Protocol

Protocol for: Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. N Engl J Med 2022;387:810-23. DOI: 10.1056/NEJMoa2119430

This trial protocol has been provided by the authors to give readers additional information about the work.

Bedaquiline-Pretomanid-Linezolid for Drug-resistant Tuberculosis: Protocols and Statistical Analysis Plans

This supplement contains the following items:

1. Final protocol, original protocol, summary of changes.
2. Final statistical analysis plan, original statistical analysis plan, summary of changes.

Protocol Number	NC-007-(B-Pa-L)
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).
Drug(s)/Combination(s):	Bedaquiline (B), pretomanid (Pa) and linezolid (L)
Protocol Amendment Version/Date:	V3.0 dated 10 March 2020, (incorporating Protocol Version 1.0 dated 23 Feb 2017, Protocol Amendment 1.0 dated 13 June 2018 and Protocol Amendment 2.0 dated 10 March 2020)
Protocol Name:	ZeNix

TABLES

FIGURES

Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse drug reactions
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
AREDS2	Age related eye disease scale 2
ART	Anti-retroviral therapy
AST	Aspartate amino transferase
AT	Amino transferase
AUC_{τ}	Area under curve over a dosing interval
B	Bedaquiline
BMI	Body mass index
bpm	Beats per minute
BPNS	Brief peripheral neuropathy scale
C	Clofazimine
CFU	Colony forming units
CK(-MB)	Creatine kinase (-MB isoenzyme)
$C_{(max), (min)}$	Plasma concentration (maximum), (minimum)
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CS	Clinically significant
C_{trough}	Plasma concentration trough
CYP3A4	Cytochrome P450 3A4
DMID	Division of microbiology and infection disease
DNA	Deoxyribonucleic acid
DOH	Department of health
DILI	Drug induced liver injury
DSMC	Data safety monitoring committee
DST	Drug susceptibility testing
E	Ethambutol
EBA	Early bactericidal activity
EC	Ethics committee
ECG	Electrocardiogram
EFV	Efavirenz
(e)CRF	Electronic case report form
FQ	Fluoroquinolone
FTC	Emtricitabine
g/L	Grams per liter
GI	Gastrointestinal
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMR	Geometric mean ratio
H	Isoniazid
hERG	Human *ether-à-go-go* related gene
HIV	Human immunodeficiency virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
ICF	Informed consent form
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
IRB	Institutional review board

IUATLD	International Union Against Tuberculosis and Lung Disease
IXRS	Interactive Voice and Web Response System
kg	Kilogram
/L	Liter
L	Linezolid
LLN	Lower Limit of Normal
LPV	Lopinavir
M	Moxifloxacin
MAO(I)	Monoamine oxidase (Inhibitor)
MBD	Minimum bactericidal dose
MIC	Minimum inhibitory concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi drug resistant tuberculosis
MGIT	Mycobacterial growth inhibiting tube
mITT	Modified intent to treat
mL	Milliliter
ms	Millisecond
NCS	Not clinically significant
NEJM	New England Journal of Medicine
NVP	Nevirapine
NO	Nitric oxide
NOAEL	No observed adverse effect level
NRTI	(Triple) nuleosidase reverse transcriptase inhibitor
Pa	Pretomanid
PD	Pharmacodynamic
PP	Per protocol
PK	Pharmacokinetic
PR	PR interval
QD	Once daily
R	Rifampicin
S	Streptomycin
SAE	Serious adverse event
SAP	Statistical analysis plan
SIRE	Streptomycin isoniazid rifampicin ethambutol
SOC	System organ class
TB	Tuberculosis
TBL	Serum total bilirubin
TDF	Tenofovir
TEAE	Treatment emergent adverse events
T>MIC	Time above minimum inhibitory concentration
t.i.w.	Three times a week
(BA) TTP	(Bacteriocidal activity) time to positivity
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis
µg	Microgram
Z	Pyrazinamide

1 Synopsis

1.1 Synopsis Summary

<table>
<tr><td>Name of Sponsor/Company</td><td>Global Alliance for TB Drug Development</td></tr>
<tr><td>Name of Finished Products:</td><td>bedaquiline (B), pretomanid (Pa) and linezolid (L)</td></tr>
<tr><td>Protocol Number/Title:</td><td>NC-007: 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)</td></tr>
<tr><td>Treatment Indication:</td><td>Pulmonary XDR-TB, pre-XDR-TB, and treatment intolerant or non-responsive MDR-TB</td></tr>
<tr><td>Trial Objective:</td><td>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.</td></tr>
<tr><td>Trial Design:</td><td>A phase 3, multi-center, partially-blinded, randomized clinical trial in four parallel treatment groups. 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 14 days and will be randomized to receive one of the 4 active treatment arms. Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive voice and web response system (IXRS) which will utilize a randomization system using stratification with a random element to allocate participants evenly across the arms by HIV status and type of TB.

Each participant will receive 26 weeks of treatment. If participant's sputum sample is culture positive between the 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 with and approved by the Sponsor Medical Monitor before implementation.

Participants will be followed for 78 weeks after end of treatment.</td></tr>
<tr><td>Patient Population:</td><td>A total of up to 180 participants, male and female, aged 14 and over Sponsor may consider replacement of late screen failure and un-assessable (as detailed in the statistical analysis plan) participants.</td></tr>
<tr><td>Test product, Dose and Mode of Administration:</td><td>The regimen will be supplied as the following:
<table>
<tr><th>Product</th><th>Tablet Strength</th><th>Abbreviation</th></tr>
<tr><td>Bedaquiline</td><td>100 mg</td><td>(B)</td></tr>
<tr><td>Pretomanid</td><td>200 mg</td><td>(Pa)</td></tr>
<tr><td>Linezolid (scored)</td><td>600 mg</td><td>(L)</td></tr>
<tr><td>Placebo Linezolid (scored)</td><td>placebo</td><td>(L)</td></tr>
<tr><td>Linezolid 600 mg half tablet (pre-cut)</td><td>300 mg</td><td>(L)</td></tr>
</table></td></tr>
</table>

Placebo linezolid half tablet (pre-cut)	placebo	(L)

Linezolid treatment will be supplied as 2 rows of full tablets (active or placebo) and one row of half-tablets (active or placebo) to allow for all possible dosing options while maintaining the blind.

Instructions for Dosing:
Treatment will be administered orally, once daily, with a full glass of water and a meal in the following dosing schemes (treatment arms):

Participants will receive the following:
- Bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;
- Pretomanid 200 mg once daily for 26 weeks plus;
- Linezolid- participants will be randomly assigned to receive one of the following four blinded linezolid treatment doses and durations:

Linezolid 1200 mg daily for 26 weeks
- 2 linezolid 600 mg active tablets once daily for 26 weeks
- ½ (one half) placebo linezolid tablet once daily for 26 weeks

Linezolid 1200 mg daily for 9 weeks
Weeks 1-9
- 2 linezolid 600 mg active tablets once daily for 9 weeks
- ½ (one half) placebo linezolid tablet once daily for 9 weeks

Weeks 10-26
- 2 placebo linezolid tablets once daily for 17 weeks
- ½ (one half) placebo linezolid tablet once daily for 17 weeks

Linezolid 600 mg daily for 26 weeks
- 1 linezolid 600 mg active tablet once daily for 26 weeks
- 1 placebo linezolid tablet once daily for 26 weeks
- ½ (one half) placebo linezolid tablet once daily for 26 weeks

Linezolid 600 mg daily for 9 weeks
Weeks 1-9
- 1 linezolid 600 mg active tablet once daily for 9 weeks
- 1 placebo linezolid tablet for 9 weeks
- ½ (one half) placebo linezolid tablet once daily for 9 weeks

Weeks 10-26
- 2 placebo linezolid tablets once daily for 17 weeks
- ½ (one half) placebo linezolid tablet once daily for 17 weeks

Treatment Modifications:
The above treatment schemes may require modification due to toxicities as noted below. All dose modifications should be discussed with the Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation

	In the event of linezolid specific toxicities, the following should be considered and implemented per guidance in the monitoring and safety for specific toxicities section (8.3) of protocol:
	
	• **Blinded** one step reductions (maximum 2 steps) in the dose of linezolid managed by the IXRS as per instructions in pharmacy manual and/or IXRS user manual.
	  ○ 1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or
	  ○ 600 mg QD to 300 mg QD, 300mg QD to placebo
	• Temporary pause of linezolid.
	• Permanent discontinuation of linezolid.
	• Participants who have a linezolid reduction can go back to a higher dose (1 step or 2 steps) post discussion with and approval by the Sponsor Medical Monitor.
	
	For participants experiencing suspected drug related toxicities due to other drugs in the regimen (B-Pa), the full regimen may be halted for up to 35 consecutive days.
	
	Interruptions/pauses of all Investigational Medicinal Product (IMP) must not exceed 8 weeks (56 days) cumulatively.
	
	When treatment is extended to 39 weeks, interruptions/pauses of all IMP must not exceed 13 weeks (91 days) cumulatively.
	
	When the total of missed dosing days of the prescribed regimen and/or pauses is greater than 7 days, the same number of missed doses should be dispensed/treatment extended to make up for the total missed doses.
	
	At no time should the participant be treated with a single agent.
	
	Every effort should be made for participants to receive a total of 9 weeks of linezolid, even if pauses are required

Criteria for Evaluation:

Primary Endpoint:

Incidence of bacteriologic failure or relapse, or clinical failure at 26 weeks after the end of treatment.

Abbreviated Definitions, full definitions will be described in the Statistical Analysis Plan (SAP):

- Bacteriologic failure: During the treatment period, failure to attain or maintain culture conversion to negative.
- Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status, with culture conversion to positive status with a strain of *Mycobacterium tuberculosis* (MTB) genetically identical to the infecting strain at baseline.
- Clinical failure: A change from protocol-specified TB treatment to a new regimen before end of protocol specified treatment due to treatment failure, retreatment for TB during follow up, or TB-related death.

Note:

- Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.
- Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit.

Further details of definitions to be provided in the SAP.

Secondary Endpoints:

- Incidence of bacteriologic failure or relapse, or clinical failure through follow up until 78 weeks after the end of treatment.
- Time to sputum culture conversion to negative status through the treatment period.
- Proportion of participants with sputum culture conversion to negative status at weeks 4, 6, 8, 12, 16 and end of treatment.
- Change from baseline TB symptoms.
- Change from baseline in Patient Reported Health Status.
- Change from baseline weight.

Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD):
Plasma concentrations of bedaquiline and its M2, pretomanid and linezolid from sparse sampling (see Table 1.2) will be measured and used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, and linezolid to further evaluate the effects of covariates on model parameters in this study population. PK data from the current trial may be combined with prior data (e.g., from the NiX-TB trial) to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{trough}, C_{max}, AUC_T, C_{mean}, and T>MIC) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

Safety and Tolerability:
These data will be presented as descriptive analyses, and no inferential tests will be carried out.

