Title Page

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

Protocol Number: Gates MRI-TBD03-201

Original Protocol (Version 1): 03 Apr 2019

Amendment 1 (Version 2): 17 Apr 2019

Amendment 2 (Version 3): 25 Sep 2019

Amendment 3 (Version 4): 07 Jul 2020

Compound Name: TBA-7371

Study Phase: 2a

Short Title: Early bactericidal activity of TBA-7371 in pulmonary tuberculosis

Sponsor Name: Bill & Melinda Gates Medical Research Institute

Legal Registered Address: One Kendall Square, Building 600, Suite 6-301, Cambridge, MA 02139

Regulatory Agency Identifier Number(s): N/A

NOTE

This study was paused for screening and randomization by the sponsor, effective 19 March 2020, due to the Coronavirus Disease 2019 (COVID-19) pandemic and the Government of South Africa declaring a National Disaster on 15 March 2020. Shortly thereafter a first lockdown (stay-at-home order) was enacted on 26 March 2020. On 13 May 2020, TB and HIV-related research was deemed essential by government directive. As a result, this amendment was implemented to enhance safety measures to include screening and monitoring for SARS-CoV-2 infection to mitigate risks of transmission among patients and staff moving forward. Additional guidance is provided in Sections 1 and 8 of this document.

NCT Number: NCT04176250
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

Sponsor Signatory

See appended electronic signature page

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Bill & Melinda Gates Medical Research Institute

Date

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List of Abbreviations

ADR	Adverse Drug Reaction(s)
AE	Adverse Event(s)
AESI	Adverse Event(s) of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	ALanine aminoTransferase
AST	ASpartate aminoTransferase
AP	Antero-Posterior
AUC_{inf}	AUC from 0 to Infinity
AUC_{last}	AUC from 0 to Last Quantifiable Concentration
AUC_{tau}	AUC from time 0 to Tau (tau represents the dosing interval of 24 hours)
BA_{CFU}	Slope of the log CFU counts
BA_{LAM}	Slope of the log LAM measurements (pg/mL)
BA_{TTP}	Slope of Time to (sputum culture) Positivity (days) in Mycobacteria Growth Indicator Tube system
βHCG	beta Human Chorionic Gonadotropin
BID	Bis in Die (latin for twice a day)
bpm	beats per minute
BT	Body Temperature
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CFU	Colony Forming Units
C_{last}	Last Quantifiable Concentration
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum Observed Plasma Concentration
CONSORT	CONsolidated Standards of Reporting Trials
COVID-19	COronaVIrus Disease caused by SARS-CoV-2 infection-19
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DDI	Drug Interaction
DNA	DeoxyriboNucleic Acid
DprE1	Deca-prenylphosphoryl-β-D-ribose 2′-epimerase 1
EBA	Early Bactericidal Activity
EC90	Expected Concentration Associated with 90% of the Maximal Effect
EDC	Electronic Data Collection
EWV	Early Withdrawal Visit
FOCBP	Female Of Childbearing Potential
Gates MRI	Bill & Melinda Gates Medical Research Institute
GCP	Good Clinical Practices
h	Hour
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRZE	Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E)
ICH	International Council for Harmonization of technical requirements for pharmaceuticals for human use
IDMC	Independent Data Monitoring Committee

List of Abbreviations

IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUATLD	International Union Against Tuberculosis and Lung Disease
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LAM	LipoArabinoMannan
LTBI	Latent TB Infection
MAD	Multiple Ascending Dose
MBC	Minimum Bactericidal Concentration
mg	Milligrams
MGIT	Mycobacteria Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
min	Minute
mITT	modified Intention to Treat
mL	milliLiter
Mtb	Mycobacterium tuberculosis
PA	Posterior-Anterior
PCR	Polymerase Chain Reaction
PD	PharmacoDynamics
PE	Physical Examination
PI	Principal Investigator
PK	PharmacoKinetics
PP	Per Protocol
QD	Quaque Die (latin for once a day)
RR	Respiratory Rate
SAD	Single Ascending Dose
SAE	Serious Adverse Event(s)
SAHPRA	South African Health Products Regulatory Authority
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome COronaVirus 2
SBP	Systolic Blood Pressure
SoA	Schedule of Activities
SSAP	Scientific Statistical Analysis Plan
STP	Study Treatment Phase
TB	TuBerculosis
TEAE	Treatment-Emergent Adverse Event
TID	Ter in Die (latin for three times a day)
T_{last}	Time at Last Quantifiable Concentration
T_{max}	Time at Maximum Plasma Concentration
TTP	Time To (sputum culture) Positivity
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization
XDR-TB	eXtensively Drug Resistant TuBerculosis

1. Protocol Summary

1.1. Synopsis

1.1.1. Protocol Title

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

1.1.2. Short Title

Early bactericidal activity of TBA-7371 in pulmonary tuberculosis.

1.1.3. Overall Goals

Assess the safety, EBA and PK of TBA-7371 in adult patients with rifampicin-sensitive TB and select dose regimen(s) for future studies.

1.1.4. Objectives and Endpoints

All objectives will be assessed in adult patients with rifampicin-sensitive pulmonary TB (see inclusion/exclusion criteria, Sections 5.1 and 5.2).

1.1.4.1. Primary Objectives and Endpoints

Table 1. Primary Objectives and Endpoints (Synopsis Overview)

Objectives	Endpoints
Bactericidal activity	
Demonstrate the 14-day EBA from screening ("0") to Day 14 (EBA 0-14) of 5 dose regimens of TBA-7371 monotherapy, and of isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) (HRZE) as assessed by colony forming unit (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 CFU counts.
Safety	
Assess the severe/serious adverse event (SAE) 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 SAEs from Day 1 through Day 15.

1.1.4.2. Secondary Objectives and Endpoints

Table 2. Secondary Objectives and Endpoints (Synopsis Overview)

Objectives	Endpoints
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 ("0") to Day 2 [BA_{CFU} (0-2)] and from Day 2 to Day 14 [BA_{CFU} (2-14)] of the log CFU counts.
Demonstrate the bactericidal activity 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	• Slope of the time to sputum culture positivity (TPP) in the MGIT system from screening ("0") to Day 14 [BA_{TTP} (0-14)], from screening to Day 2 [BA_{TTP} (0-2)], and from Day 2 to Day 14 [BA_{TTP} (2-14)]. • Slope of the log concentration of sputum LAM from screening ("0") to Day 14 [BA_{LAM} (0-14)], from screening to Day 2 [BA_{LAM} (0-2)], and from Day 2 to Day 14 [BALAM (2-14)].
Safety	
Assess the 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 body system, 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-7371 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. • 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, and severe)
Assess the impact on heart rate, blood pressure and 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 (vital signs), after at least 10 minutes in supine position ("manual, supine");

Objectives	Endpoints
	▪ manual, after 2 (±0.5) minutes in standing position ("manual, 2-min standing"); ▪ HR from ECG, supine position ("ECG, supine") • Frequency of participants with ≥ 25 % increase in HR, decrease 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, QTcF values from baseline ECG.
Assess whether there is tachyphylaxis over the 14-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 the measurement methods described above. • 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 Day 1 to Days 4, 7, 10, 14 and 15.
Assess whether cardiovascular and/or ophthalmic AEs persist or recur up to 4 weeks after discontinuation of treatment with TBA-7371.	• Mean change in HR, SBP and DBP from screening to Days 28 and 42 and from Day 14 to Days 28 and 42 for each of the measurement methods described above. • 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 PK of TBA-7371 monotherapy over the 14-day treatment period.	• TBA7371 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.
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})

1.1.4.3. 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 DeoxyriboNucleic Acid (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 (MIC);
- population PK modeling

1.1.5. Design

This is an interventional, 5-cohort, 3-step dose escalation clinical trial in adult patients,18 to 60 years of age, with rifampicin-sensitive TB. The escalation will occur sequentially in 3 steps: from Cohort I to Cohorts II and III, from Cohort III to Cohort IV and from Cohort IV to Cohort V (see below). Within the 2nd 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 as control. Rifafour® e-275 (Sanofi) tablets, a commercial presentation of HRZE approved and available in South Africa, will be used in this study [1, 2]. 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 Independent Data Monitoring Committee (IDMC) will make dose escalation decisions. After the last Cohort I participant completes the Study Treatment Phase (Day 14), the IDMC will decide 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” decision 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 instead be masked (blinded) for personnel involved in the conduct of all other laboratory procedures (including those for the primary endpoint).

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.

Study procedures are summarized in the Schedule of Activities (SoA) flow-charts (Table 3 and Table 4) in Section 1.3. below.

1.1.6. Study Population and Number of Participants

Adult subjects between 18 and 60 (inclusive) years of age of both sexes will be eligible for the study if they have untreated, rifampicin-sensitive, bacteriologically confirmed, *Mycobacterium tuberculosis* pulmonary TB, without other clinically significant medical conditions (including extra-thoracic TB and active eye disease) or ECG abnormalities, are not of childbearing potential or are using effective methods of birth control, are capable of and willing to provide informed consent. Human Immunodeficiency Virus (HIV) positive subjects may be enrolled if CD4+ T-cell count is ≥350 cells/μL and there is no Acquired Immune Deficiency Syndrome (AIDS)-defining opportunistic infection or malignancy. The complete list of inclusion and exclusion criteria can be found in Sections 5.1 and 5.2.

Candidates will be screened to achieve 90 randomized study participants. Within each dose escalation cohort, 18 participants will be randomly assigned 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 during the Study Treatment Phase. Drop-outs from the 3rd subject 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.

1.1.7. Intervention Groups

During the Screening Phase participants will not receive TB treatment.

Eligible participants will be enrolled in one of 5 cohorts in 3 sequential escalation steps as follows.

Cohort I: TBA-7371 oral suspension 100 mg once daily (100 QD) for 14 days or HRZE fixed dose combination tablets (H: 75 mg / R: 150 mg / Z: 400 mg / E: 275 mg [Rifafour® e-275]) QD for 14 days.

- **First escalation step: from Cohort I to Cohorts II and III**
  Participants will be randomized to either Cohort II or Cohort III.

  Cohort II: TBA-7371 oral suspension 100 mg twice daily (100 BID) for 14 days or HRZE fixed dose combination tablets (Rifafour® e-275) QD for 14 days.

  Cohort III: TBA-7371 oral suspension 200 mg QD for 14 days or HRZE fixed dose combination tablets (Rifafour® e-275) QD for 14 days.

- **Second escalation step: from Cohort II/III to Cohort IV**
  Cohort IV: TBA-7371 oral suspension 100 mg three times daily (100 TID) for 14 days or HRZE fixed dose combination tablets (Rifafour® e-275) QD for 14 days.

- **Third escalation step: from Cohort IV to Cohort V**
  Cohort V: TBA-7371 oral suspension 400 mg QD for 14 days or HRZE fixed dose combination tablets (Rifafour® e-275) QD for 14 days.

The 1st dose of study drug will be administered at the same time each day for the individual participant. Subsequent doses will be administered 12 hours after 1st dose for BID schedules and 7 hours and 14 hours after 1st dose TID schedule. All doses of study drug will be taken under direct observation of a study staff member.

Weight-based dosage for HRZE (Rifafour® e-275) will be as follows, in line with Package Insert[1] instructions:

- 40-54 kg: 3 tablets
- 55-70 kg: 4 tablets
- 71 kg and over: 5 tablets

On Day 15 all patients will be switched to standard of care TB treatment as determined by the National Health System.

1.1.8. Timing

Each participant will remain in the study for up to seven weeks, which consists of up to 7 days for the Screening Phase, 2 weeks for the Study Treatment Phase and 4 weeks for the Follow-up Phase.

The escalation go / no-go decisions will be taken by the IDMC based on safety data after the last subject of Cohort I (1st step), Cohorts II and III (2nd step) and Cohort IV (3rd step) will have completed the Study Treatment Phase.

The estimated duration of the study (first subject first visit [FSFV] to last subject last visit [LSLV]) was originally expected to be approximately 1 year. The duration of the study will however be extended as necessary due to COVID-19 pandemic-related restrictions.

1.1.9. Statistical Methods

This section provides a brief overview of the statistical methods to support the primary objectives, including sample size considerations. Details on statistical methods to support the secondary objectives and sensitivity analyses are provided in Section 9.4.

1.1.9.1. Bactericidal activity

The $\log_{10}$ CFU counts vs. time profiles over 14 days of treatment may be biphasic, i.e. the rate of change in $\log_{10}$ CFU changes over time. A simple solution is to characterize the subject-specific $\log_{10}$ 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.

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

The primary endpoint will be the slope of the log CFU counts from screening to Day 14 [BA_{CFU}(0-14)], i.e., average change in log CFU count per day over 14 Days, where sputum for primary endpoint is collected twice during the screening phase and daily thereafter. This can be estimated for each subject, *i*, as the mean of the slopes over each day, i.e.,

$$BA_{CFU}(0-14)_i = \sum_{t=1}^{14} \hat{\beta}_{it}/14,$$

where $\hat{\beta}_{it}$ is the estimated slope for subject *i* at time *t*. For each subject, 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 subject. The log CFU screening measurement used in the model will be the average of the two individual screening measurements. If the bilinear regression model is selected, the average change in log CFU count per day over 14 days will be estimated by:

$$BA_{CFU}(0-14)_i = \sum_{t=1}^{14} \left[\hat{\beta}_{1i} I(t \le \hat{\kappa}_i) + \hat{\beta}_{2i} I(t > \hat{\kappa}_i)\right]/14,$$

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 estimated 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. If the linear regression model is selected, the average change in log CFU count per day over 14 days will be estimated by the constant linear regression slope over time, $\hat{\beta}_i$. BA_{CFU}(0-14) will be calculated for each patient 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 CFU 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).

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 dose 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.

Primary efficacy analyses will be performed in the modified Intention-to-Treat (mITT) population.

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.

1.1.9.2. Safety

The frequency of patients who experience one or more severe and/or serious SAEs will be summarized by treatment group with 95% CIs. The proportion of patients with this endpoint within each of the TBA-7371 treatment groups will not be formally compared to the control arm given limitations due to small sample sizes. The primary safety analysis will be performed in the Safety population.

1.1.9.3. Power and Sample Size Considerations

Bactericidal Effect

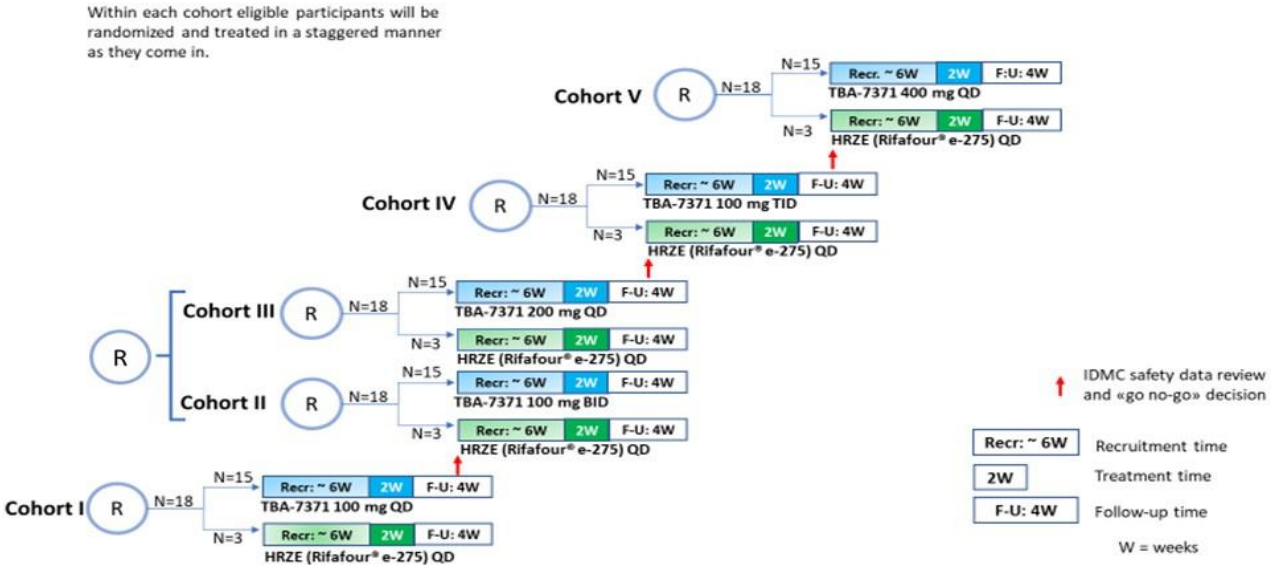
Based on Diacon et al, 2013[3], standard deviations associated with $BA_{CFU}(0\text{-}14)$ were relatively consistent across 5 treatment groups, ranging from 0.05 to 0.08. If we assume conservatively that the true standard deviation of the $BA_{CFU}(0\text{-}14)$ measures for the TBA-7371 treatment 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[3] were 0.040, 0.056, 0.077, 0.104, and 0.112 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%.

1.2. Schema

Figure 1. Schema



1.3. Schedule of Activities (SoA)

Table 3. Scheduled Visits and 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
Study drug (IMP) administration [11]				X	X	X	X	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	
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).
   - 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).
   - 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), 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).
    - 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 from Day 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 at the same time each Day for the individual participant. Subsequent doses will be administered as follows (see Table 4):
    - 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**. Overnight 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 Day 15. Drug susceptibility testing for isoniazid and rifampicin, and minimum inhibitory concentrations (MIC) of TBA-7371 will be performed on either of Day -2 or Day -1, and again on Day 14. Aliquots from each sample, as well as MTB isolates from cultures, will be stored and may be used for exploratory measurements.
13. **Spot sputum collection for exploratory measurements.** The participant should spontaneously produce (i.e., not induced) a spot sputum specimen for collection into RNA preservation media. If specimen cannot be collected due to participant inability to produce sputum, or due to operational limitations with RNA media collection kits, it is not considered a protocol deviation.
14. **Recording of AE, SAE (including serious ADR) and AESI; recording of concomitant treatments.** Adverse events (AE), serious adverse events (SAE), including serious adverse drug reactions (ADR), adverse events of special interest (AESI) and concomitant treatments will be recorded from the time each participant has signed the informed consent form (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). 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]
17. **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.

Table 4. Timing of Measurements on Days 1, 3, 4, 7, 10, and 14 of Study Treatment Phase (STP)

Time	T_0	T_0 + 0.5 h ± 5 min	T_0 + 1 h	T_0 + 2.5 h	T_0 + 3 h	T_0 + 4 h	T_0 + 6 h	T_0 + 7 h	T_0 + 9.5 h	T_0 + 10.5h	T_0 + 12 h	T_0 + 14 h	T_0 + 16.5 h	EWV[a]	Comments
			± 15-minute												
Study drug OD schedules	X														
Study drug BID schedules	X										X				
Study drug TID schedules	X							X				X			
ECG recording	X *			X						X			X	X	* before dosing
Vital signs recording	X *+			X						X			X	X	* before dosing + body weight
Blood/serum for clinical safety assessments	[X] *													X	* before dosing [X]: only Days 3 and 7 of STP
Blood/serum for PK measurements	X *	[X]	[X]	[X]	[X]	[X]	[X]	[X]		[X]	[X]		[X]	X	**Only TBA-7371 pts.** * Before dosing on Days **1,** 2, **4, 7, 14** of STP [X]: only Days 1, 7 &14 of STP. For patients on BID dosing, 12h timepoint will be collected before dosing, and 16.5h timepoint will not be collected. For patients on TID dosing, 7h timepoint will be collected before dosing, and 9.5h, 12h and 16.5h timepoints will not be collected.
Blood/serum/ plasma for exploratory measurements	[X] *														* before dosing [X]: only Days 1 and 7 of STP
Urine for clin safety assessments	[X]													X	[X]: only Days 3 and 7 of STP

Time	T_0	T_0 + 0.5 h ± 5 min	T_0 + 1 h	T_0 + 2.5 h	T_0 + 3 h	T_0 + 4 h	T_0 + 6 h	T_0 + 7 h	T_0 + 9.5 h	T_0 + 10.5h	T_0 + 12 h	T_0 + 14 h	T_0 + 16.5 h	EWV[a]	Comments
			± 15-minute												
Eye assessment (vis. acuity, color vision symptoms)				X										X	
Spot sputum collection	X														
Overnight sputum collection	→			→					→						From 3 PM to 7 AM of the following Day
AE, SAE, AESI	Collected at any time														

a. **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 the 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.

2. Introduction

TBA-7371 is a non-covalent inhibitor of mycobacterium tuberculosis (Mtb) deca-prenylphosphoryl-β-D-ribose 2′-epimerase 1 (DprE1), an enzyme involved in mycobacterial cell wall synthesis. TBA-7371 demonstrates potent bactericidal anti-Mtb activity in vitro, with a minimum bactericidal concentration (MBC) similar to its minimum inhibitory concentration (MIC) against replicating Mtb. It has a narrow spectrum, with activity limited to mycobacteria. Like other cell-wall biosynthesis inhibitors, TBA-7371 is not active against low-oxygen induced non-replicating bacteria. TBA-7371 was highly active against a panel of 96 clinical Mtb isolates representative of global phylogeny and geographical origin, and with differing drug-susceptibility profiles, including extensively drug-resistant TB (XDR-TB). The MIC90 of TBA-7371, i.e. the MIC for at least 90% of isolates of this panel, is 0.64 μg/mL and the MIC range is 0.04-5.12 μg/mL, where the distribution of MICs is unrelated to the drug-susceptibility or genotype of the strain, suggesting utility globally, and against drug-sensitive and drug-resistant TB. Activity against drug-resistant Mtb isolates is expected for TBA-7371 because its drug target, DprE1, is novel, compared to those of currently used TB drugs. Mtb mutants resistant to TBA-7371 are selected at a frequency of 4-7 x 10^{-7}, similar to the reported *in vitro* resistance frequency for clinically relevant anti-TB agents like ethambutol.

