16.1.9 Documentation of Statistical Methods

ZeNix SAP Safety, Version 1.0, 27Oct2017

ZeNix SAP Efficacy, Version 1.0, 15Sep2017

ZeNix SAP, Version 2.0, 11Aug2020

ZeNix SAP, Version 3.0, Jan2021

Global Alliance for TB Drug Development

NC-007-(B-Pa-L)

A Phase 3 partially-blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).

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Final Safety Statistical Analysis Plan

Version *1.0*

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DOCUMENT REVISION HISTORY

Version	Date	Remarks
0.1	17AUG2017	Initial version
0.2	08SEP2017	Updates based on client review of initial version
0.3	26OCT2017	Updates based on client comments on Version 0.2
1.0	27OCT2017	Final version

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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
AT	Aminotransferase
AUC_{τ}	Area Under Curve Over a Dosing interval
B	Bedaquiline
BMI	Body Mass Index
bpm	Beats per Minute
BPNS	Brief Peripheral Neuropathy Scale
CK(-MB)	Creatine Kinase(-MB isoenzyme)
$C_{(max), (min)}$	Plasma Concentration (maximum), (minimum)
CO_2	Carbon Dioxide
CPK	Creatine Phosphokinase
C_{trough}	Trough Plasma Concentration
DMID	Division of Microbiology and Infection Disease
DSMC	Data Safety Monitoring Committee
DST	Drug Sensitivity Testing
ECG	Electrocardiogram
(e)CRF	(electronic) Case Report Form
GGT	Gamma-glutamyl Test
HIV	Human Immunodeficiency Virus
HGB	Hemoglobin
ITT	Intent to Treat
IXRS	Interactive Voice and Web Response System
kg	Kilogram
L	Linezolid
LDH	Lactate dehydrogenase
MIC	Minimum Inhibitory Concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi Drug Resistant Tuberculosis
mg/dl	Milligrams per Deciliter
MGIT™	Mycobacterial Growth Indicator Tube
mITT	Modified Intent to Treat
Pa	Pretomanid
PD	Pharmacodynamic
PP	Per Protocol
PK	Pharmacokinetic
PR	PR Interval
RBC	Red Blood Cell

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Events
T>MIC	Time Above Minimum Inhibitory Concentration
(BA) TTP	(Bacteriocidal Activity) Time to Positivity
ULN	Upper Limit of Normal
WHO	World Health Organization
WBC	White Blood Cell
XDR-TB	Extensively Drug Resistant Tuberculosis

1. Introduction

This study is being conducted under the sponsorship of TB Alliance. The clinical monitoring, data management, and statistical analysis are being performed under contract with PPD, in collaboration with TB Alliance. A separate analysis plan for evaluation of efficacy will be developed and will not be included in this statistical analysis plan (SAP).

The Clinical, Data Management, and Biostatistics departments at PPD will work diligently and collaboratively, internally and with the Sponsor, to ensure that the data collected and analyzed for this study are of the highest quality possible. This will be accomplished in part by having thorough edit checks written, programmed, and updated as needed to guarantee high quality data. Edit checks will be reviewed by the statistician on an ongoing basis to evaluate whether any need to be added.

This SAP is based on the protocol versions 1.0 dated 23Feb2017 and 1.0 RUS/BEL dated 28Feb2017.

Tuberculosis (TB) is the world's leading infectious disease killer and is responsible for more deaths than Human Immunodeficiency (HIV). It is the leading cause of death among HIV-infected individuals, and there is more TB in the world today than at any other time in history. As a result of poor treatment adherence, in addition to primary transmission, drug resistance is becoming more common and fears of an epidemic with strains of extensively drug resistant TB (XDR-TB) that is very difficult to treat are growing. Novel drugs and regimens for TB are needed for the growing number of patients with XDR-TB.

The regulatory approvals of bedaquiline and delamanid have given hope that outcomes for patients with XDR-TB might be improved when added to background regimens. Linezolid was identified in a small study as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen and this drug has increasingly been added to complex regimens to treat patients with multi-drug resistant tuberculosis (MDR-TB). With the current availability of three drugs for which there is little, if any, pre-existing resistance among strains of *Mycobacterium tuberculosis* (MTB) (pretomanid [Pa], bedaquiline [B], and linezolid [L]), there is the opportunity to evaluate a new regimen that may be administered orally once daily to treat patients with XDR-TB. A key advantage of this regimen over standard of care for MDR-TB, as well as XDR-TB, is that this is an all-oral daily regimen for 6 months of treatment, in comparison to standard regimens of 6-8 drugs over 9-30 months of treatment that include daily injections for a minimum of 6 months.

This trial will provide a regimen containing 3 drugs against which there is no expected MTB resistance in the community for patients with limited treatment options, while simultaneously gathering important efficacy and safety data on a regimen that could potentially treat all strains of MTB. Data from previous trials shows that the combination of B-Pa is well tolerated and has the potential to shorten treatment in patients who are susceptible to the drugs. The ongoing Nix-TB trial has shown that the B-Pa-L regimen has manageable toxicity and encouraging efficacy as an all oral 6 month regimen administered to patients with XDR-TB. This current trial will provide important information on the toxicity and efficacy of the regimen under alternate doses and durations of linezolid to optimize the dosing scheme for the best benefit to risk balance.

2. Objectives

The objective of this study is to evaluate the efficacy, safety and tolerability of various doses and durations of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with either pulmonary XDR-TB, pre-XDR-TB, or treatment intolerant or non-responsive MDR-TB.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 3, multi-center, partially-blinded, randomized clinical trial conducted in 4 treatment groups (Section 3.3). Patients, trial investigators and staff, including laboratory staff, will be blinded to dose and scheduled duration of linezolid. Bedaquiline and pretomanid dosing will not be blinded.

The trial will be performed at multiple centers located in South Africa, Eastern Europe and Russia. A total of 120 XDR-TB and up to 60 Pre-XDR/MDR treatment intolerant or non-responsive patients who meet all of the inclusion criteria and none of the exclusion criteria, aged 14 and over (aged 18 and over in Russia and Belarus), will be randomized to receive 1 of the 4 active treatment arms. Enrolment will stop when 120 XDR-TB patients are randomized. Patients will be randomized after they have given written informed consent and met all eligibility criteria.

Each patient will receive 26 weeks of treatment. If a patient's week 16 sample remains culture positive, the Investigator may consider an option to extend current treatment to 39 weeks, in consultation with the Sponsor Medical Monitor. Patients will be followed for 78 weeks after end of treatment. The schedule of events at Section 1.2 of the protocol provides more details.

3.2. Study Endpoints

3.2.1. Primary Endpoint

Details of the primary endpoint can be found in the Efficacy SAP.

3.2.2 Secondary Endpoints

Details of the secondary endpoints can be found in the Efficacy SAP.

3.2.3 Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD)

This SAP will only handle descriptive summaries of plasma drug concentrations and PK parameters. Details on further analysis of PK and PK/PD endpoints can be found in the PK/PD modelling SAP.

3.2.4 Safety and Tolerability

- All-cause mortality.
- Incidence of treatment emergent adverse events (TEAEs) by drug relatedness and seriousness, leading to early withdrawal from treatment, leading to pauses of linezolid, leading to linezolid reductions and leading to death.
- Quantitative and qualitative clinical laboratory result measurements, including observed and change from baseline.

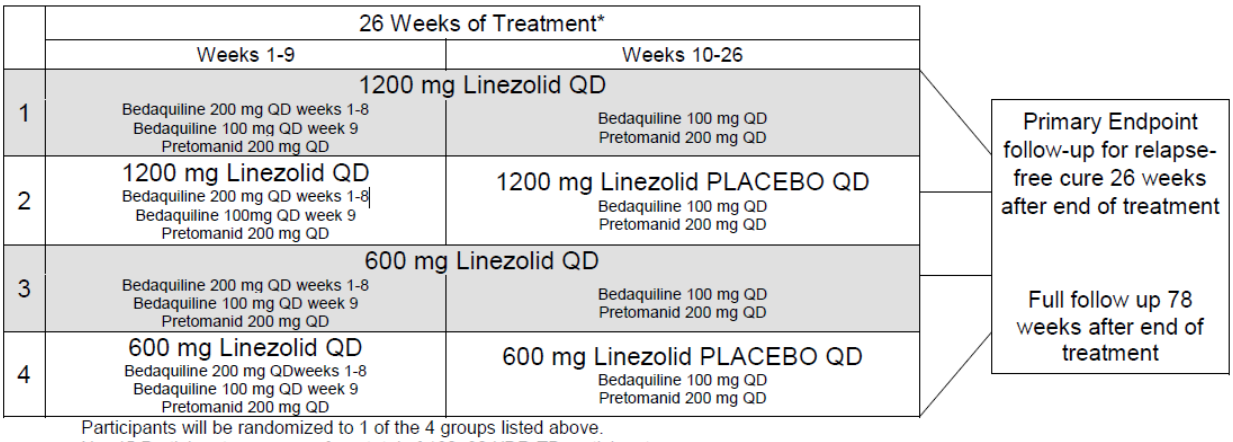
- Quantitative and qualitative measurement of electrocardiogram (ECG) results read by a central cardiology service, including observed and change from baseline.
- Ophthalmology slit lamp examination results (age related eye disease study 2 [AREDS2]) lens opacity classification and grading) for the right and left eye, including observed and change from baseline.
- Changes in ophthalmic exam for visual acuity and color vision, including observed and change from baseline.
- Changes noted in peripheral neuropathy signs and symptoms, including observed and change from baseline.

3.3 Treatments

The test product will be supplied as:

- bedaquiline 100 mg tablets
- pretomanid 200 mg tablets
- linezolid (scored) 600 mg tablets
- placebo linezolid (scored) 600 mg tablets
- linezolid half tablet (pre-cut) 300 mg (needed for blinded dose reductions)
- placebo linezolid half tablet (pre-cut) 300 mg (needed for blinded dose reductions)

Linezolid treatment will be supplied as 2 rows of full tablets and one row of half-tablets to allow for all possible dosing options while maintaining the blind. Treatment will be administered orally, once daily, with a full glass of water and a meal in the following dosing schemes (treatment groups):



Participants will be randomized to 1 of the 4 groups listed above.
N = 45 Participants per group for a total of 180. 30 XDR-TB participants per group
* Treatment will be extended to 39 weeks for participants who have a positive culture at week 16

4 General Statistical Considerations

All summary tables will be presented by treatment group and total, unless otherwise specified. The treatment grouping will be:

Linezolid 1200mg		Linezolid 600mg		Total
26 weeks (N=XXX)	9 weeks (N=XXX)	26 week (N=XXX)	9 weeks (N=XXX)	(N=XXX)

The following conventions will be used for all data presentations and analyses unless otherwise specified.

Variables will be summarized by scheduled study visit where appropriate. If there are multiple assessments in a visit, the latest non-missing value within a visit will be used in the summaries. For the categorical variables, the counts and percentages of each possible value will be tabulated by treatment group and total. For continuous variables, summaries will include the number of patients with non-missing values (n), mean, median, SD, minimum, and maximum values. Change from baseline values will be summarized where applicable. Means and medians will be presented to 1 more decimal place than the recorded data. Standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Minimum and maximum values will be reported with the same precision as the raw data.

All data from all sites will be pooled. No inferential tests will be carried out.

There will be no specific strategy to deal with missing data. In categorical summaries, a missing category will be included if and only if any data for the given endpoint are missing.

Percentages will be computed based on the number of non-missing data points for patients in the applicable analysis set. Percentages will be reported to one decimal place, and 0% will not be presented.

For the individual patient listings, all data will be listed by treatment group, center, patient identifier (ID), HIV status, and XDR status. Study day will be presented where appropriate. Any repeat assessments or additional assessments, along with any unscheduled visits, will be presented in the listings. Sort order of data listings will be treatment group, ID, and visit date.

All statistical safety analyses tables, listings and figures will be produced using SAS® Version 9.2, or higher.

A separate document, as an appendix to this SAP, will contain the mockup tables, listings, and figures (TLF shells).

4.1 Definition of Study Days and Baseline

Study Day 1 is defined as the date on which a patient 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 the endpoints, baseline is defined as the last non-missing measurement prior to first dose of study treatment unless otherwise stated.

4.2 Sample Size

In order to fulfil the objective of the study, it is planned to randomize 30 XDR-TB patients per treatment group and up to 15 pre-XDR and/or MDR treatment intolerant/non-responsive -TB patients per group. A sample size of 30-45 per arm will provide more than 90% power to demonstrate that the lower bound of the 95% confidence interval of this estimate is greater than 50%, using a 2-sided 5% significance level. This assumes that the true cure rate is 80 percent.

4.3 Randomization, Stratification, and Blinding

Patients will be randomized to 1 of the 4 regimens in a 1:1:1:1 ratio, using an interactive voice/web response system (IXRS), stratified by HIV status and type of TB. A total of up to 180 patients will be enrolled: 120 (30 per treatment arm) XDR-TB patients, and up to 60 (15 per arm) pre-XDR or treatment intolerant/non-responsive MDR pulmonary tuberculosis patients, male and female, aged 14 and over. Replacement of late screen failure and un-assessable patients may be considered by the Sponsor.

The blind must not be broken except in the case of a medical emergency, where treatment of the patient is influenced by the knowledge of what dose and duration of linezolid the patient is receiving. It is requested that the Investigator make every effort to contact the Sponsor Medical Monitor (or designee) prior to breaking the blind. IWRS will be programmed with blind-breaking instructions, described in the user manual. The Sponsor reserves the right to break the blind in order to fulfil any regulatory requirements regarding reporting of serious adverse events (SAEs).

