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Protocol Title

An Open-Label, Partially Randomised Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).

Protocol Name and Number: SimpliciTB NC-008 (B-Pa-M-Z)

Statistical Analysis Plan

Version 3.0

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List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AREDS2	Age Related Eye Disease Scale 2
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
B	Bedaquiline
BLQ	Below the Limit of Quantitation
BMI	Body Mass Index
BPaMZ	Combination of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide
CPK	Creatinine Phosphokinase
DMID	Division of Microbiology and Infectious Disease
DSMC	Data Safety Monitoring Committee
DR-TB	Drug-resistant tuberculosis
DS-TB	Drug-sensitive tuberculosis
ECG	Electrocardiogram
(e)CRF	(electronic) Case Report Form
GGT	Gamma-glutamyl Transferase
HeR	Heart Rate
HIV	Human Immunodeficiency Virus
HGB	Hemoglobin
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
HR	Isoniazid plus Rifampicin combination tablet
ITT	Intent to Treat
IMP	Investigational Medication Product
IWRS	Interactive Web Response System
MeDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MDR-TB	Multi Drug Resistant Tuberculosis
MGIT™	Mycobacterial Growth Indicator Tube
Pa	Pretomanid
PD	Pharmacodynamic
PP	Per Protocol
PK	Pharmacokinetic
PT	Preferred term
PR	PR interval – time from start of P wave to start of QRS complex on ECG
QT	QT interval – time from start of Q wave to end of T wave on ECG
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QRS	QRS complex (ventricular depolarization) on ECG
RBC	Red Blood Cell
RR	RR interval – time between two QRS complexes on ECG
SAP	Statistical Analysis Plan
SOC	System Organ Class
TB	Tuberculosis
TB-mITT	TB Specific Modified Intent to Treat
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cell
XDR-TB	Extensively Drug Resistant Tuberculosis

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1. Introduction

This document outlines the statistical analysis for both efficacy and safety. This includes, but is not limited to, the efficacy primary endpoint, secondary efficacy and safety endpoints, populations, TB symptoms, EQ5D, adherence and weight. Summaries of plasma drug concentrations and PK parameters will also be described.

SimpliciTB is a multi-centre, open-label, randomised clinical trial in drug sensitive tuberculosis (DS-TB). DS-TB participants should be sensitive to rifampicin and isoniazid and either newly diagnosed for tuberculosis (TB) or have a history of being untreated for at least 3 years after cure from a previous episode of TB.

Participants who are drug resistant (DR-TB) will also be enrolled into the study and will receive the same experimental treatment, except that they will be treated for a longer period of time due to the high degree of pyrazinamide resistance expected in this group. These participants will not be randomised. DR-TB participants should be resistant to rifampicin or isoniazid.

SimpliciTB will evaluate and support that, in addition to previous studies evaluated with BPaMZ, the drug regimen (BPaMZ) will be safe, effective, and well-tolerated and could potentially shorten the current treatment duration compared to standard HRZE/HR treatment for participants with DS-TB disease. This trial will also evaluate if this drug regimen (BPaMZ) given for 6 months will be safe and effective in DR-TB disease. All participants will be followed for 2 years after enrolment.

For participants with DS-TB, the experimental arm (4BPaMZ) will be compared to the control arm (HRZE/HR) in all analyses (unless otherwise stated). There will be no formal comparisons for participants with DR-TB.

While SimpliciTB is an open label study, only members of the Data Safety Monitoring Committee (DSMC) and the unblinded statistician(s) will have access to data grouped by study arm. Access to data grouped by study arm by investigators, CRO and TB Alliance study team should not occur. In addition, site staff will be strongly discouraged from attempting to aggregate data by treatment arm at a site level. In order to protect the safety of study participants, TB Alliance staff who do not work directly with study conduct will require access to aggregated safety data as part of study safety oversight and for the purpose of making strategic study decisions. In addition, if there are identified potential safety concerns that warrants a more frequent look at aggregated data compared to the DSMC meeting frequency, the medical monitoring team will require access to aggregated safety data.

Note: The protocol refers to three analysis populations (ITT, mITT and PP). In this SAP these are referred to as mITT, TB-mITT and PP. There are also two additional analysis populations outlined in the SAP. This is described in Table 1.

Table 1: Analysis populations according to protocol and SAP

Analysis Populations	
Protocol	**Statistical Analysis Plan**
All randomised*	Intent to treat (ITT)
Safety*	Safety
Intent to treat (ITT)	Modified intent to treat (mITT)
Modified intent to treat (mITT)	TB-specific mITT (TB-mITT)
Per protocol (PP)	Per Protocol (PP)

*Not formally defined in the protocol

1.1. Trial Intervention

Participants with DS-TB who are randomised to the intervention arm will receive: bedaquiline (200 mg daily for 8 weeks then 100 mg daily for 9 weeks); and pretomanid (200 mg daily), moxifloxacin (400 mg daily) and pyrazinamide (1500 mg daily) for 17 weeks (4BPaMZ).

Participants with DS-TB who are randomised to the control arm will receive the standard dose of isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) for 8 weeks followed by 18 weeks of isoniazid and rifampicin. This regimen will be administered according to weight band (HRZE/HR).

Participants with DR-TB will be treated with bedaquiline (200 mg daily for 8 weeks then 100 mg daily for 18 weeks); and pretomanid (200 mg daily), moxifloxacin (400 mg daily) and pyrazinamide (1500 mg daily) for 26 weeks (6BPaMZ).

1.2. Randomisation, Stratification and Blinding

Eligible participants with DS-TB will be randomised in the ratio 1:1 using an interactive web response system and stratified according to:

- HIV status (positive vs. negative)
- Cavitation (yes vs. no)

Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment allocation during the treatment phase of the trial. See blinding plan for more detail.

2. Outcome Measures

2.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be time to culture negative status in liquid media, up to 8 weeks. This will be assessed for superiority. The hypothesis is that the 4-month treatment regimen will be superior to control for participants with DS-TB. A modified intent-to-treat (mITT) analysis will be performed (as defined in §6.1).

2.2. Key Secondary Efficacy Endpoint

A key secondary efficacy endpoint will be the proportion of participants who have an unfavourable outcome at 12 months. This will be assessed for non-inferiority using the 12% margin. The difference in proportions of unfavourable status at 12 months post-randomisation (non-inferiority comparison) will be performed for participants with DS-TB for the mITT, TB-mITT and PP analysis populations (as defined in §6.1).

2.3. Secondary Safety and Tolerability Outcomes

All safety summaries in this section will be presented for all participants in the Safety population, as defined in §5, unless otherwise stated.

Adverse event verbatim reported terms will be coded by system organ class (SOC) and preferred term (PT) using the latest version of MedDRA.

Adverse events are defined as either:

1. Treatment emergent adverse events (TEAEs) which are adverse events (AEs) which started or worsened on or after the first administration of IMP up to and including 14 days after the last study drug administration, or
2. Post-treatment AEs which are AEs that start or worsen more than 14 days after the last administration of IMP.

Secondary safety and tolerability outcomes are outlined below in §2.3.1-2.3.7. These data will be presented as descriptive analyses, and no inferential tests will be carried out.

2.3.1. All-cause mortality

The proportion of participants who died from any cause during the study.

2.3.2. Treatment emergent adverse events (TEAEs)

2.3.2.1. Incidence

The proportion of participants who experienced at least one treatment-emergent adverse event (TEAE).

2.3.2.2. Severity

Of those experiencing at least one TEAE the highest grade experienced. The highest grade experienced is defined as the most extreme severity captured on the Adverse Event CRF page. The possible severities are 'Grade 1: Mild,' 'Grade 2: Moderate,' 'Grade 3: Severe', and 'Grade 4: Potentially life-threatening.'

2.3.2.3. Drug relatedness

Proportion of participants experiencing at least one TEAE related to any study medication. A related AE is defined as 'Possibly', 'Probably', or 'Certainly' related to study medication.

2.3.2.4. Seriousness

Proportion of participants experiencing at least one serious TEAE. A serious AE (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, is a congenital anomaly/birth defect, requires in-participant hospitalisation or prolongation, results in significant disability/incapacity, or is a medically important event.

2.3.2.5. Leading to treatment discontinuation

Proportion of participants experiencing a TEAE that lead to treatment discontinuation. This will be AEs where action taken with study treatment is 'Permanently Discontinued' for BPaMZ or HRZE/HR.