No active metabolites of TBA-7371 have been identified thus far.

More information on the PK and pharmacodynamics (PD) of TBA-7371 is provided in the Investigator Brochure.

2.1. Study Rationale

The current treatments for TB have a lengthy duration, involve multi-drug regimens, must be taken multiple times per day and have non-trivial unwanted effects. [4,5] Furthermore, some of the available drugs are expensive. Two of the main consequences of this profile are - first, TB treatments require large commitments of resources and infrastructure, typically lacking in the countries where TB is most prevalent, and second, poor compliance is common, which results in increased severity of disease and mortality and in the emergence of drug-resistant strains. [4-6]

The shortcomings of the available treatments, combined with massive prevalence, health impact and mortality of TB (see below), make a strong case for the discovery and development of novel TB drugs and drug regimens that will address the challenges of current treatments through one or more of the following features: shorter treatment duration, reduced dosing frequency, improved safety and tolerability profile, improved efficacy, greater affordability, suitability for pediatric use and for co-administration with antiretroviral therapy in individuals co-infected with Mtb and HIV.

Encouraging preclinical data and a sustainable safety and tolerability profile (see Section 2.3) of the first trial in healthy volunteers (TBA7371-001) justify the evaluation of TBA-7371 in an EBA trial in adult patients with untreated, drug-sensitive pulmonary TB.

2.2. Background

2.2.1. Tuberculosis

Tuberculosis in humans is an infectious disease caused by Mtb, which typically affects the lungs (pulmonary TB) but can affect other sites as well (extrapulmonary TB). It is an airborne disease transmitted by inhalation of infective droplets containing Mtb and expelled into the air by a person with active TB via coughing, sneezing, or even talking. The unique cell wall of Mtb, which has a waxy coating primarily composed of mycolic acids, allows the bacillus to lie dormant in some individuals for many years (i.e., latent TB infection). Latent TB infection (LTBI) is not associated with symptoms and is not infectious. However, approximately 10% of individuals with LTBI will develop active disease during their lifetime (i.e., a 10% lifetime risk of activation), often years or even decades after the initial infection and most of these cases will themselves become infectious.[7] Individuals with LTBI who are co-infected with HIV are at an increased risk of developing active TB; such individuals are estimated to have an 8% annual risk of reactivating LTBI. [8,9] Tuberculosis is currently one of the top three killer infectious diseases, and there is more TB in the world today than at any other time in history. While TB is found in every country in the world, it disproportionately affects people in resource poor settings, particularly those in Asia and Africa. Nevertheless, TB outbreaks still occur in industrialized nations. The World Health Organization (WHO) estimates that 2 billion people, approximately one-third of the world's population, are infected with Mtb worldwide. In 2015, there were an estimated 10.4 million new incident cases of TB (11% co-infected with HIV), and 1.4 million people died from TB. [10]

2.2.2. Early Bactericidal Activity Clinical Studies

The ability of EBA studies to quantify the bactericidal action of anti-TB agents alone or in combination was established following a pioneering study in 1980. [11] In these studies, which typically have treatment periods ranging from 2 to 14 days, the ability of various agents and combinations of agents to decrease the number of CFU of Mtb present in the sputum of study participants serves as an indication of the anti-TB activity of the treatment. A review of EBA studies conducted on the key anti-TB drugs has shown the value these studies offer to demonstrate the early anti-TB effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in patients. [12]

2.3. Benefit/Risk Assessment

In this trial patients with untreated, drug-sensitive pulmonary TB will receive for 14 days either the test drug TBA-7371 in 1 of 5 regimens (from 100 mg QD to 400 mg QD) or commercial HRZE fixed combination (Rifafour® e-275) as control drug, dosed as recommended in the package insert. [1]

HRZE is a first line treatment for drug sensitive TB with a well-established, generally favorable, yet not straightforward, benefit-risk profile. The most common AEs associated with HRZE are peripheral neuropathy, optic neuritis, hepatitis, and gastro-intestinal AEs (see Package Insert [1] and 2018 Safety Update [2] enclosed in study specific manual(s)).

TBA-7371 was tested in adult healthy volunteers in 1 clinical trial (TBA7371-001), composed of three parts: a single ascending dose (SAD) part where single doses from 100 to 800 mg were

tested, a multiple ascending dose (MAD) part where 100, 200 and 400 mg QD were taken for 14 days and a drug-drug interaction (DDI) part. The most common treatment-emergent adverse events (TEAEs) were increase in heart rate associated with decrease in blood pressure and eye symptoms (blurred vision, photophobia, altered color vision, increased lacrimation). The frequency of such events was dose related, starting at doses above 100 mg /day. Most were mild and transient. In particular, vision-related AEs were of short duration, resolved before the next dose and were not persistent changes. Furthermore, tachyphylaxis to changes in heart rate and blood pressure appeared to occur in the MAD part of the trial.

The eye symptoms appeared to be associated with C_{max}. It is therefore possible that the tolerability profile could improve with fractionation of the daily dose. This justifies the inclusion of the BID and TID dosing regimens in this trial.

There is no information on the efficacy of TBA-7371 in humans. PK/PD modelling from animal experiments, supplemented with additional PK data from healthy human subjects, suggests that bactericidal effect could be present at 100 mg/day and then increase with dose.

More information on TBA-7371 is provided in the Investigator Brochure.

The overall risks associated with TBA-7371 at or below 400 mg QD are considered low and are mitigated by the following design features of the present protocol:

- throughout the 14-day Treatment Phase eye symptoms, visual acuity and color vision, ECG will be assessed/recorded every 3-4 days, vital signs daily;
- the escalation from QD dose level to the next will be staggered, and escalation decisions will be taken by an IDMC based on full unmasked safety data from the lower dose cohort(s);
- it is possible that patients will experience no meaningful bactericidal effect for the duration of treatment with TBA-7371 of 14 days. Participants will thus be kept under close observation in hospital for the entire period so that in case of progression of disease, effective treatment can be initiated without delay;
- at the end of Study Treatment Phase patients will be switched to standard of care TB treatment, trained on the importance of compliance and proper follow-up and followed for an additional 28 days (Follow-up Phase of the study).

Given the safety profile observed thus far and the design features described above, the benefit-risk assessment for this trial is considered favorable.

3. Objectives and Endpoints

3.1. Primary Objectives and Endpoints

Table 5. Primary Objectives and Endpoints

Objectives	Endpoints
Bactericidal activity	
Demonstrate the 14-day EBA from screening ("0") to Day 14 (EBA 0-14) 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 CFU counts.
Safety	
Assess the severe/SAE 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 AEs (≥ grade 3) and/or SAEs from Day 1 through Day 15.

3.2. Secondary Objectives and Endpoints

Table 6. Secondary Objectives and Endpoints

Objectives	Endpoints
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 ("0") to Day 2 [0-2)] and from Day 2 to Day 14 [BA_{CFU} (2-14)] of the log CFU counts.
Demonstrate the bactericidal activity of 5 dose regimens of TBA-7371 monotherapy and of HRZE, as assessed by alternative methods: ▪ time to sputum culture positivity (TTP) in (MGIT) culture ▪ LAM assay	• Slope of the time to sputum culture positivity (TTP) in the MGIT system from screening ("0") to Day 14 [BA_{TTP} (0-14)], from screening to Day 2 [BA_{TTP} (0-2)], and from Day 2 to Day 14 [BA_{TTP} (2-14)]. • Slope of the log concentration of sputum LAM from screening ("0") to Day 14 [BA_{LAM} (0-14)], from screening to Day 2 [BA_{LAM} (0-2)], and 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 body system, 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-7371 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.

Objectives	Endpoints
	• 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).
Assess the impact on heart rate, blood pressure and 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 HR, SBP and DBP as measured by the following 2 (BP) or 3 (HR) methods: ▪ manual (vital signs), after at least 10 minutes in supine position ("manual, supine"); ▪ manual, after 2 (±0.5) minutes in standing position ("manual, 2-min standing"); ▪ HR from ECG, supine position ("ECG, supine") • Frequency of participants with ≥ 25 % increase in HR, decrease 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, QTcF values from baseline ECG.
Assess whether there is tachyphylaxis over the 14-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 the measurement methods described above. • Change in frequency of participants with eye symptoms (all, severe, serious) and change in mean visual acuity score and frequency of color vision changes 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 screening to Days 28 and 42 and from Day 14 to Days 28 and 42 for each of the measurement methods described above. • Change in frequency of participants with eye symptoms (all, severe, serious) and change in mean visual acuity score and frequency of

Objectives	Endpoints
	color vision changes 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.	• TBA7371 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.
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 (EC90)

3.3. 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 (MIC);
- population PK modeling.

4. Study Design

4.1. Overall Study Design

This is an interventional, 5-cohort, 3-step dose escalation clinical trial in adult patients between 18 to 60 years of age with rifampicin-sensitive pulmonary 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 below). Within the 2nd 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 this study. [1,2]

Each participant will undergo 3 study phases: up to a 7-day Screening Phase 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.

The doses and dose schedules of the 5 TBA-7371 cohorts will be as follows: Cohort I: 100 mg QD, Cohort II: 100 mg BID, Cohort III: 200 mg QD, Cohort IV: 100 mg TID, Cohort V: 400 mg QD. For HRZE, the dose will be weight-based as per package insert. [1]

An IDMC will make dose escalation recommendations. After the last Cohort I participant completing the Study Treatment Phase (Day 14), the IDMC will decide whether Cohort II and Cohort III can start enrolment (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" decision will be based on accumulating safety data. Additional data (e.g. PK) may be provided 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 CRO personnel.

The study will instead be masked (blinded) for personnel involved in the conduct of all other laboratory procedures (including those for the primary endpoint).

Study participants will be hospitalized during 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 during 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.

4.2. Scientific Rationale for Study Design

The dose escalation approach, with go/no-go decision on each escalation step to be taken by the IDMC based on the complete safety dataset from lower dose cohort(s), has been chosen to maximize the safety of participants, against the background of the safety and tolerability profile observed in study TBA-7371-001. As mentioned above, the two most frequent treatment emergent adverse events, namely heart rate increase and eye symptoms, had a dose-dependent (above 100 mg QD) frequency and were mostly mild and transient.

The level of masking, in this study, which includes all personnel involved in CFU counts for the primary endpoint (see Section 6.3.2), ensures balance of methodological excellence and feasibility, and is considered adequate for the stage of development of TBA-7371.

Whereas the 3 dose escalation steps will be conducted in an open-label manner, within the 2nd escalation, participants will be randomized to Cohort II or Cohort III. This approach is justified because Cohorts II and III have the same total daily dose of TBA-7371 (200 mg) and strengthens the design of the study.

Within each cohort, participants will be randomized to TBA-7371 or HRZE control with a 5:1 ratio (15 TBA-7371 vs. 3 HRZE). This unequal randomization is justified by the fact that HRZE data from all cohorts will be pooled; hence, if all 5 cohorts will be allowed to enter the trial, the target size of the control group (N=15) will be the same as the TBA-7371 groups.

The target population is adult males and females with untreated, rifampicin-sensitive, uncomplicated pulmonary TB. This population is ideal for the assessment of the bactericidal activity of a new drug.

In this trial, QD, BID and TID schedules will be tested. The scientific rationale is that some symptoms appear to be associated with C_{max}. It is therefore possible that fractionation of the daily dose could improve the tolerability profile and the benefit-risk ratio.

Primary endpoints are: 1) EBA of TBA-7371 as determined by the slope of log CFU count on solid media culture from screening though Day 14; and 2) frequency of participants with serious and/or severe (≥ Grade 3) AEs throughout the treatment. The value of EBA to predict clinical efficacy is outlined in Section 2.2.2. Combined SAEs and severe AEs are considered the best indicators of the overall burden and acceptability of the treatment to patients.

The scientific rationale for secondary endpoints is as follows:

- EBA as assessed by alternative methods [TTP in MGIT culture and LAM assay]. MGIT culture and LAM assay are easier to conduct compared to solid media culture. Hence, insight into the suitability of such methods to replace solid media culture will be useful for this and other TB drug development programs.
- Full AE assessment. All AE will be assessed by seriousness, intensity (severity), relationship to study drug and expectedness based on the information provided in the

Investigator Brochure and summarized by body system and preferred medical term. This will allow the full safety and tolerability profiling of TBA-7371.

- Assessment of heart rate and blood pressure via vital signs and ECG, eye symptoms, visual acuity and color vision. These measurements were selected based on the safety profile that emerged from animal studies and from phase 1 study TBA7371-001 (see above). Multiple assessment methods will be carried out for cardiovascular variables to maximize the sensitivity of the study. Eye symptoms will be assessed by non-leading questions delivered by trained staff based on a standardized script. Visual acuity and color vision will be assessed through standardized procedures. The possibility of decrease (tachyphylaxis) or increase over time of these unwanted effects, as well as their persistence or recurrence in the month following discontinuation of study drug, will also be assessed: results of study TBA7371-001 suggest changes over time during treatment with TBA-7371 of cardiovascular (decrease) and eye (increase) adverse events. It should be noted that all eye symptoms reported study TBA7371-001 were transient.

PK profile and relationship between exposure and magnitude of EBA. So far, the PK profile of TBA-7371 has been only studied in animals and in healthy volunteers. This study allows the confirmation of the PK profile in TB patients. The relationship between exposure and bactericidal response will guide the selection of the dose regimen(s) for further development of TBA-7371. No active metabolite of TBA-7371 has been identified so far, and no major metabolite seen in humans has been detected at more than 10% of parent TBA-7371. Therefore, TBA-7371 metabolism will not be examined further in this study.

Additional measurements may be added as exploratory endpoints. Exploratory endpoints will be the object of separate documents.

4.3. Justification for Dose

In this study 5 dose regimens of TBA-7371 will be tested over a 14-day treatment period: 100 mg QD, 100 mg BID, 200 mg QD, 100 mg TID and 400 mg QD.

From a safety perspective the dose selection is justified by the fact that in study TBA7371-001 single doses of 100, 200, 400 and 800 mg and multiple doses over 14 days of 100, 200 and 400 mg QD were tested: doses from 100 to 400 mg/day are considered suitable for further development assuming proper mitigation steps are in place (see Section 2.3). See Investigator Brochure for more detail.

From an activity perspective, no human data are available. PK-PD modelling of animal data, taken together with human PK data in healthy volunteers, suggest that 200 mg QD or above may be necessary to achieve a meaningful bactericidal effect.

Whereas QD dosing is an important feature of the target product profile for TBA-7371, the introduction in the study design of a twice daily (100 mg BID) and a three times daily (100 mg TID) regimen will allow assessment of the impact of daily dose fractionation vs. QD dose on the bactericidal activity and the safety/tolerability profile of TBA-7371. This information will be valuable for further development of this and other investigational drugs with similar mechanism of action.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she completes the final visit on Day 42. The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial.

5. Study Population

Prospective approvals of protocol deviations to enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

Recruitment

Participants will be recruited from communities with known high burden of TB transmission and disease. Various methods of recruitment may be used, such as community information sessions, advertising, referrals, word-of mouth, or solicitation through participants previously known to the clinical site.

Recruitment materials, if any, will be approved by the appropriate Institutional Review Board/s (IRBs) or Independent Ethics Committee/s (IECs). Interested participants will be invited to participate in the informed consent process.

5.1. Inclusion Criteria

Age

1. 18 to 60 years of age (inclusive) at the time of signing the informed consent.

Weight

2. Body weight within 40 and 100 kg (inclusive).

Disease Characteristics

3. Untreated, rifampicin-sensitive pulmonary TB, as defined by all of the following:
   a. isoniazid urine screen negativity
   b. sputum smear positivity for acid-fast bacilli using fluorescent microscopy, defined as at least 1+ on the International Union Against Tuberculosis and Lung Disease (IUATLD)/WHO scale
   c. chest X-rays which in the opinion of the investigator is consistent with TB
   d. Mtb positivity on molecular test (GeneXpert®)
   e. rifampicin sensitivity on molecular test (GeneXpert®).

Sputum Production

4. Participants must be able to produce at least 10 mL of sputum during the screening overnight sputum collection (two attempts can be made during Day -7 to -3 to meet the volume requirement if the patient is domiciled at the site for both), as assessed by a Sponsor-approved central laboratory.

Childbearing potential

5. Female and male participants should be of non-childbearing potential or using an effective method of birth control.

Non-childbearing potential is defined as follows:
   a. participant is not heterosexually active or practices sexual abstinence, OR
   b. female participant or sexual partner has undergone bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy, OR

c. female participant or sexual partner has been postmenopausal with a history of no menses for at least 12 consecutive months, OR
d. male participant or sexual partner has undergone vasectomy or bilateral orchidectomy at least three months prior to screening, OR
e. male participant with pregnant sexual partner (for duration of the study) who does not have any other sexual partners.

An effective method of birth control is defined as follows:

a. double barrier method, which can include any 2 of the following: a male condom, diaphragm, cervical cap, or female condom (male and female condoms should not be used together), OR
b. barrier method (one of the above) combined with hormone-based contraceptives or an intra-uterine device for the female participant or partner, AND
c. participant willing to continue practicing one of the above-mentioned birth control methods throughout 14-day Study Treatment Phase and for 4 weeks after the last dose of study medication or discontinuation from study medication in case of early withdrawal.

See Section 10.3 (Appendix 3) for more information on contraceptive guidance and collection of pregnancy information

Informed Consent

6. Participants must be capable of giving signed informed consent as described in Section 10.1 (Appendix 1), which includes agreeing to compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply.

Medical Conditions and History

1. Need for immediate effective anti-TB treatment as judged by the investigator.
2. Tested positive for COronaVIrus Disease-19 (COVID-19)/SARS-CoV-2 during the Screening Period with a PCR-based assay.
3. Evidence and/or history of extra-thoracic TB (e.g. miliary TB, abdominal TB, urogenital TB, osteoarthritic TB, TB meningitis, ocular TB), as judged by the investigator.
4. Evidence and/or history in the last 5 years of one or any combination of the following:
   a. uveitis;
   b. color vision deficiency;
   c. amblyopia;
   d. visual acuity worse than 20/25 after correction in either eye;
   e. any known eye disease or prior eye surgery;
   f. any systemic condition with ocular manifestations (i.e. Marfan, syphilis, diabetes, Beçhet, Vogt-Koyanagi-Harada, Lyme, or chronic inflammatory condition such as sarcoidosis, rheumatoid arthritis, psoriatic arthritis)

5. Evidence and/or history in the last 5 years of clinically significant medical condition(s) as judged by the investigator, including malignancies and unstable or uncontrolled hypertension.
6. Any current medical, psychiatric, occupational, or substance abuse problems that, in the opinion of the investigator, will make it unlikely that the participant will comply with the protocol.
7. For HIV infected participants:
   a. CD4+ count <350 cells/μL, OR
   b. AIDS-defining opportunistic infection or malignancies (except pulmonary TB).
8. Seated systolic/diastolic blood pressure assessed as vital sign (i.e. not from ECG) is less than 95/40 mmHg or greater than 145/95 mmHg at screening. Out-of-range blood pressure may be repeated twice with at least 5 minutes intervening.
9. Seated heart rate assessed as vital sign (i.e. not from ECG) is lower than 40 beats per minute (bpm) or higher than 110 bpm at screening. Out-of-range heart rate may be repeated twice with at least 5 minutes intervening.
10. A clinically significant ECG abnormality at screening. NOTE: The following can be considered not clinically significant:
    a. mild first-degree atrio-ventricular block (P-R interval <0.23 sec);
    b. right or left axis deviation;
    c. incomplete right bundle branch block;
    d. isolated left anterior fascicular block (left anterior hemiblock) in young athletic subjects.

Prior/Concomitant Therapy

See Section 10.6 (Appendix 6) for a list of commonly used prohibited medications (based on exclusion criteria # 11 to # 16). Please note that the list is not comprehensive and other medications with the features described below are also prohibited.

11. Use of medications active against Mtb within 3 months prior to the first dose of study drug.
12. Use of systemic immunosuppressive medications within 14 days prior to the first dose of study drug.
13. Use of strong inhibitors or strong inducers of cytochrome P450 (CYP) enzymes within 14 days prior to the first dose of study drug.
14. Use of inhibitors of phosphodiesterase (PDE) enzymes within 14 days prior to the first dose of study drug.
15. Use of medications known to affect the eye within 3 months prior to the first dose of study drug.
16. For HIV+ patients, use of medications listed in Section 10.6 (Appendix 6) within 3 months prior to the first dose of study drug.

Prior/Concurrent Clinical Study Experience

17. Participation in other clinical study(-ies) with investigational agent(s) within 6 months prior to trial start.

Diagnostic Assessments

18. The following laboratory values from blood collected during the Screening Phase, which represent Grade 2 or higher abnormalities per DAIDS Toxicity Table Version 2.1 (see Section 10.4, Appendix 4), will be cause for exclusion:
    - AST, ALT, alkaline phosphatase (ALP) ≥ 2.5x upper limit of normal (ULN)

- Total bilirubin ≥ 1.6x ULN
- Creatinine ≥ 1.3x ULN
- Hemoglobin < 10 g/dL (male) or 9.5 g/dL (female)
- White Blood Cell Count (WBC) < 2,000 / mm^3
- Platelets ≤ 100,000 /mm^3
- INR ≥ 1.5x ULN
- PTT ≥ 1.66 ULN
- PT ≥ 1.25x ULN

ULN= upper limit of normal for local laboratory values

Grade 2 or higher abnormalities in other laboratory parameters from blood or urine Grade 1 abnormalities, or abnormalities from laboratory parameters not included in the DAIDS Toxicity Table Version 2.1, may lead to exclusion if the investigator considers them clinically significant.