In the absence of any medical emergencies requiring a blind break, the blind for all patients will be broken once all clinical data and outcome parameters have been captured, no more data queries are pending and the statistical analysis plan has been finalized.

4.4 Analysis Set

4.4.1 Intent-to-Treat (ITT)

The ITT analysis set is defined in the efficacy SAP.

4.4.2 Safety

The safety analysis set will include all randomized patients who received at least one dose of study treatment. Patients will be analyzed as to the treatment they actually received.

4.4.3 Modified Intent-to-Treat (mITT) and Per-Protocol (PP)

The mITT and PP analysis sets are defined in the efficacy SAP.

5 Patient Disposition

5.1 Disposition

See the efficacy SAP for the details on how the patient disposition are to be presented. However, for this SAP, a listing containing all patient disposition data will be included.

5.2 Protocol Deviations

All major and minor deviations will be summarized by deviation type for all ITT patients. A listing of all protocol deviations will be provided as well. A blinded review of the deviation log collected by the clinical group, as well as a programmatic listing of study deviations to determine major and minor protocol deviations, will be conducted between soft and hard database lock. The protocol deviations will be approved by TB Alliance, and the deviation log with the classification of deviation will be provided to PPD. For the details on how the major and minor deviations determine patient exclusion and inclusion into ITT, MITT and PP analysis sets, please refer to the efficacy SAP.

6 Demographics and Baseline Characteristics

6.1 Demographics

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

Demographics will be summarized for the ITT and safety sets. A patient listing of demographics will also be provided.

6.2 Baseline Characteristics

The following baseline characteristics will be summarized using the ITT set. Number and percentage will be reported, unless otherwise noted.

- History of TB (type) (drug sensitive, MDR TB, XDR TB)
- Current TB type (MDT-TB (NR), MDR-TB (TI), pre-XDR-TB, XDR-TB)
- Smoking status (never, current, former)
    - Type (cigarettes, cigars, smokeless tobacco)
    - Amount consumed (per day, per week, per month, per year)
    - Duration of use (summary statistics)
- Alcohol use (never, current, former)
    - Type (beer, wine, spirits)
    - Amount consumed (per day, per week, per month, per year)
    - Duration of use (summary statistics)
- Screening Coached Spot Sputum result
    - Smear microscopy for acid-fast bacilli (no AFB seen, scanty positive, 1+, 2+, 3+)
    - Hain assay MTBDRplus or equivalent result (sensitive, resistant, indeterminate, not done)
    - Gene Xpert Rifampicin resistance result (sensitive, resistant, indeterminate)
- HIV status (as collected in CRF)
    - Viral load (IU/mL) (summary statistics)
    - CD4 count (cells/µL) (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 (yes, no)
    - History of trauma to their right eye (yes, no)
    - History of trauma to their left eye (yes, no)

All baseline characteristics will be presented in a listing.

6.3 Medical History

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

A patient medical history data will be presented in a listing.

6.4 Inclusion and Exclusion Criteria

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

7 Treatments and Medications

7.1 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.

7.1.1 Prior Medications

A prior medication is defined as any medication that has a stop date that was used before the start of the trial (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 patients with at least one prior medication will be summarized separately for TB medications and non-TB medications. Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification 1 and 3 and preferred drug term.

7.1.2 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. The number and percentages of patients with at least one

concomitant medication will be summarized. Concomitant medication will be summarized by ATC 1 and 3 and preferred drug term.

7.1.3 Concomitant Procedures

The number and percentages of patients with at least one concomitant procedure will be summarized. In addition, concomitant procedures will be summarized by SOC and PT and raw data will be presented in a listing.

7.2 Study Treatments

A patient'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.

The duration of exposure to study treatment by treatment will be summarized for all patients in the safety set and will be presented in a table by summary statistics. The duration of exposure will then be classified into categories "<26 weeks", "26 to ≤39 weeks", or ">39 weeks" and will be presented by number and percentage of patient in each duration category. Percentages will be computed from the number of patients in the safety set.

Drug compliance (%) for bedaquiline and pretomanid will be collected from the eCRF and summarized using descriptive statistics. Number and percentage of patients in each compliance category (<80%, 80 to <90%, ≥90%) will be presented. Percentages will be calculated out of the number of patients who were dosed at that dosing period in the safety set. Linezolid exposure data will not be included in the compliance determination since patients are allowed to stop/re-start administration.

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

- Treatment extension (number of subjects with treatment extended to 39 weeks). The treatment extension information will be retrieved from the CRF Treatment Extension page.
- Linezolid pause (number and percentage of patients with at least one dose pause, number of dose pauses, reason for dose pause). The Linezolid pause information will be retrieved from the CRF IMP Dosing pages indicated by a pause of Linezolid and scheduled dispense of Bedaquiline and Pretomanid.
- Linezolid dose reduction (number of patients with at least one dose reduction, number of patients with at least one 1-step dose reduction, number of patients with at least one 2-step dose reduction, number of dose reductions including the number of 1-step decrease in dose and 2-step decrease in dose, reason for dose reduction).
- Patients experiencing suspected drug related toxicities due to B-Pa treatments can have the full study medication paused for up to 35 consecutive days. Full regimen pauses will be summarized by number and percentage of patients with at least one full regimen pause, number of full regimen pauses and reason for regimen pause. Information related to these are found on the CRF IMP Dosing pages as pause selected on each dosing page, Linezolid, Bedaquiline and Pretomanid.

A summary of each patient's exposure will be presented in a listing.

8 Efficacy Analysis

The efficacy analysis is detailed in the efficacy SAP.

9 Safety Analysis

All safety summaries will be presented for all patients in the safety analysis set, unless otherwise stated.

9.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as adverse events (AEs) which started at or after the first administration of study treatment and includes those events started prior to the first administration of study treatment but which worsened after the first intake. Adverse events starting after the last administration of study treatment until the last scheduled visit/assessment/measurement will be regarded as treatment-emergent.

Adverse event verbatim reported terms will be coded by SOC and PT using the latest version of MedDRA.

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.

An overview summary of the number and percentage of patients with any TEAEs, severe TEAEs, drug-related TEAEs, TEAEs related to linezolid, TEAEs related to bedaquiline, TEAEs related to pretomanid, serious TEAEs, TEAEs leading to discontinuation of linezolid, TEAEs leading to discontinuation of full regimen, TEAEs leading to reduction of linezolid, TEAEs leading to interruption of linezolid, TEAEs leading to interruption of full regimen, TEAE leading to study discontinuation, and TEAE leading to death will be provided. In addition, the number and percentage of patients with the following specific TEAEs will be presented: serotonin syndrome, grade 2, 3, or 4 myalgia, grade 3 or 4 cardiac rhythm disturbances, peripheral neuropathy, optic neuropathy, myelosuppression and lactic acidosis.

9.1.1 Incidence of TEAEs

Summaries of the total number of TEAEs and the number and percentage of patients with at least one TEAE will be provided. The number and percentage of patients and the number of events will also be presented by SOC and PT. At each level of patient summarization, a patient is counted once within each PT and then each SOC if the patient reports one or more events. Percentages will be based on the number of patients in the safety set. The number of events will also be summarized.

A summary of TEAEs will also be presented in descending order based on the total for SOCs. If the total incidence for any 2 or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order.

All AEs will be presented in a listing.

9.1.2 Severity (DMID Toxicity Grade) of TEAEs

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents 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.' In the TEAE severity table, if a patient 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.

9.1.3 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 linezolid, bedaquiline, and pretomanid. The possible relationships are 'Not related', 'Unlikely', 'Possibly', 'Probably', and 'Certainly'. In the TEAE relationship table, if a patient 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.

9.1.4 Serious TEAEs

An 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-patient hospitalization or prolongation, results in significant disability/incapacity, or a medically important event.

Treatment-emergent SAEs will be categorized and presented by SOC and PT in the same manner to that described in Section 9.1.1.

9.1.5 TEAEs Leading to Treatment Discontinuation, Interruption, and Reduction

A summary of TEAEs with 'Action Taken with study treatment' as 'Permanently Discontinued' for overall, linezolid only and full regimen will be presented in a table. At each level of patient summarization, a patient is counted once if the patient reported one or more events.

The same presentation will be provided for interruption of linezolid ('Action Taken with Study Treatment Linezolid' is 'Interrupted' and action taken for Bedaquiline/Pretomanid is 'Unchanged') and Full Regimen ('Action Taken with study treatment Linezolid and Bedaquiline/Pretomanid' is 'Interrupted') and reduction of linezolid ('Action Taken with study treatment Linezolid' is 'Reduced').

Data will be categorized and presented by SOC and PT in the same manner to that described in Section 9.1.1.

9.1.6 TEAEs 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 patient summarization, a patient is counted once if the patient reported one or more events.

Data will be categorized and presented by SOC and PT in the same manner to that described in Section 9.1.1.

9.1.7 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 Section 9.1.1.

A separate 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

A detailed data listing with relevant information will be provided.

9.2 Clinical Laboratory Evaluation

A list of laboratory tests (hematology, clinical chemistry, and urinalysis) to be included in the analysis is presented in Section 7.3 of the protocol. Laboratory assessments will be done by a central laboratory. All summaries will be based on the units provided by the central laboratory, no conversion will be done. The laboratory evaluations will be summarized for baseline, post-baseline, and change from baseline at each visit. Only the scheduled measurements from central laboratory will be included in the summaries. In any case where a local laboratory needs to perform the assessment, results from this will only be presented in a listing.

Severity for laboratory parameters described in the DMID toxicity grades will be performed.

Laboratory values outside normal ranges will be identified, and the number and percentage of patients with at least one post-baseline abnormality will be summarized in shift tables comparing the baseline results to each post-baseline timepoint for those patients with results at both timepoints. All post-baseline clinical laboratory results, including scheduled and unscheduled measurements, will be included in the abnormality summaries.

Incidence of grade 3 or 4 severity for laboratory parameters according to DMID grading will be summarized by visit.

Results indicating liver-related abnormalities (i.e., ALT, AST and/or Alkaline Phosphatase) will also be summarized separately. A newly notable laboratory abnormality is defined as an abnormality observed post baseline that meets the notable criteria in Table 1 and that did not exist at baseline. Patients can still meet the criteria for a newly notable laboratory abnormality if the baseline value is missing. The table below displays the general variables and thresholds of interest. Patients are considered to have notable laboratory abnormalities if his/her response falls within the specified definitions at least once during the treatment period. In addition, total bilirubin versus ALT on the logarithmic scale will be presented in an eDISH plot. Here, 2 x ULN for total bilirubin, and 3 x ULN for ALT will be provided accordingly (using horizontal and vertical lines). The most extreme measurement up to last study drug administration for the aforementioned laboratory tests will be presented.

Table 1: Notable Criteria for Laboratory Data –Liver Function Tests

Laboratory Variable	SI Units
AST	>3 x ULN >5 x ULN >8 x ULN >10 x ULN
ALT	>3 x ULN >5 x ULN >8 x ULN >10 x ULN
Total Bilirubin	>1.5 x ULN >2 x ULN
Alkaline Phosphatase (ALP)	>2 x ULN >3 x ULN
Lipase	>2 x ULN >5 x ULN
Other: ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 5 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN and total bilirubin > 2 x ULN ALP > 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)	

Number and percentage of patients with myelosuppression as well as the number of occurrences of myelosuppression will be summarized. Patients are considered to have myelosuppression if his/her response falls within the specified criteria in Table 2 at least once during the treatment period.

Table 2: Notable Criteria for Laboratory Data –Myelosuppression

Laboratory Variable	Criteria
HGB	< 8gm/dL (Grade 3) and significantly below baseline or Hgb falls> 25% beneath baseline
ANC	< 750/mm3 (Grade 3) and significantly below baseline
Platelets	< 50,000/mm3 (Grade 3) and significantly below baseline

For each laboratory test, abnormal values will be identified as those (above/high or below/low) the reference range, and will be flagged in the data listing.

All clinical laboratory data including those assessments done by a local laboratory will be presented in data listings. Separate listings for patients with toxicity grade 3 or higher will be provided for hematology (WBC, HGB, RBC, platelets, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils, and absolute bands), chemistry (a listing displaying liver function parameters total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, GGT and ALP; and another listing for sodium, potassium, bicarbonate, urea, creatinine, glucose, calcium, total protein, albumin, LDH, CPK, uric acid, lipase, and CK-MB (if applicable)) and urinalysis (lipase, bilirubin, blood, protein, and microalbumin/creatinine ratio). A separate listing will also be provided for Hy's Law cases.

9.3 Vital Sign Measurements

Vital sign measurements include height (cm), weight (kg), body temperature (◦C), respiratory rate (breaths/min), blood pressures (mmHg) (resting more than 5 minutes), and heart rate (bpm).

These measurements will be summarized for baseline, post-baseline, and change from baseline at each visit. 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 patients with at least one post-baseline abnormality will be summarized. All post-baseline vital sign assessment results, including scheduled and unscheduled measurements, will be included in the abnormality summaries. A newly notable vital sign abnormality is defined as an abnormality observed post baseline that meets the notable criteria in Table 3 and that did not exist at baseline. Patients can still meet the criteria for a newly notable vital sign abnormality if the baseline value is missing. Table 3 displays the general variables and thresholds of interest.