2.3.2.6. Leading to study discontinuation

Proportion of participants experiencing a TEAE that lead to study discontinuation. This will be AEs where action taken with study treatment is 'Withdrawn from Study'.

2.3.2.7. Leading to death

Proportion of participants experiencing a TEAE that lead to death. This will be AEs where the answer to 'Outcome' on the AE form is 'Fatal'.

2.3.2.8. Liver-related, drug and liver-related and serious liver-related TEAEs

The proportion of participants experiencing liver related, drug and liver related and serious liver related TEAEs. Liver related AEs are those where the preferred term specifies 'Hepatic' Drug and liver related are those AEs that are liver related and related to a drug and serious liver related TEAEs are those that are liver related and the AE is considered serious (as described in § 2.3.2.4).

2.3.3. Clinical safety laboratory measurements

The incidence of newly notable (an abnormality observed post baseline that meets the notable criteria) grade 3 or 4 severity for laboratory parameters according to DMID grading. Participants are considered to have notable laboratory abnormalities if his/her response falls within the specified definitions (see Table 3 in §8.3.1) at least once during the treatment period.

2.3.4. Electrocardiogram

The electrocardiogram (ECG) results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), which are read by a central cardiology service, observed measurements and change from baseline. QT/QTc intervals, maximum change from baseline, will be categorised according to §8.4 below. The ECG results will be considered at baseline, week 8, week 17, week 26, week 39 and early withdrawal in all participants.

2.3.5. Changes in male reproductive hormones

The change in male reproductive hormones (testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin B) for all male participants in all treatment groups from baseline to end of treatment visit (week 17 or week 26 depending on treatment group) and week 39.

2.3.6. Changes in lens opacities

The change (increase or decrease) in lens opacity (cortical, nuclear and posterior subcapsular) from baseline to end of treatment (week 17 or week 26), week 39 and early withdrawal in all participants.

2.3.7. Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD)

This SAP provides descriptive summaries of plasma drug concentrations and PK parameters only. Full details on the full analysis of PK and PK/PD data can be found in the PK/PD modelling SAP.

2.4. Other Secondary Efficacy Endpoints

Other secondary endpoints which will be analysed according to the populations specified:

- Proportion of unfavourable at 24 months (mITT, TB-mITT and PP populations)
- Time to unfavourable status (mITT, TB-mITT and PP populations)
- Time to sputum culture conversion to negative status (mITT population)
- Culture conversion status at 4, 6, 12 and 17 weeks (mITT population)
- Change in weight from baseline (mITT population)
- Change in TB symptoms from baseline (mITT population)
- Change in participant reported health status from baseline (mITT population)
- Adherence (TB-mITT population)
- Baseline predictors of Favourable Status at 12 months (mITT population)

2.5. Exploratory Objectives

2.5.1. Predictors of relapse free cure

Evaluate whether any of the secondary efficacy endpoints as outlined in §2.4 predict relapse free cure at 12 months post randomisation. Potential predictors will include, but are not limited to, baseline variables (see §7.4), culture negative status at weeks 4, 6, 8, 12 and 17 as well as time to culture negativity (as a continuous variable).

2.5.2. Subgroup analyses

Subgroup analyses will be carried out and analysed for the key secondary efficacy endpoint (as described in §2.2 for the TB-mITT population). These subgroups are described in §7.4.

3. Definitions and Data Handling Issues

3.1. Positive and Negative Status

3.1.1. Positive culture

Positive culture refers to the culture being positive for *Mycobacterium Tuberculosis* (M.tb). The MGIT culture results that are positive with contamination, contaminated, or with no result will be treated as missing.

Two sputum samples per visit are collected at each visit throughout treatment and follow-up. The culture result for a given visit is established using all samples obtained for that visit. A positive culture takes precedence over a negative or contaminated culture at the same visit and a negative culture takes precedence over a contaminated culture at the same visit (Appendix §13.1).

3.1.2. Isolated Positive Cultures

It is known that occasionally participants produce sputum samples that are "isolated positives," that is, a positive culture preceded by a series of negative cultures and followed thereafter by at least two negative cultures without an intervening positive result. This phenomenon may be the result of a sealed cavity breaking down or laboratory contamination and does not in itself signify that the participant is relapsing. In the event of a single positive culture result occurring in a participant who has previously been classified as having culture negative status (in the absence of any retreatment), the participant will not be classified as a recurrence unless a second positive culture result is obtained at a separate visit (at least 7 days apart), without an intervening negative culture or unless the participant is lost to follow up or completes the study (and is unable to be brought back) before two negative cultures are obtained. As there is a higher incidence of isolated positives with liquid culture and sometimes even serial "isolated positives" [1], the clinical condition of the participant will also be considered in deciding whether the participant has an unfavourable outcome and re-treatment is indicated.

For example, if a participant after being culture negative has two positive cultures in a row, but is deemed to be doing well clinically, the investigator may choose to leave the participant untreated on clinical grounds. In such a case, so long as two consecutive negative cultures are eventually obtained in the absence of treatment, the participant will not be classified as an unfavourable outcome (defined below).

3.1.3. Culture negative status

Culture negative status is achieved when a participant produces at least two negative culture results at different visits (at least 7 days apart) without an intervening positive culture result for M.tb. The date of the first negative culture (date of collection of culture) of these two is the date at which culture negative status was obtained. Once obtained, culture negative status continues until there are two positive cultures at different visits (at least 7 days apart), without an intervening negative culture, or until there is a single positive culture not followed by two negative cultures. Culture negative status can be achieved at any time during treatment or follow-up but before any re-treatment. Culture negative status can be re-established. A single culture result or inability to produce sputum (see §3.1.4) at 8 weeks will be sufficient to count that participant as having data for endpoint classification.

Participants with two contaminated or missing samples at a given visit (from month 2 onwards) will be asked to return to produce two more sputum samples.

3.1.4. Inability to Produce Sputum

In general, inability to produce sputum is treated as being equivalent to having a negative culture result if no other sputum sample is produced at that visit. This includes:

- the rare situation where a participant who never achieves culture negative status due to the inability to produce sputum, after TB has been confirmed on the applicable baseline sample, completes follow-up without clinical or microbiological evidence of relapse.
- during the COVID-19 lockdown situation where this data is collected remotely/telephonically.

In SimpliciTB, such participants will be considered to have a favourable outcome and an inability to produce sputum with no other sputum produced at that visit will be treated as a negative culture result.

3.2. Bacteriological failure, Relapse or Reinfection

Treatment failure is defined as being declared an unfavourable outcome at or before the end of treatment (either 4 or 6 months) or failing to attain culture negative status and being declared an unfavourable outcome (§6.2) or the participant is withdrawn at or before the end of treatment for clinical (TB) reasons including being re-treated (or changing from protocol treatment) for TB.

Relapse *or* ***bacteriological relapse*** is defined as failing to maintain culture negative status or being declared an unfavourable outcome (§6.2) after the end of treatment (either 4 or 6 months) in those participants who attained culture negative status by the end of treatment and had culture conversion to positive status with an M.tb strain that is genetically identical to the infecting strain at baseline or after the end of treatment in those participants who attained culture negative status by the end of treatment and were withdrawn for clinical (TB) reasons, including being re-treated (or changing from protocol treatment) for TB. Details are given in Appendix §13.2.

Reinfection *or* ***bacteriological reinfection*** is defined as failing to maintain culture negative status or being declared an unfavourable outcome (including being withdrawn for clinical (TB) reasons including being re-treated or changing from protocol treatment for TB) after the end of treatment in those participants who attained culture negative status by the end of treatment and had culture conversion to positive status with a M.tb strain that is genetically different from the infecting strain at baseline. If reinfection cannot be distinguished from relapse, the participant will be assumed to have relapsed. A single positive sample will be sufficient for strain typing to compare to baseline. Full details are in Appendix §13.2.

3.3. Adequate Treatment

The definition of adequate treatment sets a limit for the amount of treatment missed. Participants not taking the adequate amount of treatment by this definition will be excluded from the PP analysis (see §6.2.3).

Participants allocated to a 4 month regimen, to meet the definition of adequate treatment they must have taken at least 96 doses (80%) of their allocated 119 day (17 weeks) treatment regimen within 175 days of starting therapy (i.e. 17 weeks plus an allowable 56 day halt (including a maximum of 35 consecutive days) as per the protocol).