Other Exclusion Criteria

19. History of allergy or hypersensitivity to any of the study drugs or related substances.
20. Positive urine drug screening for cocaine AND/OR amphetamines AND/OR opiates AND/OR methamphetamines. Note: screening will also be conducted for cannabinoids and results documented in the CRF; however, a positive test for cannabinoids is not an exclusion criterion.
21. Female participants currently pregnant or lactating/nursing; OR having positive serum pregnancy test during the Screening Phase OR planning a pregnancy within the 1 month after first dose of study drug. Refer to Section 10.3 (Appendix 3) for more information.

5.3. Lifestyle Considerations

Avoidance of pregnancy during the study: see Section 5.1.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (i.e. why eligibility criteria were not met) and any SAE.

Rescreening is not permitted, except in special circumstances. The investigator may review rescreening eligibility, on a case-by-case basis, with the Sponsor.

6. Study Interventions

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Two interventions will be used in this study: participants will receive either TBA-7371 oral suspension or HRZE, a fixed dose combination of isoniazid [H], rifampicin [R], pyrazinamide [Z] and ethambutol [E]) oral tablets, commercially available in South Africa (Rifafour® e-275).[1]

6.1.1. Composition

6.1.1.1 TBA-7371 Oral Suspension

The drug product is an extemporaneously compounded oral suspension.

The quantitative composition, function and quality of each ingredient in the drug product (TBA-7371 Oral Suspension, 25 mg/mL) is provided in Table 7 below.

Table 7. Composition of the TBA-7371 Oral Suspension, 25 mg/mL

Ingredient	Function	Quality Standard	Quantity per dose (100 mg)	Quantity per dose (200 mg)	Quantity per dose (400 mg)
TBA-7371 hydrochloride* equivalent to TBA-7371	Drug substance	In-house	100 mg	200 mg	400 mg
Purified water	Diluent	Commercially available	0.8 mL	1.6 mL	3.2 mL
Ora-Blend® **	Flavored oral suspending vehicle	Commercially available	Quantity required to 4 mL	Quantity required to 8 mL	Quantity required to 16 mL
Total volume			4 mL	8 mL	16 mL

*TBA-7371 hydrochloride salt is calculated using the assay value of free base from the certificate of analysis. Quantity of HCl salt (g) = amount of free base equivalent divided by % assay value as free base.
** Purified water, sucrose, glycerin, sorbitol, flavoring, micro- crystalline cellulose, carboxymethylcellulose sodium, xanthan gum, carrageenan, calcium sulfate, trisodium phosphate, citric acid and sodium phosphate as buffers, dimethicone antifoam emulsion. Preserved with methylparaben and potassium sorbate.

6.1.1.2 HRZE Tablets

HRZE is a commercially available fixed dose combination of 4 TB drugs: isoniazid (H, 75 mg), rifampicin (R, 150 mg), pyrazinamide (Z, 400 mg), and ethambutol (E, 275 mg)

Rifafour® e-275 (Sanofi) tablets, a commercial presentation of HRZE approved and available in South Africa, will be used in this study.

See package insert [1] (also enclosed in the study specific manual) for information on the composition of Rifafour® e-275 tablets.

6.1.2. Intervention Cohorts

During the Screening Phase participants will not receive TB treatment.

Participants who meet all inclusion and none of the exclusion criteria at the end of the Screening Phase will be enrolled sequentially in one of 5 cohorts in 3 escalation steps and randomized as follows.

- Cohort I: randomized to TBA-7371 oral suspension 100 mg QD OR HRZE tablets (Rifafour® e-275) QD for 14 days.
- Cohort II and Cohort III: randomized first to Cohort II OR Cohort III, and subsequently
  - Cohort II: randomized to TBA-7371 oral suspension 100 mg BID OR HRZE tablets (Rifafour® e-275) QD for 14 days.
  - Cohort III: randomized to TBA-7371 oral suspension 200 mg QD OR HRZE tablets (Rifafour® e-275) QD for 14 days.
- Cohort IV: randomized to TBA-7371 oral suspension 100 mg TID OR HRZE tablets (Rifafour® e-275) QD for 14 days.
- Cohort V: randomized to TBA-7371 oral suspension 400 mg QD OR HRZE tablets (Rifafour® e-275) QD for 14 days.

On Day 15 all participants will switch to standard of care TB treatment as determined by the National Health System.

6.1.3. Administration

Study drugs will be prepared and administered in an unmasked (unblinded) fashion based on the randomization list by authorized and trained site staff members.

All doses of study drug will be taken under direct observation of a study staff member.

TBA-7371 oral suspension will be administered every day from study Day 1 to Day 14 once (Cohorts I, II and V), twice (Cohort II) or three times (Cohort III) daily (see Section 6.1.2).

HRZE tablets (Rifafour® e-275) will be administered every day from study Day 1 to Day 14 QD as per Package Insert [1] as follows:

- 40-54 kg: 3 tablets
- 55-70 kg: 4 tablets
- 71 kg and over: 5 tablets.

If a patient's weight changes between specified weight bands during the course of the Study Treatment period, the investigator will determine which of the measured weights to use for dosing.

The 1st dose of study drug will be administered at the same time each day for the individual participant. Subsequent doses will be administered as follows:

- BID schedules: 12 hours after 1st dose
- TID schedule: 7 hours and 14 hours after 1st dose.

Fasting must occur at least 2 hours before dosing and at least 1 hour after dosing.

When the dosing timing coincides with the time of other procedures, dosing will occur after completion of the procedures. It is important that dosing occurs at the assigned time. Procedures should be timed accordingly i.e. start before dosing time as appropriate.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Preparation

TBA-7371 will be prepared extemporaneously for 250 mL or 500 mL of a 25 mg/mL suspension. Please refer to the study specific manual(s) for preparation details.

Commercial HRZE tablets (Rifafour® e-275) will be provided.

6.2.2. Handling

TBA-7371 oral suspension will be transferred and stored in Pyrex glass reagent bottles with a polypropylene screw cap without a liner. These bottles will be used for mixing, sampling and storage prior to administration. The required doses of the drug product will be dispensed using commercially available oral syringes of suitable capacity. The suspension will be dispensed just prior to dosing and not stored in the oral syringes.

6.2.3. Storage

Based upon the supportive stability study data, the recommended storage condition for batches of TBA-7371 oral suspension clinical trial material is 2-8°C (36-46°F). A do-not-use-beyond-date of 7 days after compounding has been assigned.

Rifafour® e-275 tablets will be stored in a cool place, below 25°C as per Package Insert.[1]

The study pharmacist (or designee) must confirm appropriate temperature conditions have been maintained during transit and during site storage for all study drugs received and that any discrepancies are reported and resolved before use. Upon receipt of study drug supplies, the study pharmacist (or designee) must immediately inspect supplies for damage. Any damage or discrepancy from the packing list must be documented and promptly discussed with the sponsor or CRO representative to determine the appropriate action.

6.2.4. Accountability

Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The principal investigator is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Authorization for any unused study drug and supplies to be destroyed is the responsibility of the sponsor. Unused supplies will be destroyed according to the facility's SOPs or per local regulations. Any disposal of study drug conducted at the clinical site must be documented in the study file.

Further guidance and information for the preparation, handling, storage and accountability are provided in the study specific manual(s).

6.3. Measures to Minimize Bias: Randomization and Masking

6.3.1. Randomization

Participants will be enrolled in one of 5 cohorts in 3 sequential escalation steps as follows.

- Cohort I: TBA-7371 100 mg QD or HRZE (Rifafour® e-275) QD for 14 days.

➢ First escalation step (from Cohort I to Cohorts II and III). Participants will be randomized to Cohort II OR Cohort III.

- Cohort II: TBA-7371 100 mg BID or HRZE (Rifafour® e-275) QD for 14 days.
- Cohort III: TBA-7371 200 mg QD for or HRZE (Rifafour® e-275) QD for 14 days.

➢ Second escalation step (from Cohort II and Cohort III to Cohort IV)

- Cohort IV: TBA-7371 100 mg TID or HRZE (Rifafour® e-275) QD for 14 days.

➢ Third escalation step (from Cohort IV to Cohort V)

- Cohort V: TBA-7371 400 mg 400 QD or HRZE (Rifafour® e-275) QD for 14 days.

Across Cohorts I, IV, and V, the design is non-randomized and open label, whereas the design is randomized with respect to Cohort II and III, which have the same total daily dose (200 mg). Within each cohort the design is randomized, active-controlled and open label. Within each cohort participants will be randomized unequally in a 5:1 ratio to TBA-7371 (N=15) or HRZE (N=3).

Participants will be randomized on Day -1 or Day 1 based on a randomly-generated sequence of participant identification (identifier) numbers (randomization schedule) using a validated Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and instructions for the IWRS will be provided to the study sites.

6.3.2. 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 instead be masked (blinded) for personnel involved in the conduct of all other laboratory procedures (including those for the primary endpoint).

6.3.3. Masking Break

Not applicable in this study.

6.4. Study Intervention Compliance

All doses of study drug will be taken under direct observation of a study staff member. Participant compliance with study intervention will be recorded on his/her eCRF.

6.5. Concomitant Therapy

No TB drug must be taken during the Screening Phase.

No TB drug other than study drugs (TBA-7371 and HRZE fixed dose combination) must be taken during the Study Treatment Phase (Days 1-14).

At the start of the Follow-up Phase (Day 15) participants will be switched to standard of care TB treatment.

All treatments listed in the exclusion criteria 11 to 15 are also not allowed throughout the Study Treatment Phase and Follow-up Phase (Days 1 through 42).

No vaccine should be administered during the trial.

Any allowed prescription medication, anti-inflammatory drug and antipyretic drug that the participant receives from enrollment through study Day 42 must be recorded along with reason for use, dates of administration including start and end dates and dosage information including dose and frequency.

The medical monitor may be contacted if there are any questions regarding concomitant or prior therapy.

6.6. Dose Modification

No dose modification of study drug is allowed.

6.7. Intervention after the End of the Study

There is no intervention planned after the end of the study.

7. Discontinuation of Study Drug and Participant Discontinuation/ Withdrawal

7.1. Pausing and Resumption of Study Drug and Recruitment

If any one of the conditions listed below apply, an investigator and/or the sponsor will pause enrollment and study drug administration. If an investigator observes that a pausing rule is met, he/she will inform the sponsor as soon as possible and within 24 hours of the event. The sponsor will notify all investigators and IDMC of the pause in enrollment as soon as possible and within 24 hours of the event. The IDMC will then review all relevant safety data in an ad hoc meeting and recommend to the sponsor how to proceed. If the IDMC observes that a pausing rule is met, the IDMC will inform the sponsor ASAP and within 24 hours of the observation. The IDMC charter describes these processes in more detail.

If any of the below conditions are met, enrollment and administration of study drug will be paused:

- anaphylaxis with or without bronchospasm within 4 hours of study drug intake, indicative of an immediate hypersensitivity reaction;
- 3 or more of participants in the same or different cohorts experience adverse events with Grade 3 or higher intensity, considered related to study drug and similar to one another, as assessed by the investigator and/or the IDMC and/or the sponsor;
- an AE pattern of concern, as assessed by the investigator and/or the IDMC and/or the sponsor;

The decision to pause the study will be recorded in a memorandum to the study file and will trigger IDMC review.

IDMC recommendations will be recorded in a memorandum to the study file.

The IDMC may recommend resumption of study drug administration and enrollment with or without changes to the protocol.

The final decision to resume study activities or amend the protocol will be made by the sponsor.

The clinical site will be allowed to resume activities upon receipt of written notification from the sponsor.

Upon resumption of study drug administration, participants who will have missed up to 1 treatment day will continue in the study; participants who will have missed more than 1 treatment day will be withdrawn from the study and possibly replaced if the enrollment pause results in more than 2 early withdrawals (drop-outs) in a cohort.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant will discontinue study treatment and end in-clinic hospitalization if the participant tests positive for COVID-19/SARS-CoV-2 anytime during the study treatment period, and will be referred for on-going TB treatment per national guidelines and for further evaluation for COVID-19. If the participant allows and the PI agrees, telephone follow-up may be completed in place of onsite visits on Day 28 and Day 42.

A participant may withdraw from the study at any time or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. The participant will be permanently discontinued both from the study intervention and from the study at that time.

See Section 10.1.5 (Appendix 1) regarding the participants' right to withdraw.

Participants who withdraw before Day 14 will be asked to complete the Early Withdrawal Visit assessments within 2 days of withdrawal (see Section 8.3.8).

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 a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and the eCRF.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she permanently leaves the hospital or refuses study procedures during the Study Treatment Phase or fails to return to the Day 28 and/or 42 visits during the Follow-up Phase.

In such cases the site must attempt to contact the participant and urge him/her

- to return to the hospital and resume study procedures if no or 1 treatment day have been missed, OR
- undergo the Early Withdrawal Visit, OR
- reschedule missed Day 28 or Day 42 visit as soon as possible.

Before a participant is deemed lost to follow up, the investigator or designee must make at least 3 attempts to regain contact with the participant (where possible, telephone calls and, if necessary, a home visit by a member of the study team). These contact attempts should be documented in the participant's medical record.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3, Table 3 and Table 4). Protocol waivers or exemptions are not allowed.

A ± 15-minute time window is allowed for all measurements.

8.1. Screening Assessments and Procedures

Prior to any study procedure, all eligible participants will be assigned a unique participant identifier. This participant identifier will be used throughout the study for participant identification.

Screening procedures will be conducted during the 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 and the screening sample for COVID-19/SARS-CoV-2, which must be completed on or before Day -3, and the overnight sputum collection for EBA assessment, which much be done consecutively on Day -2 and Day -1. Participants may be hospitalized for the entire screening period at the investigator's discretion, but must be hospitalized starting on Day -3. Eligibility for randomization will be based on the inclusion and exclusion criteria described in Sections 5.1 and 5.2.

Eligibility criteria will be checked during the Screening Phase and prior to study drug administration to ensure that each randomized participant meets all the inclusion criteria and none of the exclusion criteria. The investigator will also maintain a screening log to record details of all participants screened, to confirm eligibility or record reasons for screening failure, as applicable.

To evaluate eligibility criteria, the following assessments / procedures will be conducted:

- Demography and medical and treatment history
- Physical examination (PE)
- Chest x-rays
- COVID-19/SARS-CoV-2 test
- Serum HIV test and blood CD4 count
- Serum pregnancy test in female participants
- Laboratory safety tests (haematology, chemistry, coagulation, urinalysis)
- Urine isoniazid and drug screening
- Overnight sputum for eligibility assessment (sputum volume, acid-fast bacilli, Mtb positivity and rifampicin sensitivity). Sputum assessment, including volume, will be performed by a Sponsor-approved central laboratory (see laboratory study instruction document).
- Vital signs and weight
- ECG
- Eye assessment (visual acuity, color vision, eye symptoms)

Details on the assessments and procedures unique to the Screening Phase are provided in this section. Details on the assessments and procedures common to the Screening and Treatment Phase and/or Follow-up Phase are provided in the sections to follow.

8.1.1. Demography and Medical and Treatment History

Information on demographic characteristics (age, sex, place of birth, occupation, number of children) will be obtained and a medical and treatment history will be conducted during the Screening Phase to assess eligibility. All conditions that exist prior to the Screening Phase will be recorded in the medical history section of the ICF. Any clinically relevant new condition or fluctuation of existing condition observed during the Screening Phase will be recorded as AE. Day to day fluctuations in these conditions that do not represent a clinically relevant change in the participant's status should not be reported as AE (see Section 0).

8.1.2. Chest X-Rays

Good quality Posterior-Anterior (PA) chest X-rays will be accepted to assess eligibility if conducted within 1 week prior to the start of the screening period. If not available, PA chest X-rays will be conducted during the Screening Phase.

Chest X-rays consistent with TB in the investigator's opinion is one of the conditions that must be met for the diagnosis of untreated rifampicin-sensitive pulmonary TB (Inclusion Criteria, Section 5.1).

8.1.3. COVID-19/SARS-CoV-2

In accordance with the SAHPRA Policy on Conduct of Clinical Trials of Health Products during the Current COVID-19 Pandemic, issued 25 March 2020, this protocol amendment reflects the new and modified processes that were implemented in response to COVID-19. This amendment accommodates for changes related to the pandemic that are needed to minimize risk of transmission of SARS-CoV-2 among participants and staff and builds on strong infection control site practices, which are already in place, to reduce risk of TB transmission as an airborne infectious disease.

PCR-based COVID-19/SARS-CoV-2 testing will be conducted by the site and a negative result must be confirmed prior to randomization. In case of a positive COVID-19/SARS-CoV-2 test during the screening period, the participant will be excluded per the Exclusion Criterion in Section 5.2.

8.1.4. HIV Test and CD4 Count

HIV test with CD4 cell count will be conducted during the Screening Phase to assess eligibility. Details on blood/serum collection procedures, and on the laboratory are provided in the study specific manual(s). In case of positive HIV test, the participant will be excluded per the Exclusion Criteria, Section 5.2.

8.1.5. Urine Isoniazid Screening

Participants are eligible for this study if they have received no TB treatment for at least 3 months prior to Day 1 (Exclusion Criteria, Section 5.2). Urine isoniazid screening will be conducted

during the Screening Phase to support no recent TB therapy. Details on urine collection procedure, and on the laboratory are provided in the study specific manual(s).

8.1.6. Urine Drug Screening

Urine screening for cocaine, amphetamines, opiates and methamphetamines will be conducted during the Screening Phase to assess eligibility (Exclusion Criteria, Section 5.2). The same urine sample will also be screened for cannabinoids and results documented; however, a positive test for cannabinoids is not an exclusion criterion. Details on urine collection procedure and on the laboratory are provided in the study specific manual(s).

8.1.7. Overnight Sputum for Eligibility Assessment

Overnight sputum (collected from 3 PM to 7 AM of the following morning) will be collected between Day –7 and Day -3 and analyzed to assess eligibility through the sputum volume measurement, acid-fast bacilli detection and molecular tests for Mtb positivity and rifampicin sensitivity. If inclusion criteria cannot be met from the 1st overnight sputum collection, a second overnight sputum sample may be collected during Day -7 to Day -3 and one or more of the above procedures can be repeated. The patient must be domiciled at the site for the overnight sputum collection and sputum samples will be analyzed by a Sponsor-approved central laboratory.

8.1.7.1. Overnight Sputum Volume

Participants must be able to produce at least 10 mL of sputum during the overnight collection (Inclusion Criterion, Section 5.1). If this volume is not reached on the sample(s) taken between Day -7 and Day -3, the participant will be excluded. All volume assessments will be performed by a Sponsor-approved central laboratory (see laboratory study instruction document).

8.1.7.2. Acid-fast bacilli detection

Acid-fast bacilli will be sought by concentrated smear microscopy on a sputum sample obtained from the overnight collection performed between Day -7 and Day -3. In case of suboptimal 1st overnight sputum collection, the microscopy can be conducted on a 2nd overnight sputum collected between Day -7 and Day -3.

Details on the acid-fast bacilli detection methods and on the laboratory are provided in the Study Laboratory Manual.

Sputum smear positivity for acid-fast bacilli is defined as at least 1+ on the IUATLD/WHO scale. Sputum positivity for acid-fast bacilli is one of the conditions that must be met for the diagnosis of untreated rifampicin-sensitive pulmonary TB (Exclusion Criteria, Section 5.2).

8.1.7.3. Molecular tests for Mtb positivity and rifampicin sensitivity

A commercial molecular test to assess Mtb positivity and rifampicin sensitivity, GeneXpert® diagnostic system (Cepheid), will be carried out on a sputum sample obtained from the overnight collection taken between Day -7 and Day -3. In case of inconclusive results from the 1st overnight sputum sample, the GeneXpert® can be conducted on a 2nd overnight sputum collected between Day -7 and Day -3.

Mtb positivity and rifampicin sensitivity are among the conditions that must be met for the diagnosis of untreated rifampicin-sensitive pulmonary TB (Exclusion Criteria, Section 5.2).

Details on procedures for GeneXpert® test are provided in the Study Laboratory Manual.

8.2. Bactericidal Activity Assessment

8.2.1. Overnight Sputum for EBA assessment and Exploratory Measurements

Overnight sputum will be collected from 3 PM to 7 AM of the following morning.

The overnight sputum samples collected on Day -2 and Day -1 of the Screening Phase will be used to determine baseline EBA. Subsequent overnight sputum samples will be collected every day/night (Day 1 to Day 14) to assess changes in bacterial burden during the Study Treatment Phase.

Early bactericidal activity will be assessed on each sputum sample by 3 different methods: 1) CFU on solid media culture (primary), 2) time to sputum culture positivity (TTP) in MGIT culture, 3) LAM assay. Confirmation of Mtb will be performed on solid media and MGIT cultures as necessary using available commercial methods.

A commercial molecular test to assess isoniazid and rifampicin sensitivity, GenoType MTBDRplus (HAIN Lifesciences), will be utilized on positive MTB cultures from Day -2 (or, if Day -2 unavailable, Day -1) and Day 14 to assess the drug susceptibilities at each visit. In addition, MICs of TBA-7371 will be batch tested on positive MTB cultures from Day -2 (or, if Day -2 unavailable, Day -1) and Day 14.