Patients are considered to have notable vital sign abnormalities if his/her response falls within the specified definitions at least once during the treatment period.

Table 3. Clinically notable criteria for vital sign data

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

bpm: beats per minute, DBP: diastolic blood pressure, SBP: systolic blood pressure.

Patients with abnormal vital signs will be presented in a listing.

9.4 Physical Examination

Only physical examination date/time and a question of 'Were there any significant findings?' were collected on the CRF. Any abnormal findings should be captured directly on the medical history or AE pages directly as appropriate. Physical examination date/time and observed significant findings (yes/no) for all patients will be presented in a listing.

9.5 Electrocardiogram

All patients will have a standard 12-lead (ECG) assessment (heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS) performed by a central cardiologist. All summaries will be based on a central cardiologist assessment. Any assessment done by a local laboratory will only be presented in a listing.

QT intervals will be adjusted using Fridericia's correction and Bazett's correction. QT/QTc values and changes from pre-dose (average of Screening and Day 1) values at each time point will be summarized using descriptive statistics by group and time of collection.

Post-baseline QT/QTc intervals will be classified into the following categories:

- QT/QTc < 450 msec
- 450 msec ≤ QT/QTc < 480 msec
- 480 msec ≤ QT/QTc < 500 msec
- QT/QTc ≥ 500 msec

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

- increase < 30 msec,

- increase ≥ 30 msec and < 60 msec, and
- increase ≥ 60 msec.

Frequency counts will be used to summarize the number of patients at each time point according to the above categories.

Interpreted ECG results based on investigator assessment will be classified as “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant”. The number and percentages of patients with normal, abnormal not clinically significant, and abnormal clinically significant will be presented. In addition, shift tables will be provided to summarize the status changes from baseline to each scheduled post-baseline assessment.

ECG data for all patients including those assessments done by a local laboratory will be presented in a listing. A separate listing for patients with abnormal results will be provided.

9.6 Ophthalmologic Assessment

Results from the assessments of Ophthalmology slit lamp examinations (AREDS2 lens opacity classification and grading), along with visual acuity and color vision will be summarized using descriptive statistics for baseline, post-baseline, and change from baseline at each visit. Only the assessments collected at the scheduled visits or time points will be included in the summary. All ophthalmology-related results will be presented in a listing.

9.7 Peripheral Neuropathy Assessment

Descriptive summary statistics will be presented for the results of Peripheral Neuropathy Assessment for baseline, post-baseline, and change from baseline at each visit. Shift tables will be provided to summarize the status changes from baseline in signs and symptoms to each scheduled post-baseline assessment. All neuropathy-related results will be presented in a listing.

10 Data Safety Monitoring Committee

A DSMC will be appointed for the study. The primary responsibility of the DSMC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial patients by monitoring patient safety, assess patient risk versus benefit, and assess data quality and general evaluation of the trial progress. Its activities will be delineated in a DSMC charter that will define the membership, responsibilities and the scope and frequency of data reviews. The DSMC will operate on a conflict-free basis independently of the Sponsor and the study team. It will comprise at least 3 voting members that include at least 2 clinicians and one statistician. The DSMC may have an organizational meeting prior to commencement of the trial. The DSMC will have meetings where it will review unblinded data during a closed session. These meetings will be planned at regular intervals. The Sponsor or the DSMC may convene ad hoc meetings based on rates of SAEs and/or to review results of the futility analysis or if safety concerns arise during the trial. After its assessment, the DSMC will recommend to the Sponsor continuation, modification or termination of the clinical trial.

The blinded team will prepare the safety tables, listings and/or figures using the surrogate randomization and materials/kits schedule, and the unblinded team will prepare the unblinded analysis for the DSMC using the actual randomization schedule which will be provided to PPD. Only the unblinded team at PPD will receive the actual randomization schedule.

11 Pharmacokinetics/Pharmacodynamics

Derivation of PK/PD parameters described in the protocol Section 9.6 and 9.7 will be covered in a separate modeling plan, to be completed post trial start. Results will be reported in separate modeling report and provided to PPD.

Descriptive statistics (n, arithmetic mean, SD, coefficient of variation (CV%), median, minimum and maximum, geometric mean and geometric CV (%)) will be used to summarize the plasma concentration at each scheduled sampling time/window per analyte. In addition, the derived PK parameters will be summarized descriptively and reported in a listing.

12 Interim Analysis

No formal interim analyses are planned. Primary analysis will be performed on the 26 week follow-up data (after end of treatment when the last randomized patient has completed the 26 week follow-up period after end of treatment). See the efficacy SAP for details on the follow-up timing for the primary analysis. There will be 2 database locks, data analyses and trial reports generated for this trial:

1. When all patients have completed 26 weeks of follow-up after end of treatment. This will contain all data from randomization up to 26 weeks of follow-up after end of treatment.
2. When all patients have completed 78 weeks of follow-up from after 26 weeks of follow-up. This will contain all data after 26 weeks of follow-up to 78 weeks of follow-up after end of treatment.

13 Changes in the Planned Analysis

The analyses described in the statistical analysis plan do not differ from those specified in the protocol.

14 References

Lee, et al. "Linezolid for treatment of chronic extensively drug-resistant tuberculosis" N Engl J Med. 2012 Oct 18; 367(16):1508-18.

Lytvynenko N, Cherenko S, Feschenko Y, Pogrebna M, Senko Y, Barbova A, Manzi M, Denisiuk O, Ramsay A and Zachariah R (2014). “Management of multi and extensively drug resistant tuberculosis in Ukraine: how well are we doing?” IUALTD Public Health Action 4(3): S67-S72.

World Health Organization. Global Tuberculosis Report 2015, 20th ed. 2015.

15 Appendices

15.1 List of Planned Summary Tables

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16.2.5.3	Individual Plasma Concentration	PK Analysis Set
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Efficacy Statistical Analysis Plan

Protocol Title: A Phase 3 partially-blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).

Protocol Number: NC-007-(B-Pa-L).

Version: *1.0*

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0.1 07 August 2017	First version drafted
0.2 21 August 2017	Circulated to wider team after incorporating comments from DE
0.3 01 Sep 2017	Circulated to team after incorporating comments from CM and PPD
0.4 06 Sep 2017	Circulated new draft following call 06 Sept 2017

1. Introduction

This document outlines the efficacy statistical analysis plan (SAP) for the protocol ZeNix, a phase 3 partially-blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB). Bedaquiline and pretomanid treatment will not be blinded. Linezolid treatment dose and duration will be double-blinded.

Participants will have a screening period of up to 9 days and will be randomized to receive one of the following 4 active treatment arms:

1. Linezolid 1200 mg daily for 26 weeks
   - 2 linezolid 600 mg active tablets once daily for 26 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 26 weeks

2. Linezolid 1200 mg daily for 9 weeks
   Weeks 1-9
   - 2 linezolid 600 mg active tablets once daily for 9 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 9 weeks

   Weeks 10-26
   - 2 placebo linezolid 600 mg tablets once daily for 17 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 17 weeks

3. Linezolid 600 mg daily for 26 weeks
   - 1 linezolid 600 mg active tablet once daily for 26 weeks
   - 1 placebo linezolid 600 mg tablet once daily for 26 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 26 weeks

4. Linezolid 600 mg daily for 9 weeks
   Weeks 1-9
   - 1 linezolid 600 mg active tablet once daily for 9 weeks
   - 1 placebo linezolid 600 mg tablet for 9 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 9 weeks

   Weeks 10-26
   - 2 placebo linezolid 600 mg tablets once daily for 17 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 17 weeks

Participants will be randomised to one of the four regimens in a 1:1:1:1 ratio, using an interactive web response system (IWRS), stratified by HIV status and type of TB. A total of up to 180 participants will be enrolled: 120 (30 per treatment arm) XDR-TB participants, and up to 60 (15 per arm) pre-XDR or treatment intolerant/non-responsive MDR pulmonary tuberculosis Participants, male and female, aged 14 and over. . Sponsor may consider replacement of late screen failure and unassessable patients.

Each participant will receive 26 weeks of treatment. If participant's week 16 sample remains culture positive, the investigator may consider extending current treatment to 39 weeks, in consultation with the Sponsor Medical Monitor. Participants will be followed for 78 weeks after end of treatment.

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT). No formal statistical comparisons between the randomised groups will be made.

2. Primary Efficacy Endpoint

The primary efficacy endpoint will be the incidence of bacteriologic failure or relapse or clinical failure at 6 months after the end of therapy. See section 6 for the detailed definition of an "unfavourable response".

There will be three main analyses of the primary efficacy endpoint: An intent to treat (ITT) analysis; a modified intent to treat (MITT) analysis and a per protocol (PP) analysis.

The "unfavourable" rates in any defined 'ITT' population will likely be increased by factors other than bacteriologic or clinical treatment failure and relapse. The MITT analysis will therefore be considered primary for publication purposes. However, we recognize that FDA and other regulatory agencies will consider the ITT analysis primary.

NB: In the event that more than 10% of patients within any randomised group are culture positive at 4 months and have their treatment extended for a further 3 months, the primary endpoint analysis will be defined as 15 months from start of therapy for all patients. For each patient the assessment closest to this time point will be taken as this 15 month (from start of therapy) endpoint.

3. Definitions and data handling issues

3.1. Definitions

Positive culture refers to the culture being positive for M.tb. False positive or contaminated sputum cultures, without speciation data confirming presence of M.tb, will be treated as missing. Specimens classified as non-tuberculous mycobacteria (NTM) and negative for M.tb will be treated as contaminated. Full details of the bacteriology algorithm for reporting MGIT results can be found in Appendix 1. 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 culture at the same visit. (Appendix 1)

Culture negative status is achieved when a patient produces at least 2 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 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.

Patients with two contaminated or missing samples at a given visit will be asked to return to produce two more sputum samples.

Treatment failure is defined as being declared an unfavourable status (as defined in section 6) at or before the end of treatment or failing to attain culture negative status and being declared an unfavourable outcome or patient 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 is defined as failing to maintain culture negative status or being declared an unfavourable outcome after the end of treatment in those patients who attained culture negative status by the end of treatment, and had culture conversion to positive status with the **same** *Mycobacterium tuberculosis (M.tb)* strain or after the end of treatment in those patients 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 2.

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 patients who attained culture negative status by the end of treatment and had culture conversion to positive status with a *Mycobacterium tuberculosis (M.tb)* strain that is **different** from the infecting strain at baseline. If reinfection cannot be distinguished from relapse, the patient 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 2.

The ***treatment period*** is defined as 6 months (total of 26 weeks) of the B-Pa therapy (linezolid may be stopped early) plus any days made up for interrupted doses of B-Pa therapy (or 9 months in those remaining culture positive at month 4 and who are not withdrawn).

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

3.2. Inability to produce sputum

In general, inability to produce sputum is treated as being equivalent to having a negative (favourable) culture result. This includes the rare situation where a patient never achieves culture negative status due to inability to produce sputum, but completes follow-up without clinical or microbiological evidence of relapse. Such a patient will be considered to have a favourable outcome.

3.3. Isolated positive cultures

It is known that occasionally patients 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 2 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 patient is relapsing. In the event of a single positive culture result occurring in a patient who has previously been classified as having culture negative status (in the absence of any retreatment), the patient 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 patient 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 positives with liquid culture and sometimes even serial "isolated positives" the clinical condition of the patient will also be considered in deciding whether the patient has an unfavourable outcome and re-treatment is indicated.

To expand a bit, most of the experience with isolated positives has been with solid culture. Because liquid culture is more sensitive, it is possible that more than one isolated positive may occasionally occur. Therefore, the clinical condition of the patient will also be considered when deciding whether re-treatment is indicated and in determining the outcome. For example, if a patient 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 patient untreated on clinical grounds. In such a case, so long as two consecutive negative cultures are eventually obtained in the absence of treatment, the patient will not be classified as an unfavourable outcome.

3.4. Timing of events

In all analyses, visit date rather than day or week number will be used to define the timing of events. For all participants, the 6-month regimen will be taken as a total of 26 weeks, i.e. 182 dosing days (for B-Pa), from the start of therapy, after accounting for any treatment interruptions. For those who extend treatment to 9 months this will be 39 weeks (273 days) (for B-Pa) from start of therapy, again after accounting for any treatment interruptions.

For the end of treatment visit (months 6/9), a ±1-week window will be applied (as per the protocol). For the 3-monthly visits after the end of therapy, a window of ±2 weeks will be applied (as per the protocol). Additional programming will be required for cases where end of treatment date is not clearly recorded.

In the event that more than 10% of patients within any randomised group are culture positive at 4 months and have their treatment extended for a further 3 months, the primary endpoint analysis will be defined as 15 months from start of therapy for all patients. In this case the visit date for the endpoint analysis will be chosen as the one closest to 65 weeks (26+39) from start of therapy (unless patient is declared unfavourable before this date).

4. Analysis populations

Patients who are never culture positive during the baseline period, (screening through week 4) but are eligible based on documented M.tb by culture or molecular test within 3 months prior to screening will be included in all analysis populations.

The analysis populations for efficacy analyses are:

- The **Intent to treat** (**ITT)** population is defined as all randomised patients excluding late screening failures (see 4.1)
- The **Modified intent to treat** (**MITT)** population is defined as the ITT population with extra exclusions (See 4.2)
- The **Per-protocol (PP)** population is defined as the MITT population with extra exclusions (see 4.3)

Exclusions from these populations will be reported as "unassessable" status and are described below.