- All-cause mortality.
- Incidence of Treatment Emergent Adverse Events (TEAEs) will be presented 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 electrocardiogram (ECG) results read by a central cardiology service, including observed and change from baseline.
- Descriptive statistics of ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2]) lens opacity classification and grading). Categorical data for lens opacity will be summarized in a frequency table for the right and left eye, respectively, 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.

Mycobacteriology Assessments:
Sputum samples will be obtained at all scheduled visits. The following tests will be performed.

- Smear microscopy for acid-fast bacilli (AFB);
- Liquid Culture (MGIT), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP);
- GeneXpert, Hain Genotype MTBDR*plus* or an alternative molecular to confirm MTB and rifamycin resistance.
- Minimum Inhibitory concentration (MIC) of bedaquiline, pretomanid and linezolid;
- Drug Susceptibility Testing (DST) in liquid culture for rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide and second line TB drugs including fluoroquinolones and injectable;
- Genotyping.

Details on the testing and the collection and timing of samples are in sections 1.2 and 7.2

Statistical Methods:
A general description of the statistical methods planned for the primary efficacy outcome is outlined below. Specific details will be provided in the SAP.

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT). We will evaluate the hypothesis, separately for each of the experimental B-Pa-L treatment arms, that the incidence of bacteriologic and clinical cure at 26 weeks after the end of therapy is greater than 50%.

The incidence will be estimated from the binomial proportion for participants with success criteria based on the lower bound of the confidence interval for this proportion being greater than 50%.

There will not be a standard-of-care control group. A 50% treatment success rate was chosen as the target, because it is above the entire range of the historical control for cure of XDR-TB and because a cure rate of 50% in XDR, pre-XDR or MDR-TB treatment intolerant/failures with a shortened, simplified, all oral, inexpensive and safer regimen would clearly represent an important therapeutic advancement.

The primary analysis population will include both XDR and non-XDR participants (up to 45 per arm). A secondary analysis will be restricted to the XDR participants only (30 per arm). 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.

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 6 months) with the L1200 2 months 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.

Both a Modified Intent to Treat (mITT) and a Per Protocol (PP) analysis for each arm will be conducted. No formal statistical pairwise comparisons between the arms will be performed.

Trial Duration:
~4 Years (An enrolment period of approximately 24 months plus 14 days pre-treatment plus 6 months treatment period plus 18 months post treatment follow-up).

1.2 Synopsis Flowchart

Period	Screening[a]	Treatment																Visits every 3 weeks if treatment extended[b]	End of OR Early Withdrawal from Treatment[c]	Post Treatment Follow-up							
Time of Visit	Up to 14 days prior to first dose	Day 1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 23			4 weeks	8 weeks	12 weeks	26 weeks	39 weeks	52 weeks	65 weeks	78 weeks/EW[c]
Visit Window[q]	N/A	+/- 3 days									+/- 5 days							+/- 7 days	Post last dose IMP +7 days	+/- 14 days							
Informed Consent	X																										
Demography	X																										
Med/Trtmnt/Smoking History	X																										
Inclusion/Exclusion[d]	X	X																									
Randomization		X																									
Karnofsky Assessment	X																										
HIV Status[e]	X																										
CD4 Count and Viral Load[f]	X																		X								
Chest X-Ray[g]	X																		X								
Urine Pregnancy Test[h]	X	X								X				X					X								
TB Symptoms Profile	X									X				X					X				X		X		X
Patient Reported Health Status	X									X				X					X				X		X		X
Slit Lamp Exam[i]	X																		X[i]			X					
Ophthalmic Exam[j]	X					X				X		X		X		X	X	X	X	X		X					
Vital Signs	X	X	X	X		X		X		X		X		X		X		X	X			X	X	X	X	X	X
Single 12-LeadECG[k]	X	X	X			X				X				X					X			X	X	X	X	X	X
Limited Physical Exam[l]			X	X		X		X		X		X		X		X		X				X	X	X	X	X	X
Full Physical Exam[l]	X	X																	X								
Laboratory Safety Tests (includes Full Blood Count)[m]	X	X	X	X	X	X		X		X		X		X		X	X	X	X								
Full Blood Count							X		X		X		X		X												
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication/Compliance[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
PK Sampling[o]		X		X						X		X				X			X[o]								
Early Morning & Spot Sputum[r]	X	X	X	X	X	X		X		X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Peripheral Neuropathy Assessment	X					X				X		X		X		X	X	X	X			X	X		X		X
Investigator Assessment[p]																							X				X

GENERAL: Vital signs, ECGs and blood draws are to be performed pre-dosing unless otherwise specified. Vital signs and/or ECGs should be done prior to blood draws (safety and PK) on days with those assessments.

a. **Screening:** Screening assessments can occur on different days within 14 days prior to Day 1 dosing (randomization). If a participant fails screening, a full re-screen may occur at a later date. **All** screening procedures must be repeated at re-screen visit, with the exception of the slit lamp examination, which can be used from a previous screening if within 8 weeks of anticipated randomization.
b. **Visit Schedule:** If the duration of treatment is extended (see section 6.3, Treatment Modifications for details), unscheduled visits should be added every 3 weeks (+/- 7 days).
    1. End of treatment visit (final treatment visit) should be done within 7 days **AFTER** the last dose of IMP.
    2. If participant completes 26 weeks of therapy at week 33 due to full regimen pauses, an EXAMPLE of visit scheduling would be weeks 26, 29 and 33 (3 weeks from week 29 plus 7-day window). In this scenario, the week 33 visit would be the end of treatment visit and should be completed within 7 days after last dose.
    3. If participant completes treatment at week 39 due to treatment extension, an example of visit scheduling would be visits at weeks 26, 29, 32, 35 and 39/End of treatment (3 weeks plus 7-day window).
    4. Follow-up visits should be scheduled based on timing of last dose of IMP (e.g., 4-week follow-up to be scheduled 4 weeks after last dose of IMP).
c. **Follow-up Visits Early Withdrawal Participants:** Once a participant has been discontinued, they will be **required to attend an Early Withdrawal visit.** If participant:
    1. Received/took ≤ 14 doses, no additional follow-up visits are required.
    2. Received 15 or more doses and is withdrawn during treatment, follow-up after end of treatment/EW visit at week 12, week 26 (if not already performed) and week 78 are required. The week 12 visit will only require the ophthalmologic exams. The week 26 and 78 follow-up visits will be to collect Serious Adverse Event (SAE) information (including verification of survival) and patient reported TB outcome information only and may be telephonic, a home or a site visit. This includes participants who are *withdrawn from the trial due to meeting the treatment failure endpoint*. Participant may need to return for visits to collect sputum samples to determine outcome status.
    3. For participants who are withdrawn during post treatment follow-up, site should perform study procedures required for week 78 post treatment follow-up visit. If participant will not return for visit, site should obtain information on SAE and patient reported TB outcome as noted above in no 2.
d. **Inclusion/Exclusion:** to be confirmed at screening and prior to randomization.
e. **HIV testing:** If HIV status is a confirmed known positive, repeated HIV test is not needed provided that a documented HIV test result (ELISA, Western Blot or Electro-Chemiluminescence) is available. If HIV status is unknown or suspected negative, HIV test will be requested. If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated if documentation of testing method and negative HIV results can be provided. Repeated HIV testing, during the Screening period is permitted for indeterminate HIV results.
f. **CD4 count and viral load:** Required for all HIV-positive participants, viral load and CD4 required at screening, CD4 will be tested at end of treatment or early withdrawal from treatment visit.
g. **Chest X-Ray:** A chest x-ray (digital image) within 6 months prior to or at screening, will be obtained and read locally by Investigator or designee. Digital images will be provided to Sponsor, this process will be described in a separate document, the Radiology Manual.
h. **Urine Pregnancy:** Women of child-bearing potential only, whether they are sexually active or not.

i. **Slit-Lamp Exam:** Slit Lamp examination will be performed by an Ophthalmologist with AREDS2 training:
   1. For participants who receive ≤ 14 doses of IMP, exam at: Screening only.
   2. For participants who receive 15 days to ≤ 12 weeks of treatment, exams at: Screening and the 12-week post treatment follow-up visit.
   3. Participants who complete > 12 weeks of treatment exams at: Screening, End of Treatment or Early Withdrawal and the 12-week post treatment follow-up.

j. **Ophthalmic Exam:** to include Ophthalmologic Medical history at Screening; All exams to include Visual Acuity (distance testing) and Colour Vision assessment. Can be done by any trained study staff throughout study. Screening exam must be done by Ophthalmologist in addition to trained study staff that will perform exams throughout the study.

k. **Single 12-Lead ECG:** When possible, should be performed at approximately the same time of day (+/- 1 hours) and in the same fed/fasted state throughout the trial (e.g. 4 hours after lunch). Central ECG analysis will be performed. Central reading of screening results will be used to determine eligibility.

l. **Physical Exam:** Limited Physical exams should include weight and a gross neurological, pulmonary, cardiovascular and abdominal exam. Height will only be collected as part of full exam at screening.

m. **Safety Laboratory Assessments/Urine Drug Screen**: The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
   - Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count).
   - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO2, creatine phosphokinase (CPK). GGT will be done at screening.
   - When managing participants with elevated liver enzymes at an unscheduled visit, the Investigator can request additional tests, in addition to the repeated LFT [e.g. Gamma Glutamyl Transferase, screening for hepatitis A, B, C; to assist in ruling out other causes of abnormal liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection).
   - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis.
   - Urine Drug Screen: Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at **Screening only.** Investigator to utilize to determine whether participant meets Exclusion criteria 2. Positive results will **not** automatically exclude participant from the trial.

n. **Study Medication/Compliance:** Study medication administration will be supervised per local site practice to assure compliance to regimen.

o. **PK Sampling:** The dates and times of the two doses of IMP taken prior to all pre-dose PK samples will be collected in the eCRF.
   Specific PK blood draws will be obtained as follows (pre-dose to be done after ECGs):
   1. Day 1; pre-dose (within 2 hours prior to dosing)
   2. Week 2: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose
   3. Week 8: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose
   4. Week 12: pre-dose (within 2 hours prior to dosing)
   5. Week 20 or at early withdrawal if prior to week 20: pre-dose (within 2 hours prior to dosing) and 2–3 hours post-dose

- When participant is discharged and seen as an outpatient, site should make every effort to collect 6-8 hour sample at week 8 when operationally and logistically feasible.
- Hospitalization information (e.g. discharge date) will be collected in the eCRF.
- If the full regimen or linezolid is paused, PK sampling should be delayed until full regimen or linezolid are resumed.
- PK sampling should be completed even if the participant's linezolid dose has been lowered or linezolid has been permanently discontinued.
- Sites may bring participant back at a scheduled or unscheduled visit (can occur outside of visit windows) to collect PKs to ensure draw is done when IMP is administered.

p. **Investigator Assessment:** Principal Investigator to review participant status and assess whether TB treatment at current visit is considered a "success" or "failure". If considered a failure, should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration. To be completed at 26 and 78 week post treatment follow-up visits and at any time Investigator determines that participant fulfills criteria for outcome of treatment failure.

q. **Visit Windows:** the windows noted on the flowchart for timing of visit also apply to timing ***within a visit***. **For example**, procedures that are difficult to schedule such as ophthalmology exams, should be scheduled within +/- 3 days of scheduled visit from Day 1 to Week 8 or +/- 14 days within scheduled visit at the week 12 post treatment follow-up visit. Sites should make every effort to ensure all other procedures are done on the same day when possible.

r. Sputum Sampling:

Visit	Sample			Tests						
	EMS	SPOT	ISOLATE*	AFB Smear microscopy	MGIT culture, speciation	Molecular testing	MIC: B, Pa, L	MGIT DST	Genotyping	Extended DST (paired with baseline isolate)
Screening (Day -14 to -1)		● ●		S	S	S				
Baseline (Day 1) or 1st positive between screening and wk4 if Day 1 negative or contaminated			●				C	C	C	L (when applicable, with isolate below)
All Visits Post Screening	●	●			S					
1st positive for MTB at/after week 16 for participant not responding to therapy and/or 1st positive during follow-up for potential new infection			●			S	C	C	C	L

C – Central Mycobacteriology Laboratory (specialized facility)
S – Study Mycobacteriology Laboratory (facility that receives sputum samples directly from site)
L – Lab (as applicable per Country) that performs extended DST beyond panel at Central lab
*Preferably from EMS Sample when available. Alternate isolate can be requested if initial one is contaminated, or the test needs to be repeated.