Extra samples from overnight sputum collections, as well as MTB isolates from cultures, will be stored for potential assessment of exploratory endpoints (see Section 8.10).

Details on sputum collection, handling and testing procedures, and on the laboratory are provided in the laboratory study instruction document.

8.2.2 Samples for exploratory endpoints

Daily urine samples will be collected and stored for exploratory biomarker development that may include establishing the kinetics of LAM reduction following treatment.

Daily spot sputum samples will be collected into RNA preservation media (e.g., GTC-TCEP) and stored for measurements of transcriptomic-based biomarkers, which may include mycobacterial as well as host transcription markers. The participant should spontaneously produce (i.e., not induced) a spot sputum specimen for collection into RNA preservation media at each specified visit. If the specimen cannot be collected due to participant inability to produce sputum, or due to operational limitations with RNA media collection kits, it is not considered a protocol deviation and participants remain eligible for trial participation.

Serum samples will be stored for potential assessment of the alteration of mycobacterial and host proteins following treatment.

Additional exploratory biomarkers may be evaluated. 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.

8.3. Safety Assessments

Immediate safety concerns should be discussed with the sponsor and/or CRO immediately upon occurrence or awareness.

d. Adherence to the requirements of the study protocol, including those specified in the SoA (Section 1.3, Table 3 and **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.

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

f. **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.

18. **Written informed consent** will be given before any screening procedure is started.
19. **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.
20. **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.
21. **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.
22. **Blood/serum sample collection for clinical safety laboratory assessment.** The Day 3 and 7 sampling will occur before the 1st dose of study drug.
23. **Urine sample collection drug screening**: cannabinoids, cocaine, amphetamines, opiates, methamphetamines.
24. **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.
25. **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).
- 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.

26. **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).
    - 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.
27. **Eye assessment.** A trained staff member will assess: i) eye symptoms using a standardized script (Section 10.5, Appendix 5), 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).
    - Follow-up Phase: Days 15, 28 and 42 during the visit.
    - EWV: if the participant withdraws from the study between Days 1 and 14.
28. **Study drug (IMP) administration.** Study drug (TBA-7371 or HRZE) will be administered from Day 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 at the same time each Day for the individual participant. Subsequent doses will be administered as follows (see Table 4):
    - 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.
29. **Overnight sputum collection for EBA assessment and exploratory measurements**. Overnight 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 Day 15. Drug susceptibility testing for isoniazid and rifampicin, and minimum inhibitory concentrations (MIC) of TBA-7371 will be performed on either of Day -2 or Day -1, and again on Day 14. Aliquots from each sample, as well as MTB isolates from cultures, will be stored and may be used for exploratory measurements.
30. **Spot sputum collection for exploratory measurements.** The participant should spontaneously produce (i.e., not induced) a spot sputum specimen for collection into RNA preservation media. If specimen cannot be collected due to participant inability to produce sputum, or due to operational limitations with RNA media collection kits, it is not considered a protocol deviation.
31. **Recording of AE, SAE (including serious ADR) and AESI; recording of concomitant treatments.** Adverse events (AE), serious adverse events (SAE), including serious adverse drug reactions (ADR), adverse events of special interest (AESI) and concomitant treatments will be recorded from the time each participant has signed the informed consent form (ICF) until he/she has completed the last follow- up visit (Day 42) or the Early Withdrawal Visit (EWV).
32. **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). 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.

33. **Blood/serum/plasma sample collection for exploratory measurements.** Timing of sampling will be as follows:
    - Study Treatment Phase: Day 1 and 7 before administration of the 1st daily dose of study drug (see Table 4).
    - Follow-up Phase: Day 15 in the morning at approximately the same time study drug was administered.
34. **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.

Table 4) is essential and required for study conduct.

Safety outcomes will include AE and SAE described in Section 8.4 and Section 10.2 (Appendix 2).

8.3.1. Physical Examination

A full PE, including height, will be conducted during the Screening Phase to assess eligibility.

A focused PE will be performed as directed by medical history on Days 7, 15, 28 and 42. If early withdrawal occurs between Day 1 and Day 14, a focused PE should be conducted at the Early Withdrawal Visit. A focused PE may be conducted during an unscheduled visit at the discretion of the investigator.

8.3.2. COVID-19/SARS-CoV-2

PCR-based COVID-19/SARS-CoV-2 testing will be conducted at Day 7 (±2 Days), on Day 14 OR Day 15 before discharge, and/or at any other time that infection is suspected. In case of positive COVID-19/SARS-CoV-2 test during the study treatment period, the participant will discontinue study treatment, will end in clinic hospitalization, and will be referred for on-going TB treatment per national guidelines and for further evaluation for COVID-19. In case of a positive COVID-19/SARS-CoV-2 test on Day 14 or Day 15 at the end of the study treatment period, participants will be referred for on-going TB treatment per national guidelines and for further evaluation for COVID-19.

8.3.3. Pregnancy Status Assessment

A serum beta human chorionic gonadotropin (βHCG) test will be performed during the Screening Phase to assess eligibility, on Day 15, (the day after the last dose of study drug) and on Day 42 (end of the Follow-up Phase). The test will also be conducted during the Early Withdrawal Visit if the participant withdraws from the study between Day 1 and 14.

Details on serum collection procedures and on the laboratory are provided in the study specific manual(s).

If a pregnancy is reported during the study, the investigator should inform the local medical monitor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.3 (Appendix 3).

If a participant becomes pregnant during the study, she will be withdrawn from study drug and from all study procedures going forward. If the pregnancy is discovered during the Treatment Phase, the participant will undergo the Early Withdrawal Visit and thereafter be discharged from the hospital. However, she will be encouraged to undergo the Day 28 and Day 42 visits.

Investigators must make an effort to collect outcomes of pregnancies discovered during the study and communicate them to the sponsor and/or CRO.

8.3.4. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will be performed during the Screening Phase to assess eligibility, during the Treatment Phase on Day 3 and 7, and during the Follow-up Phase on Days

15 and 42. If early withdrawal occurs between Day 1 and Day 14, clinical safety laboratory assessments should be conducted at the Early Withdrawal Visit.

Clinical safety laboratory parameters include:

- haematology: complete blood count (red blood cells, haemoglobin, platelets and white blood cells) and differential (absolute counts) including neutrophils, lymphocytes, monocytes, eosinophils and basophils;
- serum chemistry: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), ALP, total bilirubin, creatinine, blood urea nitrogen (BUN), sodium, and potassium;
- serum coagulation: PT, PTT, INR
- urinalysis: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase.

Details on blood/serum and urine collection procedures and on the laboratory are provided in the study specific manual(s).

Refer to DAIDS Table in Section 10.4 (Appendix 4), pages 25-31, for intensity (severity) grading of common laboratory tests.

Certain clinical safety laboratory values from the samples collected during the Screening Phase, i.e. before randomization, that are outside the normal range with intensity (severity) Grade 2 or above, will lead to exclusion from study enrollment, as described in Section 5.2. Grade 1 abnormalities or other Grade 2 and higher abnormalities will not lead to exclusion, unless the investigator considers them clinically significant.

Abnormal results and findings that make the participant ineligible will be discussed with the participant and the participant will be referred for follow-up care with their healthcare provider if necessary.

For laboratory values from the samples collected after randomization, the investigator will record any clinically significant change in the AE section of the CRF [see Section 10.2.1 (Appendix 2)]. DAIDS intensity (severity) grading of common laboratory tests reported in Section 10.4 (Appendix 4), DAIDS Table, pages 25-31) will help the investigator in deciding whether or not a given laboratory finding is clinically significant and therefore qualifies as an AE. However, the investigator is not obliged to follow these criteria and his/her medical judgement should prevail.

Abnormal laboratory findings are associated with an underlying disease are not clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition [see Section 10.2.1 (Appendix 2)].

The laboratory reports must be filed with the source documents.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

If laboratory values from non-protocol specified clinical safety laboratory assessments require a change in participant management or are considered clinically significant by the investigator (e.g., AE or SAE), then the results must be recorded in the eCRF.

8.3.5. Vital signs and body weight

The following 5 vital signs will be measured: axillary BT, respiratory rate (RR), HR, SBP, DBP. Body weight (BW) will also be measured with vital signs

g. Vital sign and body weight recording will occur as follows (see Section 1.3, Table 3 and **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.

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

i. **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.

35. **Written informed consent** will be given before any screening procedure is started.
36. **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.
37. **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.
38. **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.
39. **Blood/serum sample collection for clinical safety laboratory assessment.** The Day 3 and 7 sampling will occur before the 1st dose of study drug.
40. **Urine sample collection drug screening**: cannabinoids, cocaine, amphetamines, opiates, methamphetamines.
41. **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.
42. **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 <u>once every morning (Days 1 to 14) before</u> administration of the 1st daily dose of study drug; <u>in addition, on Days 1, 4, 7, 10 and 14</u> vital signs will also collected 2.5h, 10.5h and 16.5h <u>after</u> the time of 1st daily dose of study drug (see Table 4).

- 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.

43. **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).
    - 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.
44. **Eye assessment.** A trained staff member will assess: i) eye symptoms using a standardized script (Section 10.5, Appendix 5), 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).
    - Follow-up Phase: Days 15, 28 and 42 during the visit.
    - EWV: if the participant withdraws from the study between Days 1 and 14.
45. **Study drug (IMP) administration.** Study drug (TBA-7371 or HRZE) will be administered from Day 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 at the same time each Day for the individual participant. Subsequent doses will be administered as follows (see Table 4):
    - 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.
46. **Overnight sputum collection for EBA assessment and exploratory measurements**. Overnight 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 Day 15. Drug susceptibility testing for isoniazid and rifampicin, and minimum inhibitory concentrations (MIC) of TBA-7371 will be performed on either of Day -2 or Day -1, and again on Day 14. [redacted]
47 [redacted]
48. **Recording of AE, SAE (including serious ADR) and AESI; recording of concomitant treatments.** Adverse events (AE), serious adverse events (SAE), including serious adverse drug reactions (ADR), adverse events of special interest (AESI) and concomitant treatments will be recorded from the time each participant has signed the informed consent form (ICF) until he/she has completed the last follow- up visit (Day 42) or the Early Withdrawal Visit (EWV).
49. **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). 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.

50. [redacted]

51. **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.

Table 4).

Screening Phase

Vital signs and body weight 1 to 3 times (see below) in the morning at approximately the same time the 1st daily dose study drug will be administered.

SBP, DBP and HR assessed as vital sign (i.e. not from ECG) will be used to assess eligibility (Exclusion Criteria, Section 5.2). An out-of-range value may be repeated twice with at least 5 minutes intervening

Study Treatment Phase

Vital signs and body weight 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 be collected 2.5h, 10.5h and 16.5h after the time of 1st daily dose of study drug (see Table 5).

Follow-up Phase

Vital signs and body weight on Day 15 in the morning before 1st daily dose of standard of care medication

Vital signs and body weight on Days 28 and 42 during the visit.

Early Withdrawal Visit

Vital signs and body weight if the participant withdraws from the study between Day 1 and 14.

At each assigned time point, BT, RR and BW will be measured once, whereas HR, SBP and DBP will be measured twice as follows:

- after at least 10 minutes in supine position ("manual, supine")
- after 2 minutes in standing position ("manual, 2-min standing")

If the rhythm is regular, manual measurement or automated blood pressure equipment may be used for HR and SBP/DBP determination. Pulse oximeter HR data should not be used. If the rhythm is irregular, the measurements should be done manually.

When ECG, vital signs and/or blood/serum samples are to be obtained at the same time point, ECG will be recorded first after 10 minutes of supine rest, followed by the vital signs and then the blood draw(s) within 5 minutes of each other.

The investigator must record any clinically significant abnormalities in vital signs occurring during the study as AE. DAIDS intensity (severity) grading of adverse events reported in Section 10.4 (Appendix 4, page 7) may help the investigator in deciding whether or not a given finding is clinically significant and therefore qualifies as an AE. However, the investigator is not obliged to follow these criteria and his/her medical judgement should prevail.

A HR, SBP or DBP AE emerging from both vital sign and ECG recording at the same time point must be reported only once, with the highest intensity and seriousness grading.

Participants with vital signs-related AEs classified as ≥ Grade 3 severity and/or serious will contribute to the primary safety end-point (see Section 3.1, Table 1).

Participants with ≥ 25% increase in HR, and /or ≥ 25 % decrease in SBP and/or ≥ 25% decrease in DBP from baseline (Day 0) detected through vital signs measurements will contribute to secondary safety end-points (see Section 3.2, Table 2).

Increases in HR and decreases in SBP and/or DBP from vital signs and/or ECG qualifying as AEs ≥ Grade 2 and/or serious are considered adverse events of special interest based on the outcomes of the Phase I trial TBA7371-001 [AESI, see Section 10.2.5, (Appendix 2)].

8.3.6. ECG

Centralized ECG reading will be used. Details on centralized ECG procedures are provided in the study specific manual(s).

One ECG recording will occur at each of the following time points (see Section 1.3, Table 3 and Table 4):

Screening Phase

Once in the morning at approximately the same time the 1st daily dose study drug will be administered.

This tracing will be used to assess eligibility (Exclusion Criteria, Section 5.2). 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 after the time of 1st daily dose of study drug (see Table 4).

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.

Early Withdrawal Visit

If the participant withdraws from the study between Day 1 and 14.

When ECG, vital signs and/or blood/serum samples are to be obtained at the same time point, ECG will be recorded first after 10 minutes of supine rest, followed by the vital signs and then the blood draw(s) within 5 minutes of each other.

The investigator must record any clinically significant ECG abnormality occurring during the study as adverse events (AE). DAIDS intensity (severity) grading of cardiovascular adverse events reported in Section 10.4 (Appendix 4, page 7) may help the investigator in deciding whether or not a given finding is clinically significant and therefore qualifies as an AE. However, the investigator is not obliged to follow these criteria and his/her medical judgement should prevail. Important: a HR, SBP or DBP AE emerging from both vital signs and ECG recorded at the same time point must be reported only once, with the highest intensity and seriousness grading.

Participants with ECG-related AEs classified as ≥ Grade 3 and/or serious contribute to the primary safety end-point (see Section 3.1, Table 5).

Participants with ≥ 25% increase in HR, and /or ≥ 25 % decrease in SBP and/or ≥ 25% decrease in DBP from baseline detected through ECG recordings contribute to secondary safety end-points (see Section 3.2, Table 6).

PR, RR, QRS, QT, QTcF intervals from ECG contribute to secondary safety end-points (see Section 3.2, Table 6)

Increases in HR and decreases in SBP and/or DBP from vital signs and/or ECG qualifying as AEs ≥ Grade 2 and/or serious are considered AESI based on the outcomes of the Phase I trial TBA7371-001 [AESI, see Section 10.2.5 (Appendix 2)].

8.3.7. Eye Assessment

On each eye assessment day participants will undergo the following 3 eye assessment procedures (always in this order):

i) Eye symptom assessment using the standardized script provided in Section 10.5 (Appendix 5)
ii) Visual acuity test by means of the Rosenbaum Pocket Eye Screener on each eye.
iii) Color vision by means of the Waggoner Computerized Color Vision Test on each eye.

The visual acuity test and Waggoner Computerized Color Vision Test (updated computerized version of the paper-based ColorDX test) will be conducted by staff members trained by an ophthalmologist. Whenever possible the same staff member should conduct all eye assessment procedures on an individual participant.

Details on use of the Rosenbaum Pocket Eye Screener and Waggoner Computerized Color Vision Test are provided in the study specific manual(s).

The 3 eye assessment procedures will be conducted on each of the eye assessment days as follows:

Screening Phase

Once in the AM.

This assessment will be used to assess eligibility (Exclusion Criteria, Section 5.2).

Study Treatment Phase

On Days 1, 4, 7, 10 and 14, 2.5 hours after the 1st daily dose of study drug (see Table 4).

Follow-up Phase

On Days 15, 28 and 42 during scheduled visit.

Early withdrawal visit

If the participant withdraws from the study between Day 1 and 14.

Regarding eye symptoms, based on the outcome of study TBA7371-001, special attention will be paid to blurred vision, photophobia, altered color vision and increased lacrimation, but any other eye symptom will be assessed if it occurs (see Section 10.5, Appendix 5).

Intensity (severity) grading of eye symptoms reported in Section 10.4 (Appendix 4, page 20) may help the investigator. However, the investigator is not obliged to follow these criteria and his/her medical judgement should prevail. The visual acuity and color vision tests will complement the clinical assessment of eye symptoms in the assessment of AE intensity and seriousness.

Any eye symptom and/or abnormal visual acuity / color vision test outcome considered clinically meaningful by the investigator must be recorded as AE.

Participants with eye symptom-related AE classified as severe (≥ Grade 3) and/or serious will contribute to the primary safety end-point (see Section 3.1, Table 5).

Participants with any eye symptom will contribute to secondary safety end-points (see Section 3.2, Table 6).

Eye symptoms ≥Grade 2 intensity (severity) and/or severe are considered adverse events of special interest based on the outcome of the Phase I trial TBA7371-001 [AESI, see Section 10.2.5 (Appendix 2)].

8.3.8. Early Withdrawal Visit

Participants who withdraw from the study before Day 14 will be asked to complete the Early Withdrawal Visit assessments within 2 days of withdrawal. These are as follows (see Table 4):

- Focused PE (see Section 0)
- Pregnancy status assessment (see Section 8.3.3)
- Clinical Safety laboratory assessments (see Section 8.3.4)
- Vital signs and body weight (see Section 8.3.5)
- ECG (see Section 0)
- Eye assessment (see Section 8.3.7)
- AE and SAE (see Section 0)
- Concomitant treatments (see Section 8.5).

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 a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and the eCRF.

If a patient is withdrawn from the study due to a positive COVID-19/SARS-CoV-2 test and maintains consent, a telephone follow-up may be documented on Day 28 and Day 42.

8.3.9. Unscheduled Visit

Procedures and assessments conducted during an unscheduled visit will be at the discretion of the investigator in consultation with the medical monitor.

8.3.10. Participant Follow-Up

During the Follow-Up Phase participants will be instructed to contact by phone a study team member to report new or worsening AEs, as well as new diagnoses, and to come to the study clinic if medical attention is needed.

On Day 15, participants will be transferred to the local TB clinic, following completion of all study assessments. Unscheduled assessments may be performed, following transfer, for purposes of safety follow-up.

In exceptional circumstances as assessed by the investigator in consultation with the medical monitor (e.g. issues related to COVID-19/SARS-CoV-2, etc.), participants may have telephone follow up for Day 28 and Day 42.

All deviations from protocol procedures, evaluations, and/or visits will be documented.

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs, SAEs, serious adverse drug reactions (Serious ADRs) and AESI can be found in Section 10.2.1, 10.2.2, 10.2.4, and 10.2.5 (Section 10.2, Appendix 2), respectively.

Study nurses and physicians are responsible for collecting and documenting information and events that would potentially meet the definition of an AE. However only the investigator (study physician) is responsible for assessment, including assignment of causality seriousness and intensity, reporting and management of all AE. The investigator is responsible for following up AE that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (Section 7).

8.4.1. Time Period for Collecting AE Information

AE, SAE (including Serious ADR) and AESI will be collected from the time each participant has signed the ICF until he/she has completed the last follow-up visit (Day 42) or the EWV.

All SAE (including Serious ADR) and AESI will be reported to the sponsor or designee within 24 hours, as indicated in Section 10.2.5 (Appendix 2). The investigator will submit any updated SAE/AESI data to the sponsor or designee within 24 hours of it being available.

The investigator is not obligated to actively seek AE or SAE after conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Methods of Detection of AE and SAE

The methods of detection, recording and follow-up of AE and SAE are provided in detail in Section 10.2.5 (Appendix 2), which includes assessments of intensity (severity), causality, expectedness and outcome of AEs and SAE.

8.4.2.1. Recording of AE and SAE

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event and record all relevant information in the appropriate section of the CRF.

Care should be taken not to introduce bias when detecting AE and SAE/AESI: open-ended and non-leading questions are the preferred method to inquire about AE occurrences.

Refer to Section 10.2.5 (Appendix 2), Follow-up of AE and SAE/AESI.

After the initial AE/SAE/AESI report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAE will be followed until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3).

Refer to Section 10.2.5 (Appendix 2). Assessment of Intensity (Severity) of AE and SAE/AESI.

Clinical signs and symptoms that constitute AE/SAE/AESI will be classified by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), potentially life threatening (Grade 4), death (Grade 5). Refer to Section 10.2 (Appendix 2).

Grading criteria reported in in the DAIDS Table, Section 10.4 (Appendix 4) may help in the assessment of intensity of AEs. Additional grading criteria reported in Section 10.5 (Appendix 5) may help in the assessment of intensity of selected eye symptoms. However, the investigator is not obliged to follow these criteria and his/her medical judgement should prevail.

Participants with AE classified as severe (Grade 3 and above) will contribute to the primary safety end-point (see Section 3.1, Table 5).

8.4.2.2. Assessment of Causality of AE and SAE

All AE will be evaluated by the principal investigator (PI) or by a medically qualified designee (i.e. investigator, study physician) to assess the relationship between study intervention and each occurrence of each AE/SAE/AESI. Careful medical judgement should be exercised to determine the level of causal relationship between an AE and the study intervention. The causality assessment will be determined using a two-level scale: related or not related.