4.1. Exclusions from ITT analysis (late screening failures)

1. Patients withdrawn from treatment because they were found to be ineligible (late exclusions from the study), based on data collected prior to randomisation, including patients who do not have documented evidence of M.tb within 3 months of screening. Note, reinfections will not be excluded from the ITT population and will be considered unfavourable. All patients without a proven favourable outcome will be considered unfavourable.

4.2. Additional exclusions from MITT analysis

1. Patients 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. Patients who die 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.

4. Patients who die 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), and who have not already been classified as unfavourable.

5. Patients who, after being classified as having culture negative status, are re-infected with a new strain different from that with which they were originally infected. Reinfection will be defined specifically as a patient infected with a strain that is genetically different from the initial strain (see Appendix 2).

6. Patients who are able to produce sputum at their primary endpoint visit, whose sputum samples are all contaminated or missing, who cannot be brought back for repeat cultures, provided they have not already been classified as unfavourable and provided their last positive culture was followed by at least two negative cultures. N.B.: This does not apply to patients who are unable to produce sputum at 6 months after end of treatment, or to patients who are able to be brought back subsequently and produce negative cultures.

Patients in categories 1-6 above who had already been classified as having an unfavourable outcome will not be excluded.

4.3. Additional exclusions from PP analysis

1. Patients lost to follow-up or withdrawn before the end of treatment due to reasons other than treatment failure, unless they have already been classified as having an unfavourable outcome.

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

3. Patients not meeting the definition of having received an adequate amount of their allocated study regimen (see section 4.5 for definition), provided this is not due to unfavourable outcome.

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

A list of all protocol deviations will be compiled throughout the course of the study.

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 patients will be included in the ITT and MITT analyses, but not in the Per Protocol analysis. A list of all major protocol deviations for analysis will be approved by the study Coordinating Investigator before database lock.

4.4. Lost to Follow-up or Early Withdrawal

Lost to Follow-up or Early Withdrawals *before* the end of the treatment (month 6 or 9) are considered as unfavourable outcomes for ITT and MITT. However, these patients will be excluded from the Per Protocol analysis. The MITT and Per Protocol analyses will consider Lost to Follow-up *after* end of treatment as unassessable unless at the time of default from follow-up the patient a) was already classified as having an unfavourable outcome, b) did not have culture negative status, or c) had a positive culture result ("isolated positive culture") not followed by at least two negative culture results at different visits (at least 7 days apart), in which cases the patient will be classified as having an unfavourable outcome. We believe this is the most appropriate approach for the primary analysis because together with the non-tuberculosis deaths, this group is likely to considerably out-number the bacteriological failures and relapses. These patients will be considered as having an unfavourable outcome in the ITT analysis.

There is a clear precedent for this analytic approach in other TB trials, and these trials also provide examples of why the inclusion of the losses to follow-up as unfavourable greatly affects 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.
In the Priftin trial bacteriological relapses occurred in 5% of patients on the rifampicin based regimen compared to 11% on the rifapentine based regimen. Approximately one third of patients were lost to follow-up and when this group combined with patients 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 patients 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 had an unfavourable outcome and finally assuming all losses had a favourable outcome.

In the study conducted by the IUATLD the published failure/relapse rates 12 months after stopping treatment based on 1044 assessable patients were 4% for the control regimen and 10% and 14% in each of the experimental arms. If the 311 unassessable patients were considered to have an unfavourable outcome these rates would increase to 24%, 32% and 35% respectively. The 311 unassessable patients 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.

4.5. Definition of adequate treatment

The definition of adequate treatment sets a limit for the amount of treatment missed. Patients not taking the adequate amount of treatment by this definition will be excluded from the PP analysis.

Patients treated for 6 months with no treatment extension, 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 242 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).

For patients who have their treatment extended to 9 months (39 weeks), to meet the definition of adequate treatment, they must have taken at least 219 doses (80%) within 333 days.

A dose is defined as taking the required daily dose of both pretomanid and bedaquiline.

4.6. Determining cause of death

A list of all ***TB-related*** and ***non-TB-related deaths*** will be generated and approved by a review committee of physicians not associated with the trial before database lock. Similarly, a list of violent or accidental deaths will be generated.

5. Baseline comparisons of key characteristics

The following baseline characteristics of patients will be summarised: age, gender, race, site, weight, height, BMI, smoking status, TB type (XDR /non-XDR), HIV status/CD4 count/on ARV, cavitation, initial bacterial load in sputum as indicated by baseline Time to Positivity (TTP) result from MGIT, drug resistance.

6. Classification of primary endpoint status

Patients will be classified as having a favourable, unfavourable or unassessable status at 6 months after the end of therapy. Patients excluded from analysis are considered unassessable.

6.1.1. Favourable status (all analyses)

Patients with a negative culture status at 6 months from end of therapy who had 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.

6.1.2. Unfavourable status in ITT population

Patients in the ITT analysis population who do not have a favourable outcome at 6 months from end of therapy will be considered to have an unfavourable response in the ITT analysis.

6.1.3. Unfavourable status in MITT population

1. Patients not classified as having achieved or maintained culture negative status when last seen, or
2. Patients previously classified as having culture negative status who, following the end of treatment, have two positive cultures without an intervening negative culture, (however, see Section 3.3 for an exception), or
3. Patients who had a positive culture not followed by at least two negative cultures when last seen, or
4. Patients dying from any cause during treatment, except from violent or accidental cause (e.g. road traffic accident) not including suicide (i.e., suicide will be considered an unfavourable outcome) or
5. Patients definitely or possibly dying from TB related cause during the follow-up phase or
6. Patients 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. Patients lost to follow up or withdrawn from the study before the end of treatment
8. If patient has surgery and the resected tissue is cultured and is positive for MTB

6.1.4. Unfavourable status in PP population

1. Patients not classified as having achieved or maintained culture negative status when last seen, or
2. Patients previously classified as having culture negative status who, following the end of treatment, have two positive cultures without an intervening negative culture, (however, see Section 3.3 for an exception), or
3. Patients who had a positive culture not followed by at least two negative cultures when last seen, or
4. Patients dying from any cause during the treatment phase, except from violent or accidental cause (e.g. road traffic accident) not including suicide (i.e., suicide will be considered an unfavourable outcome), or
5. Patients definitely or possibly dying from TB related cause during the follow-up phase, or
6. Patients requiring a restart or a change of treatment because of an unfavourable outcome with or without bacteriological confirmation, i.e. on bacteriological, radiographic or clinical grounds, unless due to reinfection with a new organism
7. If patient has surgery and the resected tissue is cultured and is positive for MTB

7. Primary endpoint analysis

The MITT analyses will be considered primary.

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT) including all TB types. A key secondary analysis will be restricted to the XDR participants only (30 per arm).

We will evaluate the hypothesis, separately for each of the experimental B-L-Pa treatment arms, that the incidence of bacteriologic failure or relapse or clinical failure (including mortality) -unfavorable outcome - at 6 months (26 weeks) after the end of therapy is less than 50%.

Given the uncertainty about the dosing and duration of linezolid and effect on efficacy and safety and to control the overall type I error rate the following analysis strategy will be adopted for both the primary and secondary analysis populations:

The primary comparison will be for the linezolid 1200mg taken for 26 weeks arm (L1200 26 weeks) with the L1200 9 weeks and L600 26 weeks only being tested if L1200 26 weeks is a success. Similarly, L600 9 weeks will only be tested if L600 26 weeks is a success. A Bonferroni adjustment will be made for comparing the L1200 9 weeks and L600 26 weeks arms simultaneously, using $p<0.025$. For these comparisons the lower bound of the 97.5% confidence interval will need to exceed 50% for success.

No formal statistical pairwise comparisons between the arms will be performed.

The proportion of assessable patients with a favourable and unfavourable outcome, with 95% and 97.5% confidence intervals, will be presented. For success, the lower bound of the 95% confidence interval (or 97.5% as applicable) for a favourable outcome should be above 50%.

This MITT analysis is consistent with the TB literature over the past 50 years. **However, we recognise that FDA and other regulatory agencies will consider the ITT analysis primary, where all patients who are not proven to have a favourable outcome will be classified as having an unfavourable outcome.**

8. Sensitivity analyses of primary endpoint analysis

In addition to analysing the primary endpoint data by ITT, MITT and PP and separately for XDR-TB patients (key secondary efficacy analyses), it is planned to conduct the following sensitivity analyses:

1. An analysis of patients in the MITT and PP populations where reinfections are classified as unfavourable outcomes

2. An analysis of the MITT and PP populations treating all deaths as unfavourable

3. An analysis of the ITT, MITT and PP populations excluding patients who were never culture positive during the baseline period (screening through week 4), but were eligible based on documented M.tb by culture or molecular test within 3 months prior to screening

9. Secondary efficacy analyses of primary endpoint

The following analyses will be performed on MITT and PP populations only unless otherwise stated.

9.1. Time to event unfavorable outcome analysis

Time to an unfavourable outcome will be analysed with Kaplan Meier plots and Cox's proportional-hazards regressions analysis. These analyses will be performed according to ITT, MITT and PP endpoint 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 6 month after end of therapy visit.

10. Secondary efficacy endpoints

10.1. Incidence of bacteriologic failure or relapse at 24 months after the end of treatment

Efficacy analyses as described for the primary endpoint will be repeated for the 24 month after the end of treatment endpoint as a confirmatory analysis.

10.2 Time to sputum culture conversion to negative status

For patients with positive baseline culture results, 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.

10.3 Culture conversion status at 4, 6, 8, 12 and 16 weeks

Patients will be classified as being culture positive, culture negative, dead or unassessable at 4, 6, 8, 12 and 16 weeks. Every effort will be made to obtain a sputum sample from all patients, but it is recognised that some patients may not have produced any sputum in the preceding week and may be unable to do so when requested. Patients who cannot produce sputum will be classified as being culture negative at that time point. The proportion culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis.

10.4 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, 6 and 24 months from end of treatment.

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.

10.5 Patient reported health status

Patient reported health status is measured by the 5 domains of EQ5D. These will be summarised at baseline, week 8, end of treatment, 6 and 24 months from end of treatment by randomised group and change from baseline at each follow-up assessment by mean, median, IQR and range by randomised group.

10.6 Weight

Baseline weight and change from baseline weight throughout treatment and at 6 and 24 months after the end of therapy will be summarised by mean, median, IQR and range

11 Pharmacokinetics-Pharmacodynamics (PK-PD)analyses

Details of the PK parameter estimation and analysis are detailed in a separate PK SAP. PK-PD analyses will be described in a separate PK-PD SAP.

12 Sub-group analyses

To assess consistency of results, exploratory sub-group analyses of the primary endpoint on the MITT analysis population will be considered. For example, depending on numbers consideration will be given to subgroup analyses by: age; gender; race; smoking status; HIV status/CD4 count; cavitation, initial bacterial load in sputum as indicated by baseline TTP result from MGIT; ARV taken or not during the treatment period.

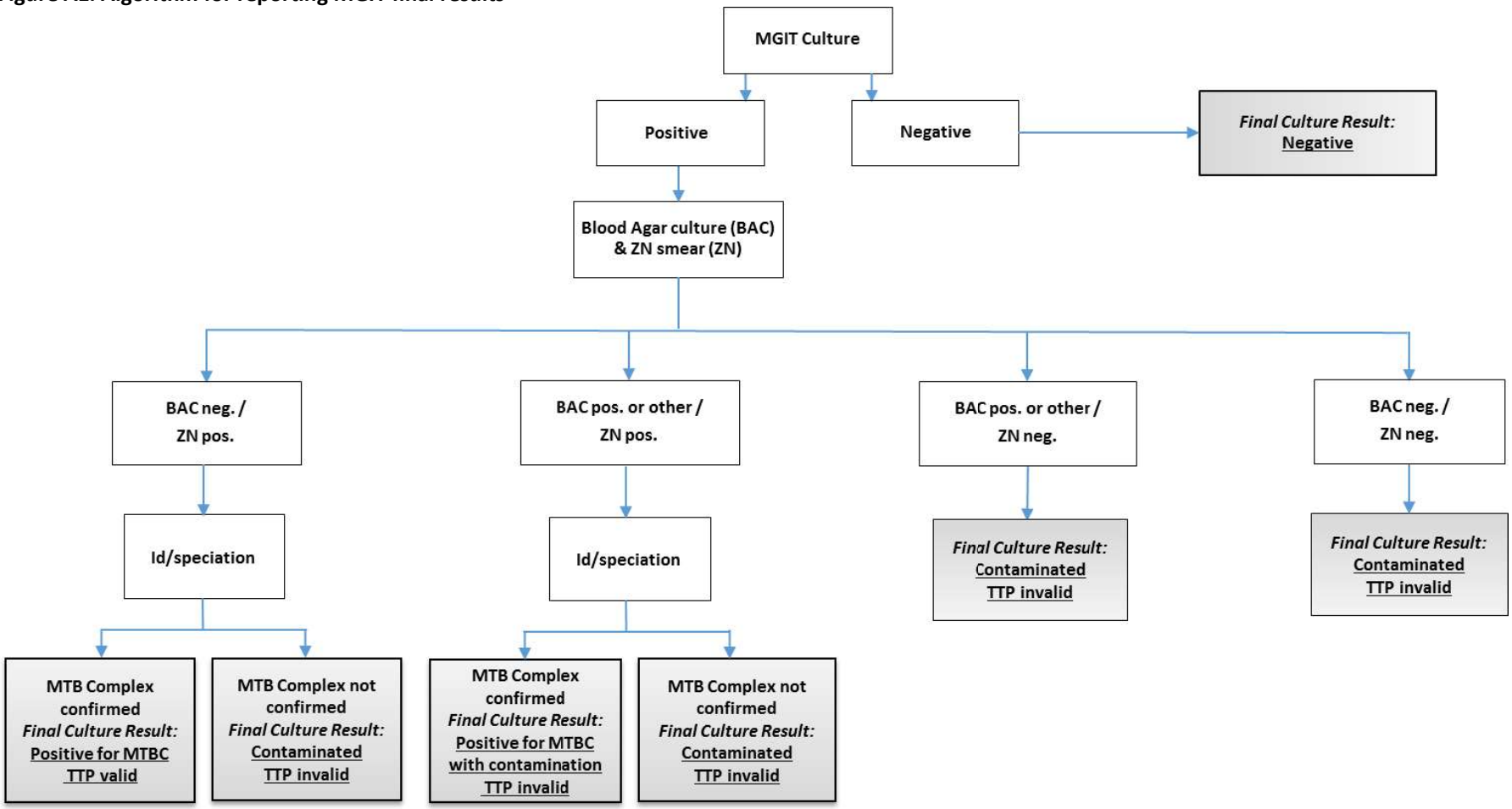
13 Reasons for treatment failure as determined by the local PI

Reason(s) that led the site investigator to conclude that an individual patient failed treatment or relapsed will be classified as a) bacteriology alone, b) clinical deterioration alone, c) radiological deterioration alone, d) bacteriology plus clinical deterioration, e) bacteriology plus radiological deterioration, f) clinical deterioration plus radiological deterioration, or g) bacteriology plus clinical deterioration plus radiological deterioration. These classifications will be tabulated and compared to outcomes derived from the algorithm described in section 6.

