at EWV if the participant discontinues between Day 1 and Day 14. Focused PE may be conducted during an unscheduled visit at the discretion of the investigator.
4. **Chest X-rays.** Good quality Posterior-Anterior chest X-rays will be accepted if conducted within 1 week prior to Day -7. If not available, chest X-rays will be conducted during the Screening Phase.
5. **Blood/serum sample collection for clinical safety laboratory assessment.** The Day 3 and 7 sampling will occur before the 1st dose of study drug.
6. **Urine sample collection drug screening**: cannabinoids, cocaine, amphetamines, opiates, methamphetamines.
7. **Overnight sputum collection for eligibility assessment.** Sputum assessment, including volume, will be performed by a Sponsor-approved central laboratory (see laboratory study instruction document). The 1st of the 3 overnight sputum collections (Day -7 to Day -3) conducted during the Screening Period will be used to assess eligibility as follows: sputum volume (must be at least 10 mL), acid-fast bacilli detection, *Mycobacterium tuberculosis* (Mtb) positivity and rifampicin sensitivity via the GeneXpert® diagnostic system (Cepheid). In case inclusion criteria cannot be met from the 1st overnight sputum collection, one or more of the above procedures can be conducted on a 2nd overnight sputum collected during the Day -7 to -3 screening period if the patient is domiciled at the site for both.
8. **Vital sign and body weight recording.** The following 5 vital signs will be recorded: axillary body temperature (BT), respiratory rate (RR), heart rate (HR), systolic blood pressure, (SBP), diastolic blood pressure (DBP). Body weight (BW) will also be recorded with vital signs. Vital signs and body weight will be recorded as follows:
   - Screening Phase: vital signs and BW once in the morning at approximately the same time the 1st daily dose study drug will be administered. SBP, DBP and HR can be repeated twice if exclusion criteria are met.
   - Study Treatment Phase: vital signs and BW once every morning (Days 1 to 14) before administration of the 1st daily dose of study drug; in addition, on Days 1, 4, 7, 10 and 14 vital signs will also collected 2.5h, 10.5h and 16.5h after the time of 1st daily dose of study drug (see Table 4 of the protocol).
   - Follow-up Phase: vital signs and BW on Day 15 in the morning before 1st daily dose of SoC medication; on Days 28 and 42 during the visit.
   - EWV: vital signs and BW if the participant withdraws from the study between Day 1 and 14.

   At each time point BT, RR and BW will be measured once, whereas HR, SBP and DBP will be measured twice as follows: after 10 min supine ("manual, supine") and after 2 (±0.5) min standing ("manual, 2-min standing"). When ECG, vital signs and/or blood/serum samples are to be obtained at the same time point, the following order must be followed: ECG, vital signs, blood/serum sample, within 5 min of each other.
9. **ECG recording**. 12-lead ECG will be recorded once at each time point after at least 10 minutes of supine rest as follows:
   - Screening Phase: once in the morning at approximately the same time the 1st daily dose study drug will be administered.
   - Study Treatment Phase: on Days 1, 4, 7, 10 and 14 before administration of the 1st daily dose of study drug and 2.5h, 10.5h and 16.5h thereafter (see Table 4 of the protocol).
   - Follow-up Phase: on Day 15 in the morning before 1st daily dose of standard of care medication; on Days 28 and 42 during the visit.

- EWV: if the participant withdraws from the study between Day 1 and 14.

10. **Eye assessment.** A trained staff member will assess: i) eye symptoms using a standardized script (Section 10.5, Appendix 5 of the protocol), ii) visual acuity by means of the Rosenbaum Pocket Eye Screener, iii) color vision by means of the Waggoner Computerized Color Vision Test and as follows:
    - Screening Phase: once in the AM.
    - Study Treatment Phase: Days 1, 4, 7, 10, and 14, 2.5h after 1st daily dose of study drug (see Table 4 of the protocol).
    - Follow-up Phase: Days 15, 28 and 42 during the visit.
    - EWV: if the participant withdraws from the study between Days 1 and 14.
11. **Study drug (IMP) administration.** Study drug (TBA-7371 or HRZE) will be administered fro ay 1 to Day 14 based on the randomization list by an authorized and trained site staff member. The 1st dose of study drug will be administered t .e same time each Day for the individual participant. Subsequent doses will be administered as follows (see Table 4 of the protocol):
    - Twice daily (BID) schedules: 12h after 1st dose
    - Three times (TID) daily schedule: 7h and 14h after 1st dose