The sponsor or designee will have the opportunity to confirm the seriousness and case causality based on the clinical judgement of the medical monitor and sponsor designee. If a SAE is considered unrelated by the investigator but the sponsor believes that there is a reasonable possibility that the event is related, the sponsor will upgrade the case to a ‘related’ status. The sponsor or designee will never downgrade a case from serious to non-serious or related to not related.

Refer to Section 10.2.6.4 (Appendix 2).

8.4.2.3. Assessment of AE/SAE Expectedness

Each SAE will be evaluated by the sponsor. based on applicable product information (e.g. Investigator Brochure or Package Insert).

Refer to Section 10.2.6.5 (Appendix 2).

8.4.2.4. Assessment of SAE Outcome

The outcome of each SAE must be reported to the sponsor, even if this extends beyond the SAE reporting period (i.e., after the final study visit).

Refer to Section 10.2.6.6 (Appendix 2).

8.4.3. Reporting Requirements for SAE, Serious ADR, AESI and Other Events

Prompt notification (within 24 hour) by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and potentially other regulatory agencies about the safety of the study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.

All fatal and life-threatening serious unexpected ADR are to be reported to South African Health Products Regulatory Authority (SAHPRA) within 7 calendar days after first knowledge with a complete report to be submitted within an additional 8 calendar days. Serious, unexpected ADRs that are not fatal or life threatening are to be reported to SAHPRA no later than 15 calendar days after first knowledge. An investigator who receives a Serious, unexpected ADR report or other specific safety information (e.g., summary or listing of SAEs/SADRs) from the sponsor will review and file it. A tracker of all such reports received from the CRO will be maintained by the site. The PI will notify the IRB/IEC, if appropriate and according to local requirements. IRB/IEC submissions will be conducted per the local IRB/IEC SOP.

Certain events other than SAEs and ADRs require immediate reporting to the Sponsor. These include withdrawal of consent, emergency unmasking, protocol violation affecting safety, AE thought to be an allergic reaction to study drug, event precluding further administration of study drug in the investigator's opinion, pregnancy. Reporting of these events will be conducted through the Immediately Reportable Event Form.

Refer to Sections 10.2.6.1, 10.2.6.2, and 10.2.6.3 and to the schema in Section 10.2.6.4 (Appendix 2).

8.4.4. Death Events

Any untoward medical occurrence resulting in death is reported as SAE. Any event resulting in death without identification of medical occurrence must also be reported as SAE; such event will be coded as "death NOS" (No Other Specified") until the medical event is identified.

8.5. Concomitant Treatments

Concomitant treatments will be recorded during the Screening Period to assess eligibility. Any change to concomitant treatments throughout the study from Day -1 (signed ICF) to Day 42 or EWV, will be recorded. If a concomitant treatment that would have precluded enrollment (see Exclusion criteria in Section 5.2 and Section 10.6, Appendix 6) is deemed necessary during the Study Treatment Phase, the participant will be discontinued from the study.

8.6. Treatment of Overdose

All participants will be hospitalized during the entire Study Treatment Phase. The study drug will be administered by trained staff. Hence, overdose is considered unlikely.

In case of overdose, appropriate medical treatment will be instituted, guided by a full PE. The study participant will be discontinued from the study and will remain in hospital until symptoms

of overdose have disappeared or in the investigator's opinion it is safe to discharge the participant.

8.7. Pharmacokinetics

Blood/serum samples for PK measurements WILL BE CONDUCTED ONLY IN PARTICIPANTS RANDOMIZED TO TBA-7371. Timing of sampling will be as follows (see Section 1.3, Table 3 and Table 4).

Study Treatment Phase

- Days 1, 2, 4, 7 and 14 before administration of the 1st daily dose of study drug.

j. In addition, on Days 1, 7 and 14 samples will also be collected at 30 min, 1h, 2.5h, 3h, 4h, 6h, 7h, 10.5h, 12h, 16.5h after 1st daily dose of study drug. (see **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.

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

l. **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.

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

53. **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.

54. **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.

55. **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.

56. **Blood/serum sample collection for clinical safety laboratory assessment.** The Day 3 and 7 sampling will occur before the 1st dose of study drug.

57. **Urine sample collection drug screening**: cannabinoids, cocaine, amphetamines, opiates, methamphetamines.

58. **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.

59. **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).
    - 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.
60. **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).
    - 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.
61. **Eye assessment.** A trained staff member will assess: i) eye symptoms using a standardized script (Section 10.5, Appendix 5), 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).
    - Follow-up Phase: Days 15, 28 and 42 during the visit.
    - EWV: if the participant withdraws from the study between Days 1 and 14.
62. **Study drug (IMP) administration.** Study drug (TBA-7371 or HRZE) will be administered from Day 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 at the same time each Day for the individual participant. Subsequent doses will be administered as follows (see Table 4):
    - 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.
63. **Overnight sputum collection for EBA assessment and exploratory measurements**. Overnight 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 Day 15. Drug susceptibility testing for isoniazid and rifampicin, and minimum inhibitory concentrations (MIC) of TBA-7371 will be performed on either of Day -2 or Day -1, and again on Day 14. [redacted]
64. **Spot sputum collection for exploratory measurements.** The participant should spontaneously produce (i.e., not induced) a spot sputum specimen for collection into RNA preservation media. If specimen cannot be collected due to participant inability to produce sputum, or due to operational limitations with RNA media collection kits, it is not considered a protocol deviation.

65. **Recording of AE, SAE (including serious ADR) and AESI; recording of concomitant treatments.** Adverse events (AE), serious adverse events (SAE), including serious adverse drug reactions (ADR), adverse events of special interest (AESI) and concomitant treatments will be recorded from the time each participant has signed the informed consent form (ICF) until he/she has completed the last follow- up visit (Day 42) or the Early Withdrawal Visit (EWV).
66. **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). 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.
67. **Blood/serum/plasma sample collection for exploratory measurements.** Timing of sampling will be as follows:
    - Study Treatment Phase: Day 1 and 7 before administration of the 1st daily dose of study drug (see Table 4).
    - Follow-up Phase: Day 15 in the morning at approximately the same time study drug was administered.
68. **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.

- Table 4).
- 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.

Follow-up Phase

On Day 15 in the morning before 1st daily dose of standard of care medication;

When ECG, vital signs, or blood/serum samples are to be obtained at the same time point, ECG will be done first after 10 minutes of supine rest, followed by the vital signs and then the blood draw(s) within 5 minutes of each other.

Concentrations of TBA7371 will be measured, and the following PK parameters calculated 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.

Details on serum collection procedures, and on the laboratory are provided in the study specific manual(s).

8.8. Pharmacodynamics

No pharmacodynamic parameter other than those included in the efficacy or safety assessments will be evaluated in this EBA study.

8.9. Transcriptomics, Genetics and Epigenetics

Refer to Section 8.10.

8.10. Biomarkers and Other Exploratory Measurements

Participants will be explicitly asked to consent for storage and use of biological samples for biomarker and other exploratory measurements not included in the present protocol.

Blood/serum and urine samples for biomarker and other exploratory measurements will be collected on Day 1 before administration of the 1st daily dose of study drug and on Day 15 in the AM, if the participant gives his/her consent. If not, such samples will not be collected.

Details on blood/serum and urine collection procedures are provided in the study specific manual(s).

Samples for biomarkers and other exploratory measurements will also be obtained from overnight sputum collection (Section 8.2.1).

A spot sputum collection will also be collected at screening and then daily from Day 1 to Day 15 for exploratory assessments. Collection procedures are provided in the study specific manual(s).

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 measurements may include but are not limited to: mycobacterial cell-free DNA, ribosomal RNA ratio assay, gene expression profiles, serum cytokines or other proteins, urine

LAM, bacterial genotypic evaluations for emergence of resistance; susceptibility testing to TBA7371 (MIC); population PK models.

8.11. Health Economics

Not applicable to this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

Primary: at least one of the TBA-7371 treatment groups has an average log CFU counts per day reduction from screening to Day 14 [BA_{CFU}(0-14)] that is greater than zero, with an acceptable safety profile.

9.2. Sample Size Determination

Approximately 90 participants will be randomized 5:1 to either intervention arm, totaling N = 15 for each TBA-7371 treatment and control groups.

Bactericidal effect

Based on Diacon et al. (2013) [3], standard deviations associated with BA_{CFU}(0-14) were relatively consistent across 5 treatment groups, ranging from 0.05 to 0.08. If we assume conservatively that the true SD of the BA_{CFU}(0-14) 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}(0-14) reduction of 0.067 (0.079), using a 1-sided alpha = 5%. For reference, the observed BA_{CFU}(0-14) reduction in Diacon et al, 2013 [3] were 0.040, 0.056, 0.077, 0.104, and 0.112 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%.

9.3. Populations for Analyses

Analysis populations are shown in Table 8.

Table 8 Populations for Analyses

Population	Description
Modified intention to treat (mITT) efficacy population	All participants randomly assigned to study intervention, who received 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 and unmasking. Participants will be analyzed according to the intervention they actually received.
Safety	All participants randomly assigned to study intervention and who received 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 TBA7371 and have at one blood sample with measurable concentrations

9.4. Statistical Analyses

A detailed statistical analysis plan (SAP) centered on primary and secondary endpoints will be developed and finalized prior to initiation of enrollment and will further describe the participant populations to be included in each analysis, details of the statistical methods, including procedures for accounting for missing, unused, and spurious data. Primary and secondary analyses are summarized in Table 9.

Exploratory endpoint analyses will be described in a separate exploratory scientific SAP(s) (exploratory SSAP). Specific objectives and hypotheses related to exploratory biomarker analyses will be documented in this exploratory SSAP prior to full data unmasking and analysis.

Results from the exploratory analyses may be reported in a separate results memo and included as an addendum to the clinical study report (CSR).

Table 9. Summary of Primary and Secondary Endpoints and Analyses

Endpoint	Statistical Analysis
Primary Bactericidal Effect	
Slope i.e. average change per day from screening ("0") to Day 14 [BA_{CFU}(0-14)] of the log CFU counts.	For each patient, linear and bilinear regression models will be fit, and the better fit model based on lower AIC will be used to estimate [BA_{CFU}(0-14)] of log CFU counts from screening to Day 14. The log CFU screening measurement used in the model will be the average of the two individual screening measurements. An 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). Multiplicity will be handled by means of a step-down sequential approach. 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.
Primary Safety	
Frequency of study participants who experienced one or more severe AEs and/or SAEs	The frequency of patients who experienced one or more severe and/or serious AE will be summarized by treatment group.
Secondary Bactericidal Effect	
Slope i.e. average change per day from screening ("0") to Day 2 [BA_{CFU} (0-2)] and from Day 2 to Day 14 [BA_{CFU} (2-14)] of the log CFU counts.	For each patient, linear and bilinear regression models will be fit, and the better fit model based on lower AIC will be used to estimate BA_{CFU}(0-2) and BA_{CFU}(2-14) of log CFU counts from screening to Day 2 and Day 2 to Day 14, respectively. An ANCOVA model will be used to quantify the evidence that the each of the treatment group means BA_{CFU}(0-2) and BA_{CFU}(2-14) is less than 0.
Slope of the time to sputum culture positivity (TTP) in the MGIT system from screening to Day 14 [BA_{TTP} (0-14)], from screening to Day 2 [BA_{TTP} (0-2)], and from Day 2 to Day 14 [BA_{TTP} (2-14)].	For each patient, linear and bilinear regression models will be fit, and the better fit model based on lower AIC 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. An ANCOVA model will be used to quantify the evidence that the each of the treatment group means BA_{TTP}(0-14), BA_{TTP}(0-2) and BA_{TTP}(2-14) is less than 0.

Endpoint	Statistical Analysis
Slope of the log concentration of sputum LAM from screening to Day 14 [BA_{LAM} (0-14)], from screening to Day 2 [BA_{LAM}(0-2)], and from Day 2 to Day 14 [BA_{LAM} (2-14)].	For each patient, linear and bilinear regression models will be fit, and the better fit model based on lower AIC 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. An ANCOVA model will be used to quantify the evidence that the each of the treatment group means BA_{LAM}(0-14), BA_{LAM}(0-2) and BA_{LAM}(2-14) is less than 0.
Secondary Safety	
Frequency of participants with adverse events (AEs) and frequency of AEs: overall, by seriousness, severity, body system, preferred term and relatedness to study drug.	The frequency of participants with and frequency of AEs will be summarized by treatment group. The incidence of AEs by seriousness, severity, body system, preferred term and relatedness to study drug will be summarized by treatment group.
• Frequency of participants with any new (vs. baseline) 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.	The incidence of new eye symptoms, mean and frequency distribution of duration of each eye symptom, and mean and frequency distribution of percentage of days with any eye symptom and each of the eye symptoms will be summarized by treatment group.
• Mean/median change in visual acuity from screening (s) 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)	Mean and median changes in visual acuity from screening to lowest score will be summarized by treatment group. Frequency of participants with any new color vision abnormalities, as well as the specific type of abnormality (tritan, protan, deutan) will be summarized by the number of eyes the abnormality occurs in (one or both), severity (mild, moderate, severe) and treatment group.
• Mean and frequency distribution of changes from Day 1 to 15 in HR, systolic blood pressure (SBP) and DBP as measured by the following 2 (BP) or 3 (HR) methods: ▪ manual (vital signs), after at least 10 minutes in supine position ("manual, supine"); ▪ manual, after 2 (±0.5) minutes in standing position ("manual, 2-min standing"); ▪ HR from ECG, supine position ("ECG, supine") • Frequency of participants with ≥ 25 % increase in HR, decrease in SBP, decrease	Mean and frequency distribution of changes from Day 1 through Day 15 in HR, SBP and DBP will be provided by treatment group and by each method measured. The frequency of participants with ≥ 25 % increase in HR, decrease in SBP, decrease in DBP vs. baseline as measured with any of the methods will be provided by treatment group. The mean and frequency distribution of percentage of days with ≥ 25% increase in HR, decrease in SBP, decrease in DBP vs. baseline will be provided by treatment group. The mean and median RR, QRS, QT, QTcF values from ECG will be provided by treatment group.

Endpoint	Statistical Analysis
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 RR, QRS, QT, QTcF values from ECG	
• Mean change in HR, SBP and DBP from Day 1 to Days 4, 7, 10, 14 and 15 for each of the measurement methods described above. • 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 Day 1 to Days 4, 7, 10, 14 and 15.	The mean change in HR, SBP and DBP from Day 1 to Days 4, 7, 10, 14 and 15 will be provided by treatment group and by each method measured. Frequency of participants with any new color vision abnormalities, as well as the specific type of abnormality (tritan, protan, deutan) will be summarized by the number of eyes the abnormality occurs in (one or both), severity (mild, moderate, severe) and treatment group.
• Mean change in HR, SBP and DBP from baseline (Day 0) to Days 28 and 42 and from Day 14 to Day 28 and 42 for each of the measurement methods described above. • Change in frequency of participants with eye symptoms (all, severe, serious) and change in frequency of participants with any new color vision abnormalities (tritan, protan, deutan) in one or both eyes and degree of severity (mild, moderate, severe) from baseline (Day 0) to Days 28 and 42 and from Days 1-15 (combined) to Days 28-42 (combined).	The mean change in HR, SBP and DBP from baseline (Day 0) to Days 28 and 42, and from Day 14 to Days 28 and 42 will be provided by treatment group and by each method measured. Frequency of participants with any new color vision abnormalities, as well as the specific type of abnormality (tritan, protan, deutan) will be summarized by the number of eyes the abnormality occurs in (one or both), severity (mild, moderate, severe) and treatment group.
• Mean, median and range of each blood/serum and urine safety parameter at screening, Day 3, Day 7, Day 14, and Day 42 • Mean, median and range of the changes in each blood/serum and urine safety parameter from screening to Day 3, Day 7, Day 14 and Day 42.	The mean, median and range of each blood/serum and urine safety parameter at screening, Day 3, Day 7, Day 14 and Day 42 will be provided by treatment group. The mean, median and range of the changes in each blood/serum and urine safety parameter from screening to Day 3, Day 7, Day 14 and Day 42 will be provided by treatment group. Changes may be assessed on the raw (difference) or log (fold change) scale, depending on which scale the distribution of the measure is more appropriately described by a normal distribution.

Endpoint	Statistical Analysis
Secondary PK and PK/PD	
TBA7371 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.	Individual values will be listed for each PK parameter by treatment group, and the following (non-model-based) descriptive statistics will be provided: N, arithmetic mean, standard deviation, arithmetic percent CV, median, minimum, maximum, geometric mean, and geometric percent CV.
Correlation between TBA-7371 AUC, C_{max}, T>MIC and CFU counts on solid media culture.	Spearman correlations, simple linear regressions and graphical visualizations will be used to summarize correlations.
Expected concentration associated with 90% of the maximal TBA-7371 EBA effect (EC90)	EC90 will be estimated from exposure-response E_{max} model fits.

9.4.1. Bactericidal Activity Analyses

9.4.1.1. Primary Bactericidal Activity Analyses

The primary endpoint will be the slope of the log CFU counts from screening to Day 14 [BA_{CFU}(0-14)], i.e., average change in log CFU count per day over 14 days, where sputum is collected twice during the screening phase and daily thereafter. The $\log_{10}$ CFU counts vs. time profiles over 14 days of treatment may be biphasic, i.e. the rate of change in $\log_{10}$ CFU changes over time. A simple solution [3] is to characterize the subject-specific $\log_{10}$ 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. However, it is also likely that the some of the subject-specific $\log_{10}$ CFU count vs. time profiles will be better characterized using a simple linear regression model.

The average slope can be estimated for each subject, *i*, as the mean of the slopes over each day, i.e.,

$$BA_{CFU}(0-14)_i = \sum_{t=1}^{14} \hat{\beta}_{it}/14,$$

where $\hat{\beta}_{it}$ is the estimated slope for subject *i* at time *t*. For each subject, 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 subject. The log CFU screening measurement used in the model will be the average of the two individual screening measurements. If the bilinear regression model is selected, the average change in $\log_{10}$ CFU per day over 14 days will be estimated by:

$$BA_{CFU}(0-14)_i = \sum_{t=1}^{14}\left[\hat{\beta}_{1i} I(t \le \hat{\kappa}_i) + \hat{\beta}_{2i} I(t > \hat{\kappa}_i)\right]/14,$$

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 estimated 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. If the linear regression model is selected, the average change in $\log_{10}$ CFU count per day over 14 days will be estimated by the constant linear regression slope estimate, $\hat{\beta}_i$. BA_{CFU}(0-14) will be calculated for each patient 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 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 $BA_{CFU}(0\text{-}14)$ 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.

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 and acceptable safety profile.

9.4.1.2. Secondary Bactericidal Activity Analyses

EBA measures ($BA_{CFU}(0\text{-}2)$ and $BA_{CFU}(2\text{-}14)$) will be calculated from the regression models and assessed similarly as described above for $BA_{CFU}(0\text{-}14)$. MGIT TPP and concentrations of LAM will also be assessed similarly. For all secondary EBA measurements there will be no adjustment for multiple comparisons and no formal success criteria.

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

One of the limitations of the primary analysis method is that each individual subject must have enough data to fit a bilinear regression model in order to be included in the primary analysis. More sophisticated statistical models, such as a Bayesian nonlinear mixed-effects regression model [13] do not have this same limitation, and will therefore be examined through sensitivity analyses to assess the robustness of the primary model fits. The Bayesian model jointly fits the data from all patients and treatment groups and comprises the joint bilinear regression model as a special case. In addition, similar bilinear and linear regressions will also be fit directly to the change from screening response variable to further assess the robustness of the results.

9.4.2. Safety Analyses

9.4.2.1. Primary Safety Analyses

The frequency of patients who experienced one or more severe AEs and/or SAEs will be summarized by treatment group with 95% CIs. The proportion of patients with this endpoint within each of the TBA-7371 treatment groups will not be formally compared to the control arm given limitations due to small sample sizes. The primary safety analysis will be performed in the Safety population.

9.4.2.2. Secondary Safety Analyses

Individual safety parameters of interest, e.g., mean HR over time, mean SBP and DBP over time, and incidence of and frequency of eye symptoms and other adverse events will be summarized by treatment group. The incidence of AEs by seriousness, severity, body system, preferred term and relatedness to study drug will be summarized by treatment group.

Mean and frequency distribution of changes from baseline through Day 15 in HR, SBP and DBP will be provided by treatment group and by each method measured. The frequency of participants with ≥ 25 % increase in HR, decrease in SBP, decrease in DBP vs. baseline as measured with any of the methods will be provided by treatment group. The mean and frequency distribution of percentage of days with ≥ 25% increase in HR, decrease in SBP, decrease in DBP vs. baseline will be provided by treatment group. The mean and median RR, QRS, QT, QTcF values from ECG will be provided by treatment group.

The mean change in HR, SBP and DBP from Day 1 to Days 4, 7, 10, 14 and 15 will be provided by treatment group and by each method measured. The change in frequency of participants with eye symptoms (all, severe, serious) and abnormal visual acuity and abnormal color vision scores from Day 1 to Days 4, 7, 10, 14 and 15 will be provided by treatment group. The mean change in HR, SBP and DBP from screening to Days 28 and 42, and from Day 14 to Days 28 and 42 will be provided by treatment group and by each method measured. The change in frequency and duration of eye symptoms (all, severe, serious) and/or abnormal visual acuity and/or abnormal color vision scores from screening to Days 28 and 42, and from Days 1-14 (combined) to Days 28-42 (combined) will be provided by treatment group.