14 APPENDICES

14.1 Appendix 1: Algorithm for Interpretation of Positive MGIT Results

Figure A1. Algorithm for reporting MGIT final results



Note: MGIT cultures with no ID/speciation will be treated as a missing result.

Table A1. 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/Contaminated	Contaminated

14.2 Appendix 2: Interpretation of Relapse/Re-infection using Whole Genome Sequence (WGS)

The purpose of the WGS analysis is to determine if the two M. tuberculosis strains from a given patient (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** (re-infection/bacteriological re-infection). 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 and RIFAQUIN trials) that show a clear genetic distinction between relapse and re-infection cases of M.tb infection.

- ≤12 SNPs different = Relapse
- ≥100 SNPs different = Reinfection
- >12 and <100 SNPs different = Indeterminate. These 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 re-infection' based on this further review. A patient will be considered a relapse unless there is sufficient evidence to support a classification of re-infection.

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Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
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Efficacy Statistical Analysis Plan

Protocol Title: A Phase 3 partially-blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).

Protocol Number: NC-007-(B-Pa-L).

Version: 2.0

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Table of Contents

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0.1 07 August 2017	First version drafted
0.2 21 August 2017	Circulated to wider team after incorporating comments from DE
0.3 01 Sep 2017	Circulated to team after incorporating comments from CM and PPD
0.4 06 Sep 2017	Circulated new draft following call 06 Sept 2017
1.1 2019	new draft with updates, removal of original appendix 1, and addition of week 26 analysis
1.2 March 2020	General corrections
1.3 April 2020	Added surgery clause
1.4 26 May 2020	Added COVID clause
1.5 June 2020	Minor amendments after review meeting
2.0 August 2020	Up versioned v1.5 to v2.0

1. Introduction

This document outlines the efficacy statistical analysis plan (SAP) for the protocol ZeNix, a phase 3 partially-blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB). Bedaquiline and pretomanid treatment will not be blinded. Linezolid treatment dose and duration will be double-blinded.

Participants will have a screening period of up to 9 days and will be randomized to receive one of the following 4 active treatment arms:

1. Linezolid 1200 mg daily for 26 weeks
   - 2 linezolid 600 mg active tablets once daily for 26 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 26 weeks

2. Linezolid 1200 mg daily for 9 weeks
   Weeks 1-9
   - 2 linezolid 600 mg active tablets once daily for 9 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 9 weeks

   Weeks 10-26
   - 2 placebo linezolid 600 mg tablets once daily for 17 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 17 weeks

3. Linezolid 600 mg daily for 26 weeks
   - 1 linezolid 600 mg active tablet once daily for 26 weeks
   - 1 placebo linezolid 600 mg tablet once daily for 26 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 26 weeks

4. Linezolid 600 mg daily for 9 weeks
   Weeks 1-9
   - 1 linezolid 600 mg active tablet once daily for 9 weeks
   - 1 placebo linezolid 600 mg tablet for 9 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 9 weeks

   Weeks 10-26
   - 2 placebo linezolid 600 mg tablets once daily for 17 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 17 weeks

Participants will be randomised to one of the four regimens in a 1:1:1:1 ratio, using an interactive web response system (IWRS), stratified by HIV status and type of TB. A total of up to 180 participants, male and female, aged 14 and over, will be enrolled.

Each participant will receive 26 weeks of treatment. If participant's sputum sample is culture positive between week 16 and week 26 treatment visits and their clinical condition suggests they may have an ongoing TB infection, Investigator may consider extending current treatment to 39 weeks. If the culture results between week 16 and week 26 are contaminated, missing or considered an isolated positive without clinical significance, available culture results should be used to make this decision. All decisions regarding treatment extension should be discussed and approved by the Sponsor Medical Monitor before implementation. Participants will be followed for 78 weeks after end of treatment.

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT). No formal statistical comparisons between the randomised groups will be made.

2. Primary Efficacy Endpoint

The primary efficacy endpoint will be the incidence of bacteriologic failure or relapse or clinical failure at 6 months after the end of therapy. See section 6 for the detailed definition of an "unfavourable response".

There will be three main analyses of the primary efficacy endpoint: An intent to treat (ITT) analysis; a modified intent to treat (MITT) analysis and a per protocol (PP) analysis.

The "unfavourable" rates in any defined 'ITT' population will likely be increased by factors other than bacteriologic or clinical treatment failure and relapse. The MITT analysis will therefore be considered primary for publication purposes. However, we recognize that FDA and other regulatory agencies will consider the ITT analysis primary.

NB: In the event that more than 10% of patients within any randomised group are culture positive at 4 months and have their treatment extended for a further 3 months, the primary endpoint analysis will be defined as 15 months from start of therapy for all patients. For each patient the assessment closest to this time point will be taken as this 15 month (from start of therapy) endpoint.

3. Definitions and data handling issues

3.1. Definitions

Positive culture refers to the culture being positive for M.tb. False positive or contaminated sputum cultures, without speciation data confirming presence of M.tb, will be treated as missing. Specimens classified as non-tuberculous mycobacteria (NTM) and negative for M.tb will be treated as contaminated. Two sputum samples per visit are collected at each visit, excluding at Week 5,7,14 & 18, 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 culture at the same visit. Refer to Appendix 1 for further details.

Culture negative status is achieved when a patient produces at least 2 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 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.

Patients with two contaminated or missing samples at a given visit will be asked to return to produce two more sputum samples.

Treatment failure is defined as being declared an unfavourable status (as defined in section 6) at or before the end of treatment or failing to attain culture negative status and being declared an unfavourable outcome or patient 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 is defined as failing to maintain culture negative status or being declared an unfavourable outcome after the end of treatment in those patients who attained culture negative status by the end of treatment, and had culture conversion to positive status with the **same** *Mycobacterium tuberculosis (M.tb)* strain or after the end of treatment in those patients 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 2.

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 patients who attained culture negative status by the end of treatment and had culture conversion to positive status with a *Mycobacterium tuberculosis (M.tb)* strain that is **different** from the infecting strain at baseline. If reinfection cannot be distinguished from relapse, the patient 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 2.

The ***treatment period*** is defined as 6 months (total of 26 weeks) of the B-Pa therapy (linezolid may be stopped early) plus any days made up for interrupted doses of B-Pa therapy (or 9 months in those who are extended).

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

3.2. Inability to produce sputum

In general, inability to produce sputum is treated as being equivalent to having a negative (favourable) culture result. This includes:

- the rare situation where a patient never achieves culture negative status due to inability to produce sputum, but completes follow-up without clinical or microbiological evidence of relapse.
- during the COVID-19 lockdown situation where this data is collected remotely/telephonically

Such patients will be considered to have a negative (favourable) outcome.

3.3. Isolated positive cultures

It is known that occasionally patients 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 2 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 patient is relapsing. In the event of a single positive culture result occurring in a patient who has previously been classified as having culture negative status (in the absence of any retreatment), the patient 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 patient 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 positives with liquid culture and sometimes even serial "isolated positives" the clinical condition of the patient will also be considered in deciding whether the patient has an unfavourable outcome and re-treatment is indicated.

To expand a bit, most of the experience with isolated positives has been with solid culture. Because liquid culture is more sensitive, it is possible that more than one isolated positive may occasionally occur. Therefore, the clinical condition of the patient will also be considered when deciding whether re-treatment is indicated and in determining the outcome. For example, if a patient 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 patient untreated on clinical grounds. In such a case, so long as two consecutive negative cultures are eventually obtained in the absence of treatment, the patient will not be classified as an unfavourable outcome.

3.4. Timing of events

In all analyses, visit date rather than day or week number will be used to define the timing of events. For all participants, the 6-month regimen will be taken as a total of 26 weeks, i.e. 182 dosing days (for B-Pa), from the start of therapy, after accounting for any treatment interruptions. For those who extend treatment to 9 months this will be 39 weeks (273 days) (for B-Pa) from start of therapy, again after accounting for any treatment interruptions.

For the end of treatment visit (months 6/9), a ±1-week window will be applied (as per the protocol). For the 3-monthly visits after the end of therapy, a window of ±2 weeks will be applied (as per the protocol). Additional programming will be required for cases where end of treatment date is not clearly recorded.

In the event that more than 10% of patients within any randomised group have their treatment extended for a further 3 months, the primary endpoint analysis will be defined as 15 months from start of therapy for all patients. In this case the visit date for the endpoint analysis will be chosen as the one closest to 65 weeks (26+39) from start of therapy (unless patient is declared unfavourable before this date).

4. Analysis populations

Patients who are never culture positive during the baseline period, (screening through week 4) but are eligible based on documented M.tb by culture or molecular test within 3 months prior to screening will be included in all analysis populations.

The analysis populations for efficacy analyses are:

- The **Intent to treat** (**ITT)** population is defined as all randomised patients excluding late screening failures (see 4.1)
- The **Modified intent to treat** (**MITT)** population is defined as the ITT population with extra exclusions (See 4.2)
- The **Per-protocol (PP)** population is defined as the MITT population with extra exclusions (see 4.3)

Exclusions from these populations will be reported as "unassessable" status and are described below.

4.1. Exclusions from ITT analysis (late screening failures)

1. Patients found to be ineligible (late exclusions from the study), based on data collected prior to randomisation, including patients who do not have documented evidence of M.tb within 3 months of screening.

4.2. Additional exclusions from MITT analysis

1. Patients 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. Patients with suspected/confirmed COVID19 during treatment and stop their allocated treatment

4. Patients who die 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. Patients who die 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), and who have not already been classified as unfavourable.

6. Patients who, after being classified as having culture negative status, are re-infected with a new strain different from that with which they were originally infected. Reinfection will be defined specifically as a patient infected with a strain that is genetically different from the initial strain (see Appendix 2).

7. Patients who are able to produce sputum at their primary endpoint visit, whose sputum samples are all contaminated or missing, who cannot be brought back for repeat cultures, provided they have not already been classified as unfavourable and provided their last positive culture was followed by at least two negative cultures. N.B.: This does not apply to patients who are unable to produce sputum, or to patients who are able to be brought back subsequently and produce negative cultures.

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

4.3. Additional exclusions from PP analysis

1. Patients lost to follow-up or withdrawn before the end of treatment due to reasons other than treatment failure, unless they have already been classified as having an unfavourable outcome.

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

3. Patients not meeting the definition of having received an adequate amount of their allocated study regimen (see section 4.5 for definition), provided this is not due to unfavourable outcome.

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

A list of all protocol deviations will be compiled throughout the course of the study.

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 patients will be included in the ITT and MITT analyses, but not in the Per Protocol analysis. A list of all major protocol deviations for analysis will be approved by a review committee before all planned analyses.

4.4. Lost to Follow-up or Early Withdrawal

Lost to Follow-up or Early Withdrawals *before* the end of the treatment (month 6 or 9) are considered as unfavourable outcomes for ITT and MITT. However, these patients will be excluded from the Per Protocol analysis. The MITT and Per Protocol analyses will consider Lost to Follow-up *after* end of treatment as unassessable unless at the time of default from follow-up the patient a) was already classified as having an unfavourable outcome, b) did not have culture negative status, or c) had a positive culture result ("isolated positive culture") not followed by at least two negative culture results at different visits (at least 7 days apart), in which cases the patient will be classified as having an unfavourable outcome. We believe this is the most appropriate approach for the primary analysis because together with the non-tuberculosis deaths, this group is likely to considerably out-number the bacteriological failures and relapses. These patients will be considered as having an unfavourable outcome in the ITT analysis.