SPUTUM SAMPLES GENERAL: If EMS (early morning sputum) is not available, site should make every attempt to collect two spot samples at least 30 minutes apart.

PRE-SCREENING SAMPLES: If consent granted by participant, and when applicable, site can request pre-screening culture/isolate/DNA from current TB diagnosis/disease course to be sub-cultured and shipped and/or tested:

- at the study lab if/when those samples could support inclusion in trial.
- at the study/central lab for relevant participants with no baseline (no positive cultures from screening through week 4).

MOLECULAR TESTING:

- At Screening: GeneXpert, Hain MTBDR*plus* or equivalent to determine MTB complex and Rifampicin resistance.
- Positive MTB at/after week 16: Hain MTBDR*plus* and HainMTBR*sl*

LIQUID DST: for SIRE, Z and second line anti-TB drugs, including but not limited to fluoroquinolones and injectables.

STORAGE: MTB isolates from all positive cultures to be stored at the study laboratory until trial closure for the applicable study tests. The cultures as well as the extracted MTB DNA from the applicable baseline and follow-up isolates will also be stored at the central lab for potential further work to validate new assay tools for 5 years after trial closure.

CENTRAL LAB: Results from testing at central lab (MIC, DST and genotyping) will not routinely be provided to sites. In the event that results are necessary to determine appropriate participant treatment, Sponsor will provide available drug susceptibility results to the site. Genotyping will be performed on paired DNA extracts to determine if the participant was a relapse or reinfection (See SAP for details).

EXTENDED DST TESTING: Paired isolates from baseline and at/after week 16 should be shipped to a relevant lab (as applicable/available per Country) for DST extending beyond the panel of drugs tested at the central lab. Extended results will be provided to the site to inform appropriate participant treatment.

2 Introduction and Rationale

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in many countries. TB is now the world's leading infectious disease killer and is responsible for more deaths than HIV.[43] 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.

Outcomes of treatment for XDR-TB using the best available treatments have traditionally been very poor. The best treatment historically has been to use available second line drugs individually tailored based on drug susceptibility testing in an inpatient setting to assure adherence with treatment lasting from 24 months to much longer for patients without culture conversion. The most detailed report using this approach with long term follow-up prior to the use of linezolid, bedaquiline or delamanid in regimens has come from South Africa, where the HIV co-infection rate among patients with XDR-TB ranges from 40 to 70%. A cohort study of 107 patients with XDR-TB found cure or completion of therapy at 24 months to be 16%, with 46% having died.[28] In another report from South Africa of 114 patients with XDR-TB, 22% completed treatment successfully.[21] The largest evaluation of treatment outcomes was noted in the WHO 2014 annual tuberculosis report of 1269 patients in 40 countries, where 22% of patients with XDR-TB completed treatment successfully and 35% died.[42] A meta-analysis of 397 patients with XDR-TB from 31 centers, with HIV coinfection <10%, reported 32% treatment success.[17] Reports of the outcome of XDR-TB treatment from Peru (43 patients, 42% treatment success)[2] and Ukraine (114 patients, 22% treatment success)[11] have been similar. Based on these reports, the success of traditionally available drug therapies for treating XDR-TB infection is substantially less than 50% and in the most detailed and largest reports is less than 25%.

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. Experience recently published from the C209 uncontrolled study of bedaquiline given on a background of multiple drugs notes that the subset of 38 patients with XDR-TB had rates of sputum culture conversion to negative of 62.2%.[29] However, in this study only one patient with XDR-TB was co-infected with HIV. All participants were required to have Mycobacterium tuberculosis (MTB) isolates susceptible to at least 3 drugs at enrolment, and patients had a median of only 5.4 months of treatment-free follow-up. This study added bedaquiline for 6 months to a background regimen of many drugs given for 18 months or longer.

While treatment success for MDR-TB is better than for XDR-TB, overall success in treating MDR-TB is still approximately 50% according to the World Health Organization 2015 Global TB Report.[43] This report presented that overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, 10% failed treatment, and for 8% there was no outcome information.

With such poor historical outcomes for patients with XDR-TB and with the complexity, expense and toxicity of treatments for all forms of drug resistant TB, novel drug combinations are

desperately needed to improve treatment outcomes. Linezolid was identified in a small study as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen[9] and this drug has increasingly been added to complex regimens to treat patients with MDR-TB.

With the current availability of three drugs for which there is little, if any, pre-existing resistance among strains of 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. Mice infected with MTB had relapse-free cures with 3 months of treatment with a B-Pa-L regimen. While it is not known whether that treatment duration will translate to humans, it is hypothesized in the design of the ongoing Nix-TB clinical study that patients with pulmonary XDR-TB may have relapse-free cure after as little as 6 months' treatment with the B-Pa-L regimen. Therefore, since 2015, the TB Alliance has sponsored a study with a 6 month treatment duration with the B-Pa-L regimen in participants with XDR-TB or MDR TB not responsive to or intolerant to therapy (the Nix-TB study).[1]

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 includes daily injections for a minimum of 6 months. The NC-007 trial takes this regimen into a randomized Phase 3 trial to optimize the dosing scheme for linezolid and the benefit relative to risk, and to expand the patient population to include individuals with pre-XDR TB.

The information presented below first details the trial rationale, then key preclinical information and human efficacy and safety information for each of the drugs in the regimen and then presents preclinical and clinical data to support the combination of these drugs in a regimen to treat patients with XDR, pre-XDR and MDR treatment intolerant/failure-TB.

2.1 Trial Rationale

2.1.1 Trial Design Rationale

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.

2.1.2 Trial Drug Rationale

2.1.2.1 Bedaquiline

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this study bedaquiline will be administered as 200 mg daily for 8 weeks, followed by 100 mg daily for the remaining 18 weeks or 30 weeks if treatment is extended. This daily dosing scheme will allow more convenient dosing that should ultimately enhance patient adherence and may allow the formulation of fixed dose

combinations with other drugs. This daily dosing regimen is supported by safety and efficacy demonstrated in the NC-005 study that administered bedaquiline 200 mg daily over 8 weeks, and by pharmacokinetic modelling and simulation of the daily dosing scheme. This supportive information is detailed below.

The NC-005 study allows the efficacy and safety to be compared for treatment arms that dosed bedaquiline at the currently registered dose and at 200 mg daily for the 8 weeks of the trial. Briefly, Study NC-005 evaluated a regimen in patients with drug susceptible pulmonary TB given bedaquiline with pretomanid and pyrazinamide over an 8 week period. One arm was to enroll 60 patients who were to be given this regimen with bedaquiline dosed as approved for marketing (referred to as the B (loading dose/t.i.w.) PaZ arm), and another 60 patients were to be enrolled who would be given the regimen with bedaquiline dosed at 200 mg daily (referred to as the B (200mg) PaZ arm). Another group of patients with DS TB were randomized to treatment with standard HRZE therapy. Patients with MDR-TB were given the regimen with bedaquiline dosed at 200 mg daily in addition to moxifloxacin (referred to as the B (200 mg) MPaZ MDR-TB arm). The primary endpoint was The Bactericidal Activity (BATTP (0-56)) as determined by the rate of change in time to sputum culture positivity (TTP) over 8 weeks of treatment in the Mycobacterial Growth Indicator Tube system, represented by the model-fitted log (TTP) results as calculated by the regression of the observed log (TTP) results over time. The assessments of safety and tolerability included the incidence of Treatment Emergent Adverse Events (TEAEs) presented by severity (DMID Grade), by drug relatedness and seriousness, and for those leading to early withdrawal and leading to death, by group. In addition, quantitative and qualitative clinical laboratory result measurements were evaluated, including group summaries of observed values and changes from baseline. Pharmacokinetics for all participants included pre-dose samples on 9 days during and one day following dosing with the regimen. Fifteen PK Sub-study participants in each treatment arm had in addition intense PK sampling on Days 14 and 56.

<u>Efficacy of bedaquiline 200 mg daily dose vs the marketed dosing scheme over 8 weeks</u>

In the efficacy analysis of the NC-005 trial, based on liquid media collected from overnight sputum samples, the B(200 mg)MPaZ MDR-TB treatment group showed the highest bactericidal activity over the 8-week treatment period, followed by that of B(200 mg)PaZ, B(loading dose/t.i.w.)PaZ and then HRZE. It appears clear that the daily dosing regimen for bedaquiline provided at least as good a result in the primary efficacy analysis as the registered dosing scheme for bedaquiline.

<u>Safety of bedaquiline 200 mg daily dose vs the marketed dosing scheme</u>

Adverse events, including serious adverse events and Grade III/IV adverse events were similar among groups. In particular, the mean change from baseline in the corrected QTc intervals was numerically less in the participants given bedaquiline daily than in the participants given bedaquiline with the labelled dosing scheme. Measures of potential hepatic toxicity, including participants with greater than 3 fold or 10 fold elevations in aminotransferase levels, were numerically greater in participants given the labelled dosing scheme than subjects given daily doses of bedaquiline.