Participants allocated to a 6 month regimen, to meet the definition of adequate treatment they must have taken at least 146 doses (80%) of their allocated 182 day (26 weeks) treatment regimen within 238 days of starting therapy (i.e. 26 weeks plus an allowable 56 day halt (including a maximum of 35 consecutive days) as per the protocol).

Participants in the control arm are additionally required to have taken at least 80% of their allocated intensive treatment.

3.4. Determining Cause of Death

A list of all ***TB-related*** and ***non-TB-related deaths*** will be generated and approved by a review committee **blind to randomised arm** before database lock. Similarly, a list of violent or accidental deaths will be generated (see study Death Adjudication Manual).

3.5. Major Protocol Deviations for Analysis

A major protocol deviation for analysis is defined as a serious protocol deviation which is likely to affect to a significant degree the scientific value of the trial. These participants will be included in the mITT and TB-mITT analyses, but not in the PP analysis (see §6.2). A list of all major protocol deviations for analysis (blinded to treatment arm) will be approved by a review committee prior to database lock.
Note: participants attending a long term outcome visit outside the specified window will be evaluated and considered for potential major protocol violator. Visits within 2 weeks of the window opening will be considered *minor* protocol violators.

3.6. Trial Timings

Study Day 1 is defined as the date on which a participant is administered the first dose of the study medication. Other study days are defined relative to the Study Day 1 with Day 2 being the day after Study Day 1 and Day -1 being the day prior to Study Day 1.

For all safety endpoints, baseline is defined as the last non-missing measurement prior to first dose of study treatment unless otherwise stated.

In all analyses, visit date rather than day or week number will be used to define the timing of events. For participants treated with the 6-month regimens (HRZE/HR for DS-TB participants and 6mBPaMZ for DR-TB participants) this will be taken as a total of 26 weeks, i.e. 182 dosing days. For DS-TB participants randomised to 4 months of BPaMZ a total of 17 weeks (119 dosing days) is taken. As per the protocol, assessments should be collected as follows:

- Within ± 3 days of scheduled visit from day 1 to week 8
- Within ± 5 days of scheduled visit from week 12 to week 26
- Within ± 14 days of scheduled visit during the follow-up phase at or after month 6 to month 24.

Unscheduled visits and visits outside of these windows will be slotted into windows as appropriate. Visits falling outside of the defined protocol visit windows will be put into separate visits so that all data, both collected at scheduled and unscheduled time points, are used.

The ***treatment period*** is defined as either 17 or 26 weeks from start of therapy depending on allocated treatment regimen.

The ***follow-up period*** is defined as the period after the end of treatment to the end of follow-up.

3.7. General Statistical Considerations for Safety Analysis

If there are multiple assessments in a visit, the highest grade non-missing value within a visit will be used in the summaries, however all will be shown in the listings. If numeric data is beyond range of lab detectability and result is showed as "<XX" or ">XX" then the numeric XX value will be used for summary statistics.

There will be no specific strategy to deal with missing data i.e. it will not be imputed. A complete case analysis will be performed. For example when modelling the data based on a specific outcome only participants with complete data will be included.

Baseline is defined as last available measurement prior to dosing and post baseline abnormalities are included in the summary if the subject did not meet the abnormality criteria at baseline or toxicity grade at post baseline is higher than that on baseline.

All statistical analyses tables, listings and figures will be produced using STATA Version 16.0 or higher.

3.8. Newly notable abnormalities

A newly notable laboratory abnormality is defined as an abnormality observed post baseline that meets the notable criteria in Table 3 and that did not exist at baseline. Participants can still meet the criteria for newly notable laboratory if the baseline value is missing.

4. Sample Size

For the primary endpoint, time-to-negative culture conversion at 8 weeks, 150 participants per arm (DS-TB participants) will provide more than 99% power (5% two-sided significance) to detect a hazard ratio (HR) of at least 2 (for 4BPaMZ vs. HRZE), assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 93% power to detect a HR of least 2. Note, non-randomised MDR participants will not be formally compared to any randomised group.

For the key secondary efficacy endpoint of clinical outcome at 12 months from randomisation, 150 participants per arm will provide 74% power at the two-sided 5% significance level based on assumptions using data from the largest most recently completed phase 3 TB treatment trial which used the same control arm [2]. That is, assuming 16% of participants in the control arm are unfavourable and 13% are unassessable at 12 months post randomisation. A non-inferiority margin of 12% is chosen and justified below.

This trial aims to demonstrate that the experimental regimen administered for 4 months to participants with DS-TB is not inferior to the standard 6-month control regimen using a non-inferiority margin of 12%, chosen based on the following rationale. The best estimate for the treatment effect (also known as M1 in guidance documents for non-inferiority trials) of the current standard treatment (HRZE) is derived from modern clinical trials of this treatment compared to historical, natural history trials. Based on the above reference, an estimate of the favourable rate observed with standard HRZE therapy of 84% is used. The WHO estimates that the case fatality rate for untreated smear positive pulmonary tuberculosis is 70%, and this estimate was confirmed in a systematic review in 2011 [3]. Therefore, an estimate of 30% for the favourable rate of placebo may be contrasted with the 84% favourable rate of the standard HRZE therapy. Based on these data, the best available point estimate for M1 (the overall treatment effect of HRZE, expressed as a risk difference) is 54%. A selection of 12% for M2 (the non-inferiority margin) would represent less than 25% of the point estimate of M1, thus assuring that the lower bound of the NI margin preserves more than 75% of the estimated treatment effect of the HRZE regimen.

5. Analysis Populations

Analysis populations are:

- The **Intent to treat** (**ITT)** population, defined as all participants who were enrolled, whether or not they started treatment.

- The **Safety** population, defined as all enrolled participants who received at least one dose of study treatment. Participants will be analysed as to the treatment they actually received regardless of given allocation.

- The **Modified intent to treat** (**mITT)** population, defined as all participants who were enrolled and started treatment, excluding any late screening failures.

- The **TB-specific modified intent to treat (TB-mITT)** population, defined as the mITT population with additional exclusions (see below).

- The **Per-protocol (PP)** population, defined as the TB-mITT population with additional exclusions (see below).

For ITT, mITT, TB-mITT and PP; participants will be analysed as to the treatment they were randomised to receive.

For short-term culture conversion endpoints, only the mITT population will be examined.

The TB-mITT population is unique to the TB field and is outlined here (with further details provided in Appendix §13.3). TB-mITT is a key analysis that has been used in the literature of long-term outcome trials of durable cure in TB, although it has generally been referred to simply as the 'mITT analysis'. This analysis excludes participants based on data collected post-randomisation. A true mITT analysis, as recognised by regulatory authorities, does not exclude any participants due to missing data post-enrollment.

Thus, for the long-term endpoint of durable cure, the TB-mITT analysis will be considered primary for the purposes of publication, to allow comparison with the rest of the literature in the TB field. However, for regulatory purposes, we recognise that regulatory agencies will consider the mITT analysis primary.

6. Endpoint definitions

6.1. Short term endpoints

6.1.1. mITT Population

Participant status is defined in §3.1.

6.1.1.1. Unassessable status (late exclusions)

1. Participants enrolled and later found to be ineligible because of a protocol violation at enrolment (based on data collected prior to enrolment).
2. Participants without culture confirmation of M.tb at Day 1 (baseline) sputum samples (or screening or out to Week 4 if the baseline is contaminated or negative). These participants will be late exclusions from the study.

6.2. Long term endpoints

Favourable status (all analysis populations)

Participants with culture negative status at the time of the endpoint (at 12 or at 24 months), who have not already been classified as having an unfavourable outcome and whose last positive culture result ("isolated positive culture") was followed by at least two negative culture results. For participants who are missing culture status at the 12 month endpoint but who have a culture result at a future timepoint will be considered culture negative status at 12 months if both the previous and future culture results are negative.

6.2.1. mITT Population

6.2.1.1. Unassessable status (late exclusions)

1. Participants enrolled and later found to be ineligible because of a protocol violation at enrolment (based on data collected prior to enrolment).

2. Participants without culture confirmation of M.tb at Day 1 (baseline) sputum samples (or screening or out to Week 4 if the baseline is contaminated or negative). These participants will be late exclusions from the study.