There is a clear precedent for this analytic approach in other TB trials, and these trials also provide examples of why the inclusion of the losses to follow-up as unfavourable greatly affects 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.
In the Priftin trial bacteriological relapses occurred in 5% of patients on the rifampicin based regimen compared to 11% on the rifapentine based regimen. Approximately one third of patients were lost to follow-up and when this group combined with patients 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 patients 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 had an unfavourable outcome and finally assuming all losses had a favourable outcome.

In the study conducted by the IUATLD the published failure/relapse rates 12 months after stopping treatment based on 1044 assessable patients were 4% for the control regimen and 10% and 14% in each of the experimental arms. If the 311 unassessable patients were considered to have an unfavourable outcome these rates would increase to 24%, 32% and 35% respectively. The 311 unassessable patients 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.

4.5. Definition of adequate treatment

The definition of adequate treatment sets a limit for the amount of treatment missed. Patients not taking the adequate amount of treatment by this definition will be excluded from the PP analysis.

For patients treated for 6 months with no treatment extension, 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).

For patients who have their treatment extended to 9 months (39 weeks), to meet the definition of adequate treatment, they must have taken at least 219 doses (80%) of their allocated 273 day (39 weeks) treatment within 364 days (i.e. 39 weeks plus an allowable 91 day halt (including a maximum of 35 consecutive days) as per the protocol).

A dose is defined as taking the required daily dose of both pretomanid and bedaquiline.

4.6. Determining cause of death

A list of all ***TB-related*** and ***non-TB-related deaths*** will be generated and approved by a review committee of physicians not associated with the trial before database lock. Similarly, a list of violent or accidental deaths will be generated.

5. Baseline comparisons of key characteristics

The following baseline characteristics of patients will be summarised: age, gender, race, site, weight, height, BMI, smoking status, TB type (XDR /non-XDR), HIV status/CD4 count/on ARV, cavitation, initial bacterial load in sputum as indicated by baseline Time to Positivity (TTP) result from MGIT, baseline drug resistance.

6. Classification of primary endpoint status

Patients will be classified as having a favourable, unfavourable or unassessable status at 6 months after the end of therapy. Patients excluded from analysis are considered unassessable.

6.1.1. Favourable status (all analyses)

Patients with a negative culture status at 6 months from end of therapy who had 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.

6.1.2. Unfavourable status in ITT population

Patients in the ITT analysis population who do not have a favourable outcome at 6 months from end of therapy will be considered to have an unfavourable response in the ITT analysis.

6.1.3. Unfavourable status in MITT population

1. Patients not classified as having achieved or maintained culture negative status when last seen, or
2. Patients previously classified as having culture negative status who, following the end of treatment, have two positive cultures without an intervening negative culture, (however, see Section 3.3 for an exception), or
3. Patients who had a positive culture not followed by at least two negative cultures when last seen, or
4. Patients dying from any cause during treatment, except from violent or accidental cause (e.g. road traffic accident) not including suicide (i.e., suicide will be considered an unfavourable outcome) or
5. Patients definitely or possibly dying from TB related cause during the follow-up phase or
6. Patients 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. Patients lost to follow up or withdrawn from the study before the end of treatment
8. Patients who have had surgery and the resected tissue is cultured and is positive for MTB.

6.1.4. Unfavourable status in PP population

1. Patients not classified as having achieved or maintained culture negative status when last seen, or
2. Patients previously classified as having culture negative status who, following the end of treatment, have two positive cultures without an intervening negative culture, (however, see Section 3.3 for an exception), or
3. Patients who had a positive culture not followed by at least two negative cultures when last seen, or
4. Patients dying from any cause during the treatment phase, except from violent or accidental cause (e.g. road traffic accident) not including suicide (i.e., suicide will be considered an unfavourable outcome), or
5. Patients definitely or possibly dying from TB related cause during the follow-up phase, or
6. Patients requiring a restart or a change of treatment because of an unfavourable outcome with or without bacteriological confirmation, i.e. on bacteriological, radiographic or clinical grounds, unless due to reinfection with a new organism
7. Patients who have had surgery and the resected tissue is cultured and is positive for MTB.

7. Primary endpoint analysis

The MITT analyses will be considered primary.

The primary efficacy analysis will be conducted using culture results including all TB types.

We will evaluate the hypothesis, separately for each of the experimental B-L-Pa treatment arms, that the incidence of bacteriologic failure or relapse or clinical failure (including mortality) -unfavorable outcome - at 6 months (26 weeks) after the end of therapy is less than 50%.

Given the uncertainty about the dosing and duration of linezolid and effect on efficacy and safety and to control the overall type I error rate the following analysis strategy will be adopted for both the primary and secondary analysis populations:

The primary comparison will be for the linezolid 1200mg taken for 26 weeks arm (L1200 26 weeks) with the L1200 9 weeks and L600 26 weeks only being tested if L1200 26 weeks is a success. Similarly, L600 9 weeks will only be tested if L600 26 weeks is a success. A Bonferroni adjustment will be made for comparing the L1200 9 weeks and L600 26 weeks arms simultaneously, using $p<0.025$. For these comparisons the lower bound of the 97.5% confidence interval will need to exceed 50% for success.

No formal statistical pairwise comparisons between the arms will be performed.

The proportion of assessable patients with a favourable and unfavourable outcome, with 95% and 97.5% confidence intervals, will be presented. For success, the lower bound of the 95% confidence interval (or 97.5% as applicable) for a favourable outcome should be above 50%.

This MITT analysis is consistent with the TB literature over the past 50 years. **However, we recognise that FDA and other regulatory agencies will consider the ITT analysis primary, where all patients who are not proven to have a favourable outcome will be classified as having an unfavourable outcome.**

8. Sensitivity analyses of primary endpoint analysis

In addition to analysing the primary endpoint data by ITT, MITT and PP and separately for XDR-TB patients (key secondary efficacy analyses), it is planned to conduct the following sensitivity analyses:

1. An analysis of patients in the MITT and PP populations where reinfections are classified as unfavourable outcomes

2. An analysis of the MITT and PP populations treating all deaths as unfavourable

3. An analysis of the ITT, MITT and PP populations excluding patients who were never culture positive during the baseline period (screening through week 4), but were eligible based on documented M.tb by culture or molecular test within 3 months prior to screening

9. Secondary efficacy analyses of primary endpoint

The following analyses will be performed on ITT, MITT and PP populations only unless otherwise stated.

9.1. Time to event unfavorable outcome analysis

Time to an unfavourable outcome will be analysed with Kaplan Meier plots. These analyses will be performed according to ITT, MITT and PP endpoint 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 6 month after end of therapy visit.

10. Secondary efficacy endpoints

10.1. Incidence of bacteriologic failure or relapse at 18 months after the end of treatment

Efficacy analyses as described for the primary endpoint will be repeated at the 18 month after the end of treatment endpoint as a confirmatory analysis.

10.2 Time to sputum culture conversion to negative status

For patients with positive culture results from day 1 to week 4 (baseline excluding screening), time to culture negative status (first of two negative cultures without an intervening positive culture) will be analysed using survival analysis techniques and Kaplan Meier plots.

10.3 Culture conversion status at 4, 6, 8, 12, 16 and 26 weeks

Patients will be classified as being culture positive, culture negative, dead or unassessable (including those without positive culture results from day 1 to week 4) at 4, 6, 8, 12, 16 and 26 weeks. Every effort will be made to obtain a sputum sample from all patients, but it is recognised that some patients may not have produced any sputum in the preceding week and may be unable to do so when requested. Patients who are unable to produce sputum will be classified as being culture negative at that time point. The proportion of culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis.

10.4 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, week 16, end of treatment, 6 and 18 months from end of treatment.

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.

10.5 Patient reported health status

Patient reported health status is measured by the 5 domains of EQ5D. These will be summarised at baseline, week 8, week 16, end of treatment, 6 and 18 months from end of treatment by randomised group and change from baseline at each follow-up assessment by mean, median, IQR and range by randomised group.

10.6 Weight

Baseline weight and change from baseline weight throughout treatment and at 6 and 24 months after the end of therapy will be summarised by mean, median, IQR and range

11 Week 26 analysis

This analysis is culture conversion status at week 26 with details outlined in section 10.3 above, with the inclusion of culture conversion status at weeks 20 and 23.

This week 26 analysis will only be performed once all patients have reached the week 26 timepoint.

12 Pharmacokinetics-Pharmacodynamics (PK-PD) analyses

Details of the PK parameter estimation and analysis are detailed in a separate PK SAP. PK-PD analyses will be described in a separate PK-PD SAP.

13 Sub-group analyses

To assess consistency of results, exploratory sub-group analyses of the primary endpoint on the MITT analysis population will be considered. For example, depending on numbers consideration will be given to subgroup analyses by: age; gender; race; smoking status; HIV status; cavitation, initial bacterial load in sputum as indicated by baseline TTP result from MGIT; ARV taken or not during the treatment period, geographical location.

14 Reasons for treatment failure as determined by the local PI

Reason(s) that led the site investigator to conclude that an individual patient failed treatment or relapsed will be classified as a) bacteriology alone, b) clinical deterioration alone, c) radiological deterioration alone, d) bacteriology plus clinical deterioration, e) bacteriology plus radiological deterioration, f) clinical deterioration plus radiological deterioration, or g) bacteriology plus clinical deterioration plus radiological deterioration. These classifications will be tabulated and compared to outcomes derived from the algorithm described in section 6.

15 APPENDICES

Appendix 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/Contaminated	Contaminated

Appendix 2: Interpretation of Relapse/Re-infection using Whole Genome Sequence (WGS)

The purpose of the WGS analysis is to determine if the two M. tuberculosis strains from a given patient (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** (re-infection/bacteriological re-infection). 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 and RIFAQUIN trials) that show a clear genetic distinction between relapse and re-infection cases of M.tb infection.

- ≤12 SNPs different = Relapse
- ≥100 SNPs different = Reinfection
- >12 and <100 SNPs different = Indeterminate. These 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 re-infection' based on this further review. A patient will be considered a relapse unless there is sufficient evidence to support a classification of re-infection.

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Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	8/11/2020 8:07:33 AM
Certified Delivered	Security Checked	8/11/2020 10:09:31 AM
Signing Complete	Security Checked	8/11/2020 10:09:55 AM
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Statistical Analysis Plan

Protocol Title: A Phase 3 partially-blinded, randomised trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).

Protocol Number: NC-007-(B-Pa-L).

Version: 3.0

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Version History:

Version Number/Date	Change
0.1 07 August 2017	First version drafted
0.2 21 August 2017	Circulated to wider team after incorporating comments from DE
0.3 01 Sep 2017	Circulated to team after incorporating comments from CM and PPD
0.4 06 Sep 2017	Circulated new draft following call 06 Sept 2017
1.1 2019	new draft with updates, removal of original appendix 1, and addition of week 26 analysis
1.2 March 2020	General corrections
1.3 April 2020	Added surgery clause
1.4 26 May 2020	Added COVID clause
1.5 June 2020	Minor amendments after review meeting
2.0 August 2020	Up versioned v1.5 to v2.0
2.1 November 2020	Combining efficacy and safety SAP
2.2 November 2020	Incorporation of comments after review meeting
2.3 December 2020	New round of comments
2.4 January 2021	New round of comments
2.5 January 2021	New round of comments
3.0 January 2021	Last comments (about ECG) incorporated, upversioned to 3.0

List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
B	Bedaquiline
BLQ	Below the Limit of Quantitation
BMI	Body Mass Index
BPaL	Combination of Bedaquiline plus Pretomanid plus Linezolid
DMID	Division of Microbiology and Infectious Disease
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
(e)CRF	(electronic) Case Report Form
GGT	Gamma-glutamyl Transferase
HeR	Heart Rate
HIV	Human Immunodeficiency Virus
HGB	Hemoglobin
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
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
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cell
XDR-TB	Extensively Drug Resistant Tuberculosis

CONTENTS

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.

ZeNix is a phase 3 partially-blinded, randomised trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).

1.1 TRIAL INTERVENTION

Participants will have a screening period of up to 9 days and will be randomised to receive one of the following 4 active treatment arms:

1. Linezolid 1200 mg daily for 26 weeks
   - 2 linezolid 600 mg active tablets once daily for 26 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 26 weeks

2. Linezolid 1200 mg daily for 9 weeks
   Weeks 1-9
   - 2 linezolid 600 mg active tablets once daily for 9 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 9 weeks

   Weeks 10-26
   - 2 placebo linezolid 600 mg tablets once daily for 17 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 17 weeks

3. Linezolid 600 mg daily for 26 weeks
   - 1 linezolid 600 mg active tablet once daily for 26 weeks
   - 1 placebo linezolid 600 mg tablet once daily for 26 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 26 weeks

4. Linezolid 600 mg daily for 9 weeks
   Weeks 1-9
   - 1 linezolid 600 mg active tablet once daily for 9 weeks
   - 1 placebo linezolid 600 mg tablet for 9 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 9 weeks

   Weeks 10-26
   - 2 placebo linezolid 600 mg tablets once daily for 17 weeks
   - 1 placebo linezolid 300 mg half tablet once daily for 17 weeks

1.2 RANDOMISATION, STRATIFICATION AND BLINDING

Participants will be randomised to one of the four regimens in a 1:1:1:1 ratio, using an interactive web response system (IWRS), stratified by HIV status (positive vs. negative) and type of TB (XDR-TB vs. MDR-TB). A total of up to 180 participants, male and female, aged 14 and over, will be enrolled. Bedaquiline and pretomanid treatment will not be blinded. Linezolid treatment dose and duration will be double-blinded. After all participants complete their treatment phase, the statisticians will no longer be blinded to treatment allocation (see blinding plan for more detail).