<u>Pharmacokinetics of bedaquiline 200 mg daily dose vs the marketed dosing scheme</u>

A population PK model published by McLeay in 2014 was used with PK data from Study NC-005 to simulate the expected bedaquiline exposures when dosed at 200 mg daily followed by 100 mg

daily for the remainder of the study in comparison to the labelled dosing scheme with bedaquiline administered for 6 months.[14] The key findings from the simulations of the proposed dosing scheme for NC-007 of bedaquiline administered 200 mg daily over 8 weeks followed by 100 mg daily for an additional 16 weeks are:

- The exposures of the proposed dosing scheme ($C_{max,\ mean}$ or $_{trough}$) are not expected to exceed the exposures associated with the labelled scheme on Day 14 at the end of the 400 mg daily dose. With the labelled dosing scheme, the highest exposures are on Day 14 at the end of the 400 mg daily loading dose.
- The average daily exposures with the proposed dosing scheme over 6 months are within (or not substantially different from) the range of exposures over 6 months of the labelled dosing scheme.
- The cumulative exposure, in terms of AUC over time, is similar between the proposed dosing scheme and the labelled scheme

2.1.3 Pretomanid

Pretomanid has demonstrated good microbicidal activity at the 200mg daily dose as monotherapy in studies PA-824-CL-007 and PA-824-CL-010, in combination with either bedaquiline or pyrazinamide over 14 days in the early bacteriocidal activity (EBA) Study NC-001-(B-M-Pa-Z), in combination with either bedaquiline and/or pyrazinamide and/or clofazimine over 14 days in the EBA Study NC-003-(B-C-Pa-Z), and in combination with bedaquiline and linezolid over 6 months in the Nix-TB study. In the EBA Study PA-824-CL-010 the 100mg dose demonstrated similar microbicidal activity to the 150 and the 200mg daily dose over 14 days. The Phase 2 trial NC-002-(M-Pa-Z) evaluated this regimen at doses of pretomanid of both 100 mg and 200 mg relative to the HRZE control. In this trial the efficacy results were similar between participants treated with 100 mg/day and 200 mg/day of pretomanid in the regimen, although for the primary endpoint, reduction in colony forming units of MTB from sputum, only the 200 mg/day dose group was statistically significantly better than the group randomized to standard HRZE therapy. Safety was also similar between the groups, although the 200 mg/day group had more grade 2 adverse events than either the 100 mg/day group or the HRZE control group. Because sterilizing relapse-free cure of TB in patients with XDR-TB may ultimately require a regimen with higher drug exposures, the 200mg dose was chosen for evaluation in the Nix-TB study of the B-Pa-L regimen. The manageable toxicity of the regimen and very encouraging efficacy in the Nix-TB trial support taking the 200 mg dose of pretomanid forward in the NC-007 trial.

2.1.4 Linezolid

The standard dose of linezolid for a multitude of indications is 400mg or 600mg BID. Doses of linezolid used to treat pulmonary TB in reported observational trials and case series range from 300 mg to 1200 mg per day over periods of up to 20 months of treatment. While the development of adverse events is generally higher with higher doses, the adverse events often ameliorate with a reduction of the dose or discontinuation of drug for several weeks and then reintroduction at a lower dose. No controlled trials have clearly identified differences in anti-TB effect across a range of doses over long term treatment of TB.

In this trial, each arm will vary the linezolid dosing to identify the optimal ratio of efficacy to adverse events as noted below. The 4 arms, to which participants will be randomly assigned in a blinded manner, are:

- Linezolid 1200 mg orally once daily for 26 weeks, with the ability to interrupt or reduce the dose if needed based on toxicity.
- Linezolid 1200 mg orally once daily for the first 9 weeks, with the ability to interrupt or reduce the dose if needed based on toxicity.
- Linezolid 600 mg orally once daily for 26 weeks, with the ability to interrupt or reduce the dose if needed based on toxicity.
- Linezolid 600 mg orally once daily for the first 9 weeks, with the ability to interrupt or reduce the dose if needed based on toxicity.

These dosing schemes for linezolid are chosen based on clinical experience in the Nix-TB trial, the company's linezolid early bactericidal activity (EBA) study findings in the Lin CL-001 study, and preclinical data in the mouse model of infection. While the EBA study showed that a modestly greater bactericidal effect over 14 days at the highest 1200 mg daily dose (see further details below in Section 2.2.3), this dose appears to be associated in the Nix-TB trial and in published literature with a greater incidence of unwanted neuropathic and myelosuppressive effects than the 600 mg daily dose. While a full 6 months of linezolid therapy in the regimen may give greater culture conversion and avoid relapse, the mouse model found that linezolid dosing of only 1 or 2 months, when B and Pa were given continuously for a total of 3 months, maximized relapse-free cure; in other words, similar to pyrazinamide in the present first line HRZE therapy, more than 2 months of linezolid when combined with B and Pa does not increase relapse-free cure in the mouse model. Thus, the 4 treatment arms in this study will give randomized comparative information about the optimal duration and dose of linezolid in the regimen relative to efficacy and toxicity.

The decision to give linezolid as a single daily dose is based on the results of the linezolid EBA study that showed over 14 days that similar bactericidal activity was noted whether the drug was given as a single daily dose or divided in to 2 doses. A single daily dose will ultimately enhance patient adherence and will reduce the total time the drug concentration is greater than the calculated concentration associated with mitochondrial toxicity (which we hypothesize to be the likely mechanism for the toxicities of peripheral neuropathy and myelosuppression).

2.2 Agents to be Studied

2.2.1 Bedaquiline

Bedaquiline is being developed as part of combination therapies for pulmonary TB due to MDR-TB and approved in 2012 in the USA under the provisions of accelerated approval regulations. Bedaquiline received conditional Marketing Authorization in the EU in 2014 and is approved in over 40 countries (EU countries counted individually). The approved indication may vary per country. Bedaquiline is marketed under the trade name SIRTURO™. Bedaquiline has a novel mechanism of action as it specifically inhibits mycobacterial ATP synthase, an enzyme that is essential for the generation of energy in MTB The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.

In the placebo-controlled Phase 2b study C208 conducted in newly-diagnosed patients with sputum smear-positive pulmonary MDR-TB (including pre-XDR-TB), the addition of bedaquiline to a preferred background regimen of MDR-TB treatment resulted in a decreased time to culture conversion and improved culture conversion rates compared to placebo. Median time to culture conversion according to the primary analysis method was 83 days for the bedaquiline group compared to 125 days for the placebo group ($p<0.0001$; hazard ratio, 95% CI: 2.44 [1.57; 3.80]). The proportion of patients in the mITT population with sputum culture conversion after 24 weeks of treatment with bedaquiline or placebo in combination with background regimen (with patients who discontinued considered as non-responders), was 52/66 (78.8%) in the bedaquiline group and 38/66 (57.6%) in the placebo group. Durability of response seen in the bedaquiline treatment group was supported by the results at Week 120. The proportion of responders (with patients who discontinued considered as non-responders) at Week 120 was 41/66 (62.1%) in the bedaquiline group and 29/66 (43.9%) in the placebo group.

In the Phase 2b, open-label study C209, conducted in 233 patients with sputum smear positive pulmonary MDR-TB, the median time to sputum culture conversion excluding patients with DS-TB and those that did not have a positive sputum culture at screening and/or baseline (mITT; 205 patients), was 57 days. At Week 24, 163 of 205 (79.5%) patients responded to bedaquiline treatment as determined by sputum culture conversion rates. Conversion rates at Week 24 were highest (87.1%; 81/93) in patients with MDR-TB resistant to only RMP and INH, 77.3% (34/44) in pre-XDR-TB patients and lowest (54.1%; 20/37) in XDR-TB patients.

The average terminal half-life of bedaquiline, is about 5.5 months. After reaching C_{max}, however, there is initially a fairly rapid reduction in plasma bedaquiline concentrations over the dosing interval (with an estimated half-life of about 13 hours). Four weeks after ceasing bedaquiline intake, the mean bedaquiline concentrations were reduced by approximately 40% compared to the end of the bedaquiline treatment period in the C208 study. Administration of bedaquiline with food increased the relative bioavailability by about 2-fold compared to administration under fasted conditions. It is therefore recommended to take bedaquiline with food to enhance its oral bioavailability.

CYP3A4 is the major CYP isoenzyme involved *in vitro* in the metabolism of bedaquiline. Drug-drug interaction (DDI) studies have showed reduced exposure to bedaquiline during combination with a strong or moderate inducer of CYP3A4 metabolism (i.e., rifampicin) and increased exposure during combination with a strong or moderate inhibitor of CYP3A4 metabolism (i.e., ketoconazole). Potential drug interactions with anti-retroviral drugs have been evaluated in three studies. In an interaction study of single-dose bedaquiline and multiple-dose Lopinavir/ritonavir, exposure (AUC) to bedaquiline was increased by 22% (90% CI: 11-34). Co-administration of single-dose bedaquiline and multiple-dose nevaripine did not result in clinically relevant changes in the exposure to bedaquiline. Co-administration of a single dose of bedaquiline and multiple-dose efavirenz (EFV) resulted in approximately a 20% decrease in the AUC_{inf} of bedaquiline with no alteration in the C_{max}. Modeling based on the data from this DDI study predicts average steady-

state concentrations of bedaquiline and M2 to be reduced by 52% with chronic co-administration of bedaquiline and EFV.[5]

Safety of Bedaquiline

The Investigator's Brochure for bedaquiline provides detailed safety information.[5]

Data were used from 14 completed clinical studies to identify Adverse Drug Reactions (ADRs) according to the ICH guideline entitled, E6: Good Clinical Practice, Consolidated Guideline (ICH, 1996): "…all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out."

The ADRs were identified from the pooled safety database of reported AEs in the Phase 2b clinical studies with bedaquiline, based upon a systematic well-documented approach and are presented for study C208 below in Table 1. None of the ADRs reported in the controlled studies during the Investigational Treatment phase were considered serious.

Table 1: ADRs C208 Stage 1 and Stage 2

Adverse Drug Reactions (ADRs) in the Controlled Studies (C208 Stage 1 and Stage 2) During the Investigational Treatment Phase			
ADR (Grouped term), n (%)	**Frequency**	**Any BDQ N=102**	**Any Placebo N=105**
Nervous system disorders			
Headache	Very Common	24 (23.5)	12 (11.4)
Dizziness	Very Common	13 (12.7)	12 (11.4)
Cardiac disorders			
ECG QT prolonged	Common	3 (2.9)	4 (3.8)
Gastrointestinal disorders			
Nausea	Very Common	36 (35.3)	27 (25.7)
Vomiting	Very Common	21 (20.6)	24 (22.9)
Diarrhea	Common	6 (5.9)	12 (11.4)
Hepatobiliary disorders			
Transaminases increased[a]	Common	7 (6.9)	1 (1.0)
Musculoskeletal and connective tissue disorders			
Arthralgia	Very Common	30 (29.4)	21 (20.0)
Myalgia	Common	6 (5.9)	7 (6.7)

a. Different AE preferred terms (i.e., transaminases increased, aspartate aminotransferase [AST] increased, alanine aminotransferase [ALT] increased, hepatic enzyme increased, and hepatic function abnormal) contribute to this ADR, while for the other ADRs the ADR is the preferred term.