6.2.1.2. Unfavourable status

Participants in the mITT analysis population who do not reach the time of the endpoint (12 or 24 months depending on the endpoint) or who are not culture negative status at the time of the endpoint (12 or 24 months) and whose last positive culture result ("isolated positive culture") was not followed by at least two negative culture results.

6.2.2. TB-mITT Population

6.2.2.1. Unassessable status (additional exclusions from mITT)

In addition to those excluded from the mITT analysis (see §6.2.1.1), the following participants will be excluded:

1. Participants who, having completed treatment, are lost to follow-up or withdrawn from the study, their last status being culture negative and their last positive culture result ("isolated positive culture") followed by at least two negative culture results at different visits (at least 7 days apart, without an intervening positive culture).

2. Women who become pregnant during treatment and stop their allocated treatment.

3. Participants with suspected/confirmed COVID-19 during treatment and who stop their allocated treatment.

4. Participants who died during treatment from violent or accidental cause (e.g. road traffic accident). N.B.: This does not include death from suicide, which will be considered an unfavourable outcome.

5. Participants who died during follow-up (after the end of treatment) with no evidence of failure or relapse of their TB, their last status being culture negative and their last positive culture result ("isolated positive culture") followed by at least two negative culture results at different visits (at least 7 days apart).

6. Participants who, after being classified as having culture negative status are deemed culture positive and are infected with a new strain that is different from that with which they were originally infected. Reinfection will be defined specifically as a participant infected with a strain that is genetically different from the initial strain (see Appendix §13.2).

7. Participants who are able to produce sputum at the endpoint visit, but whose endpoint visit sputum samples are all contaminated or missing, who cannot be brought back for repeat cultures, provided their last positive culture was followed by at least two negative cultures. N.B.: This does not apply to participants who are unable to produce sputum at the given endpoint (see §3.1.4), or to participants who are able to be brought back subsequently and produce negative cultures.

Participants in categories 1-7 above who have already been classified as having an unfavourable outcome will not be excluded.

6.2.2.2. Unfavourable status

1. Participants not classified as having achieved or maintained culture negative status when last seen, or

2. Participants previously classified as having culture negative status who, following the end of treatment, have two positive cultures without an intervening negative culture (however, see §3.1.2 for an exception), or

3. Participants who had a positive culture not followed by at least two negative cultures when last seen, or

4. Participants dying from any cause during treatment, except from violent or accidental cause (e.g. road traffic accident), not including suicide (e.g., suicide will be considered an unfavourable outcome), or

5. Participants definitely or possibly dying from TB related cause during the follow-up phase, or

6. Participants requiring an extension of their treatment beyond that permitted by the protocol a restart or a change of treatment for any reason except reinfection or pregnancy, or

7. Participants lost to follow up or withdrawn from the study before the end of treatment.

6.2.3. PP Population

6.2.3.1. Unassessable status (additional exclusions from TB-mITT)

In addition to those already excluded from the mITT (see §6.2.1.1) and the TB-mITT (see §6.2.2.1) analyses, the following participants will be excluded from the PP analysis:

1. Participants lost to follow-up or withdrawn for reasons other than treatment failure (e.g. participant consent or relocation) before the end of treatment, unless they have already been classified as having an unfavourable outcome.

2. Participants whose treatment was modified or extended beyond what is permitted in the protocol for reasons other than an unfavourable therapeutic response to treatment (e.g. an adverse drug reaction), unless they have already been classified as having an unfavourable outcome.

3. Participants not meeting the definition of having received an adequate amount of their allocated study regimen (see §3.3), provided this is not due to an unfavourable outcome.

4. Participants who are classified as "major protocol deviations for analysis" (see §3.5), unless they have already been classified as having an unfavourable outcome on the basis of data obtained prior to the protocol deviation

6.2.3.2. Unfavourable status

Points 1-6 in §6.2.2.2 Unfavourable status in the TB-mITT Population section above

7. Efficacy Statistical Analysis

All efficacy outcomes will be analysed for superiority with the exception of the proportion of participants who have an unfavourable outcome at 12 months and at 24 months. These will be analysed for non-inferiority with a non-inferiority margin of 12%.

All superiority analyses for efficacy, apart from the interim analysis (see §7.3), will be two-sided and considered statistically significant at the 5% level.

All efficacy analyses will be adjusted for the stratification variables (HIV status and cavitation) unless otherwise stated and considered primary. Unadjusted analyses will also be considered for key endpoints.

Additional baseline covariates listed in §7.4 will be considered for a secondary adjusted analysis for key efficacy endpoints.

7.1. Primary Efficacy Endpoint

Time to culture negative status in liquid media over 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio. This model assumes proportional hazards. This means that the hazard rates for participant subgroups are proportional over time during participant follow-up. A program that tests the proportional hazards assumption in the Cox model (estat phtest for Stata) will be used. In the case where there is adequate evidence that the proportional hazard assumptions are violated at the 5% level (i.e. $p<0.05$), then the restricted mean survival time method (RMST) will be used. Data will be described using Kaplan-Meier plots.

For the 8 week culture conversion endpoint the time will be taken from randomisation until the first occurrence of achieving culture negative status in liquid media over 8 weeks. For participants who do not achieve culture negative status, time will be taken from randomisation to 8 weeks (and censored). Participants who die or are lost to follow up/withdrawn will be considered as not achieving culture negative status unless they have achieved a culture negative status prior to death or being lost to follow up/withdrawn. The last known visit date will be taken for any participants who are missing the date of their 8-week visit. Participants negative at baseline (but eligible for the trial based on a positive result at screening) will not be included in this primary time-to-event analysis.

7.1.1. Sensitivity Analyses of Primary Efficacy Endpoint

As a sensitivity analysis for the primary efficacy endpoint, multiple imputation [under the missing at random (MAR) assumption] will be used to account for missing culture results at missing visits, defined as missing when there are no culture results for any sample at a visit. Note: a contaminated result will be considered as such, up to and including week 8, after which it will be considered missing (for statistical analysis purposes). A seed of 102079 will be used, and 20 imputed values will be created for each missing observation in the multiple imputation model.

7.2. Secondary endpoints

7.2.1. Key Secondary Endpoint: Unfavourable Status at 12 months (Non-inferiority Comparison)

For the proportion of participants who have an unfavourable outcome at 12 or 24 months, non-inferiority will be determined using the upper bound of the (two-sided) 95% confidence interval of the difference, relative to the 12% margin. If the upper bound of the two-sided 95% confidence limit for the difference (proportion with unfavourable outcome in the intervention arm less the proportion with unfavourable outcome in the control arm) is less than 12% (the margin of non-inferiority), the intervention will be considered to be non-inferior to the control arm on that comparison.

The difference in proportions of an unfavourable status at 12 months will be analysed using the Cochran-Mantel-Haenszel test.

7.2.1.1. Secondary Bayesian analysis of Unfavourable Status at 12 months

A Bayesian analysis of the key secondary endpoint will also be performed (as a secondary analysis) with the posterior distribution of the effect size graphed under different prior distributions (for example, sceptical, uninformative and optimistic). This analysis has advantages over a more standard frequentist analysis as direct probability statements can be made about the effect size and in addition, prior information about the size of the effect can be formally incorporated into the posterior estimation. While the uninformative prior will yield similar results as a standard frequentist analysis (i.e. with a point estimate and confidence interval), the Bayesian analysis provides a more intuitive interpretation about the effect of the intervention compared to control.

7.2.1.2. Sensitivity Analyses for Unfavourable Status at 12 months

The following sensitivity analyses on the key secondary endpoint are planned:

1. An analysis of participants in the TB-mITT and PP populations where reinfections are re-classified as unfavourable outcomes.
2. An analysis of the TB-mITT and PP populations treating all deaths as unfavourable.

7.2.2. Unfavourable Status at 24 months

Unfavourable status at 24 months will be analysed as described in the first two paragraphs of §7.2.1 for unfavourable status at 12 months.

7.2.3. Time to Unfavourable Status

Time to an unfavourable outcome will be analysed using a Cox proportional-hazards regression analysis. These analyses will be performed according to the mITT, TB-mITT and PP classifications. Time to event will be calculated in days from the date of enrolment up to the first date associated with the reason for unfavourable status or (if favourable) the date of the 12 months post randomisation visit or date last seen if they did not reach 12 month follow-up. Kaplan Meier plots will also be presented.