Each participant will receive 26 weeks of treatment. If participant's sputum sample is culture positive between week 16 and week 26 treatment visits and their clinical condition suggests they may have an ongoing TB infection, Investigator may consider extending current treatment to 39 weeks. If the culture results between week 16 and week 26 are contaminated, missing or considered an isolated positive without clinical significance, available culture results should be used to make this decision. All decisions regarding treatment extension should be discussed and approved by the Sponsor Medical Monitor before implementation. Participants will be followed for 18 months after end of treatment.

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT). No formal statistical comparisons between the randomised groups will be made.

2 OUTCOME MEASURES

2.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint will be the incidence of bacteriologic failure or relapse or clinical failure at 6 months after the end of therapy. See section 6 for the detailed definition of an "unfavourable response".

There will be three main analyses of the primary efficacy endpoint: An intent to treat (ITT) analysis; a modified intent to treat (MITT) analysis and a per protocol (PP) analysis.

The "unfavourable" rates in any defined 'ITT' population will likely be increased by factors other than bacteriologic or clinical treatment failure and relapse. The MITT analysis will therefore be considered primary for publication purposes. However, we recognize that FDA and other regulatory agencies will consider the ITT analysis primary.

NB: In the event that more than 10% of participants within any randomised group are culture positive at 4 months and have their treatment extended for a further 3 months, the primary endpoint analysis will be defined as 15 months from start of therapy for all. For each participant the assessment closest to this time point will be taken as this 15 month (from start of therapy) endpoint.

2.2 SECONDARY EFFICACY ENDPOINTS

Secondary endpoints which will be analysed according to the MITT population (unless otherwise stated) include:

- Proportion of favourable at 18 months after the end of treatment (ITT, MITT and PP populations)
- Incidence of bacteriologic failure or relapse, or clinical failure through follow up until 18 months after the end of treatment.
- Time to unfavourable status (ITT, MITT and PP populations)
- Time to sputum culture conversion to negative status through the treatment period
- Culture conversion status at 4, 6, 8, 12, 16 and 26 weeks (ITT population)
- Change in weight and BMI from baseline
- Change in TB symptoms from baseline
- Change in participant reported health status from baseline

2.3 SECONDARY SAFETY AND TOLERABILITY OUTCOMES

All safety summaries in this section will be presented for all participants in the Safety analysis set, 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:

- 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
- Post-treatment AEs which are AEs that start or worsen more than 14 days after the last administration of IMP.

Secondary safety and tolerability are outlined below in §2.3.1-2.3.6. 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*

The 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 by the investigator.

2.3.2.4 *Seriousness*

The 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*

The proportion of participants experiencing a TEAE that led to discontinuation of the whole treatment and the proportion of participants experiencing a TEAE that led to the discontinuation of linezolid only. This will be AEs where action taken with study treatment is 'Permanently Discontinued' for BPaL, or for linezolid alone.

2.3.2.6 *Leading to study discontinuation*

The proportion of participants experiencing a TEAE that led to study discontinuation. This will be AEs where action taken with study treatment is 'Withdrawn from Study' or 'Other Action'.

2.3.2.7 *Leading to pauses of linezolid*

The proportion of participants experiencing a TEAE that led to a pause in linezolid.

2.3.2.8 *Leading to linezolid reductions*

The proportion of participants experiencing a TEAE that led to a reduction in linezolid dose.

2.3.2.9 *Leading to death*

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

2.3.2.10 *Liver-related, liver and drug 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 ('Possibly', 'Probably', and 'Certainly') 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 Tables 1 and 2 in §8.2.1) at least once during the treatment period.

2.3.4 Electrocardiogram

ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTcF interval), which are read by a central cardiology service, observed measurements and change from baseline. QT/QTcF intervals and their change from baseline will be categorised according to §8.4 below. The EGC results will be considered at baseline, week 8, week 16, end of treatment (week 26 or 39), and early withdrawal in all participants.

2.3.5 Peripheral neuropathy

The observed and change from baseline in peripheral neuropathy (from the peripheral neuropathy assessment form) at week 8, week 16, end of treatment (week 26 or 39), month 6 follow-up and early withdrawal.

2.3.6 Changes in ophthalmology

The change (increase or decrease) in visual acuity and colour vision, and lens opacity from baseline at end of treatment (week 26 or 39), follow-up (week 4 and 12, respectively) and early withdrawal.

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 EXPLORATORY OBJECTIVES

2.4.1 Subgroup analyses

Subgroup analyses will be carried out and analysed for the primary efficacy endpoint (as described in §2.1 for the MITT population). These subgroups are described in §7.4.

3 DEFINITIONS AND DATA HANDLING ISSUES

3.1 DEFINITIONS

3.1.1 Positive culture

Positive culture refers to the culture being positive for MTB.

The MGIT culture results that are positive with contamination, contaminated, or with no result will be treated as missing.

Two sputum samples are collected at each scheduled visit, excluding at weeks 5,7,14 and 18, 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 culture at the same visit. Refer to Appendix 12.1 for further details.

3.1.2 Culture negative status

Culture negative status is achieved when a participant produces at least 2 negative culture results at different visits (at least 7 days apart) without an intervening positive culture result for MTB. The date of the first negative 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.

Participants with two contaminated or missing samples at a given visit will be asked to return to produce two more sputum samples.

3.2 BACTERIOLOGICAL FAILURE, RELAPSE OR REINFECTION

3.2.1 Treatment failure

Treatment failure is defined as being declared an unfavourable status (as defined in §6) at or before the end of treatment or failing to attain culture negative status and being declared an unfavourable outcome or 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.

3.2.2 Relapse

Relapse is defined as

- failing to maintain culture negative status or
- being declared an unfavourable outcome 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 an MTB strain that is genetically identical to the infecting strain at baseline or
- being declared an unfavourable outcome 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 12.2.

3.2.3 Reinfection

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 MTB 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 12.2.

3.2.4 Inability to produce sputum

In general, inability to produce sputum is treated as being equivalent to having a negative culture result (if and only if no other culture result is produced at that visit)

. This includes:

- the rare situation where a participant never achieves culture negative status due to inability to produce sputum, but completes follow-up without clinical or microbiological evidence of relapse.
- during the COVID-19 lockdown situation where this data is collected remotely/telephonically

3.2.5 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 2 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 positives with liquid culture and sometimes even serial "isolated positives" the clinical condition of the participant will also be considered in deciding whether the participant has an unfavourable outcome and re-treatment is indicated.

To expand a bit, most of the experience with isolated positives has been with solid culture. Because liquid culture is more sensitive, it is possible that more than one isolated positive may occasionally occur. Therefore, the clinical condition of the participant will also be considered when deciding whether re-treatment is indicated and in determining the outcome. 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.

3.3 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 ITT and MITT analyses, but not in the Per Protocol analysis. A list of all major protocol deviations for analysis will be approved by a review committee before all planned analyses.

3.4 TRIAL TIMINGS

In all analyses, visit date rather than day or week number will be used to define the timing of events. For all participants, the 6-month regimen will be taken as a total of 26 weeks, i.e. 182 dosing days (for B-Pa), from the start of therapy, after accounting for any treatment interruptions. For those who extend treatment to 9 months this will be 39 weeks (273 days) (for B-Pa) from start of therapy, again after accounting for any treatment interruptions.

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.

For the end of treatment visit (months 6/9), a ±1-week window will be applied (as per the protocol). For the 3-monthly visits after the end of therapy, a window of ±2 weeks will be applied (as per the protocol). Additional programming will be required for cases where end of treatment date is not clearly recorded.

In the event that more than 10% of participants within any randomised group have their treatment extended for a further 3 months, the primary endpoint analysis will be defined as 15 months from start of therapy for all participants. In this case the visit date for the endpoint analysis will be chosen as the one closest to 65 weeks (26+39) from start of therapy (unless participant is declared unfavourable before this date).

The ***treatment period*** is defined as 6 months (total of 26 weeks) of the B-Pa therapy (linezolid may be stopped early) plus any days made up for interrupted doses of B-Pa therapy (or 9 months in those who are extended).

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

3.5 DEFINITION OF 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.

For participants treated for 6 months with no treatment extension, 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).

For participants who have their treatment extended to 9 months (39 weeks), to meet the definition of adequate treatment, they must have taken at least 219 doses (80%) of their allocated 273 day (39 weeks) treatment within 364 days (i.e. 39 weeks plus an allowable 91 day halt (including a maximum of 35 consecutive days) as per the protocol).

A dose is defined as taking the required daily dose of both pretomanid and bedaquiline.

3.6 DETERMINING CAUSE OF DEATH

A list of all ***TB-related*** and ***non-TB-related deaths*** will be generated and approved by a review committee of physicians not associated with the trial before database lock. Similarly, a list of violent or accidental deaths will be generated.

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. A complete case analysis will be performed.

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

3.8 Newly notable abnormalities

Newly notable laboratory abnormality is defined as an abnormality observed post baseline that meets the notable criteria in Table 1 and that did not exist at baseline. Participants can still meet the criteria for a newly notable laboratory abnormality if the baseline value is missing.

4 Sample Size

In order to fulfil the objective of the study, it is planned to randomise 45 XDR-TB, pre-XDR and/or MDR treatment intolerant/non-responsive -TB participants per group. A sample size of 45 per arm will provide more than 90% power to demonstrate that the lower bound of the 95% confidence interval of this estimate is greater than 50%, using a 2-sided 5% significance level. This assumes that the true cure rate is 80 percent.

5 ANALYSIS POPULATIONS

Participants who are never culture positive during the baseline period, (day 1 through week 4) but are eligible based on documented MTB by culture or molecular test within 3 months prior to screening will be included in all analysis populations.

The analysis populations for efficacy analyses are:

- The **Intent to treat (ITT)** population is defined as all randomised participants excluding late screening failures (see §6.1)
- The **Modified intent to treat (MITT)** population is defined as the ITT population with extra exclusions (See §6.2)
- The **Per-protocol (PP)** population is defined as the MITT population with extra exclusions (see §6.3)
- The **Safety** population, defined as all randomised participants who received at least one dose of study treatment. Participants will be analysed as to the treatment they actually received regardless of randomised allocation.

Exclusions from these populations will be reported as "unassessable" status and are described below.

6 ENDPOINT DEFINITIONS

Participants will be classified as having a favourable, unfavourable or unassessable status at 6 months after the end of therapy. Participants excluded from analysis are considered unassessable.

6.1 ITT POPULATION

The ITT population is defined as all randomised participants excluding late screening failures.

6.1.1 Unassessable status (late exclusions)

Participants found to be ineligible (late exclusions from the study), based on data collected prior to randomisation, including participants who do not have documented evidence of MTB within 3 months of screening.

6.1.2 Favourable status (all analysis populations)

Participants with a negative culture status at 6 months from end of therapy who had 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.

6.1.3 Unfavourable status

Participants in the ITT analysis population who do not have a favourable outcome at 6 months from end of therapy will be considered to have an unfavourable response in the ITT analysis.

6.2 MITT POPULATION

6.2.1 Unassessable status (additional exclusions from MITT analysis)

In addition to those excluded from the ITT analysis (see §6.1.1), 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 COVID19 during treatment and 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 die 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), and who have not already been classified as unfavourable.
6. Participants who, after being classified as having culture negative status, are re-infected with a strain that is genetically different from the initial strain (see Appendix 12.2).
7. Participants who are able to produce sputum at their primary endpoint visit, whose sputum samples are all contaminated or missing, who cannot be brought back for repeat cultures, provided they have not already been classified as unfavourable and 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, or to participants who are able to be brought back subsequently and produce negative cultures.

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

6.2.2 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 who have had surgery and the resected tissue is cultured and is positive for MTB.
8. Participants lost to follow up or withdrawn from the study before the end of treatment.

6.3 PP Population

6.3.1 Unassessable status (additional exclusions from PP)

In addition to the exclusions from the MITT population, the following will apply to the PP population:

1. Participants lost to follow-up or withdrawn before the end of treatment due to reasons other than treatment failure, 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 (e.g. an adverse drug reaction) other than an unfavourable therapeutic response to treatment, 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 §3.7 for definition), provided this is not due to unfavourable outcome.
4. Participants who are classified as "major protocol deviations for analysis" (see §3.3), unless they have already been classified as having an unfavourable outcome on the basis of data obtained prior to the protocol deviation.

A list of all protocol deviations will be compiled throughout the course of the study.

6.3.2 Unfavourable status

Points 1-7 in §6.2.2 Unfavourable status in the MITT Population section above.

6.4 LOST TO FOLLOW-UP OR EARLY WITHDRAWAL

Lost to Follow-up or Early Withdrawals before the end of the treatment (month 6 or 9) are considered as unfavourable outcomes for ITT and MITT. However, these participants will be excluded from the Per Protocol analysis. The MITT and Per Protocol analyses will consider Lost to Follow-up after end of treatment as unassessable unless at the time of default from follow-up the participant a) was already classified as having an unfavourable outcome, b) did not have culture negative status, or c) had a positive culture result ("isolated positive culture") not followed by at least two negative culture results at different visits (at least 7 days apart), in which cases the participant will be classified as having an unfavourable outcome. We believe this is the most appropriate approach for the primary analysis because together with the non-tuberculosis deaths, this group is likely to considerably out-number the bacteriological failures and relapses. These participants will be considered as having an unfavourable outcome in the ITT analysis.