    Fasting must occur at least 2 hours before dosing and at least 1 hour after dosing. Study drug administration will be followed by 200 mL water.
12. **Overnight sputum collection for EBA assessment and exploratory measurements**. Overnigh+ sputum will be collected from 3 PM to 7 AM of the following Day (16 hours) on Days -2 and -1 during Screening Phase and on 14 consecutive Days during the Study Treatment Phase (Days 1 to 14) for EBA assessment. The last collection will finish at 7 AM of D , 15. tibility t sting for isoniazid and rifampicin, and minimum inhibitory concentrations (MIC) of TBA-7371 will be performed o ither of Day -2 or Day -1 and again on Day 14. [redacted]
13. [redacted]
14. **Recording of AE, SAE (including serious ADR) and AESI; recor ing of concomitant treatments.** Adverse events (AE), serious adverse events (SAE), including serious adverse drug reactions (A R), adverse ev nts of special interest (AESI) and concomitant treatments will be recorded from the time each participant has signed the informed con ent forr (ICF) until he/she has completed the last follow- up visit (Day 42) or the Early Withdrawal Visit (EWV).
15. **Blood/serum sample collection for PK measurements**. WILL BE CONDUCTED ONLY IN PARTICIPANTS RANDOMIZED TO TBA-7371. Timing of sampling will be as follows:
    - Study Treatment Phase: Days 1, 2, 4, 7 and 14 before administration of the 1st daily dose of study drug; in addition, on Days 1, 7 and 14 samples will also collected 30 min (+/- 5 min) and at 1h, 2.5h, 3h, 4h, 6h, 7h, 10.5h, 12h, 16.5h (+/- 15 min) after 1st daily dose of study drug. (see Table 4 of the protocol). Patients assigned to BID dosing will not have collections at 16.5h, and the 12h sample will be taken prior to the second daily dose. Patients assigned to TID dosing will not have collections at 10.5h, 12h and 16.5h, and the 7h sample will be taken prior to the second daily dose.

    When timing coincides, samples must always be taken after recording of ECG and vital signs.
16. [redacted]

[redacted]

Coronavirus Disease (COVID-19) / Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 Testing). COVID-19 testing will be conducted via PCR using a test product authorized by SAHPRA at an accredited public or private sector laboratory. A specimen will be collected during the screening period between Day-7 to Day -3, and a negative result must be confirmed prior to randomization. For safety monitoring purposes, testing will also be performed at Day 7 (±2 Days), on Day 14 OR Day 15 before discharge, and/or at any other time that infection is suspected.

Appendix 2 Imputation Rules for Missing or Partial Dates for AEs

Date	Situation	Imputation Rule
AE Start Date	Only month and year are known and month is prior to first dose date	Use the first day of the month
	Only month and year are known and month is the same as first dose date	Use the first dose date
	Only month and year are known and month is after first dose date	Use the first day of the month
	Only year is known and year is after first dose date	Use Jan 1 of that year
AE End Date	Only month and year are known and month is prior to last dose date	Use the last day of the month
	Only month and year are known and month is the same as last dose date	Use the last dose date
	Only month and year are known and month is after last dose date	Use the first day of the month
	Only year is known and year is before last dose date	Use Dec 31 of that year
	The estimated stop date is before a complete or imputed AE start date	Use the last day of the month of the AE start date

AE = adverse event

Note: The imputation of end date must be later than start date.

Appendix 3 Imputation Rules for Missing or Partial Dates for Concomitant Medications

Imputation rules for missing or partial dates (D=day, M=month, Y=year, T=time)			
Parameter	**Missing**	**Additional conditions**	**Imputation Rule**
Start date	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as M and Y of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D and Y	None--date completely missing	Date of first dose of study drug
Stop date	D only	M and Y same as M and Y of end of study	Date of end of study
		M and/or Y not same as M and Y of nd of study	Last day of month
	M and D	Y same as Y of end of study	Date of last dose of study drug
		Y not same as Y of end of study	Use Dec 31 of Y
	M, D and Y	Medications that are not marked as ongoing - date completely missing	Date of end of study

Appendix 4 SAS Code

SAS code for computing 95% confidence interval for single proportion based on the mid-P method:

```
proc freq data=<dataset> order=freq;
   tables category / binomial (CL=MIDP) alpha=0.05;
   weight Count;
run;
```