The mean, median and range of each blood/serum and urine safety parameter at screening, Day 3, Day 7, Day 14 and Day 42 will be provided by treatment group. The mean, median and range of the changes in each blood/serum and urine safety parameter from screening to Day 3, Day 7, Day 14 and Day 42 will be provided by treatment group. 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.

Bayesian linear and nonlinear mixed effects models will be utilized to characterize the profile of continuous variables (e.g., heart rate, blood pressure) over time, and the proportion of patients in the population reaching clinically relevant thresholds will be estimated. From these models, the likelihood of tachyphylaxis can be characterized by the posterior probability that the mean heart rate decreases from Day 1 to Day 14, the posterior probability that the mean blood pressure on decreases from Day 1 to Day 14, and the posterior probability that the frequency of patients with eye symptoms (all, severe, serious) decreases from Day 1 to Day 14.

9.5. PK Analyses

Concentration data will be summarized by treatment group using nominal time points. Individual and mean concentration versus nominal time plots will be presented by treatment groups. PK parameters will be summarized by treatment group.

The relationship of each TBA7371 PK parameter (AUC, C_{max}, T>MIC) and CFU counts (e.g. BA_{CFU}(0-14), CFU change) will be explored graphically for the treatment groups combined. The PK and CFU data used in the correlations will also be presented in tabular format. If a correlation

is observed, further analysis may be performed to identify exposure targets for response. Details of such analysis will be provided in the analysis plan.

9.6. Demographic and Compliance Analyses

Demographic parameters (age, sex, and race/ethnicity) and other baseline characteristics will be summarized by treatment group for all participants in the safety population.

Listings of randomized participants with protocol deviations (to be defined in the SAP) will be presented by treatment group.

9.7. Interim Analyses

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.

9.7.1. Independent Data Monitoring Committee (IDMC)

The independent IDMC will be established to oversee the safety of this study and to make a go / no-go decision at each dose escalation step.

The IDMC will operate according to a charter. The IDMC structure, participants and other details will be provided in the charter. The charter will be available prior to study start.

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

During active enrollment, the IDMC will meet at least once before each of the 3 dose escalation steps, unless a decision is made to stop recruitment earlier. The IDMC reviews will include vital signs, ECG and eye symptoms / visual acuity and color vision tests, and safety laboratory tests as well as solicited and unsolicited AE and SAE. All procedures associated with these reviews, including objectives, data handling, elements included for review, and recommendations will be documented.

The IDMC will make a formal recommendation on the continued enrolment into the trial after each safety review.

The IDMC charter will provide meeting information and other details.

If study drug administration is paused by the local medical monitor or the principal investigator, the IDMC will convene on an ad hoc basis.

The recommendation of the IDMC, along with the sponsor’s decision, will be communicated to the investigators and the IRB/IEC and the national regulatory authorities as required. The sponsor or its designee agrees to abide to any directives issued by the national regulatory authority of the IRB.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, and other relevant documents (e.g., diary cards) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

10.1.2. Study Oversight

The study sponsor, the IRB/IEC, the institution through which the research is performed, and all members of the principal investigator's clinical team and the national regulatory authority share responsibility for ensuring the safety of participants in this trial.

The principal investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently, in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH and GCP guidelines, SAHPRA Regulations the IRB/IEC, and all other applicable country and local regulations.
- Closely monitoring study participants and taking whatever measures necessary to ensure their safety. The principal investigator may delay an individual's study drug administration or pause study drug administration altogether if the investigator is concerned that the study drug might place a participant or participants at significant risk. Where specified, the responsibilities of the principal investigator may be delegated to a medically qualified team member (designee). The investigator determines severity and causality with respect to the study drug for each AE.

The sponsor has an institutional responsibility to ensure participant safety and is ultimately accountable for safety oversight. Local medical monitors and the IDMC play an important role in this regard and support the sponsor.

The local medical monitor is the sponsor's representative and is a physician or surgeon in their country of residence. The local medical monitor:

- reviews the safety of the product for protocols in a specific region and, in conjunction with the sponsor, determines expectedness of AEs.
- Is responsible for safety oversight in-country and plays an important role in the reporting of SAEs, ADRs and pregnancies, as described in the protocol
- in consultation with the sponsor, may assess the severity and causality for AEs and may upgrade the degree of severity and causality determined by the principal investigator or designee

The IRB or EC has institutional responsibility for the safety of research participants. The IRB or EC has the authority to terminate, suspend or require changes to a clinical trial.

The national regulatory authority, SAHPRA, has the authority to terminate, suspend or require changes to a clinical trial.

10.1.3. Financial Disclosure

Include text related to financial disclosure if not included in another document.

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4. Informed Consent Process

Written informed consent will be obtained prior to conducting any study-related procedures.

Participants must be informed that their participation is voluntary. The principal investigator or designee will explain the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The principal investigator or designee will conduct the consent discussions on an individual basis with each participant Adequate time will be allowed for all questions to be addressed. Potential participants will be interviewed to ensure that they meet all entry criteria relating to history.

10.1.5. Informed Consent Forms

Informed consent for study participation

Participants will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The informed consent will be obtained by the use of a written consent form approved by the IRB or IEC.

Consent for HIV testing will also be obtained prior to enrollment.

Other consents will be presented to the participant which are optional and if not signed, would not exclude the participant from the study:

- consent to collect, store and testing of samples for research not described in the protocol;
- consent to allow any remaining specimens originally taken for mandatory testing to be used for research not described in the protocol
- consent to genetic testing.

Sample testing will be in line with the consent of the participant.

A copy of the signed consent forms shall be given to the participant prior to conducting any study-related procedures.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If there is a change to the ICF during the conduct of the study, participants must be re-consented to the most current version of the ICF.

Any withdrawal of consent for sample testing will be documented in the eCRF.

Laboratory assays for primary and secondary endpoints will be carried out in South Africa. Participants will be informed that some of the assays for exploratory endpoints may be carried out in laboratories outside South Africa. If participants will be asked to consent to optional exploratory research using the remainder of mandatory samples, include text that addresses the use of remaining mandatory samples for optional exploratory research.

Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.6. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant record or dataset that is transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the sponsor.

The participant must be informed that his/her study-related data will be used by the sponsor in accordance with local data protection law. The level of data disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.7. Dissemination of Clinical Study Data

Study information from this protocol will be posted on publicly available clinical trials registers (clinicaltrials.gov and the South African registry) before enrolment of participants begins.

The final study report will include all available safety data, clinical assessments, and concomitant medications through the final study visit. The database will be locked prior to unmasking and preparation of the final study report when all of the above data have been

entered, reviewed, and all queries related to the data have been addressed. Modifications or additions to the analyses will be included in the relevant SAP. Any decisions to deviate from the planned analyses described in the protocol and in the SAP will be described in detail in the final study report.

The final clinical study report will be reviewed and approved by the sponsor signatory and the principal investigator.

Summaries of the results of the study will also be posted on the same websites.

10.1.8. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF using an Electronic Data Capture (EDC) system, unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (Appendix 1, Section 10.1.9) that supports the information entered in the CRF.

The study will be monitored regularly by the sponsor or its designee throughout the study period. The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source Documents

Source documentation consists of existing medical records and/or study records developed and maintained by the investigator. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.

Data recorded on source documents will be transcribed onto case report forms (CRFs) or entered using electronic case report forms (eCRFs) using an EDC system.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.

For the purpose of monitoring and auditing the study, source documentation will consist of existing medical records and/or study records developed and maintained by the investigator.

10.1.10. Study and Site Closure

The sponsor designee reserves the right to close the study site(s) or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

At the discretion of the sponsor, all materials and supplies provided to the investigator will be returned or disposed of in compliance with local regulatory requirements upon authorization from the sponsor, upon study completion. The investigator or designated clinical site staff will notify the IRB/IEC when the study has been completed.

10.1.11. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (e.g. hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements, eye symptom or findings), including those that worsen from baseline, **considered clinically significant** in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study start even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected DDI.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Lack of efficacy per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of ADR

- "Adverse drug reaction" or "adverse reaction" means a response to a medicine in humans which is noxious and unintended and which occurs at any dose and which can also result from overdose, misuse or abuse of a medicine. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

10.2.3. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a medically significant / important event or reaction:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.2.4. Definition of Serious Adverse Drug Reaction (Serious ADR)

When an adverse event is judged to be serious and related (see Section 10.2.6.4) to an investigational product, it is referred to as Serious ADR and is subject to expedited reporting (see Section □).

10.2.5. Definition of AESI

Adverse events of special interest (AESIs) are adverse events that the sponsor wants to monitor carefully and which are subject to expedited reporting (within 24 hours) from the investigator to the Sponsor or representative following the same process and timelines than the SAEs.

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

- Anaphylactic reaction
- ≥Grade 2 intensity (severity) and/or serious AE related to increase of heart rate (HR);
- ≥Grade 2 intensity (severity) and/or serious AE related to decrease of SBP;
- ≥Grade 2 intensity (severity) and/or serious AE related to decrease of DBP;
- ≥Grade 2 intensity (severity) and/or serious eye symptom-related AE.

10.2.6. Recording and Follow-up of AEs and SAEs

10.2.6.1. AE and SAE Recording

- Care will be taken not to introduce bias when detecting AE and SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- AE will be reported on the AE CRF using a recognized medical term or diagnosis that accurately reflects the event.
- AE evaluations will be reviewed by the principal investigator or a medically qualified delegate. AE CRF pages are to be completed by members of the study team designated in writing by the principal investigator. The onset and resolution dates of an AE and action taken in response to the AE will be documented.
- After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAE and non-serious AESI will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the medical monitor, the IDMC or the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- SAE will be assessed for severity and causal relationship to the study investigational medicinal product.

10.2.6.2. Follow-up of AEs and SAEs and Resolution

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.
- The onset and resolution dates of the event and medical care taken in response to the event will be documented.
- AEs will be considered resolved when the condition returns to normal or returns to the participant's baseline status as established during the Screening Phase, or when the condition has stabilized with the expectation that it will remain chronic
- If the event has not resolved by the final study visit, it will be documented as "ongoing" on the eCRF, however, follow-up of the SAE must continue until resolved or the condition has stabilized. Information recorded on the CRF must be substantiated in the source documents.
- The resolution date to be recorded on the CRF is the last date on which the participant experienced the AE.

10.2.6.3. Assessment of AE/SAE Intensity

The investigator will assess intensity (severity) for each AE and SAE reported during the study and assign 1 of 5 grades:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Potentially life-threatening
- Grade 5: Death (where applicable)

It is recommended that definitions provided in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 of July 2017 (reported in Section 10.4, Appendix 4) be followed. The DAIDS Table provides definitions of intensity grades 1 to 4 for numerous major clinical conditions and laboratory parameters, organized by body system. Furthermore, for conditions and parameters not specifically identified, the DAIDS

It should be noted that the investigator is not obliged to use the definitions reported in Appendix 4 and medical judgement should prevail.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (see Section 10.2.2), **not** when it is rated as severe.

10.2.6.4. Assessment of AE/SAE Causality (Relatedness)

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The causality assessment will be determined using a two-level scale: related or not related.
- An AE/SAE is considered related to study intervention if there is a reasonable possibility that the study intervention contributed to the AE.
- Not-related means there is no reasonable possibility that the AE is causally related to administration of the study intervention. There are other more likely causes for the AE.
- The investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data.**

- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements (see Section 10.2.6).

10.2.6.5. Assessment of AE/SAE Expectedness

Expected adverse events are adverse events consistent with the applicable product information provided by the sponsor (investigator brochure for TBA-7371 and package insert for Rifafour® e-275 HRZE).

10.2.6.6. Assessment of SAE Outcome

The outcome of each SAE must be reported to the sponsor, even if this extends beyond the SAE reporting period (i.e. after the final study visit).

For analysis purposes, the outcome for SAE will be determined on the final study visit.

Outcome of all AE will be classified as one of the following:

- Resolved
- Resolved with sequelae
- Ongoing
- Death

10.2.7. Reporting of SAE, Serious ADR, AESI and Other Events

10.2.7.1. Reporting to Sponsor Delegate's (CRO Safety Team) Via the Electronic Data Collection Tool

- The primary mechanism for reporting an SAE by the investigator to the sponsor or delegate (e.g. CRO safety team) will be the electronic data collection tool.
- The site will enter the SAE data into the electronic system as soon as it is identified.
- All SAE (related and unrelated) and AESI must be reported to the sponsor or delegate throughout the study.
- Serious ADRs are reported to the sponsor or delegate even after the trial is over, if the sponsor, Medical Monitor or PI become aware of them.
- The investigator must not wait to collect additional information to fully document the event before notifying the CRO Safety team of an SAE. The initial notification should include at least the following:
    - Protocol number and name and contact number of the investigator
    - Participant ID number (and initials and date of birth, if available)

- Date participant received study investigational medicinal product.
- SAE and date of event onset
- Current status of participant

NOTE: the reporting must be done anyway even if one or more of the above items are missing

- The investigator is responsible for applicable expedited safety report submission to the sponsor or delegate and the sponsor or delegate reports to SAHPRA within specific time periods of being notified of the event. Therefore, it is important that the investigator submit additional information requested as soon as it becomes available.
- All fatal and life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) are to be reported to SAHPRA with 7 calendar days after first knowledge with a complete report to be submitted within an additional 8 calendar days. Non-fatal and life-threatening SUSARs need to be reported to SAHPRA no later than 15 calendar days after first knowledge. The same timelines apply to follow-up information received for the SUSARs.
- The sponsor will notify the IDMC of all SUSARs within the same timelines the report is send to investigators, health authorities, IEC and other relevant parties. Any follow-up report will be sent with the same timelines.
- If the electronic system is unavailable, the site may use the paper SAE data collection tool (see Section 10.2.6.2) instead of the electronic data collection tool, in order to report the event within 24 hours of becoming aware.
- After the study is completed at a given site, if used, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see Section 10.2.6.2).
- Contacts for SAE reporting and for all safety personnel are contained in the Team Contact List which will be maintained by the study sponsor.

- Refer to Section 10.2.6.4 for the reporting schema.

10.2.7.2. SAE Reporting via paper CRF

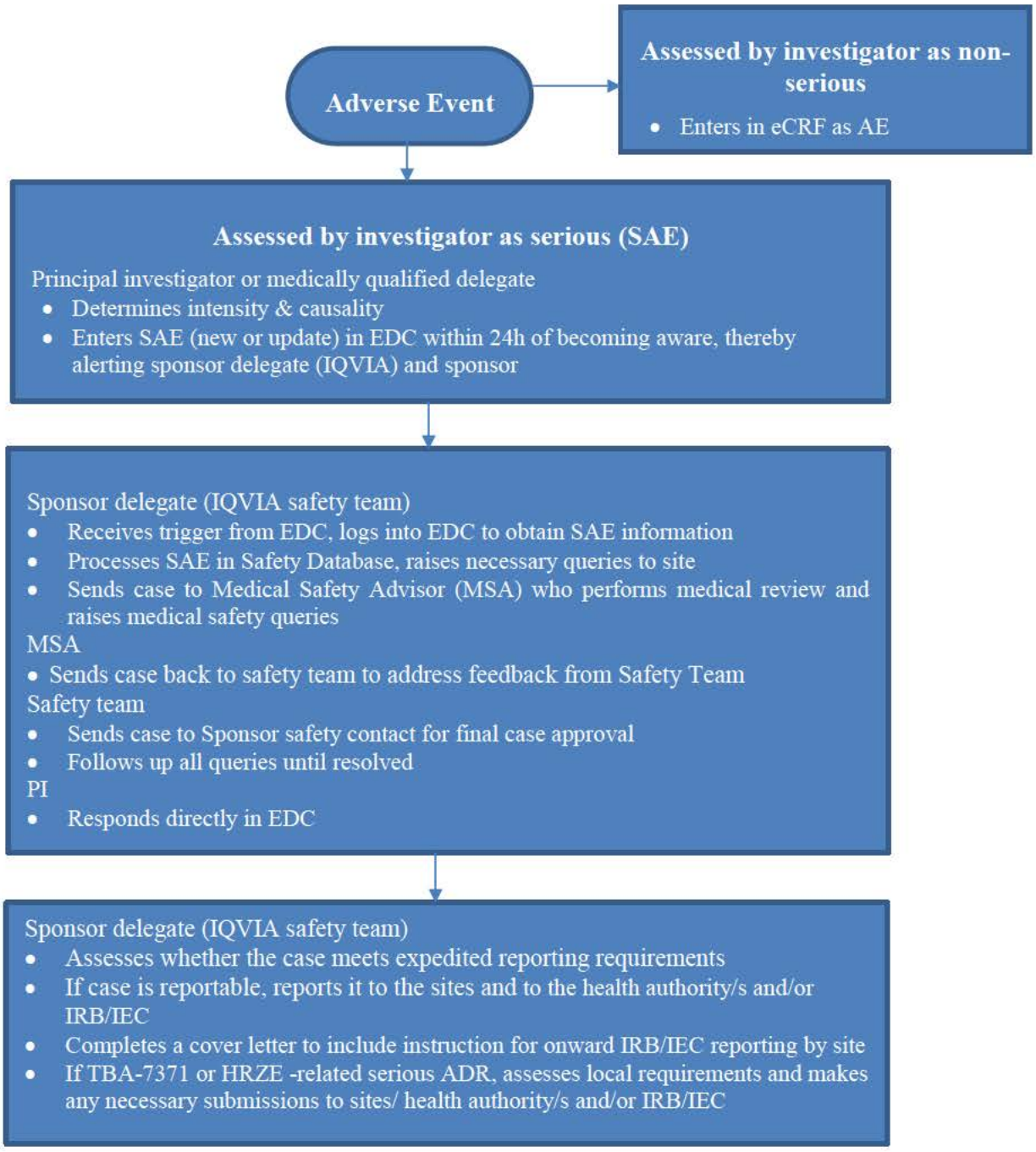
- If the CRF cannot be completed, the Supplemental SAE Report (paper form) should be completed by the PI or his/her designee, and scanned and emailed, or faxed to the CRO Safety Team. The investigator is responsible for ensuring an adequate transmission of the fax and will store the distribution confirmation in the study file.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE report form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

10.2.7.3. Other Events Requiring Immediate Reporting

- The investigator must report the following events by scanning and emailing, or faxing the appropriate form to the local medical monitor within 24 hours of becoming aware of the event:
  - Withdrawal of consent during the study for medical reasons (Immediately Reportable Event Form)
  - Emergency unmasking (unblinding) (Immediately Reportable Event Form) (not applicable for this trial)
  - Protocol violation affecting the safety of a participant (Immediately Reportable Event Form)
  - Any event that, in the opinion of the investigator, precludes further administration of the study drug (Immediately Reportable Event Form, unless meets SAE criteria)
  - Pregnancy (Immediately Reportable Event Form, and Pregnancy Notification Form)

10.2.7.4. SAE and Serious ADR Reporting Schemes



10.3. Appendix 3. Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Female of Childbearing Potential (FOCBP)

A female is considered fertile following menarche. If fertility is uncertain (e.g. amenorrhea in adolescents) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered. If in doubt, the participant should be considered fertile.

Women in the following categories are not considered FOCBP

1. Premenarchal
2. Documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

Contraception Guidance:

Women physically capable of pregnancy must agree to use an acceptable method of avoiding pregnancy **for 1 month after the last dose of study medication**.

Male participants of childbearing potential must agree to use an acceptable method of contraception for 3 months after the last dose of the study medication and must also refrain from sperm donation through 3 months after receiving the last dose of study medication.

Acceptable methods of avoiding pregnancy include:

- sexual abstinence (not engaging in sexual intercourse)
- a confirmed sterile partner

Or at least 2 of the below contraceptive methods

- hormonal contraceptives (oral, injection, transdermal patch, or implant)
- Intra Uterine Device (IUD)
- male or female condom
- diaphragm

Collection and Reporting Pregnancy Information

Male and female participants will be provided with information on acceptable methods of contraception as part of the informed consent process and will be asked to sign the ICF stating that they understand the requirements for avoidance of pregnancy.

In the event of a pregnancy by a female participant or pregnancy by a sexual partner of a male participant, the processes outlined below must be followed.

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- Investigators must make an effort to collect outcomes of pregnancies discovered during the study and communicate them to the sponsor and/or CRO. The health status of the mother and child, the date of delivery, and the child's sex, birth weight and multiparity should be recorded and be reported to the medical monitor after delivery. If delivery occurs before the last scheduled study visit, the participant should continue to be followed to determine the outcome of the pregnancy, and for SAEs through the final study visit unless withdrawal of consent has occurred. If delivery occurs after the final study visit, the investigator should attempt to maintain contact with the participant to obtain information after delivery.
- The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Any post-study pregnancy-related SAE considered related to the study intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.4. Appendix 4. Division of AIDS (DAIDS) Table for Grading Intensity (Severity) of Adverse Events

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1
July 2017

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

Table of Contents

Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (*serum glutamic pyruvic transaminase)*
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (*serum glutamic-oxaloacetic transaminase)*
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young Children Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

DAIDS AE Grading Table Corrected Version 2.1- July 2017
Page 2

Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

Instructions for Use

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage
Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies
In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

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Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

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Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

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Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

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Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

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Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

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Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures *New Onset Seizure ≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

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Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

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Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

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Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

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Systemic

Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

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Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

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*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

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Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ 7 days of age	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ 7 days of age	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] **or eGFR, Low** **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

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Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

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Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

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Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

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Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

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Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], High (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

10.5. Appendix 5. Eye Symptom Assessment Forms

10.5.1. Study TBA7371-002, Eye Symptom Assessment Form, Screening Phase

THE ASSESSOR WILL ASK THE PARTICIPANT QUESTIONS (*ITALICS*) AND REPORT ANSWERS AS INDICATED

Special attention should be paid to the following symptoms offered by the participant**:** blurred vision with glasses/contact lenses on, photophobia (sensitivity to light), increased lacrimation (tearing, not to be confused with crying), decreased color vision.