There is a clear precedent for this analytic approach in other TB trials, and these trials also provide examples of why the inclusion of the losses to follow-up as unfavourable greatly affects 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.

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 had an unfavourable outcome and finally assuming all losses had a favourable outcome.

In the study conducted by the IUATLD the published failure/relapse rates 12 months after stopping treatment based on 1044 assessable participants were 4% 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 increase 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.

6.5 BASELINE COMPARISONS OF KEY CHARACTERISTICS

The following baseline characteristics of participants will be summarised: age, sex, race, geography, weight, height, BMI, smoking status, alcohol use, TB type (XDR /non-XDR), HIV status/CD4 count/on ARV, cavitation, initial bacterial load in sputum as indicated by baseline Time to Positivity (TTP) result from MGIT, baseline drug resistance.

7 EFFICACY STATISTICAL ANALYSES

7.1 PRIMARY ENDPOINT ANALYSIS

The MITT analyses will be considered primary.

The primary efficacy analysis will be conducted using culture results including all TB types.

We will evaluate the hypothesis, separately for each of the experimental B-L-Pa treatment arms, that the incidence of bacteriologic failure or relapse or clinical failure (including mortality) -unfavorable outcome - at 6 months (26 weeks) after the end of therapy is less than 50%.

Given the uncertainty about the dosing and duration of linezolid and effect on efficacy and safety and to control the overall type I error rate the following analysis strategy will be adopted for both the primary and secondary analysis populations:

The primary comparison will be for the linezolid 1200mg taken for 26 weeks arm (L1200 26 weeks) with the L1200 9 weeks and L600 26 weeks only being tested if L1200 26 weeks is a success. Similarly, L600 9 weeks will only be tested if L600 26 weeks is a success. A Bonferroni adjustment will be made for comparing the L1200 9 weeks and L600 26 weeks arms simultaneously, using $p<0.025$. For these comparisons the lower bound of the 97.5% confidence interval will need to exceed 50% for success.

No formal statistical pairwise comparisons between the arms will be performed.

The proportion of assessable participants with a favourable and unfavourable outcome, with 95% and 97.5% confidence intervals, will be presented. For success, the lower bound of the 95% confidence interval (or 97.5% as applicable) for a favourable outcome should be above 50%.

This MITT analysis is consistent with the TB literature over the past 50 years. **However, we recognise that FDA and other regulatory agencies will consider the ITT analysis primary, where all participants who are not proven to have a favourable outcome will be classified as having an unfavourable outcome.**

7.1.1 Sensitivity analyses of primary endpoint

In addition to analysing the primary endpoint data by ITT, MITT and PP and separately for XDR-TB participants (key secondary efficacy analyses), it is planned to conduct the following sensitivity analyses:

1. An analysis of participants in the MITT and PP populations where reinfections are classified as unfavourable outcomes

2. An analysis of the MITT and PP populations treating all deaths as unfavourable

3. An analysis of the ITT, MITT and PP populations excluding participants who were never culture positive during the baseline period (day1 through week 4), but were eligible based on documented MTB by culture or molecular test within 3 months prior to screening

7.1.2 Secondary efficacy analyses of primary endpoint

7.1.2.1 *Time to event unfavourable outcome analysis*

Time to an unfavourable outcome will be analysed with Kaplan Meier plots. These analyses will be performed according to ITT, MITT and PP endpoint 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 6 month after end of therapy visit.

7.2 SECONDARY EFFICACY ENDPOINTS

The following analyses will be performed on ITT only unless otherwise stated.

7.2.1 Incidence of bacteriologic failure or relapse at 18 months after the end of treatment

Efficacy analyses as described for the primary endpoint will be repeated at the 18 month after the end of treatment endpoint as a confirmatory analysis, for ITT, MITT and PP populations

7.2.2 Time to sputum culture conversion to negative status

For participants with positive culture results from day 1 to week 4 (baseline excluding screening), time to culture negative status (first of two negative cultures without an intervening positive culture) will be analysed using survival analysis techniques and Kaplan Meier plots. This analysis will be done for the MITT population.

7.2.3 Culture conversion status at 4, 6, 8, 12, 16 and 26 weeks

Participants will be classified as being culture positive, culture negative, dead or unassessable (including those without positive culture results from day 1 to week 4) at 4, 6, 8, 12, 16 and 26 weeks. Every effort will be made to obtain a sputum sample from all participants, but it is recognised that some participants may not have produced any sputum in the preceding week and may be unable to do so when requested. Participants who are unable to produce sputum will be classified as being culture negative at that time point. The proportion of culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died.

7.2.4 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, week 16, end of treatment, 6, 12 and 18 months from end of treatment.

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.

7.2.5 Participant reported health status

Participant reported health status is measured by the 5 domains of EQ5D. These will be summarised at baseline, week 8, week 16, end of treatment, 6, 12 and 18 months from end of treatment by randomised group and change from baseline at each follow-up assessment by mean, median, IQR and range by randomised group.

7.2.6 Weight and BMI

Baseline weight and BMI and their change from baseline at weeks 8 and 16, end of treatment, and at 6 and 18 months after the end of therapy will be summarised by mean, median, IQR and range

7.3 WEEK 26 ANALYSIS

This analysis is culture conversion status at week 26 with details outlined in §7.2.3 above, with the inclusion of culture conversion status at weeks 20 and 23.

This week 26 analysis will only be performed once all participants have reached the week 26 time point.

7.4 SUB-GROUP ANALYSES

To assess consistency of results, exploratory sub-group analyses of the primary endpoint on the MITT analysis population will be considered. For example, depending on numbers consideration will be given to subgroup analyses by:

- age
- sex
- race
- smoking status
- alcohol use
- HIV status
- cavitation
- initial bacterial load in sputum as indicated by baseline TTP result from MGIT
- ARV taken or not during the treatment period
- geographical location
- Baseline resistance to Bedaquiline (pending numbers)

7.5 REASONS FOR TREATMENT FAILURE AS DETERMINED BY THE LOCAL PI

Reason(s) that led the site investigator to conclude that an individual participant failed treatment or relapsed will be classified as a) bacteriology alone, b) clinical deterioration alone, c) radiological deterioration alone, d) bacteriology plus clinical deterioration, e) bacteriology plus radiological deterioration, f) clinical deterioration plus radiological deterioration, or g) bacteriology plus clinical deterioration plus radiological deterioration. These classifications will be tabulated and compared to outcomes described in §7.1.

7.6 MINIMUM INHIBITORY CONCENTRATIONS

Minimum Inhibitory Concentrations (MICs) for all three drugs will be tabulated separately. Baseline and week 16 values will be tabulated for all participants that have them measured. If multiple visits have the measures, week 16 will be used. For descriptive purposes only. A listing will be provided for the participants who have MICs for both time points.

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.

8.1.1 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. Serious SAEs will be presented in the data listing.

8.1.2 TEAEs Leading to Early Withdrawal

A summary of TEAEs with 'Action Taken with study treatment' as 'Permanently Discontinued' will be presented. 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 linezolid ('Action Taken with Study Treatment Linezolid' is 'Interrupted' and action taken for Bedaquiline/Pretomanid is 'Unchanged') and Full Regimen ('Action Taken with study treatment Linezolid and Bedaquiline/Pretomanid' is 'Interrupted') and reduction of linezolid ('Action Taken with study treatment Linezolid' is 'Reduced').

8.1.3 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 categorised and presented by SOC and PT in the same manner to that described in §8.2.1.

A separate 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 was violent or accidental (excluding suicide)
- Death was due to suicide

8.1.4 Liver-related TEAEs

A summary of TEAEs that has preferred terms under "Hepatic" according to MedDRA dictionary will be presented by SOC and PT in the same manner to that described in §8.2.1.

8.1.4.1 *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 each treatment drug (Bedaquiline, Pretomanid, and Linezolid) in the same manner to that described in §8.2.1.

8.1.4.2 *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 participants with treatment emergent serious adverse events that have toxicity grade 3 or higher for either AST, ALT, ALP or total bilirubin.

8.1.4.3 *Incidence of hepatotoxicity*

Proportion of participants experiencing at least one liver function test (AST or ALT) that is >3 x ULN or at least one hepatic SAE (as described in §8.2.1).

8.1.5 Additional TEAE summary

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.

8.1.6 Additional AE summary after 14 days post end of treatment

The number and percentage of participants that had an AE graded 3 or 4 after 14 days post end of treatment.

8.2 CLINICAL EVALUATION

8.2.1 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 day 1, week8, end of treatment, month 6 follow-up and month 18 follow-up.

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 1: 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 and ≤5 x ULN >5xULN

8.2.2 Myelosuppression

Number and percentage of participants with myelosuppression as well as the number of occurrences of myelosuppression will be summarised. Participants are considered to have myelosuppression if his/her response falls within the specified criteria in Table 2 at least once during the treatment period.

Table 2: Notable Criteria for Laboratory Data – Myelosuppression

Laboratory Variable	Criteria
HGB	<8g/dL (Grade 3) and significantly below baseline or HGB falls >25% beneath baseline
ANC	< 750/mm^3 (Grade 3) and significantly below baseline
Platelets	< 50,000/mm^3 (Grade 3) and significantly below baseline

8.2.3 Vital Sign Measurements

Vital sign measurements include body temperature (◦C), respiratory rate (breaths/min), blood pressures (mmHg) (resting more than 5 minutes), and heart rate (bpm).

These measurements will be summarised for baseline and change from baseline at week8, end of treatment, month 6 follow-up and month 18 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.

8.3 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 prior to dosing at each time point will be summarised using descriptive.

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

- increase > 60 msec.

Frequency counts will be used to summarize the number of participants at each time point according to the above categories.

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 post-baseline assessments.

Participants with any QTcF values ≥ 500 will be presented in a figure.

8.4 Ophthalmology Tests

Results from the assessments of Ophthalmology slit lamp examinations (lens opacity classification and grading), visual acuity and colour vision will be summarised for baseline, end of treatment, and follow-up.

8.5 Peripheral Neuropathy

Peripheral neuropathy assessments as reported by the participants (from the peripheral neuropathy assessment form) will be summarised at baseline, week 8, end of treatment, and month 6 follow-up.

8.6 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 and minor 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/m2) 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 (Black or African American, White), country, 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 (MDR-TB (NR), MDR-TB (TI), pre-XDR-TB, XDR-TB)
- Smoking status (never, current, former)
- Alcohol status (never, current, former)
- Screening Coached Spot Sputum result
    - Smear microscopy for acid-fast bacilli (no AFB seen, scanty positive, 1+, 2+, 3+)

    - Hain assay MTBDRplus or equivalent result (sensitive, resistant, indeterminate, not done)
    - Gene Xpert Rifampicin resistance result (sensitive, resistant, indeterminate)
- Serology
    - HIV status (positive, negative as collected in CRF)
    - CD4 count (summary statistics)
    - Viral load (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

Participants who violate 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.

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 for TB medications and non-TB medications.

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.

11.1.3 Concomitant Procedures

The number and percentages of participants with at least one concomitant procedure (defined similarly as concomitant medications above) will be summarised.

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 will be summarised for all participants in the safety set and will be presented in a table by summary statistics. The groupings are
1. <9 or <26 weeks (less than allocated)
2. 9 or 26 weeks (as expected)
3. 9 or 26 weeks to 38 weeks (missed dose extension)
4. 39 weeks (official treatment extension)

Drug compliance (%) for bedaquiline and pretomanid will be collected from the eCRF and summarised using descriptive statistics. Number and percentage of participants in each compliance category (<80%, 80 to <90%, ≥90%) will be presented. Percentages will be calculated out of the number of participants who were dosed at that dosing period in the safety set. Linezolid exposure data will not be included in the compliance determination since participants are allowed to stop/re-start administration.

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

- Treatment extension (number of participants with an official treatment extension to 39 weeks).
- Linezolid pause (number and percentage of participants with at least one dose pause, number of dose pauses, reason for dose pause). The Linezolid pause information will be retrieved from the CRF IMP Dosing pages indicated by a pause of Linezolid and scheduled dispense of Bedaquiline and Pretomanid.
- Linezolid dose reduction (number of participants with at least one dose reduction, number of participants with at least one 1-step dose reduction, number of participants with at least one 2-step dose reduction, number of dose reductions including the number of 1-step decrease in dose and 2-step decrease in dose, reason for dose reduction).
- Participants experiencing suspected drug related toxicities due to B-Pa treatments can have the full study medication paused for up to 35 consecutive days. Full regimen pauses will be summarised by number and percentage of participants with at least one full regimen pause, number of full regimen pauses and reason for regimen pause. Information related to these are found on the CRF IMP Dosing pages as pause selected on each dosing page, Linezolid, Bedaquiline and Pretomanid.

12 APPENDICES

12.1 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/Contaminated	Contaminated

12.2 Interpretation of Relapse/Re-infection using Whole Genome Sequence (WGS)

The purpose of the WGS analysis is to determine if the two MTB 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 (re-infection/bacteriological re-infection). To do this, WGS of the two MTB 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 and RIFAQUIN trials) that show a clear genetic distinction between relapse and re-infection cases of MTB infection.

- ≤12 SNPs different = Relapse
- ≥100 SNPs different = Reinfection
- >12 and <100 SNPs different = Indeterminate.

These 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 re-infection' based on this further review. A participant will be considered a relapse unless there is sufficient evidence to support a classification of re-infection