SAS code for response-exposure E_{max} model:

```
ods output fitstatistics=<Data with aic>;
ods output parameterestimates=<Data with slope estimates>;
proc nlmixed data=<dataset>;
  by <treatment group>;
  parms Emax=<numeric>
        EC50=<numeric>
        s2=<numeric>;
  mu=(Emax*Cmax)/(EC50+Cmax);
  model <Avg. Slope(0-14)> ~ normal(mu,s2);
run;
```

SAS code for bilinear regression model with kar a as one of the parameters:

```
ods output fitstatistics=<Data with aic>;
ods output parameterestimates=<Data with slope estimates>;
ods output additionalestimates=<Data with BA(0-14) estimate>;
run;
proc nlmixed data=<dataset>;
  by <subject ID>;
  parms alpha=4 to 8 by 0.5   beta1=-0.3 to 0.3 by 0.05
beta2=-0.3 to 0.3 by 0.05   kappa=2 to 10 by 1   s2=0.05 to 0.3
by 0.05 / best=1;
  bounds alpha >0,   1 < kappa < 14,   s2>0; * Add constraints to
parameters to improve convergence;
  if day <= kappa then mu = alpha + beta1*day;
  else if day > kappa then mu = alpha + beta1*kappa +
beta2*(day-kappa);
  model logCFU ~ normal(mu,s2);
  estimate 'BAcfu(0-14)' (kappa*beta1 + (t_last-
kappa)*beta2)/t_last;*Estimate BA(0-14);
run;
```

SAS code for bilinear regression model with kappa fixed at 2:

```
ods output fitstatistics=<Data with aic>;
ods output parameterestimates=<Data with slope estimates>;
proc nlmixed data=<dataset>;
  by <subject ID>;
  parms alpha=4 to 8 by 0.5   beta1=-0.3 to 0.3 by 0.05
beta2=-0.3 to 0.3 by 0.05 s2=0.05 to 0.3 by 0.05 / best=1;
  bounds alpha >0,   s2>0; * Add constraints to parameters to
improve convergence;
  if day <= 2 then mu = alpha + beta1*day;
  else if day > 2 then mu = alpha + beta1*2 + beta2*(day-2);
  model logCFU ~ normal(mu,s2);
  run;
```

SAS code for simple regression model:

```
ods output fitstatistics=<Data with aic>;
ods output parameterestimates=<Data with slope estimates>;
proc nlmixed data=<dataset>;
  by <subject ID>;
  parms alpha=4 to 8 by 0.5  beta1=-0.3 to 0.3 by 0.05  s2=0.05
to 0.3 by 0.05  / best=1;
  mu = alpha + beta1*day;
  model logCFU ~ normal(mu,s2);
run;
```

SAS code for ANCOVA (`lsmeans` statement used to estimate 90% CIs, `lsmestimate` statements used for one-sided 5% p-values, trt = treatment group with HRZE as reference):

```
proc mixed data=<dataset>;
  class <treatment group>(ref=HRZE);
  model <Avg. Slope(0-14)> = <treatment group> + <screening
logCFU> /
* LSmeans used to obtain 90 Cis;
  lsmeans <treatment group> / cl alpha=0.1;
* 6 LSMestimate statements used to obtain 1-sided p-values -
NOTE: HRZE will refer to #6 below if used as reference, the #1-5 will
be as indicated in model;;
  lsmestimate <trt> 'trt #1' 1 0 0 0 0 0 / lower alpha = 0.05;
  lsmestimate <trt>  'trt #2' 0 1 0 0 0 0 / lower alpha = 0.05;
  lsmestimate <trt>  'trt #3' 0 0 1 0 0 0 / lower alpha = 0.05;
  lsmestimate <trt>  'trt #4' 0 0 0 1 0 0 / lower alpha = 0.05;
  lsmestimate <trt>  'trt #5' 0 0 0 0 1 0 / lower alpha = 0.05;
  lsmestimate <trt>  'trt #6' 0 0 0 0 0 1 / lower alpha = 0.05;
run;
```