Date (MM/DD/YYYY) _____Time (h.min) _____Study Day (-1, -2, -3)_____

Assessor 's name _____

1) History

- *Have you had any eye problems in one or both eyes <u>in the last month?</u>* (yes/no)

If no, go to point 2)

If "yes":

- *What were you experiencing?*
- *Did you see an eye doctor?*
- *Has it resolved?*

(Assessor to report patient's feedback; record relevant patient quotes)

_____

_____

_____

_____

_____

2) Current

- *Are you having any problems in one or both eyes now or in the last 24 hours?*
  - *Now?* (yes/no) _____
  - *In the last 24 hours?* (yes/no) _____

If no:

- *The assessment is complete. We are done for today!*

If yes:

- *In your own words, please describe each eye symptom and answer the questions I will ask as precisely as you can.*

FIRST SYMPTOM

- *Describe this eye symptom* (Assessor to report relevant participant quotes):
  _____
  _____
  _____
  _____
  _____

  Medical term (Assessor to provide preferred medical term for the symptom):
  _____

- *One or both eyes? If one, which one?* _____

- *When did it start?* (dd/mm/yyyy) _____ time (h.min)_____

- *Is it still ongoing*? (yes no) _____

- If no, *how long did it last?* _____hours, _____minutes

- *What made it better?* _____
  _____
- *What made it worse?* _____
  _____
- *Are you currently receiving any treatment for this?* (yes/no)

- *If yes, what treatment(s)?* (Assessor to report brand and/or generic name[s])
  _____
  _____
  _____

- Assessor to define seriousness of symptom (non-serious/serious) based on definitions provided in Section 10.2.2. _____

- Assessor to define intensity (severity) of symptoms based on grading provided in Section 10.2.5.3 and definitions provided in Section 10.4 (Appendix 4, page 20).

  _____

SECOND SYMPTOM

- *Describe this eye symptom* (Assessor to report relevant participant quotes):
  _____
  _____
  _____
  _____
  _____

  Medical term (Assessor to provide preferred medical term for the symptom):
  _____

- *One or both eyes? If one, which one?* _____

- *When did it start?* (dd/mm/yyyy) _____ time (h.min)_____

- *Is it still ongoing*? (yes no) _____

- If no, *how long did it last?* _____hours, _____minutes

- *What made it better?* _____
  _____
- *What made it worse?* _____
  _____
- *Are you currently receiving any treatment for this?* (yes/no)

- *If yes, what treatment(s)?* (Assessor to report brand and/or generic name[s])
  _____
  _____
  _____

- Assessor to define seriousness of symptom (non-serious/serious) based on definitions provided in Section 10.2.2. _____

- Assessor to define intensity (severity) of symptoms based on grading provided in Section 10.2.5.3 and definitions provided in Section 10.4 (Appendix 4, page 20).
  _____

[Add #] SYMPTOM

(Assessor to add more pages like this one if the participant reports more than 3 symptoms).

- *Describe this eye symptom* (Assessor to report relevant participant quotes):
  _____
  _____
  _____
  _____
  _____

  Medical term (Assessor to provide preferred medical term for the symptom):
  _____

- *One or both eyes? If one, which one?* _____
- *When did it start?* (dd/mm/yyyy) _____ time (h.min)_____
- *Is it still ongoing*? (yes no) _____
- If no, *how long did it last?* _____hours, _____minutes
- *What made it better?* _____
  _____
- *What made it worse?* _____
  _____
- *Are you currently receiving any treatment for this?* (yes/no)
- *If yes, what treatment(s)?* (Assessor to report brand and/or generic name[s])
  _____
  _____
  _____
- Assessor to define seriousness of symptom (non-serious/serious) based on definitions provided in Section 10.2.2. _____
- Assessor to define intensity (severity) of symptoms based on grades provided in Section 10.2.5.3 and definitions provided in Section 10.4 (Appendix 4, page 20).
  _____

10.5.2. Study TBA7371-002, Eye Symptoms Assessment

Study Treatment Phase (Days 1, 4, 7, 10, 14) and Follow-up Phase (Days 15, 28, 42)

THE ASSESSOR WILL ASK THE PARTICIPANT QUESTIONS (*ITALICS*) AND REPORT ANSWERS AS INDICATED

Special attention should be paid to the following symptoms offered by the participant**:** blurred vision with glasses/contact lenses on, photophobia (sensitivity to light), increased lacrimation (tearing, not to be confused with crying), reduced color vision.

Date (MM/DD/YYYY) _____Time (h.min) _____

Study Day (1, 4, 7, 10, 14, 15, 28, 42, Early Withdrawal Visit) _____

Assessor ‘s name _____

- *Are you having any problems in one or both eyes now?* (yes/no)
- *Have you had any problem since the last eye check?* (yes/no)

If no to both questions:

- *The assessment is complete. We are done for today!*

If yes to one or both questions:

- *In your own words, please describe each eye symptom and answer the questions I will ask as precisely as you can.*

FIRST SYMPTOM

- *Describe this eye symptom* (Assessor to report relevant participant quotes):
  _____
  _____
  _____
  _____

  Medical term (Assessor to provide preferred medical term for the symptom):
  _____

- *One or both eyes? If one, which one?* _____
- *When did it start?* (dd/mm/yyyy) _____ time (h.min) _____
- *Is it still ongoing*? (yes no) _____
- If no, *how long did it last*? _____hours _____minutes
- *Is it the same, better or worse compared to last time?* _____
- *What made it better?* _____
  _____
- *What made it worse?* _____
  _____
- Assessor to define seriousness of symptom (non-serious/serious) based on definitions provided in Section 10.2.2. _____
- Assessor to define intensity (severity) of symptoms based on grades provided in Section 10.2.5.3 and definitions provided in Section 10.4 (Appendix 4, page 20).
  _____

SECOND SYMPTOM

- *Describe this eye symptom* (Assessor to report relevant participant quotes):
  _____
  _____
  _____
  _____

  Medical term (Assessor to provide preferred medical term for the symptom):
  _____

- *One or both eyes? If one, which one?* _____
- *When did it start?* (dd/mm/yyyy) _____ time (h.min) _____
- *Is it still ongoing*? (yes no) _____
- If no, *how long did it last*? _____hours _____minutes
- *Is it the same, better or worse compared to last time?* _____
- *What made it better?* _____
  _____
- *What made it worse?* _____
  _____
- Assessor to define seriousness of symptom (non-serious/serious) based on definitions provided in Section 10.2.2. _____
- Assessor to define intensity (severity) of symptoms based on grades provided in Section 10.2.5.3 and definitions provided in Section 10.4 (Appendix 4, page 20).
  _____

[Add #] SYMPTOM

(Assessor to add more pages like this one if the participant reports more than 3 symptoms).

- *Describe this eye symptom* (Assessor to report relevant participant quotes):
  _____
  _____
  _____
- Medical term (Assessor to provide preferred medical term for the symptom):
  _____
  - *One or both eyes? If one, which one?* _____
  - *When did it start?* (dd/mm/yyyy) _____ time (h.min) _____
  - *Is it still ongoing*? (yes no) _____
  - If no, *how long did it last*? _____hours_____minutes
  - *Is it the same, better or worse compared to last time?* _____
  - *What made it better?* _____
    _____
  - *What made it worse?* _____
    _____
  - Assessor to define seriousness of symptom (non-serious/serious) based on definitions provided in Section 10.2.2. _____
  - Assessor to define intensity (severity) of symptoms based on grades provided in Section 10.2.5.3 and definitions provided in Section 10.4 (Appendix 4, page 20)
    _____

10.6. Appendix 6. List of Prohibited Medications

The list is not comprehensive and other medications with the features listed below are also prohibited. As outlined in Section 4.1 regarding overall study design, Rifafour® is allowed for patients randomized to receive HRZE during the 14-day Study Treatment Phase.

Category	Drugs
Medications active against Mtb (exclusion criteria, Section 5.2	**isoniazid**, **ethambutol**, amikacin, bedaquiline, **clofazimine**, cycloserine, delamanid, fluoroquinolones, rifabutin, rifampicin, streptomycin, kanamycin, para-aminosalicylic acid, rifapentine, pyrazinamide, thioacetazone, capreomycin, thioamides, metronidazole**, linenezolid**, **rifater.**
Systemic immunosuppressive medications (exclusion criteria, Section 5.2	TNF-alpha inhibitors, systemic corticosteroids, cyclosporine.
Strong inhibitors and strong inducers of CYP450 enzymes* (exclusion criteria, Section 5.2	
Strong inhibitors of CYP1A2	ciprofloxacin, enoxacin, fluvoxamine, clinafloxacin, rofecoxib, zafirlukast, oltipraz.
Strong inhibitors of CYP2B6	ticlopidine, thiotepa.
Strong inhibitors of CYP2C8	gemfibrozil, clopidogrel.
Strong inhibitors of CYP2C9	Miconazole.
Strong inhibitors of CYP2C19	fluconazole, fluvoxamine, ticlopidine, fluoxetine.
Strong inhibitors of CYP2D6	bupropion, fluoxetine, paroxetine, quinidine, dacomitinib.
Strong inhibitors of CYP3A	boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquenavir, telaprevir, telithromycin, voriconazole, cobicistat, troleandomycin.
Strong inducers of CYP2B6	Carbamazepine.
Strong inducers of CYP3A	avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort, rifabutin, phenobarbital, mitotane, enzalutamide.
Inhibitors of PDE enzymes (exclusion criteria, Section 5.2	
Inhibitors of PDE5	sildenafil, avanafil, tadalafil and vardenafil.

Inhibitors of other PDE	PDE1: amantadine, deprenyl, nimodipine. PDE3: inamrinone (amrinone), cilostazol, milrinone. PDE4: cilomilast, roflumilast, rolipram.
Medications known to affect the eye (exclusion criteria, Section 5.2	chloroquine derivatives (i.e. hydroxychloroquine), phenothiazines (i.e. thioridazine, chlorpromazine), tamoxifen, canthaxanthine, desferrioxamine, digitalis, systemic isotretinoin, PDE5 inhibitors noted above, drugs active against Mtb highlighted in bold above.
HIV antiviral medications (exclusion criteria, Section 5.2	Cobicistat, efavirenz, indinavir, nelfinavir, nevirapine, ritonavir (including any ritonavir combination, e.g. danoprevir/ritonavir, darunavir/ritonavir, eltegravir/ritonavir, indinavir/ritonavir, lopinavir/ritonavir, tipranoavir/ritonavir), saquinavir

*No common medications are identified as strong inducers of CYP1A2, CYP2C8, CYP2C9, and CYP2C19

10.7. Appendix 7. Document History

DOCUMENT HISTORY	
Document	**Date**
Original Protocol (Version 1):	03 Apr 2019
Amendment 1 (Version 2):	17 Apr 2019
Amendment 2 (Version 3):	25 Sep 2019
Amendment 3 (Version 4):	07 Jul 2020

Changes in Version 2:

- Updated protocol number (Title Page)
- Extended screening period to 7 Days (Table 4, Section 1.1.8, Section 8)
- Changed PK sampling schema (Tables 4 and 5 and Section 8.7)
- Eliminated late PK sampling timepoints for patients receiving BID and TID dosing (Tables 4 and 5 and Section 8.7)
- Changed laboratory I/E criteria to specify lab values that are exclusionary for DAIDS Grade 2 or greater abnormalities (Section 5.2, Section 8.3.3)
- Updated masking rules (Section 6.3.2)
- Eliminated time of Day window for first dose administration (Table 4, Section 6.1.3)
- Safety labs added on Day 3 and updates to exploratory biomarker collection (Table 4)
- [redacted]

Changes in Version 3:

- Protocol title updated in bold print (Title Page)
- Table of Abbreviations:
  - Acronym of “GMRI” changed to “Gates MRI” and definition changed from “Gates Foundation Medical Research Institute” to “Bill & Melinda Gates Medical Research Institute” (Page 6)
  - Definition of mg as “milligrams” added to Table (Page 7)
  - Definition of PA as “Posterior-Anterior” regarding chest X-rays added (Page 7)
- Changed text for weight-based dosage for HRZE (Rifafour® e-275) from "> 70 kg: 5 tablets" to "71 kg and over: 5 tablets" specifically as stated in the Commercial Package Insert. (Page 13)
- In Table 4:
  - For “Overnight sputum collection for eligibility assessment”, adjusted formatting so all elements are legible. (Page 17)
  - For “Blood/serum sample collection for PK measurements”, removed PK draw scheduled during screening period as it is deemed not necessary for PK analysis. (Page 18)
  - For footnote #2 regarding “Hospital admission and discharge” text clarified from - Study participants will be hospitalized “before start of Screening Phase” to “by Day -3 of the Screening Phase” (Page 18)

  - For footnote #4 regarding "Chest X-rays", text corrected from "Good quality Antero-Posterior (AP) chest X-rays" to read "Good quality Posterior-Anterior chest X-rays", as Posterior-Anterior is the correct orientation for a standard chest X-ray. (Page 18)
  - In footnote #7, spelling of "Cephaid" corrected to "Cepheid". (Page 19)
  - In footnote #12, regarding "Overnight sputum collection for EBA assessment and exploratory measurements", text corrected to refer reader to footnote #7 (overnight sputum collection) instead of footnote #6 (urine collection) for details on how the first overnight sputum will be used. (Page 20)
  - In footnote #14, regarding "Blood/serum sample collection for PK measurements", as performed in the table, the text outlining the blood sampling for PK scheduled for the screening period has been deleted as the sample is not needed for the PK analysis, so the text ". (Page 20)
- In Section 2.1, text refined here to clarify issues with current TB treatment – changed from "Two are the main consequences of this profile. First, TB treatments require large commitments of resources and infrastructure, typically lacking in the countries where TB is most prevalent. Second,…" to "Two of the main consequences of this profile are - first, TB treatments require large commitments of resources and infrastructure, typically lacking in the countries where TB is most prevalent, and second,…" (Page 23)
- In Section 4.1:
  - "Overall Study Design", changed text from - An IDMC will make "dose escalation recommendations" to "dose escalation recommendations"; the sponsor ultimately makes the decision to escalate using the IDMC recommendation as an important part of the decision making process. (Page 30)
  - To clarify text, "during" was added to "Within each cohort, there will be no replacement for the first 2 early withdrawals (drop-outs) occurring during the during the Treatment Phase." (Page 31)
- In Section 5.2, "Exclusion Criteria", Criteria #18 - #21, correctly re-numbered as Criteria #17 - #20. (Page 37)
- In Section 6.1.3 "Administration":
  - Changed text for weight-based dosage for HRZE (Rifafour® e-275) from "> 70 kg: 5 tablets" to "71 kg and over: 5 tablets" specifically as stated in the Commercial Package Insert. (Page 40)
  - Text added to clarify how to handle if a patient's weight changes between specified weight bands during the course of the Study Treatment period; the investigator will determine which of the measured weights to use for dosing. (Page 41)
- In Section 6.2 "Preparation/Handling/Storage/Accountability" for consistent instructions across trial related trial documents, changes made:
  - Section 6.2.1 "Preparation", text clarified as "TBA-7371 will be prepared extemporaneously for 250 mL or 500 mL of a 25 mg/mL suspension" (Page 41)
  - In Section 6.2.3 "Storage", The "do-not-use-beyond-date of 14 Days after compounding has been assigned" corrected to be "7 Days after compounding has been assigned." (Page 41)

- Section 8.1.2 “Chest X-Rays” – text corrected from “Anterior-Posterior” to “Posterior-Anterior” which is the correct orientation for standard chest X-rays. (Page 48)
- Section 8.1.5 “Urine Drug Screening” – text corrected to refer reader to renumbered exclusion criterion #19 (from previously #20). (Page 48)
- Section 8.1.6.2 “Acid Fast Bacilli Detection” – text clarified to reflect proper laboratory evaluation planned for trial with “direct microscopy” changed to “concentrated smear microscopy” and also with “on direct microscopy” deleted from paragraph 3. (Page 49)
- Section 8.2.1 “Overnight Sputum for EBA assessment and Exploratory Measurements”, changed “The first (Day -7 to -3) and second (Day-2) overnight sputum samples” to “The first (Day -7 to -3) or second (Day-2) overnight sputum samples” to indicate either can be used to assess eligibility. (Page 49).
- Section 8.3.1 “Physical Examination”, measuring height was deleted from “A focused physical examination will be performed as directed by medical history on Days 7, 15, 28 and 42”; height only needs to be assessed during the screening period, not in subsequent focused physical examinations. (Page 50)
- In Section 8.5 “Concomitant Treatments”, text added to specify that if a concomitant treatment that would have precluded enrollment is deemed necessary “during the Study Treatment Phase”, the participant will be discontinued from the study. (Page 59)
- In Section 8.7 “Pharmacokinetics”, blood sampling original planned during the screening period for the morning at approximately the same time the 1st daily dose study drug will be administered was deleted as the sample is not necessary for the PK analysis; a pre 1st dose blood sample is already planned. (Page 60)
- In Section 9.7.1 “Independent Data Monitoring Committee (IDMC)”, redundant text, “The IDMC may request additional information, or a pause in recruitment and vaccination, while safety data are being evaluated”, deleted from 5th paragraph; text already stated earlier in 3rd paragraph. (Page 72)
- Section 10.2.4 “Definition of AESI”, text correction made – from “≥Grade 2 intensity (severity) and/or serious AR related to decrease of diastolic blood pressure (DBP)” to “≥Grade 2 intensity (severity) and/or serious AE related to decrease of diastolic blood pressure (DBP)”. (Page 81)
- In Appendix 3. Contraceptive Guidance and Collection of Pregnancy, text added to cover both contraception requirements for male participants and the course of action for pregnancies of partners of male participants has been added: (Page 88)
- Male contraception:
    - Male participants of childbearing potential must agree to use an acceptable method of contraception for 3 months after the last dose of the study medication and must also refrain from sperm donation through 3 months after receiving the last dose of study medication.
    - Male and female participants will be provided with information on acceptable methods of contraception as part of the informed consent process and will be asked to sign the ICF stating that they understand the requirements for avoidance of pregnancy.

  - Pregnancies of partners of male participants: In the event of a pregnancy by a female participant or pregnancy by a sexual partner of a male participant, the processes outlined below must be followed.
- Section 10.6 "Appendix 6 – List of Prohibited Medications" (Page 132)
  - Redundant confusing text "..and other the list is not comprehensive" deleted
  - Text was added to indicate that Rifafour® as anti-TB medication is allowed for patients randomized to receive HRZE during the 14-Day Study Treatment Phase.
  - Delamanid which is now approved and used in South Africa was added to the list.

Changes in Version 4:

Content-related changes are outlined in the below table. In addition, updates and revisions related to grammar, punctuation, and consistency were also incorporated into this protocol amendment version.

Overall Rationale:

- Primarily as a result of the global COVID-19 pandemic, this amendment was implemented to enhance safety measures to include screening and monitoring for SARS-CoV-2 infection to mitigate risks of transmission among participants in this trial and site staff supporting it. Additionally, telephonic follow-up has been included for follow-up period visits for exceptional circumstances due to the local status of the COVID-19 pandemic to monitor patient safety while reducing risk for SARS-CoV-2 transmission.
- Additional aspects of the changes incorporated to enhance evaluation of patient safety and improve trial processes and interpretation of results include:
  - Color vision testing was changed from use of the older/former paper-based Color DX test to the computerized Color DX (Waggoner) test to allow for more standardized training of sites for administering the test and for more precise assessment of any potential color vision changes. The analysis plan has been updated accordingly.
  - Serum sodium and potassium levels were added to the regular scheduled clinical safety lab assessments to enhance interpretation of patient hemodynamic status and renal function. Assessment of these levels was inadvertently omitted from the schedule of assessments in previous versions. No additional blood sampling is required with adding these assessments to those already scheduled.
  - An additional PK sample was added for patients who withdraw from the trial during the study treatment period to enhance interpretation of any important safety findings leading to withdrawal.
  - Allowance for unscheduled visits during the follow-up period (when patients will be on regular TB treatment) was added in the event an interim safety assessment is deemed necessary by the investigator.
  - The 2 overnight sputum collection attempts used for confirming participant eligibility based on sputum volume production were shifted to the Day -7 to Day -3 period to improve screening logistics.
  - Confirmation of susceptibility to isoniazid and rifampicin for patient TB isolates from baseline and Day 15.