7.2.4. Time to Sputum Culture Conversion to Negative Status

For the mITT analysis population, time to culture negative status (first of two negative cultures without an intervening positive culture) will be analysed using survival analysis techniques, Kaplan Meier plots and Cox proportional hazard regression.

7.2.5. Culture Conversion Status at 4, 6, 12 and 17 Weeks

For the mITT analysis population, participants will be classified as being culture positive, culture negative, dead or unassessable at 4, 6, 12 and 17 weeks.

7.2.6. Adherence

The proportion of participants who have an adequate amount of treatment (see §3.3) will be tabulated. No formal comparisons will be performed.

7.2.7. Weight and BMI

Baseline weight and BMI and their change from baseline weight at week 8 and end of treatment and at 12 and 24 months after the end of therapy will be summarised by mean, median, IQR and range.

7.2.8. TB Symptoms

Each TB symptom will be summarised by n (%): none (0), mild (1), moderate (2), severe (3) at each visit collected as per the protocol: baseline, week 8, end of treatment, 12 and 24 months after the end of therapy.

In addition, baseline and change from baseline score at each time point listed above for each symptom and for total symptom score will be summarised by mean, median, IQR and range.

7.2.9. Participant Reported Health Status

Participant reported health status is measured by the 5 domains of EQ5D. These will be summarised at baseline, week 8, end of treatment and 12 month follow-up by randomised group. Change from baseline will be summarized at each follow-up assessment by mean, median, IQR and range.

7.2.10. Predictors of Favourable Status at 12 and 24 months

As an exploratory analysis, predictors of having a favourable outcome at 12 months and at 24 months will be investigated. Potential predictors will include, but are not limited to, baseline variables (see §7.4), culture negative status at weeks 4, 6, 8, 12 and 17 as well as time to culture negativity (as a continuous variable).

7.3. Interim Analyses

7.3.1. Overview

There is one planned interim analysis for efficacy data. The interim analysis is based on an intermediate outcome of time to negative culture conversion status observed by 8 weeks. Following a review of these interim findings, consideration will be given to increase the sample size (pending funding availability) to adequately power the study on the key secondary 12-month clinical outcome. This would then become the primary efficacy endpoint. This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [4-6].

The interim analysis endpoint (I) is time to negative culture conversion status observed by 8 weeks in the mITT population. The final analysis endpoint (D) is favourable status at 12 months. Therefore, as the interim endpoint is not the same as the final analysis endpoint this is denoted as $I \neq D$ i.e. interim endpoint does not equal the final endpoint.

For the interim analysis, a single culture result at week 8, with no available future culture data, is sufficient to classify culture negative status at that visit (see §3.1.3). If all culture results are contaminated at week 8 and no future culture data is available, then the week 7 result is sufficient to determine status at week 8.

7.3.2. Operating characteristics

The power at each stage has been maintained at a high level (> 0.9) to ensure an effective intervention has a high chance of proceeding beyond I (to minimise the chance of missing a result and not extending recruitment).

A 10% significance level (p=0.1 one-sided) has been chosen for the first stage to allow in an event that the intervention seems to be performing poorly then the sample size will not be increased but stay as planned. At the first stage there is less concern about extending recruitment if the observed interim result is false so a higher than the conventional 5% (2-sided) level is chosen. But, the corresponding power has been chosen as 95% so that there is a high chance of proceeding to the 2nd (and final stage) if there is an indication of a treatment effect on the intermediate outcome measure.

Positive Predictive Value of the Control (PPVC) and of the Intervention (PPVE) were assumed 95%. Other values of PPVC were also considered to explore the sensitivity of the design on this assumed value. This is from a review of the literature and analyses on previously published TB trials [7].

Table 2 outlines the operating characteristics for both I and D.

Table 2. Operating characteristics for interim and final analysis		
	Interim (Phase 2)	Final (Phase 3)
Primary Outcome	Culture negative status	Favourable rate
Follow-up length	8 weeks	12 months
Significance level (1 sided)	10%	2.5%
Power	95%	90%
Control arm event rate	50%	84%
Treatment effect under (H0)	0%	-12% (NI margin)
Treatment effect under (H1)	25%	0%
Allocation ratio (E:C)	1:1	1:1
Attrition rate (LTFU rate)	0%	13%

7.3.3. Sample size calculation

The calculation was conducted in STATA using the NSTAGEBIN command (Appendix §13.4).

Currently, no software allows for selection of a HR at the interim stage and risk difference at the final stage. As such, the treatment effect in I was transformed from a HR to a risk difference for the sample size calculation. Assuming a control event rate of 50%, a HR of 2 was equivalent to an absolute risk difference of 25%.

7.3.4. Decision

The interim analysis will occur after approximately 60 participants randomised to the control arm have reached the 8-week primary endpoint. At the interim stage, a test on the risk difference between the two treatment arms on the I-outcome measure is carried out. The design and decision rule for the first stage was made based on target effect size of 2 on the hazard ratio scale. If the p-value of the test on the I-outcome is less than 0.1, accrual to both arms may continue to the final stage when a test on the D-outcome measure is carried out. Successfully moving to the final stage will mean increasing recruitment to 225 per arm i.e. to a total of 450 DS-TB participants and up to 225 DR-TB participants (if desired). This will adequately power the trial on the new primary endpoint in D with an overall power (both stages combined) of 86%.

7.4. Subgroup Analyses

As exploratory analyses to assess consistency of outcome, the following sub-group analyses (with tests for interaction) of the primary endpoint on the mITT analysis populations will be considered according to:

- HIV status
- Cavitation (images are to be reviewed in order for these data to be considered reliable)

- Age
- Sex
- Race
- Region
- Smoking status
- Alcohol intake
- Pyrazinamide resistance (pending numbers)
- Bedaquiline resistance (pending numbers)
- Time to positivity

7.5. Minimum Inhibitory Concentrations

Minimum inhibitory Concentrations (MICs) for all drugs will be tabulated separately. Baseline will be cross tabulated against end of treatment. If measured at multiple visits, end of treatment will be used. This is for descriptive purposes only.

8. Safety Statistical Analysis

All safety endpoints will be presented descriptively, and no inferential tests will be carried out. AE duration will be calculated as (Stop Date – Start Date) + 1. Partial dates for AEs will not be imputed. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified as treatment-emergent.

At each level of participant summarisation, a participant is counted once within each PT and then each SOC if the participant reports one or more events.

8.1. All-cause mortality

A table will be presented that contains the cause of death as well as the following details about death (Yes/No):

- Death was related to TB
- Death due to treatment failure
- Death was violent or accidental (excluding suicide)
- Death was due to suicide

8.2. Treatment emergent AEs (TEAEs)

8.2.1. Incidence of TEAEs

Summaries of the total number of TEAEs and the number and percentage of participants with at least one TEAE will be provided.

8.2.2. Severity

A summary of TEAEs by maximum severity will be presented in a table. In the TEAE severity table, if a participant reported multiple occurrences of the same TEAE, only the most severe TEAE is presented. TEAEs that are missing severity will be presented in tables as 'Severe' but will be presented in the data listing with a missing severity. A separate table will be presented for 'Grade 3: Severe' or 'Grade 4: Potentially life-threatening' TEAEs.

8.2.3. Drug-related TEAEs

A summary of TEAEs by relationship to study treatment will be presented in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study treatment and specifically for bedaquiline, pretomanid, moxifloxacin, pyrazinamide, and HRZE/HR. The possible relationships are summarised as 'Not Related' (i.e. 'Not Applicable', 'Not related', 'Unlikely') and 'Related' (i.e. 'Possibly', 'Probably', and 'Certainly') in the table and their actual values (i.e. 'Not Applicable', 'Not related', 'Unlikely', 'Possibly', 'Probably', and 'Certainly') in the listing. In the TEAE relationship table, if a participant reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. All TEAEs that have a missing relationship will be presented in the summary table as "Certainly" but will be presented in the data listing with a missing relationship.

8.2.4. Serious TEAEs

Treatment-emergent SAEs will be categorised and presented by SOC and PT in the same manner to that described in §8.2.1. The same summary will be repeated for Bedaquiline, Pretomanid, Moxifloxacin and Pyrazinamide separately.

8.2.5. TEAEs leading to treatment discontinuation or interruption

A summary of TEAEs with action taken with study treatment as 'Permanently Discontinued' for BPaMZ or HRZE/HR will be presented in a table. At each level of participant summarisation, a participant is counted once if the participant reported one or more events.