SAS code for random intercepts and slopes model (day = relative to baseline study day, trt = treatment group with HRZE as reference):

```
proc mixed data=<dataset>;
  class <treatment group>(ref=HRZE) <subject>;
  model logCFU = <day> + <trt> + <day*trt> + <screening logCFU>;
  random int day / subject=<subject> type=un;
* The first 6 estimate statements used to obtain correct 1-sided p-
values - NOTE: HRZE will refer to #6 below if used as reference, the
#1-5 will be as indicated in model;
  estimate "Avg slope Tr 1" day 1 trt*day 1 0 0 0 0 0 / cl lower
alpha =0.05;
estimate "Avg slope Tr 2" day 1 trt*day 0 1 0 0 0 0 / cl lower alpha
=0.05;
estimate "Avg slope Tr 3"  day 1 trt*day 0 0 1 0 0 0 / cl lower alpha
=0.05;
estimate "Avg slope Tr 4" day 1 trt*day 0 0 0 1 0 0 / cl lower alpha
=0.05;
estimate "Avg slope Tr 5" day 1 trt*day 0 0 0 0 1 0 / cl lower alpha
=0.05;
estimate "Avg slope Tr 6"  day 1 trt*day 0 0 0 0 0 1 / cl lower alpha
=0.05;
* The next 6 estimate statements used to obtain correct 90% CIs;
estimate "Avg slope Tr 1" day 1 trt*day 1 0 0 0 0 0 / cl alpha =0.1;
estimate "Avg slope Tr 2" day 1 trt*day 0 1 0 0 0 0 / cl alpha =0.1;
estimate "Avg slope Tr 3"  day 1 trt*day 0 0 1 0 0 0 / cl alpha =0.1;
estimate "Avg slope Tr 4" day 1 trt*day 0 0 0 1 0 0 / cl alpha =0.1;
estimate "Avg slope Tr 5" day 1 trt*day 0 0 0 0 1 0 / cl alpha =0.1;
estimate "Avg slope Tr 6"  day 1 trt*day 0 0 0 0 0 1 / cl alpha =0.1;
run;
```

Appendix 5 Document History

DOCUMENT HISTORY	
Document	**Date**
Original SAP	22 Nov 2019
Amendment 1	23 Aug 2021
Amendment 2	27 June 2022

Changes in Amendment 1:

Modifications were made to the following sections of the SAP:

Section 4.0 Introduction
- Revise text with respect to the protocol amendment

Section 5.2 Objectives and Endpoint
- Revise text with respect to the protocol amendment

Section 6 Study Design Considerations
- Revise text with respect to the protocol amendment

Section 7 Study Population
- Remove completer population

Section 9 Overall Statistical Considerations
- Define baseline values of vital signs

Section 10 Statistical Analysis Methods
- Add drug susceptibilities and MIC of TBA-7371 to summary of baseline characteristics

Section 11
- Add description for computing CFU/mL

Section 12 Safety Analyses
- Clarify determination of AEs of special interest per Investigator discretion
- Add line plots of mean of intraday and daily heart rate, SBP, and DBP in supine and standing position
- Add line plots of mean of orthostatic change in intraday and daily heart rate, SBP, and DBP
- Add boxplots of intraday and daily values of QTcF
- Revise analyses for eye symptoms, visual acuity, and color vision test

- Add summary of COV-19/SARS-CoV-2 test
- Add summary of drug susceptibilities and MIC of TBA-7371

Section 16 References

- Update references

Changes in Amendment 2:

Modifications were made to the following sections of the SAP:

Section 2 Signature Page

- Author of SAP changed from [redacted] to [redacted]
- Approval changed from [redacted] to [redacted]

Section 7.1 Population for Analyses

- Randomized population definition added.
- Clarity added for the timing of PK samples to the PK population definition.

Section 11.1.1 Primary Analysis

- Clarity added for starting values for the bilinear regression model
- Clarity added regarding equations, refined definition of BAcfu(0-14) for bilinear model
- Clarity added to use of PROC NLMIXED for both linear and bilinear models

Section 11.1.2 Secondary Analysis

- Clarity added to bilinear models used for secondary analysis.

Section 11.1.3 Sensitivity Analysis

- Updated the use of Bayesian model to ANCOVA using averaged change from baseline, as well as a mixed model

Section 11.3 Subgroups

- Added HIV status at Baseline as a subgroup.

Section 13.2 Pharmacokinetic analyses

- Clarity added regarding models and statistics used for reporting

Appendix

- Updated SAS code in appendix according to updates in Sections 11.1 – 11.3

Signature Page for VV-TMF-29915 v1.0

Reason for signing: Approved	Name: [redacted] Role: Biostatistics Date of signature: 11-Oct-2022 12:45:54 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Clinical Development Date of signature: 11-Oct-2022 12:58:06 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Clinical Operations Date of signature: 11-Oct-2022 13:16:10 GMT+0000

Signature Page for VV-TMF-2 915 v1.0