Of note, 13 deaths occurred in the C208 Stage 2 study: 10 subjects (12.7%) in the bedaquiline group and 3 subjects (3.7%) in the placebo group experienced an SAE leading to death. One death (alcohol poisoning) occurred during administration of bedaquiline. The median time to death for the remaining 9 subjects was 344 days after last intake of bedaquiline. One of the 10 deaths in the bedaquiline treatment group and 1 of the 3 deaths in the placebo group occurred after the

Week 120 window. In the bedaquiline group, the most common cause of death as reported by the investigator was TB or TB-related illness (5 subjects). For all deaths due to TB, the subject's last microbiological outcome was either failure to convert or relapse. The causes of death in the remaining bedaquiline subjects varied. The investigator considered all the SAEs leading to death not or doubtfully related to bedaquiline/placebo. The imbalance in deaths is unexplained. In addition, no discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, or severity of disease was observed.

During clinical studies with bedaquiline a prolongation of QTc interval on the ECG was observed. Consequently, bedaquiline treatment initiation is not recommended in patients with, personal or family history of prolonged QT intervals, or additional risk factors for Torsades de Pointes. Detailed criteria are noted in Section 5.2 Exclusion Criteria.

Increases in transaminases were seen in clinical studies during administration of bedaquiline in combination with a background regimen. Based on a review confirmed by an external hepatologist, it was concluded that bedaquiline has a signal for liver injury manifested by increases in AST and to a lesser extent ALT. Transaminase elevations are not unexpected given the number of other hepatotoxic drugs in the background regimens in clinical trials based on the publication by Keshavjee, which describes a 16.5% incidence of hepatotoxicity during MDR-TB treatment. [7]

2.2.2 Pretomanid

As detailed in the Investigator's Brochure[6], pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazo-oxazines, which possess significant anti-tuberculosis activity and a unique mechanism of action[35]. Pretomanid demonstrated *in vitro* activity against both DS- and MDR-TB[10], and *in vivo* activity in a mouse model of tuberculosis[10, 35].

2.2.2.1 Pharmacology

2.2.2.1.1 Key in Vitro Evaluation of Pretomanid Bactericidal Activity

Non-clinical in vitro studies demonstrated that pretomanid was active against actively growing drug-sensitive and drug-resistant MTB strains as well as against non-replicating MTB The minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive MTB isolates *in vitro* was shown to be similar to the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of MTB with MIC values ranging from 0.03 to 0.53 µg/mL. The Investigator's Brochure contains further information on *in vitro* bactericidal activity. [6]

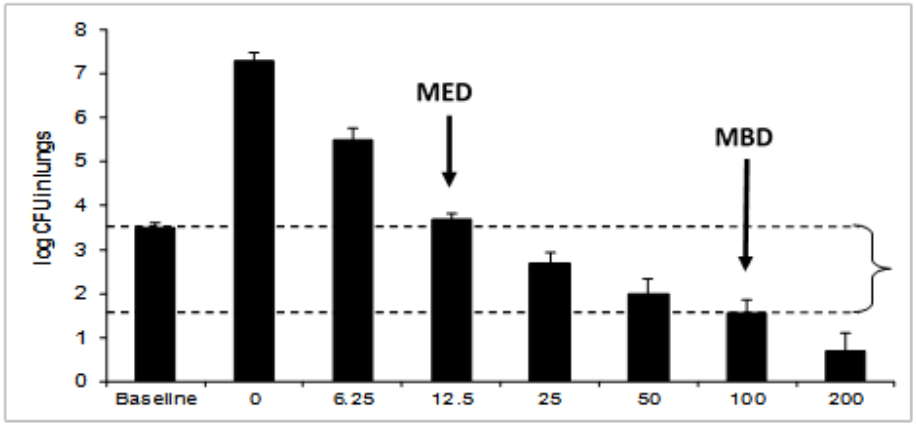
Although not thoroughly elucidated at this time, pretomanid has a novel mechanism of action that appears to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reduction of pretomanid by a deazaflavin (F420)-dependent nitroreductase has been shown to be associated with generation of reactive nitrogen species, including nitric oxide (NO), [33] although the exact target(s) of the reactive nitrogen species are not known. Transcriptional profiling studies also suggest that pretomanid affects both cell wall biosynthesis and the respiratory complex of MTB.[12,13]

2.2.2.1.2 Key Non-Clinical Studies of Pretomanid

The activity of pretomanid as a single agent or as part of a multi-drug combination regimen has been examined in a number of mouse studies.[18,19,20,36,40] In a mouse model of established TB, the activity of various doses of pretomanid (given once daily, 5 days/week, for 1 month), initiated 22 days after inhalation infection with H37Rv MTB is shown in Figure 1. In this model, the minimum effective dose (MED) for pretomanid, defined as the lowest dose able to prevent the development of gross lung lesions and splenomegaly, was 12.5 mg/kg/day, while the minimum bactericidal dose (MBD), defined as the lowest dose able to reduce lung colony forming units (CFU) by 99%, was 100 mg/kg/day. Moreover, in these experiments, the activity of pretomanid at 100 mg/kg was comparable to the activity of isoniazid at 25 mg/kg.

Figure 1: Log10 CFU Counts in Lungs

After One Month of Daily Treatment with the Indicated Dose (in mg/kg) of Pretomanid



Arrows denote the minimum effective dose (MED) and minimum bactericidal dose (MBD).

2.2.2.2 Non-Clinical Toxicology and Safety

Pretomanid has been evaluated in an ICH recommended battery of safety pharmacology studies, in repeat-dose toxicity studies in rats (2 to 26 weeks) and cynomolgus monkeys (7 days to 9 months), in 8 genotoxicity studies, and in fertility and teratology studies in rats and rabbits.

In the repeat-dose toxicity studies, the lowest no-observed adverse effect level (NOAELs) was 10 mg/kg/day in a 26-week study in rats, 50 mg/kg/day in a 13-week study in monkeys and <25 mg/kg/day (based on findings of thickening of the GI tract at all doses) in a 9-month study in monkeys. The major findings in safety and toxicity studies are listed below in Table 2 and are detailed in the Investigator's Brochure.[6]

Table 2: Key findings of Pretomanid in Safety and Toxicity Studies

Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behaviour at ≥150 mg/kg, which resolved within 24 hours. Rats given

repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.

Testicular toxicity

Although rat and rabbit embryonic development studies indicate no effects of PA-824 on fetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose toxicology studies and a Segment I fertility study. In this fertility study, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower dose not associated with testicular atrophy. A detailed study in sexually mature male monkeys demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing.

Cataracts

Cataracts developed in rats with prolonged daily administration of pretomanid at doses ≥100 mg/kg/day. In one 13-week study in monkeys, cataracts did develop at 450/300 mg/kg/day, but only by the end of a 13-week recovery period. In a second 13-week study in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.

hERG inhibition and QT prolongation

Altered ventricular repolarisation due to inhibition of hERG-mediated potassium current and manifested on the electrocardiogram (ECG) as a prolonged QT interval corrected for heart rate (QTc). Pretomanid inhibited hERG current with IC50 values of approximately 6.2 µg/mL. Following a single pretomanid dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Co-administration of pretomanid with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at pretomanid doses of ≥150 mg/kg/day.

2.2.2.3 Clinical Background Information

Pretomanid has been evaluated in 8 single- and multi-dose Phase 1 studies with healthy adult male and female subjects, with 163 subjects receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 7 days. These Phase 1 studies have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid. Two additional Phase 1 studies sponsored by the NIH included a Thorough QT study and a study

of drug interactions among pretomanid, efavirenz and ritonavir/lopinavir. Further details of the studies are in the Investigator's Brochure.

2.2.2.3.1 Pharmacokinetics

Several Phase 1 studies have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid and have demonstrated that pretomanid has a half-life of approximately 18 hours, which supports daily dosing, and an effect of food with the 200 mg dose that increases total exposure by 88%. Interaction studies with midazolam, efavirenz and ritonavir/lopinavir demonstrate effects that are not likely to be clinically significant.

Drug interaction with midazolam: Study CL-006 was an open-label, fixed-sequence drug-drug interaction study to evaluate the effects of multiple-dose administration of pretomanid on the PK of midazolam, a sensitive probe substrate and representative compound for drugs metabolised by CYP3A enzymes. Dosing with pretomanid at 400 mg/day for 14 days (to steady state) had minimal effect on the PK of midazolam and its 1-hydroxy metabolite as assessed by measurement of the Day 17: Day 1 ratios of maximum concentration (C_{max}), area under the curve to the last available time point (AUC_{0-t}), and area under the curve extrapolated to infinity (AUC_{0-inf}). The C_{max} and AUC values for midazolam after co-administration with pretomanid were approximately 85% of those observed after treatment with midazolam alone. Furthermore, midazolam and 1-hydroxy midazolam time to maximum concentration (T_{max}) and half-life ($t_{1/2}$) values were not different in the presence or absence of pretomanid. Therefore, 14 days' dosing with 400 mg/day pretomanid does not appear to significantly inhibit CYP3A4 in humans.

Drug interaction with efavirenz, ritonavir/lopinavir, and rifampicin: The US NIH sponsored this drug interaction study with rifampicin, a known hepatic enzyme inducer, and with the antiretroviral drugs efavirenz and ritonavir/lopinavir (LPV/r) in healthy subjects. Participants in Arm 1 were randomised to Sequence 1 (pretomanid 200 mg once daily for 7 days, two-week washout period, efavirenz (EFV) 600 mg once daily for 14 days, then both drugs for 7 days) or Sequence 2 (Treatment 1B: EFV, then EFV + pretomanid, washout, and pretomanid). Results indicate that comparing pretomanid given with EFV versus pretomanid alone in 16 participants, the geometric mean ratio (GMR) for the maximum concentration (C_{max}) was 0.71, the GMR for the 24-hour area under the time-concentration curve (AUC_{0-24h}) was 0.65, and the GMR for the trough concentration (C_{min}) was 0.54. Concentrations of EFV when given with pretomanid versus given alone were similar. Participants in Arm 2 were randomised to Sequence 1 (pretomanid 200 mg once daily for 7 days, then a 2-week washout period, then LPV/r 400/100 mg twice daily for 14 days, then LPV/r + pretomanid together for 7 days) or Sequence 2 (LPV/r, then LPV/r + pretomanid, washout, then pretomanid alone). Comparing pretomanid + LPV/r versus pretomanid alone from 16 PK-evaluable participants, the GMR for C_{max} was 0.87, for AUC_{0-24h} was 0.83, and for C_{min} was 0.78. In Arm 3, participants received pretomanid for 7 days, then rifampicin 600 mg for 7 days, then pretomanid + rifampicin together for 7 days. Comparing pretomanid + rifampicin versus pretomanid alone from 16 PK-evaluable participants, the GMR for C_{max}, AUC_{0-24h}, and C_{min} were 0.47, 0.34, and 0.15, respectively.