The same presentation will be provided for interruption of BPaMZ or HRZE/HR ('Action Taken with IMP' is 'Interrupted'). Data will be categorised and presented by SOC and PT in the same manner to that described in §8.2.1.

8.2.6. TEAE leading to study discontinuation

A summary of TEAEs where the answer to action taken' is 'Withdrawn from Study' will be presented in a table. At each level of participant summarisation, a participant is counted once if the participant reported one or more events. Data will be categorised and presented by SOC and PT in the same manner to that described in §8.2.1.

8.2.7. TEAEs leading to death

A summary of TEAEs where the answer to 'Outcome' in the AE form is 'Fatal' will be presented in a table. Data will be categorized and presented by SOC and PT in the same manner to that described in §8.2.1.

8.2.8. Liver-related TEAE

A summary of TEAEs that has preferred terms under "Hepatic disorders" according to MedDRA dictionary will be presented by SOC and PT in the same manner to that described in §8.2.1. In addition, any liver-related TEAE tables will be presented by region, sex, age (< vs. >median), previous alcohol intake and HIV status.

8.2.8.1. Liver and drug-related TEAEs

A summary of liver-related TEAEs that are drug related (i.e. 'Possibly', 'Probably', and 'Certainly') will be presented by SOC and PT for treatment arm and drug in the same manner to that described in §8.2.1.

8.2.8.2. Serious liver-related TEAEs

A summary of TEAEs that are liver related and serious (as described in § 2.3.2.4) will be presented by SOC and PT for treatment arm in the same manner to that described in §8.2.1. Liver enzyme profile plots will be provided for patients with treatment emergent serious adverse events that have toxicity grade 3 or higher for either AST, ALT, ALP or total bilirubin.

8.2.8.3. Incidence of hepatotoxicity

Proportion of participants experiencing at least one liver function test (LFT; AST or ALT) that is ≥3 x ULN or at least one hepatic SAE (as described in §8.2.8). This will be summarised in a table by treatment arm (and combining the BPaMZ arms to give a BPaMZ total). In addition we will summarise for those who have had a hepatotoxicity what their hepatitis status (A, B and C) was at baseline, at the time of the event and the change from baseline to time of event.

8.2.8.4. Predictors of hepatotoxicity

As an exploratory analysis, pending numbers, predictors of having a hepatotoxicity (binary outcome of at least one LFT ≥3xULN or not) will be investigated. Potential predictors will include, but are not limited to, baseline variables (see §7.4 with the addition of weight and BMI) and hepatitis (A, B or C) at baseline. Logistic regression will be used for this binary outcome. If this logistic regression analysis converges and shows any suggestion of a predictor then, pending numbers in each group an ordered logistic regression will be considered using the outcomes as described in Table 3 which lists notable criteria for AST and ALT. If there are no or very small numbers of patients with ≥8xULN then this may be combined with the ≥5-<8xULN group.

8.2.9. Additional TEAE summary

The number and percentage of participants with the following specific TEAEs will be presented: grade 2, 3, or 4 myalgia, and grade 3 or 4 cardiac rhythm disturbances, grade 3 or 4 lipase, pancreatitis, peripheral neuropathy.

All AEs will be presented in a listing, which will specify whether they are treatment emergent or not.

8.3. Clinical Evaluation

8.3.1. Clinical Laboratory Evaluation

A list of laboratory tests (haematology, clinical chemistry, and urinalysis) to be included in the analysis is presented in §7.3 of the protocol. Laboratory assessments done by a central laboratory will be summarised in tables. All summaries will be based on the units provided by the central laboratory, no conversion will be done. The laboratory evaluations will be summarised for baseline, post-baseline, and change from baseline at week 8, end of treatment (week 17 or week 26), 52 week and 104 week FU.

Laboratory values outside normal ranges will be identified, and the number and percentage of participants with at least one post-baseline abnormality will be summarised in shift tables comparing the baseline results to each post-baseline timepoint for those participants with results at both timepoints.

The table below displays the general variables and thresholds of interest. Participants are considered to have notable laboratory abnormalities if his/her response falls within the specified definitions at least once during the treatment period.

Table 3:Notable Criteria for Laboratory Data

Lab Test Type	Laboratory Variable	SI Units
Liver	AST	>3 x ULN and ≤ 5 x ULN >5 x ULN and ≤ 8 x ULN >8 x ULN
	ALT	>3 x ULN and ≤ 5 x ULN >5 x ULN and ≤ 8 x ULN >8 x ULN
	Total Bilirubin	>2 x ULN
	Alkaline Phosphatase (ALP)	>2 x ULN
Chemistry Labs	Other: ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 3 x ULN and total bilirubin > 2 x ULN and ALP < 2 x ULN (potential Hy's law case)	
	Lipase	>2xULN to ≤5XULN >5xULN

8.3.2. Vital Sign Measurements

Vital sign measurements include blood pressures (mmHg) (resting more than 5 minutes), and heart rate (bpm). These measurements will be summarised for baseline and change from baseline at week 8, end of treatment (week17 or week 26), 12 and 24 month follow-up. Only the vital signs collected at the scheduled visits or time points will be included in the summary.

Abnormal vital sign assessment results will be identified, and the number and percentage of participants with at least one post-baseline abnormality will be summarised. General variables and thresholds of interest are outlined in appendix 3 of the protocol.

8.4. Electrocardiogram

All participants will have a standard 12-lead (ECG) assessment (heart rate (HeR), PR interval, RR interval, corrected QTcF intervals (adjusted using Fridericia's correction) performed by a central cardiologist. All summaries will be based on the central cardiologist assessment.

For all ECG parameters (HeR, PR, RR, QTcF), actual values and changes from measurement closest to and prior to dosing at each time point (week 8, end of treatment (week 17 or week 26), week 39 will be summarised using descriptive statistics by treatment group and time of collection.

Post-baseline QTcF intervals will be classified into the following categories:

- QTcF ≤ 450 msec
- 450 msec < QTcF ≤ 480 msec
- 480 msec < QTcF ≤ 500 msec
- QTcF > 500 msec

QTcF changes from baseline will be classified into the following categories:

- increase > 0 msec and ≤ 30 msec,
- increase >30 msec and ≤ 60 msec, and
- increase > 60 msec.

Number and percentage of notable maximum QTcF interval and change from baseline QTcF interval will be summarised.

Interpreted ECG results based on CRF investigator assessment will be classified as "normal", "abnormal, not clinically significant", or "abnormal, clinically significant". The number and percentages of participants with normal, abnormal not clinically significant, and abnormal clinically significant will be presented. In addition, shift tables will be provided to summarise the status changes from baseline to week 8, end of treatment, 12 and 24 month follow-up assessments.

Patients with any QT or QTcF values >=500 that resulted in early withdrawal will be presented in a figure.

8.5. Male Reproductive Hormone Tests

Descriptive summary statistics by treatment arm will be presented for each of testosterone, follicle-stimulating hormone, luteinizing hormone, and inhibin B. These will only be presented for those participants who have had these tests carried out at an official timepoint. Any participant who has had these tests carried out outside the official windows will not be included. The timepoints are as follows: screening and baseline (Day 1) results to be displayed together taking the average of the two, end of treatment (week 17 or week 26) and week 39 follow-up. Change from baseline (average of screening and day 1) for each reproductive laboratory parameter will be presented at end of treatment (week 17 or week 26) and 9 month follow-up by treatment arm.

8.6. Lens Opacity Tests

Descriptive summary statistics by treatment arm will be presented for Ophthalmology slit lamp examinations (lens opacity classification and grading) for each of cortical, nuclear and posterior subcapsular lens opacities at screening, baseline (Day 1), end of treatment (week 17 or week 26) and week 39 follow-up. Change from baseline for each lens opacity parameter will be presented at end of treatment (week 17 or week 26) and 6 month follow-up by treatment arm.

8.7. Pharmacokinetics/Pharmacodynamics

Descriptive statistics (n, arithmetic mean, standard deviation (SD), coefficient of variation (CV%), median, minimum and maximum, geometric mean and geometric CV (%)) will be used to summarise the plasma concentration at each scheduled sampling time/window per analyte. The geometric mean is obtained by computing the arithmetic mean of the logarithm-transformed values of concentration and then using the exponentiation to return the computation to the original scale. Geometric CV(%) is calculated as follows: CV (%)=Square root of [exp($\hat{\sigma}^2$) – 1] * 100, where $\hat{\sigma}^2$ denotes the variance of the log-transformed values.