Section Number	Text in Amendment 2 (Version 3)	Text in Amendment 3 (Version 4)
Section 1.1.4.2 Secondary Objectives and Endpoints Safety	Mean/median changes in color vision scores from screening to lowest scores 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, and severe)
Section 3.2 Secondary Objectives and Endpoints Safety	Change in frequency of participants with eye symptoms (all, severe, serious) and change in mean visual acuity score and color vision scores from day 1 to days 4, 7, 10, 14 and 15.	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 Day 1 to Days 4, 7, 10, 14 and 15.
	Change in frequency of participants with eye symptoms (all, severe, serious) and change in mean visual acuity score and color vision scores from screening to days 28 and 42 and from days 1-15 (combined) to days 28-42 (combined).	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).
[redacted]		
Section 1.1.8 Timing	The estimated duration of the study (first subject first visit [FSFV] to last subject last visit [LSLV]) will be approximately 1 year.	The estimated duration of the study (first subject first visit [FSFV] to last subject last visit [LSLV]) was originally expected to be approximately 1 year. The duration of the study will however be extended as necessary due to COVID-19 pandemic-related restrictions.
Table 3 Scheduled Visits and Activities and		**Added:** COVID-19/SARS-CoV-2 Testing at Day -7 to -3, Day7, and Day 15 Consolidated Screening Visit days.
Table 3 Scheduled Visits and Activities Footnotes	**c. Early Withdrawal Visit (EWV)**. 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.	**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

Section Number	Text in Amendment 2 (Version 3)	Text in Amendment 3 (Version 4)
		discretion of the investigator in consultation with the medical monitor.
		Footnote #3: Added: Focused PE may be conducted during an unscheduled visit at the discretion of the investigator.
	Footnote #7 **Overnight sputum collection for eligibility assessment.** The 1st of the 3 overnight sputum collections conducted during the Screening Period (day -7 to -3) will be used to assess eligibility as follows: sputum volume (must be at least 10 mL), acid-fast bacilli detection, Mtb positivity and rifampicin sensitivity via the GeneXpert® diagnostic system (Cepheid). In case of suboptimal 1st overnight sputum collection, the above procedures will be conducted on samples from the 2nd overnight sputum collection (day -2). Also see # 12 below.	**Footnote #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.
	Footnote #10 **Eye assessment.** A trained staff member will assess: i) eye symptoms using a standardized script (Appendix 5), ii) visual acuity by means of the Rosenbaum Pocket Eye Screener, ii) color vision by means of the ColorDX Color test and as follows:	**Footnote #10** **Eye assessment.** A trained staff member will assess: i) eye symptoms using a standardized script (Section 10.5, Appendix 5), 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:
	Footnote #11 Study drug will be administered at least 1 hour before and at least 2 hours after a meal, followed by 200 mL of water.	**Footnote #11** 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.
	Footnote #12 **Overnight sputum collection for EBA assessment and exploratory measurements**. Overnight sputum will be collected from 3 PM to 7 AM of the following day (16 hours) on 3 screening days during Screening Phase (days -7 to -3, -2, -1) and on 14 consecutive days during the Study Treatment Phase (days 1 to 14). The last collection	**Footnote #12** **Overnight sputum collection for EBA assessment and exploratory measurements**. Overnight 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

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	will finish at 7 AM of day 15. All samples, except the first (day -3, see # 7 above) will be used for EBA assessment. [redacted]	(Days 1 to 14) for EBA assessment. The last collection will finish at 7 AM of Day 15. Drug susceptibility testing for isoniazid and rifampicin, and minimum inhibitory concentrations (MIC) of TBA-7371 will be performed on either of Day -2 or Day -1, and again on Day 14. [redacted]
		[redacted]
		New Footnote #15: Clarified window for blood draws
		New Footnote #17: Added **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.
Table 4 Timing of Measurements on Days 1, 4, 7, 10, and 14 of Study Treatment Phase (STP)		Clarified window for blood draws **Added:** EWV column **Added:** Blood/serum draws at EWV
Table 4 Timing of Measurements on Days 1, 4, 7, 10, and 14 of		**Added:** a. Early Withdrawal Visit (EWV) or Unscheduled Visit. Participants who withdraw before Day 14 will be asked to

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Study Treatment Phase (STP) Footnotes		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 the 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.
Section 5.1 Inclusion Criteria	**Criteria #1 - Deleted the following text:** **Weight** Consider whether any restriction on weight or BMI is needed for this study intervention/stage of development and delete if not required.	
	Criteria #2 – Deleted the following text: **Disease Characteristics** For studies in healthy volunteers, begin with this criterion. State whether rescreening will be allowed and the circumstances under which rescreening can occur (eg, laboratory value range) and cross reference Section 5.4 if appropriate:	
	Criteria #3 - Deleted the following text: • For studies in patients, provide disease-related considerations: standard, accepted diagnostic criteria (consider supplying laboratory reference ranges or clinical diagnostic criteria in an appendix). Include duration/severity of disease or disorder if appropriate. • When appropriate, specify a realistic and pragmatic inclusion range for each test or marker of interest. Take into consideration any known assay variance or error rate as well as biological variation to avoid creating protocol violation issues. • State whether rescreening will be allowed and the circumstances under which rescreening can occur (eg, laboratory value range) and cross reference Section 6.4, if appropriate. • Check whether additional information associated with the disease area can be found in the therapeutic area libraries.	

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	Criteria 3b sputum smear positivity on direct microscopy for acid-fast bacilli, defined as at least 1+ on the IUATLD/WHO scale	**Criteria 3b** sputum smear positivity for acid-fast bacilli using fluorescent microscopy, defined as at least 1+ on the International Union Against Tuberculosis and Lung Disease (IUATLD)/WHO scale
	Criteria 4 Participants must be able to produce at least 10 mL of sputum during the overnight sputum collection (day -7 to -3 or day -2 of the Screening Phase).	**Criteria 4** Participants must be able to produce at least 10 mL of sputum during the screening overnight sputum collection (two attempts can be made during Day -7 to -3 to meet the volume requirement if the patient is domiciled at the site for both), as assessed by a Sponsor-approved central laboratory.
Section 5.2 Exclusion Criteria		**Added** Criteria #2 – Tested positive for COronaVIrus Disease (COVID-19)/SARS-COV-2 during the Screening Period with a PCR-based assay.
Section 5.4 Screening Failures	Rescreening is not permitted.	Rescreening is not permitted, except in special circumstances. The investigator may review rescreening eligibility, on a case-by-case basis, with the Sponsor.
Section 6.1.3 Administration	Study drugs will be administered at least 1 hour before and at least 2 hours after a meal, followed by 200 mL of water.	Fasting must occur at least 2 hours before dosing and at least 1 hour after dosing.
Section 7.2. Participant Discontinuation/Withdrawal from the Study		**Added:** A participant will discontinue study treatment and end in clinic hospitalization, if the participant tests positive for COVID-19/SARS-CoV-2 anytime during the study treatment period, and will be referred for on-going TB treatment per national guidelines and for further evaluation for COVID-19. If the participant allows and the PI agrees, telephone follow-up may be completed in place of onsite visits on Day 28 and Day 42.
Section 8.1 Screening Assessments and Procedures	Screening assessments can be done at any time during this period, except for the written informed consent, which much 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 much be done consecutively on Day -2 and Day -1.	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 and the screening sample for COVID-19/SARS-CoV-2, which must be completed on or before Day -3, and the overnight sputum collection for EBA

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		assessment, which much be done consecutively on Day -2 and Day -1. Added the following to eligibility list • COVID-19/SARS-CoV-2 test • Sputum assessment, including volume, will be performed by a Sponsor-approved central laboratory (see laboratory study instruction document).
New Section 8.1.3 COVID-19/SARS-CoV-2		COVID-19/SARS-CoV-2 In accordance with the SAHPRA Policy on Conduct of Clinical Trials of Health Products during the Current COVID-19 Pandemic, issued 25 March 2020, this protocol amendment reflects the new and modified processes that were implemented in response to COVID-19. This amendment accommodates for changes related to the pandemic that are needed to minimize risk of transmission of SARS-CoV-2 among participants and staff and builds on strong infection control site practices, which are already in place, to reduce risk of TB transmission as an airborne infectious disease. PCR-based COVID-19/SARS-CoV-2 testing will be conducted by the site and a negative result must be confirmed prior to randomization. In case of a positive COVID-19/SARS-CoV-2 test during the screening period, the participant will be excluded per the Exclusion Criterion in Section 5.2.
New Section 8.1.7	Overnight sputum (collected from 3 PM to 7 AM of the following morning) will be collected 3 times during the Screening Phase and 14 times during the Study Treatment Phase, as described in Section 8.2.1 below. The first (between day –7 and -3) and if necessary the second (day-2) overnight sputum samples will be used to assess eligibility through the sputum volume measurement, acid-fast bacilli detection and molecular tests for Mtb positivity ad rifampicin sensitivity.	Overnight sputum (collected from 3 PM to 7 AM of the following morning) will be collected between Day –7 and Day -3 and analyzed to assess eligibility through the sputum volume measurement, acid-fast bacilli detection and molecular tests for Mtb positivity and rifampicin sensitivity. If inclusion criteria cannot be met from the 1st overnight sputum collection, a second overnight sputum sample may be collected during Day -7 to Day -3 and one or more of the above procedures can be repeated. The patient must be domiciled at the site for the overnight sputum collection and sputum samples will be analyzed by a Sponsor-approved central laboratory.

Section Number	Text in Amendment 2 (Version 3)	Text in Amendment 3 (Version 4)
New Section 8.1.7.1 Overnight Sputum Volume	Participants must be able to produce at least 10 mL of sputum during the overnight collection (inclusion criterion # 4). If this volume is not reached on the sample taken between day -7 and day -3, the sputum volume produced on day -2 will be used for eligibility. If a volume of least 10 mL is not reached again, the participant will be excluded.	Participants must be able to produce at least 10 mL of sputum during the overnight collection (Inclusion Criterion, Section 5.1). If this volume is not reached on the sample(s) taken between Day -7 and Day -3, the participant will be excluded. All volume assessments will be performed by a Sponsor-approved central laboratory (see laboratory study instruction document).
New Section 8.1.7.2 Acid-fast bacilli detection	Acid-fast bacilli will be sought by concentrated smear microscopy on a sputum sample obtained from the overnight collection performed between day -7 and day -3. If for whatever reason the sample obtained is suboptimal as specified in the laboratory manual, a sample from the day -2 overnight collection can be used.	Acid-fast bacilli will be sought by concentrated smear microscopy on a sputum sample obtained from the overnight collection performed between Day -7 and Day -3. In case of suboptimal 1st overnight sputum collection, the microscopy can be conducted on a 2nd overnight sputum collected between Day -7 and Day -3.
New Section 8.1.7.3 Molecular tests for Mtb positivity and rifampicin sensitivity	A commercial molecular test to assess Mtb positivity and rifampicin sensitivity, GeneXpert® diagnostic system (Cepheid), will be carried out on a sputum sample obtained from the overnight collection taken between day -7 and day -3. If for whatever reason the sample obtained is suboptimal, a sample from the day -2 overnight collection can be used.	A commercial molecular test to assess Mtb positivity and rifampicin sensitivity, GeneXpert® diagnostic system (Cepheid), will be carried out on a sputum sample obtained from the overnight collection taken between Day -7 and Day -3. In case of inconclusive results from the 1st overnight sputum sample, the GeneXpert® can be conducted on a 2nd overnight sputum collected between Day -7 and Day -3.
Section 8.2.1 Overnight Sputum for EBA assessment and Exploratory Measurements	Overnight sputum will be collected from 3 PM to 7 AM of the following morning. Overnight sputum collection will occur on 3 days/nights during the Screening Phase (days -7 to -3, -2 and -1) and every day/night (day 1 to day 14) during the Study Treatment Phase. The first (day -7 to -3) or second (day-2) overnight sputum samples of the Screening Phase will be used to assess eligibility as described in section 8.1.6. above. The second (day -2) and third (day -1) overnight sputum samples of the screening Phase will be used to determine baseline EBA. Early bactericidal activity (EBA) will be assessed on each sputum sample by 3 different methods: 1) colony forming units (CFU) on solid media culture (primary), 2) time to sputum culture positivity (TTP) in Mycobacteria	Overnight sputum will be collected from 3 PM to 7 AM of the following morning. The overnight sputum samples collected on Day -2 and Day -1of the Screening Phase will be used to determine baseline EBA. Subsequent overnight sputum samples will be collected every day/night (Day 1 to Day 14) to assess changes in bacterial burden during the Study Treatment Phase. Early bactericidal activity will be assessed on each sputum sample by 3 different methods: 1) CFU on solid media culture (primary), 2) time to sputum culture positivity (TTP) in MGIT culture, 3) LAM assay. Confirmation of Mtb will be performed on solid media and MGIT cultures as necessary using available commercial methods. A commercial molecular test to assess isoniazid and rifampicin sensitivity, GenoType MTBDRplus (HAIN

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	Growth Indicator Tube (MGIT) culture, 3) sputum lipoarabinomannan (LAM) assay. [redacted] Details on sputum collection, handling and testing procedures, and on the laboratory are provided in the study specific manual(s).	Lifesciences), will be utilized on positive MTB cultures from Day -2 (or, if Day -2 unavailable, Day -1) and Day 14 to assess the drug susceptibilities at each visit. In addition, MICs of TBA-7371 will be batch tested on positive MTB cultures from Day -2 (or, if Day -2 unavailable, Day -1) and Day 14. [redacted] Details on sputum collection, handling and testing procedures, and on the laboratory are provided in the laboratory study instruction document.
Section 8.2.2 Samples for exploratory endpoints		**Added:** The participant should spontaneously produce (i.e., not induced) a spot sputum specimen for collection into RNA preservation media at each specified visit. If the specimen cannot be collected due to participant inability to produce sputum, or due to operational limitations with RNA media collection kits, it is not considered a protocol deviation and participants remain eligible for trial participation.
Section 8.3.1. Physical Examination		**Added:** A focused PE may be conducted during an unscheduled visit at the discretion of the investigator.
New Section 8.3.2. COVID-19/SARS-CoV-2		**Added:** COVID-19/SARS-CoV-2 PCR-based COVID-19/SARS-CoV-2 testing will be conducted at Day 7 (±2 Days), on Day 14 OR Day 15 before discharge, and/or at any other time that infection is suspected. In case of positive COVID-19/SARS-CoV-2 test during the study treatment period, the participant will discontinue study treatment, will end in clinic hospitalization, and will be referred for on-going TB treatment per national guidelines and for further evaluation for COVID-19. In case of a positive COVID-19/SARS-CoV-2 test on Day 14 or Day 15

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		at the end of the study treatment period, participants will be referred for on-going TB treatment per national guidelines and for further evaluation for COVID-19.
New Section 8.3.7. Eye Assessment	The 3 eye assessment procedures will be conducted by staff members trained by an ophthalmologist. Details on use of the Rosenbaum Pocket Eye Screener and Color DX Color Vision Test are provided in the Study Manual.	The visual acuity test and Waggoner Computerized Color Vision Test (updated computerized version of the paper-based ColorDX test) will be conducted by staff members trained by an ophthalmologist. Details on use of the Rosenbaum Pocket Eye Screener and Waggoner Computerized Color Vision Test are provided in the study specific manual(s).
Section 8.3.8. Early Withdrawal Visit		**Added:** If a patient is withdrawn from the study due to a positive COVID-19/SARS-CoV-2 test and maintains consent, a telephone follow-up may be documented on Day 28 and Day 42.
New Section 8.3.9 Unscheduled Visit		**Added:** Procedures and assessments conducted during an unscheduled visit will be at the discretion of the investigator in consultation with the medical monitor.
New Section 8.3.10 Participant Follow-Up		**Added:** On Day 15, participants will be transferred to the local TB clinic, following completion of all study assessments. Unscheduled assessments may be performed, following transfer, for purposes of safety follow-up. In exceptional circumstances as assessed by the investigator in consultation with the medical monitor (e.g. issues related to COVID-19/SARS-CoV-2, etc.), participants may have telephone follow up for Day 28 and Day 42.
New Section 8.4.2.3 Assessment of AE/SAE Expectedness	Each AE/SAE will be evaluated by the principal investigator or medically qualified designee to assess whether it is expected based on applicable product information (e.g. Investigator Brochure or Package Insert).	Each SAE will be evaluated by the sponsor. based on applicable product information (e.g. Investigator Brochure or Package Insert).

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	The sponsor or designee will have the opportunity to confirm the expectedness based on the clinical judgement of the medical monitor and sponsor designee. If an AE is considered expected by the investigator but the sponsor believes that the event is unexpected, the sponsor will upgrade the case to 'unexpected' status. The sponsor or designee will never downgrade a case from unexpected to expected.	
Section 8.4.3. Reporting Requirements for SAE, Serious ADR, AESI and Other Events	All fatal and life-threatening serious adverse drug reactions (ADR) are to be reported to South African Health Products Regulatory Authority (SAHPRA) within 7 calendar days after first knowledge with a complete report to be submitted within an additional 8 calendar days. Serious, ADRs that are not fatal or life threatening are to be reported to SAHPRA no later than 15 calendar days after first knowledge. An investigator who receives a Serious ADR report or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and file it.	All fatal and life-threatening serious unexpected ADR are to be reported to South African Health Products Regulatory Authority (SAHPRA) within 7 calendar days after first knowledge with a complete report to be submitted within an additional 8 calendar days. Serious, unexpected ADRs that are not fatal or life threatening are to be reported to SAHPRA no later than 15 calendar days after first knowledge. An investigator who receives a Serious, unexpected ADR report or other specific safety information (e.g., summary or listing of SAEs/SADRs) from the sponsor will review and file it.
[redacted]		
New Table 9 Summary of Primary and Secondary Endpoints and Analyses Secondary Safety	**Endpoint** Mean/median changes in color vision scores from screening (s) to lowest scores during days 1-15 **Statistical Analysis** Mean and median changes in color vision scores from screening to lowest score will be summarized by treatment group.	**Endpoint** Frequency of participants with any new color vision abnormalities (tritan, protan, deutan) in one or both eyes and degree of severity (mild, moderate, severe) **Statistical Analysis** Frequency of participants with any new color vision abnormalities, as well as the specific type of abnormality (tritan, protan, deutan) will be summarized by the number of eyes the abnormality occurs in (one or both), severity (mild, moderate, severe) and treatment group.
	Endpoint Change in frequency of participants with eye symptoms (all, severe, serious) and change in mean visual acuity	**Endpoint** 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,

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	and color vision scores from day 1 to days 4, 7, 10, 14 and 15. **Statistical Analysis** The change in frequency of participants with eye symptoms (all, severe, serious) and change in mean visual acuity and color vision scores from day 1 to days 4, 7, 10, 14 and 15 will be provided by treatment group.	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. **Statistical Analysis** Frequency of participants with any new color vision abnormalities, as well as the specific type of abnormality (tritan, protan, deutan) will be summarized by the number of eyes the abnormality occurs in (one or both), severity (mild, moderate, severe) and treatment group.
	Endpoint Change in frequency of participants with eye symptoms (all, severe, serious) change in mean visual acuity and color vision scores from baseline (day 0) to days 28 and 42 and from days 1-15 (combined) to days 28-42 (combined). **Statistical Analysis** The change in frequency of participants with eye symptoms (all, severe, serious) and change in mean visual acuity and color vision scores from screening to days 28 and 42, and from days 1-15 (combined) to days 28-42 (combined) will be provided by treatment group.	**Endpoint** Change in frequency of participants with eye symptoms (all, severe, serious) and change in frequency of participants with any new color vision abnormalities (tritan, protan, deutan) in one or both eyes and degree of severity (mild, moderate, severe) from baseline (Day 0) to Days 28 and 42 and from Days 1-15 (combined) to Days 28-42 (combined). **Statistical Analysis** Frequency of participants with any new color vision abnormalities, as well as the specific type of abnormality (tritan, protan, deutan) will be summarized by the number of eyes the abnormality occurs in (one or both), severity (mild, moderate, severe) and treatment group.
Section 9.4.1.2. Secondary Bactericidal Activity Analyses	All efficacy analyses will be performed in the mITT population, with per-protocol and completer populations performed to assess the robustness of results.	All efficacy analyses will be performed in the mITT population, with sensitivity analyses performed in the per-protocol population to assess the robustness of results.
New Section 10.2.2 Definition of ADR		**Added:** Definition of ADR "Adverse drug reaction" or "adverse reaction" means a response to a medicine in humans which is noxious and unintended and which occurs at any dose and which can also result from overdose, misuse or abuse of a medicine. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
New Section 10.2.3 Definition of SAE	Other situations:	Is a medically significant / important event or reaction:

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New Section 10.2.5 Definition of AESI	Adverse events of special interest (AESIs) are adverse events that the sponsor wants to monitor carefully.	Adverse events of special interest (AESIs) are adverse events that the sponsor wants to monitor carefully and which are subject to expedited reporting (within 24 hours) from the investigator to the Sponsor or representative following the same process and timelines than the SAEs.
New Section 10.2.6.1 AE and SAE Recording	SAE will be assessed for severity, causal relationship to the study vaccine, and expectedness by the investigator.	SAE will be assessed for severity and causal relationship to the study investigational medicinal product.
New Section 10.2.7.1 Reporting to Sponsor Delegate's (CRO Safety Team) Via the Electronic Data Collection Tool	All fatal and life-threatening adverse drug reactions (ADRs) are to be reported to SAHPRA with 7 calendar days after first knowledge with a complete report to be submitted within an additional 8 calendar days. Serious ADRs that are not fatal or life threatening need to be reported to SAHPRA no later than 15 calendar days after first knowledge.	All fatal and life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) are to be reported to SAHPRA within 7 calendar days after first knowledge with a complete report to be submitted within an additional 8 calendar days. Non-fatal and life-threatening SUSARs need to be reported to SAHPRA no later than 15 calendar days after first knowledge. The same timelines apply to follow-up information received for the SUSARs.
Section 11.0 References	**Deleted:** 13. 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	

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Signature Page for Gates MRI-TBD03-201 Protocol Version 4 - 7 Jul 2020 v4.0

Approval	[redacted] Clinical Development 15-Jul-2020 17:46:53 GMT+0000

Document Number: TBD03-CLIN-000010 v4.0