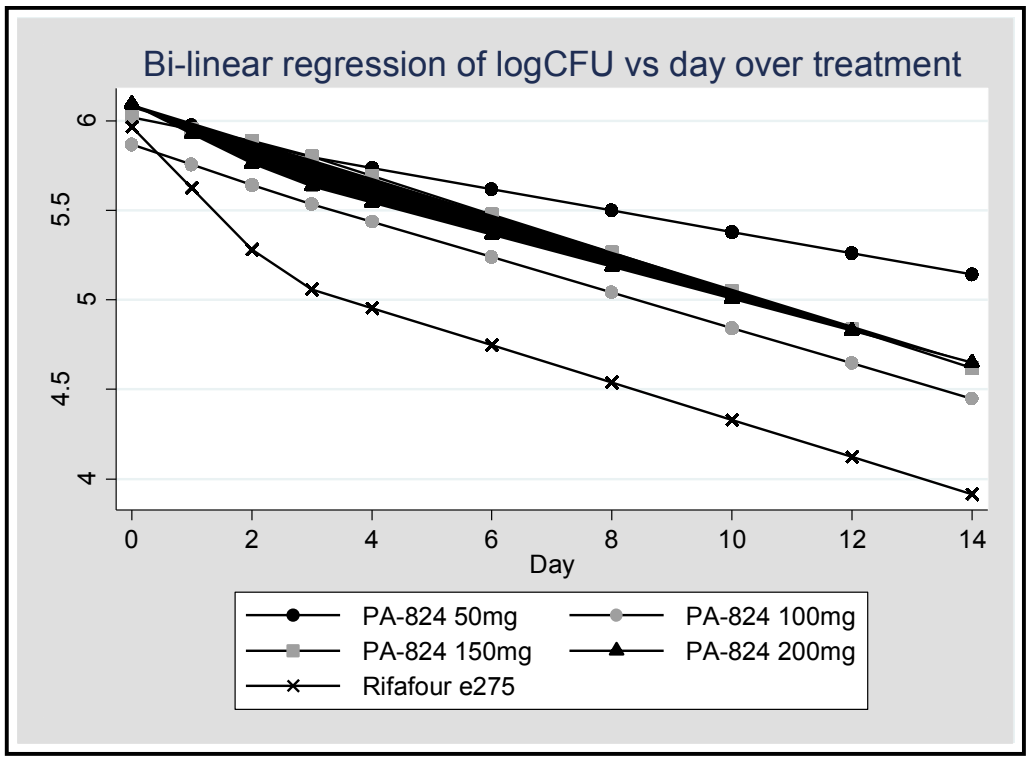
In conclusion, compared to pretomanid alone, plasma pretomanid values (based on geometric mean ratios) for maximum concentration (C_{max}), area under the concentration-time curve (AUC_{0-}

$_{24h}$), and trough concentration (C_{min}) were reduced 28%, 35%, and 46% with efavirenz; 13%, 17%, and 21% with LPV/r; and 53%, 66%, and 85% with rifampin, respectively.

2.2.2.3.2 Pretomanid Clinical Efficacy

The first two Phase 2 studies to evaluate the early bactericidal effect (EBA) of pretomanid oral monotherapy (50 to 1200 mg/day for 14 days) examined the dose-response for pretomanid in participants with newly diagnosed pulmonary TB infection. The first study (CL-007) demonstrated good EBA, but all doses in this study (200 to 1200 mg/day) had the same activity. The second study (CL-010) evaluated a lower dose range (50 to 200 mg/day) and the maximum effect on EBA was seen at a dose of 100 mg/day over 14 days [4] (Figure 2).

Figure 2: Mean log Colony Forming Unit Values over Time Study CL-010



CFU = colony-forming unit; PA-824 = pretomanid

* Day 0 = (Day -2 + Day -1)/2 = baseline measurement

Pretomanid has been evaluated in patients with TB as monotherapy for a maximum duration of 14 days, the longest considered acceptable for a TB patient to be treated in a clinical trial with a single drug. Studies of Pretomanid for both 14 days and for up to 6 months, in combination with either bedaquiline and/or linezolid, are described below in Section 2.3.2.

2.2.2.3.3 Pretomanid Clinical Safety

The pretomanid Investigator's Brochure[6] provides detailed safety information.

Across the 16 clinical studies with pretomanid completed to date, a total of 649 participants have been exposed to pretomanid, including 289 healthy subjects across the 10 Phase 1 studies and 360 participants with newly diagnosed smear positive pulmonary TB across 5 Phase 2 studies. Among the 289 healthy Subjects, 174 received exposure to a single dose of pretomanid ranging from 50 to 1500 mg and 115 received exposures to repeated daily doses of pretomanid (50 to 1000 mg) for up to 14 days. The 360 participants with newly diagnosed smear positive pulmonary TB were exposed to pretomanid either as a single agent at daily doses of 50 to 1200 mg for 14 days or in combination with other anti-TB agents (bedaquiline, moxifloxacin, pyrazinamide, linezolid and/or clofazimine) at a dose of 100 mg or 200 mg for up to 26 weeks. The overall safety profile determined from the clinical studies completed to date indicates pretomanid is well tolerated in healthy adults and in TB patients when administered alone and in combination with moxifloxacin, pyrazinamide, bedaquiline and clofazimine.

Pretomanid is an investigational drug and there is limited experience in humans; the safety database is being developed and investigators should be vigilant to any adverse events noted in clinical trials. Across these studies, the most common side effects or AEs associated with pretomanid exposure include:

- Headache
- Stomach discomfort (nausea, vomiting, flatulence, and/or diarrhea)
- Skin and subcutaneous tissue disorders

The only adverse drug reaction identified in clinical studies completed to date as likely caused by pretomanid is blood creatinine increased. A study of the effects of repeat doses of pretomanid in healthy volunteers determined that the drug does not adversely affect glomerular filtration rate, effective renal plasma flow or filtration fraction and the elevations in serum creatinine reverse.

The following parameters will be followed with particular care in the Phase 3 development program:

- Hepatic Safety – Specific guidelines are included in the protocol to assure close surveillance and careful management of participants who have elevations in aminotransferases and/or bilirubin. Serious liver injury, including death in 3 participants taking a combination of pretomanid, pyrazinamide and moxifloxacin, has occurred during clinical studies and the risk of liver injury may be higher for participants taking a combination of PA-824 and pyrazinamide than it is for the standard HRZE treatment. Therefore, close monitoring of liver function is required for participants who are administered PA-824, especially when combined with pyrazinamide. Administration of the regimen of PaMZ has been associated with death in 3 participants associated with hepatic injury. Furthermore, the HRZE control regimen, and both pyrazinamide and moxifloxacin, has been associated with drug induced liver injury and in rare cases hepatic necrosis. Consequently, hepatic safety will be under close surveillance in all clinical studies.

- Ophthalmologic Evaluations – while the detailed examinations in Phase 2 have not raised concern for humans, ophthalmologic examinations, with slit lamp exam and grading of lens opacities, will continue in all human studies that involve exposure to pretomanid longer than

14 days. These examinations will be conducted at baseline, near the end of the dosing period and 3 months after the end of study drug exposure. These examinations are to follow up on the finding of cataracts in rats exposed to pretomanid in clinical studies.

- Cardiovascular Safety – All participants will have ECGs taken at baseline and at multiple time points during the study. Although the Thorough QT Study in healthy subjects found that pretomanid did not increase corrected QT intervals in a clinically meaningful way and did not add to the known effect of moxifloxacin, the ECGs will be carefully monitored during Phase 3. All ECGs will be interpreted and conduction intervals will be confirmed by a central cardiology service.

- Central Nervous System Safety –While pretomanid alone or combined in various regimens has been well tolerated overall, one participant in Study NC-002 of the Pa-M-Z regimen had a seizure without any prior seizure history, and some animals in toxicology studies have had seizures at high drug exposures. Consequently, close surveillance will be made of participants in the Phase 3 study for seizures or any central nervous system adverse events of potential concern.

Of note, preclinical toxicology studies found that rats, but not primates, had testicular toxicity when treated with pretomanid. Clinical evaluations of potential testicular toxicity in Phase 2 studies have evaluated over 300 participants exposed to pretomanid over 2-6 months with evaluations of testosterone, LH, or Inhibin B (2 studies) or FSH values (3 studies) at baseline and after daily dosing of regimens containing pretomanid in various combinations with moxifloxacin, pyrazinamide and bedaquiline. A review of data from the 3 studies by an independent reproductive endocrine expert concluded that, based on the hormone evaluations to date, there is no evidence that PA-824 is a testicular toxicant in men at the doses and exposure times evaluated.

2.2.3 Linezolid

Linezolid is a synthetic antibacterial agent of the oxazolidanone class approved in many countries around the world for drug-resistant, gram-positive bacterial infections, including gram positive organisms such as *Staphylococcus aureus*, coagulase negative *Staphlococcus* and *Enterococcal* infections. The recommended dose for these infections is 600 mg twice daily for up to 28 days of therapy.[23,24,26] Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism.[8] Resistance of MTB to linezolid is rare, as this drug has not been widely used to treat tuberculosis. In a recent study using linezolid to treat patients with XDR-TB in Korea, none of 41 patients had resistance to linezolid at baseline.[9]

Preclinical *in vitro* data shows linezolid is active against MTB, including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1 µg/mL.[38] Recent studies of the bactericidal and sterilizing activity of linezolid in a mouse model of MTB infection have demonstrated linezolid alone causes marked reductions in lung colony forming units (CFUs) from mice following 1-3 months of therapy.[36] (Table 3, below)

Table 3: Murine Lung CFU counts during Treatment with Linezolid

Monotherapy versus Standard Therapy

	Mean lung log_{10} CFU count (± S.D.) at:			
Regimen	**D0**	**Month 1**	**Month 2**	**Month 3**
Untreated	6.17 ± 0.27	6.47 ± 0.06		
2RHZ/4RH		3.47 ± 0.37	1.59 ± 0.25	0.50 ± 0.51
L		4.97 ± 0.26		