For a concentration value below the limit of quantitation (BLQ), a concentration value of zero is included for the computation of arithmetic mean and a concentration value of 50% the lower limit of quantitation (plasma LLOQ = x.xx units) is included for the computation of geometric mean. If 50% or more of the values are BLQ at one timepoint, the arithmetic mean and geometric mean is reported as BLQ. If the calculated arithmetic mean and/or geometric mean are less than LLOQ, the arithmetic mean and/or geometric mean are reported as BLQ.

Derivation of PK/PD parameters described in the protocol Section 9.6 and 9.7 will be covered in a separate modelling SAP.

9. Participant Disposition

9.1. Participant Disposition

Participant disposition for all participants who signed informed consent will be presented as follows:

- No. of participants screened, screen failed, randomised, and received at least one dose of treatment.

- Of those receiving at least one dose, the number and proportion who completed the IMP, who discontinued IMP, who completed the study, who discontinued from the study. The reasons for discontinuation of IMP and study participation will also be summarised.

9.2. Study protocol deviations

All major deviations will be summarised by deviation type for all ITT participants.

10. Demographics and baseline characteristics

The following demographics and baseline characteristics will be summarised using the ITT population. Number and percentage will be reported, unless otherwise noted.

10.1. Demographics

Age (years), height (cm), weight (kg), and body mass index (BMI) (kg/m^2) will be summarised as continuous variables. BMI is defined as the participant's weight (kg) divided by the square of their height (m). The number and percentage of participants will be presented for categorical variables including race (Asian, Black or African American, White, Mixed Race, Native Hawaiian or Other Pacific Islander, Other), region (EMEA, EMEA (South Africa sites only), Asia, South America), and sex (male, female).

10.2. Baseline characteristics

- History of TB (type) (DS-TB, Mono-Resistant TB, MDR TB, PRE-XDR TB, XDR TB)
- Current TB type (DS-TB, DR-TB)
- Smoking status (never, current, former)
- Alcohol status (never, current, former)
- Screening mycobacteriology test result
    - Smear microscopy for acid-fast bacilli (AFB) (no AFB seen, scanty positive, 1+, 2+, 3+)
    - Rapid molecular tests for fluoroquinolones, aminoglycosides-cyclicpeptides, isoniazid, and rifampicin resistance (Hain assay MTBDRplus and MTBDRsl (sensitive, resistant, indeterminate, not done)) and MTB confirmed (Yes, No)
    - Liquid culture (MGIT) mycobacterium tuberculosis (MTB) result (negative, positive for MTB complex, positive for MTB complex with contamination, contaminated, no result) and time to positivity when positive.
- Serology
    - HIV status (positive, negative as collected in CRF)
    - CD4 count (summary statistics)
- Karnofsky performance status
- Chest X-ray (normal, abnormal)
    - Cavities (none, unilateral, bilateral)
- Ophthalmologic history
    - History of vision and/or eye disorders (yes, no)
    - Immediate family history of cataracts (yes, no)
    - History of prior eye surgery and/or trauma (yes, no)

10.3. Medical History

Medical history will be coded using the latest version of Medical Dictionary for Drug Regulatory Activities (MedDRA). The number and percentage of participants with clinically significant medical/treatment history will be summarised by system organ class (SOC) and preferred term (PT). Percentages will be calculated based on number of participants in the ITT analysis set.

10.4. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria can be referenced in the protocol, Sections 5.1 and 5.2, respectively. Any participant who violates the inclusion and/or exclusion criteria (screen failures as well as late screen failures) will be presented in a listing.

11. Treatment and Medications

11.1. Prior and Concomitant Medications

For the purpose of inclusion in prior and/or concomitant medication summary tables, incomplete medication start and stop dates will be imputed as follows:

Missing start dates will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: impute to 01-MMM-YYYY;
- UK-UKN-YYYY: impute to 01-JAN-YYYY;
- UK-UKN-UNKN: impute to date of initial screening.

Missing stop dates will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- UK-UKN-YYYY: Assume 31-DEC-YYYY;
- UK-UKN-UNKN: Assume last day of study visit.

All medications will be coded according to the latest version of World Health Organization drug dictionary. Summaries on prior and concomitant medication will be performed using the ITT set. Data on prior and concomitant medications will be presented in a listing.

11.1.1. Prior Medications

A prior medication is defined as any medication that has a stop date before the start of the study drug (prior to Day 1). Prior medications collected in the CRF will be classified as TB medications and non-TB medications. The number and percentages of participants with at least one prior medication will be summarised separately for TB medications and non-TB medications. Prior medications will be summarised by Anatomical Therapeutic Chemical classification 4 (ATC4) if used by >10% of participants. .

11.1.2. Concomitant Medications

A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of study treatment (Day 1). The number and percentages of participants with at least one concomitant medication will be summarised. Concomitant medication will also be summarised by ATC4 classification if used by >10% of participants.

11.1.3. Concomitant Procedures

A concomitant procedure is defined as any procedure that has a date that is on or after the date of first dose of study treatment (Day 1). The number and percentages of participants with at least one concomitant procedure will be summarised. Concomitant procedures will be summarised by MedDRA higher level term if carried out on >5% of participants.

11.1.4. Study Treatment Exposure

A participant's drug exposure in days will be defined as (date of last dose - date of first dose +1). Drug exposure in weeks will be calculated by dividing the exposure in days by 7. The date of last dose is the last available date in the study medication page, if missing then the date of last dose in the disposition treatment page will be used.

The duration of exposure to IMP and its category (4BPaMZ: <17 weeks, ≥17 weeks and 6BPaMZ: <17 Weeks, ≥17 to <26 Weeks, ≥26 Weeks) by treatment will be summarised for all participants in the safety set and will be presented in a table by summary statistics.

The following exposure parameters will be summarised according to the general methods:

- HRZE-HR pause (number and percentage of participants with at least one dose pause and number of dose pauses, reason for dose pause). The HRZE-HR pause information will be retrieved from the CRF Exposure HRZE-HR Dosing pages indicated by a pause.
- BPaMZ pause (number of participants with at least one dose pause and number of participants with at least one pause). The BPaMZ pause information will be retrieved from the CRF Exposure BPaMZ dosing pages indicated by a pause.

12.References

1. Phillips, P.P.J., et al., *A comparison of liquid and solid culture for determining relapse and durable cure in phase III TB trials for new regimens.* BMC Med, 2017. **15**(1): p. 207.
2. Gillespie, S.H., et al., *Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis.* N Engl J Med, 2014. **371**(17): p. 1577-87.
3. Tiemersma, E.W., et al., *Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review.* PLoS One, 2011. **6**(4): p. e17601.
4. Parmar, M.K., et al., *Testing many treatments within a single protocol over 10 years at MRC Clinical Trials Unit at UCL: Multi-arm, multi-stage platform, umbrella and basket protocols.* Clin Trials, 2017. **14**(5): p. 451-461.
5. Bratton, D.J., P.P. Phillips, and M.K. Parmar, *A multi-arm multi-stage clinical trial design for binary outcomes with application to tuberculosis.* BMC Med Res Methodol, 2013. **13**: p. 139.
6. Royston, P., et al., *Designs for clinical trials with time-to-event outcomes based on stopping guidelines for lack of benefit.* Trials, 2011. **12**: p. 81.
7. Bratton, D.J., *Design issues and extensions of multi-arm multi-stage clinical trials*. 2015, UCL (University College London).
8. Jindani, A., et al., *High-dose rifapentine with moxifloxacin for pulmonary tuberculosis.* N Engl J Med, 2014. **371**(17): p. 1599-608.
9. Lienhardt, C., et al., *Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial.* JAMA, 2011. **305**(14): p. 1415-23.

13.Appendix

13.1. Derived MGIT results per visit

Table A13.1: Derived MGIT results per visit

Derived sample Culture 1 (Visit X)	Derived Sample Culture 2 (Visit X)	Final Derived Result for Visit X
Positive	Missing/Negative/Contaminated	Positive
Negative	Missing/Contaminated	Negative
Contaminated/missing	Missing/Contaminated	Missing

13.2. Interpretation of Relapse/Reinfection using Whole Genome Sequence (WGS)

The purpose of the WGS analysis is to determine if the two M. tuberculosis strains from a given participant (positive culture at baseline and at or after the end of treatment) can be considered the **same** (treatment failure/bacteriologic failure or relapse/bacteriological relapse), or **different** (reinfection/bacteriological reinfection).

To do this, WGS of the two M. tuberculosis strains are compared, the number of SNPs/variants determined, and the criteria outlined below followed.

These cut offs have been determined from previously published reports (REMoxTB [2] and RIFAQUIN [8] trials) that show a clear genetic distinction between relapse and reinfection cases of M.tb infection.

≤12 SNPs different = Relapse

≥100 SNPs different = Reinfection

>12 and <100 SNPs different = Indeterminate

Indeterminate results will be reviewed on case by case basis and are likely to be rare.

Additional sequence analysis may be performed and/or additional samples may need to be tested.

Any additional investigations will be documented on the 'WGS Indeterminate Proforma' which also includes the final conclusion of 'relapse' or reinfection' based on this further review.

A participant will be considered a relapse unless there is sufficient evidence to support a classification of reinfection.

13.3. TB-mITT population

In the TB field, the combination of bacteriologic cure rates approaching 100% and required long-term follow up has meant that recorded negative outcomes are very much contaminated with the "noise" of missing data.

There is a clear precedent for this analytic approach, and those trials also provide examples of why the inclusion of the losses to follow-up as unfavourable outcomes can affect the results. Data from the Priftin trial which led to accelerated approval of rifapentine and a trial conducted by the International Union Against TB & Lung Disease (IUATLD) in African and Asian sites illustrate the problems associated with classifying all losses to follow-up and deaths as having an unfavourable outcome [9]. In the Priftin trial bacteriological relapses occurred in 5% of participants on the rifampicin based regimen compared to 11% on the rifapentine based regimen. Approximately one third of participants were lost to follow-up and when this group combined with participants unassessable for other reasons were added to the bacteriological failures, the rates increased to 53% and 57% respectively. The true bacteriological relapses were greatly outnumbered by these other groups. At the time of the licensing submission to the FDA it was recognised that because there were a substantial number of participants likely to be unassessable the main focus should be on the relapse rates. In the final statistical report, the results were first reported excluding those unassessable and then assuming all losses follow-up had an unfavourable outcome and finally assuming all losses to follow-up had a favourable outcome.

In a study conducted by the IUATLD the published failure/relapse rates 12 months after stopping treatment based on 1044 assessable participants were 5% for the control regimen and 10% and 14% in each of the experimental arms. If the 311 unassessable participants were considered to have an unfavourable outcome these rates would have increased to 24%, 32% and 35%, respectively. The 311 unassessable participants were not evenly distributed across the three trial arms. There were 42 deaths, of which 20 occurred in one of the experimental arms (the more efficacious of the two) and 11 in each of the other, a difference which was not considered to be due to the treatment, but due to chance. There were also imbalances among those without a bacteriological assessment (7 in one arm versus 19 and 22 in the other two arms) and in the distribution of losses to follow-up.

Hence the adaptation to this situation in publications, generally replacing what is usually considered mITT analyses in the TB field with TB-mITT analyses.

13.4. STATA code for interim analysis sample size

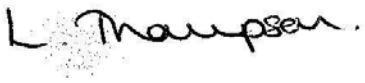
```
nstagebin, nstage(2) arms(2 2) alpha(0.1 0.025) power(0.95 0.9) theta0(0 -0.12) theta1(0.25 0)
ctrlp(0.5 0.84) ppvc(0.95) ppve(0.95) accrate(200 200) fu(0.27 1.0) extrat(0.075) ltfu(0 0.13) tunit(1)

n-stage trial design                version 1.0.1, 17 Jul 2014
----------------------------------------------------------------
Sample size for a 2-arm 2-stage trial with binary outcome based
on Bratton et al. (2013) BMC Med Res Meth 13:139
----------------------------------------------------------------

Control arm I (D) event rate = 0.50 (0.84)
Delay in observing I (D) outcome = 0.27 (1.0) years
Attrition rate for I (D) outcome = 0.00 (0.13)

Operating characteristics
------------------------------------------------------------------------
        Alpha(1S)    Power  theta|H0  theta|H1   Length*    Time*
------------------------------------------------------------------------
Stage 1     0.1000    0.950    0.000    0.250    0.945    0.945
Stage 2     0.0250    0.900   -0.120    0.000    2.375    3.320
Pairwise    0.0250    0.860                       3.320
------------------------------------------------------------------------
 *  Length (duration of each stage) is expressed in year periods

Cumulative sample sizes per arm per stage
                 ---------Stage 1---------  ---------Stage 2---------
                 Overall  Control   Exper.  Overall  Control   Exper.
--------------------------------------------------------------------------------
Number of active arms       2       1       1       2       1       1
Accrual rate*           200.0    100.0    100.0    200.0    100.0    100.0
Patients for analysis     120       60       60      392      196      196
Patients recruited**      190       95       95      450      225      225
--------------------------------------------------------------------------------
 *  Accrual rates are specified in number of patients per year
 ** Accounts for loss-to-follow-up rate and includes those recruited during follow-up periods


.
end of do-file
```

NtF1 “Positive with contamination” culture results

This is to clarify that MGIT cultures with the final result “positive with contamination” were considered to be positive when determining culture conversion status.

The SAP section 3.1.1 should read “The MGIT culture results that are contaminated or with no result will be treated as missing” instead of “The MGIT culture results that are positive with contamination, contaminated, or with no result will be treated as missing.”

The extra words were inserted in error between SAP version 2.0 (“False positive or contaminated sputum cultures, without speciation data confirming presence of M.tb, will be treated as missing.”) and version 3.0 (“The MGIT culture results that are positive with contamination, contaminated, or with no result will be treated as missing.”).

Signed  Date: 11th November 2021

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NtF2 Reporting of TEAEs under SMQs

This note to file clarifies the reporting of TEAEs under the SMQs.

The SimpliciTB SAP v3.0 (dated May 2021) section 8.2.9 states:

"The number and percentage of participants with the following specific TEAEs will be presented separately: grade 2, 3 or 4 myalgia, grade 3 or 4 cardiac rhythm disturbances, grade 3 or 4 lipase, pancreatitis, peripheral neuropathy and myelosuppression."

Section 8.2.9 should have said:

"The number and percentage of participants with the following specific TEAEs will be presented separately: grade 2, 3 or 4 myalgia, grade 3 or 4 cardiac rhythm disturbances, pancreatitis, peripheral neuropathy and myelosuppression."

In addition, the following should have been included in the SAP:

"Following an SMQ analysis of the adverse events using the online MedDRA SMQ Analysis tool, the number and percentage of participants with TEAEs falling under the following SMQs will be presented":

SMQ Category	SMQ Analysis Rule
Hepatic Event	All PTs under SMQ (hepatic disorder)
Seizure (neurological)	All PTs under SMQ (Convulsions)
Peripheral Neuropathy	All PTs under SMQ (peripheral neuropathy)
Lactic Acidosis	All PTs under SMQ (lactic acidosis)
Pancreatitis, Amylase elevation, Lipase elevation	All Narrow PTs and broad B terms under acute pancreatitis SMQ
Optic neuropathy	All PTs under SMQ (optic nerve disorder)
Myelosuppression	All PTs under SMQ (Haematopoetic cytopenias)
Cardiac Rhythm Disturbances	All PTs under SMQ (Cardiac arrhythmias)
Musculoskeletal System (Myalgia)	All PTs under SMQ (Rhabdomyolysis/myopathy), excluding the following PTs:
	Creatinine renal clearance decreased
	Hypocalcaemia

Signed L. Thompson Date: 11th November 2021

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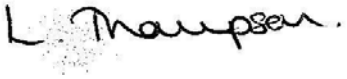
NtF3 Liver Enzyme Plots

This note clarifies the drawing of the liver enzyme plots.

The SimpliciTB SAP v3.0 (dated May 2021), section 8.2.8.2 states:

"Liver enzyme profile plots will be provided for participants with treatment emergent serious adverse events that have toxicity grade 3 or higher for either AST, ALT, ALP or total bilirubin."

This was intended to be in section 8.2.8.2 and read:
"Liver enzyme profile plots will be provided for participants with laboratory tests with toxicity grade 3 or higher for AST or ALT. These plots will include ALT, AST, ALP, and total bilirubin."

Signed  Date: 11th November 2021

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