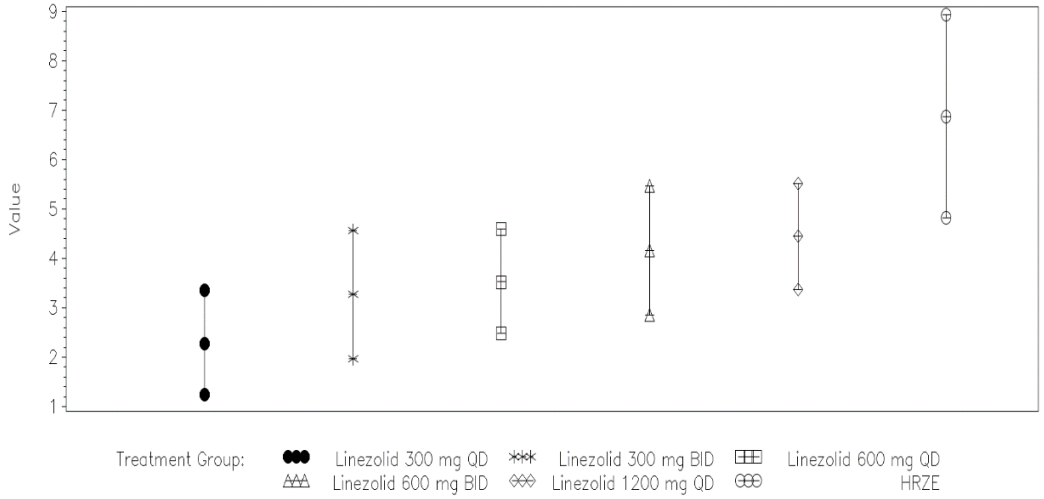
In recent years linezolid has been used to treat patients with MDR[28] and XDR-TB, although there have been no fully controlled trials of linezolid in a regimen for this indication. The World Health Organization management guidelines place linezolid in Group 5 ("Agents with unclear role in treatment of drug resistant-TB") in their groups of drugs to treat MDR-TB.[41] Over the past 10 years small retrospective observational studies have reported good results when linezolid has been added to failing regimens for patients with MDR-TB.[9, 27, 34] The most compelling recent evidence linezolid may be of benefit to patients with XDR-TB was reported by Lee and colleagues from a study in S. Korea.[9] Forty-one patients who had sputum culture–positive XDR-TB and who had not had a response to any available chemotherapeutic option during the previous 6 months were randomized to start linezolid at 600 mg daily or to delay therapy with linezolid at 600 mg daily for 2 months without changing their failing background regimen. After confirmed sputum-smear conversion, or at 4 months, patients underwent a second randomization to continued linezolid therapy at a dose of 600 mg per day or 300 mg per day for at least an additional 18 months. Thirty four of 39 (87%) of the patients had a negative sputum culture within 6 months after linezolid had been added to their drug regimen. As of the cutoff date prior to publication, of the 38 patients who received linezolid, 17 were still receiving the treatment per protocol, and 13 had completed treatment, including 6 with no relapse during the treatment period, 4 with no relapse at the 6-month follow-up, and 3 with no relapse at the 12-month follow-up (end of study).

While the standard dose of linezolid for short term use for severe bacterial infections is 600 mg bid, some clinicians and clinical trials using linezolid as Group 5 therapy to treat TB use only 300 mg or 600 mg daily due to concerns about toxicity developing when used over a period of months (see below for a review of linezolid toxicity). [9] However, there are no data to indicate what dose of linezolid is required or optimal to effectively treat TB infection. Consequently, TB Alliance has recently conducted and completed an Early Bactericidal Activity trial to evaluate the use of linezolid over 14 days in patients with newly diagnosed DS Pulmonary TB in dosing schedules including 300 mg daily, 300 mg bid, 600 mg daily, 600 mg bid, 1200 mg daily, and HRZE at standard doses daily. Preliminary unpublished in-house results using Bayesian mixed effects modelling have noted that there is a bactericidal effect of linezolid over 14 days that is substantial, but less than for the full HRZE regimen. There is little difference between daily or twice daily dosing of the same total daily dose of drug, and there is a dose-response relationship between total daily dose and daily reductions in either total CFU counts on solid culture or increases in Time to Positivity in liquid culture (a decreased load of MTB is associated with an increase in Time

to Positivity). Point estimates of the log of the daily increase in Time to Positivity over 14 days ranged from 2.278 for Linezolid 300 mg QD to 4.446 for linezolid 1200 mg QD, with the estimate of 6.860 for HRZE for reference.

Figure 3: Mean Early Bactericidal Activity Time to Positivity, Days 0 to 14, Study Lin CL-001

Bayesian Nonlinear Mixed Effects Regression Model: Posterior Estimates and 95% Bayesian Confidence Intervals



HRZE = isoniazid, rifampin, pyrazinamide, and ethambutol

2.2.3.1 Linezolid Clinical Safety

Linezolid is currently marketed globally for a variety of acute infectious diseases and has been studied for the treatment of XDR-TB in several recent trials.[3,9] The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label.[23,24,26] Of note, the approved indication for linezolid is for administration up to 28 days.

Warnings and Precautions

- Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g., phenelzine, isocarboxazid) or within 2 weeks of taking any such product.

- Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce

bone marrow suppression or those with a chronic infection who have received previous or concomitant antibiotic therapy.

- Lactic acidosis has been reported with the use of linezolid. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or low bicarbonate level while receiving linezolid should receive immediate medical evaluation.

- Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Where administration of linezolid and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).

- Peripheral and optic neuropathy has been reported in patients treated with linezolid, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with linezolid for less than 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. Visual function should be monitored in all patients taking linezolid for extended periods and in all patients reporting new visual symptoms regardless of length of therapy with linezolid. If peripheral or optic neuropathy occurs, the continued use of linezolid in these patients should be weighed against the potential risks. Additional information on the neuropathies reported in recent studies of linezolid administered over prolonged periods to patients with TB infection is presented above in Section 2.2.3.2.3.2

- Convulsions have been reported in patients when treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported.

- Postmarketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid, a reversible, nonselective MAO inhibitor. Some MAO inhibitors have been associated with hypoglycemic episodes in diabetic patients receiving insulin or hypoglycemic agents. While a causal relationship between linezolid and hypoglycemia has not been established, diabetic patients should be cautioned of potential hypoglycemic reactions when treated with linezolid.

In addition, the linezolid product label notes that there was an excess of abnormal liver function tests in comparator-controlled trials. These abnormalities were noted in 0.4% of linezolid treated

patients in trials of skin and skin structure infections vs in 0.2% of clarithromycin treated patients, and in 1.6% of patients treated with linezolid versus 0.8% of patients with other treatments in trials of all other infections.

Adverse events of linezolid long term therapy for Tuberculosis have been described in several literature reports. The most complete review is a meta-analysis by Cox which noted the proportion of adverse events necessitating treatment discontinuation was significantly different by dose: 29.49% (95%CI 3.24–55.74) for ⩽600 mg daily vs. 60.75% (95%CI 42.69–78.81) for >600 mg daily (P = 0.05). [3]

In a trial reported by Lee et al in S Korea[9], seven of 41 participants had myelosuppression, including anemia and neutropenia, primarily within the first 5 months, and only one participant withdrew due to anemia. Six had clinically significant myelosuppression: 5 in 0-4 months and 1 in 4-8 months, with 0 in 8-12 months.

Peripheral and Optic Neuropathy:

The linezolid product label notes these adverse events have been " *reported in patients, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual function should be monitored in all patients taking ZVYOX for extended periods (≥3 months) and in all patients reporting new visual symptoms, regardless of length of therapy*.[26]

In Lee, NEJM, 2012[9], the publication's Supplemental Table 3 notes that 21 patients had clinically significant peripheral neuropathy spread over 12 months: 5 in months 0-4, 10 in months 4-8 and 5 in months 8-12 (time of onset not noted for one). Participants who developed any peripheral neuropathy had their dosing of linezolid interrupted, generally for several weeks, and then resumed at the lower dose of 300 mg/day (C. Barry, personal communication). None of the participants withdrew from the study based on peripheral neuropathies. At baseline, patients received visual acuity testing, contrast sensitivity and color vision tests. Seven cases were observed as having potential effects on vision; only two of 38 patients withdrew from study due to optic neuropathy. For clinically significant optic neuropathy, one had this at 0-4 months, 2 at 4-8 months and 3 at months 8-12. Except for the 2 participants who withdrew from the study, the others resumed linezolid at the 300 mg dose after a hiatus of several weeks of treatment and completed the study with resolution of their visual acuity changes (C. Barry, personal communication).

In the Schecter California Department of Health (DOH) review[32], peripheral neuropathy developed in 5 of 30 patients (no standardized monitoring), but only one withdrew from linezolid therapy. One patient developed visual loss secondary to optic neuropathy after 10 months of linezolid therapy, but vision returned to normal 3-4 weeks after discontinuation.

In Park, 2006[27], two patients of eight in the case series developed optic neuropathy after 8-9 month and had linezolid discontinued; these patients also had peripheral neuropathy. After linezolid treatment was stopped, the optic neuropathy fully resolved after 2-3 months. A total of

4 patients developed peripheral neuropathy at 4, 5, 8, 11 months; in the patients with optic neuropathy who stopped treatment, the peripheral neuropathic symptoms continued or improved only marginally.

In Singla, 2012[34], two of 29 patients treated with linezolid, 600 mg daily over 12 months, stopped the drug because of peripheral neuritis (one patient) and optic neuritis (one patient). The time course of these adverse events was not noted.

2.3 Regimens to be Studied

The regimen included in this study (B-Pa-L) has been selected based on the performance of the regimen in non-clinical pharmacology studies and on the combination of bedaquiline and pretomanid with other drugs in clinical studies NC-001 and NC-003. In addition, improved treatment outcomes in XDR patients with the addition of linezolid to existing therapy provide support for combining linezolid with other drugs that have no pre-existing resistance. Preliminary results from the ongoing Nix-TB clinical study demonstrate the encouraging potential of this regimen.

This regimen has the potential to treat drug resistant strains of tuberculosis. This is an oral regimen, removing the need for injectables as part of drug resistant treatment, and is also projected to be markedly less expensive than current XDR-TB therapy. Treatment duration is anticipated to be shorter than current regimens for drug resistant TB, based on findings in mouse models of infection and the fact that all participants will be treated with three active drugs against TB for which there is no expected resistance.

The key data supporting the use of the B-L-Pa regimen are described below.

2.3.1 Non-Clinical Studies

In the murine model of TB, addition of bedaquiline to HRZ results in accelerated clearance of MTB [5,36] when compared to HRZ alone. While the combination of bedaquiline and pretomanid in the murine model of TB in initial studies appeared somewhat antagonistic relative to bedaquiline alone, it was as active as the triple combination of HRZ[15] and in a subsequent study it was more active in the mouse model than HRZ.[16] Thus a novel regimen with bedaquiline plus pretomanid core could be effective in the treatment of MDR-TB by providing two novel drugs for which there is no known pre-existing resistance.

Recent studies of the bactericidal and sterilising activity of linezolid in an animal model where mice were given high dose aerosol MTB infection have demonstrated that linezolid alone and in combination with bedaquiline and pretomanid causes marked reductions in lung CFUs from mice following 1 to 3 months of therapy (Table 4 below). Additionally, all mice treated daily with bedaquiline, pretomanid and linezolid (B-L-Pa) were cured of the infection after 3 months of therapy as evidenced by no MTB cultured from lungs when mice were sacrificed 3 months after the completion of therapy that lasted 3 months or more (Table 4, below). This is in contrast to the 5-6 months required in previous studies to cure all mice when treated with the standard of care isoniazid, rifampicin and pyrazinamide (HRZ; note that typically ethambutol is not used in the mouse model of infection). Additional mouse studies were performed to determine whether shorter durations of linezolid, with continuation of the other drugs, would result in relapse-free

cure in the mouse (Table 4 below). Treatment with linezolid for only the first 4 to 8 weeks of a 3-month treatment also resulted in relapse-free cure when lungs from the mice were cultured 3 months after the completion of therapy.[37]

Table 4: Murine Relapse Data

Impact of Linezolid Treatment Duration on Lung Colony Forming Unit Counts Assessed during Treatment and Proportion of Mice Relapsing after Treatment Completion

	Proportion of mice relapsing after treatment for:	
Regimen	**2 months**	**3 months**
2RHZ/RH*		8/14 **(57%)**
BPa		3/14 **(21%)**
3BPaL **	6/15 **(40%)**	0/15#† **(0%)**
2BPaL/1BPa***		0/15#† **(0%)**
1BPaL/2BPa	9/15 **(60%)**	0/15#† **(0%)**

#p = 0.11 vs. BPa; †p≤ 0.001 vs. RHZ
*2RHZ/RH means 2 months on the full regimen and a third month on only RH
**3BPaL means 3 months on the full regimen
***2BPaL/1BPa means 2 months on the full regimen and a third month on only BPa
****1BPaL/2Bpa means 1 month on the full regimen and a third month on only BPa
B – bedaquiline, H-isoniazid, L-linezolid, Pa-pretomanid, R-rifampicin, Z-pyrazinamide

In conclusion, linezolid increases the sterilising activity of the bedaquiline-pretomanid combination; no MTB could be cultured from the lungs of mice 3 months after cessation of 3 months of treatment with the combination, in contrast to MTB cultured from 13 of 15 mice treated with the standard 2RHZ/4RH regimen over 3 months. In addition, limiting the duration of linezolid to the first month of treatment does not affect linezolid's contribution to the sterilising activity of the regimen in the preclinical mouse study.

Prior to the use of pretomanid in combination with bedaquiline in clinical study NC-001, a preclinical cardiovascular safety pharmacology study was conducted in unrestrained beagle dogs with both drugs to explore the potential for additive effects on QT prolongation induced by the combination. Results indicate that administration of 100 mg/kg bedaquiline daily for 7 days causes a small increase in QTc interval by Day 6 in some animals that is not influenced by the addition of 100 mg/kg pretomanid on Day 7. The effect of pretomanid dosing alone on QT interval appeared to be due to discomfort related to the subcutaneous route of administration and not related to the plasma exposure.

2.3.2 Clinical Studies of Pretomanid in a Regimen with Bedaquiline and/or Linezolid

2.3.2.1 Clinical Study NC-001

Study NC-001 was a partially double-blind, randomized, parallel group study in adult male and female participants with newly diagnosed, uncomplicated, smear-positive, pulmonary TB. A total of 85 participants met study eligibility criteria and were randomly assigned to one of the six treatment groups. All study treatments were given once daily for 14 days. Substantial EBA activity was demonstrated across participants in all arms of the study and the daily reductions in cultured colony counts per mL of sputum are presented in Table 5 below.

Table 5: Summary Statistics for $EBA_{CFU(0-14)}$

Derived Using Bi-Linear Regression, Study NC-001

Treatment Group	N	Daily Mean (SD) $EBA_{CFU(0-14)}$
Pretomanid + pyrazinamide + moxifloxacin	13	0.23 (0.128)
Pretomanid + pyrazinamide	14	0.15 (0.040)
Pretomanid + bedaquiline	15[a]	0.11 (0.050)
Bedaquiline alone	14	0.07 (0.068)
Bedaquiline + pyrazinamide	15	0.13 (0.102)
Rifafour e-275	10	0.14 (0.094)

There were no Serious Adverse Events from the study among participants treated with pretomanid and bedaquiline. Three participants in a bedaquiline-containing treatment arm were withdrawn: one participant on the bedaquiline only arm for a Grade 3 ALT and Gamma-Glutamyl Transferase (GGT) elevation (although the elevation occurred prior to the first dose of study medication), one on a bedaquiline plus pyrazinamide (weight banded) arm for a Grade 3 ALT and AST elevation, and one on a pretomanid and bedaquiline arm for to a Grade 3 ALT elevation.

2.3.2.2 Clinical Study NC-003

Efficacy

In the 14 day EBA study NC-003 two monotherapy and four different combinations of bedaquiline, pretomanid, pyrazinamide and clofazimine were evaluated in DS-TB participants. Fifteen participants were randomized into 7 treatment arms: C, Z, B-Pa-Z-C, B-Pa-Z, B-Pa-C, B-Z-C, and HRZE control. This study demonstrated no EBA for the clofazimine monotherapy arm and modest EBA for the pyrazinamide monotherapy arm. However, all of the experimental regimens demonstrated EBA. In general, adding clofazimine to the various agents resulted in either no increase in EBA, or a decrease when compared to a similar regimen that did not include clofazimine. In this study, the experimental regimen with the best EBA was B-Pa-Z which demonstrated a rate of decrease in both $\log_{CFU}$ and $\log_{TTP}$ that was at least as good as the HRZE control. The daily $\log_{CFU}$ results are presented in Table 6. Similar results were found when TTP was used to calculate the bactericidal activity over 14 days ($BA_{(0-14)}$).

Table 6: NC-003 Efficacy Results: Daily BAlog$_{CFU(0-14)}$

Arm	logCFU
BPaZC	.124
BPaZ	.180
BPaC	.086
BZC	.098
Z	.036
C	-.025
Rifafour®	.152

Safety

Generally, the regimens in this study were well tolerated. Table 7 provides a list of the overall safety findings. The only SAE experienced in the study was in a participant in the clofazimine monotherapy arm. Otherwise, the rates of treatment emergent AEs (TEAEs) were similar across the treatment arms. One participant in the B-Pa-Z arm was withdrawn from the study due an adverse event of increased liver function tests (alanine aminotransferase (ALT), AST and GGT).

Table 7: NC-003 Safety Data

	BPaZC	BPaZ	BPaC	BZC	Z	C	HRZE	Total
N	15	15	15	15	15	15	15	105
Participants with:								
TEAEs	11	9	8	10	10	9	8	65
TEAEs leading to death:								
Serious TEAEs						1		1
TEAES leading to early withdrawal		1						1
TEAEs leading to discontinuation of study drug		1						1
Drug-related TEAES	8	5	7	3	5	6	5	39
Serious, drug-related TEAEs								
Grade III AEs		2	1	2		1		6
Grade IV AEs		1	1					2
Grade II/IV AEs		2	1	2		1		6

QT Prolongation

Because bedaquiline and clofazimine are both known to prolong the QT interval, intensive ECG monitoring was included in the study endpoints. The mean change from baseline in QTcB and QTcF tended to be larger at 5 hours than at 10 hours post-dose in the (B-Pa-Z-C) arm and in the (B-Pa-C) arm. No QTcB or QTcF ≥500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of ≥60 ms in QTcB was reported for 2 participants in the (B-Pa-C) arm and for 1 participant in the clofazimine alone arm. An increase from baseline to Visit 5 and subsequent

visits of ≥60 msec in QTcF was reported for 4 participants in the (B-Pa-C) arm and for 1 participant in the clofazimine alone arm. For both QTcB and QTcF, the (B-Pa-Z-C) arm and the (B-Pa-C) arm showed the largest increase from baseline. Clofazimine will not be used in any treatment arms in the NC-007 study.

2.3.2.3 The Nix-TB Study

The NiX-TB Study is an ongoing open-label study assessing the safety and efficacy of bedaquiline plus linezolid plus pretomanid in participants with pulmonary infection of either XDR-TB or treatment intolerant/non-responsive MDR-TB. The study regimen includes: bedaquiline 400 mg once daily for 2 weeks then 200 mg 3 times per week plus pretomanid 200 mg once daily plus linezolid 600 mg twice daily amended (22 Jan 2016 protocol) to 1200 mg once daily. Treatment duration is 6 months, although if participants are still culture positive at month 4, there is the option to extend treatment to 9 months or withdraw. The primary endpoint is the incidence of bacteriologic failure or relapse or clinical failure through follow-up until 6 months after the end of treatment. Secondary Endpoints include: incidence of bacteriologic failure or relapse or clinical failure through follow-up until 24 months after the end of treatment as a confirmatory analysis, time to sputum culture conversion to negative status through the treatment period, and the proportion of participants with sputum culture conversion to negative status at 4, 6, 8, 12, 16 and end of treatment. In addition, linezolid dosing (actual) and efficacy will be explored and changes from baseline will be evaluated for TB symptoms, Patient Reported Health Status, body weight, and measures of safety.

Efficacy Experience to Date:

Sixty-nine participants have been enrolled as of February 1, 2017, at 2 sites in South Africa. Forty-nine percent of the participants are HIV positive, 79% have XDR-TB and 21% have MDR intolerant or resistant to prior therapy. Forty have completed the 6 months of therapy with the drug regimen and 31 have been followed to the primary endpoint at 6 months after treatment. All surviving patients were culture negative by 4 months, with 74% negative at 8 wks. As of February 1, 2017, there has been 1 microbiological relapse during follow up after drug therapy and 1 participant has had a new infection during follow-up with Drug Sensitive TB. This study will continue to enrol participants until the NC-007 study is initiated.

Safety of the B-Pa-L Regimen in the Nix-TB Study: As of December 2016, four participants have died in the study. The causes of death have varied and include: 2 with multi-organ disseminated TB who died within the first 5 weeks of therapy, 1 who had a gastrointestinal bleed and 1 with multi-organ failure and disseminated TB on autopsy. No deaths or SAEs have been caused by hepatic injury. No participants have been withdrawn from the study except for the 4 who died. The expected linezolid toxicities of peripheral neuropathy and myelosuppression were common but manageable. Seventy-one percent of participants had at least one linezolid dose pause (22% of all participants due to myelosuppression and 28% due to peripheral neuropathy), during the 6 months of treatment. One had peak ALT and AST > 3 X ULN and total bili > 2X ULN, but these improved and treatment restarted without a recurrence. There were 7 cases of grade 3 or 4 transaminitis and all resolved and allowed the study regimen to be continued. There were no cases of optic neuritis. While participants have required close surveillance for signs and

symptoms of neuropathies and bone marrow suppression, these toxicities have been manageable.

2.4 Overall Benefit/Risk Assessment

The recent report of the long term outcome of patients with XDR-TB treated in S. Africa highlighted the very poor prognosis for patients with this disease. After 60 months of follow up 73% of 107 patients had died and only 11% had a favourable outcome[28]. These patients have infection with MTB resistant to many/most of the available drugs to treat tuberculosis. Patients with XDR-TB have limited treatment options due to their resistance profile, and the drugs that are typically used in Standard of Care have many side effects, some are administered as injectables and have poor treatment outcomes in XDR-TB. Similarly, patients with Pre-XDR-TB and patients with MDR-TB who are failing or are intolerant to treatment have traditionally poor outcomes and are a challenge to treat. While treatment success for MDR-TB is better than for XDR-TB, overall success in treating MDR-TB is still approximately 50% according to the World Health Organization 2015 Global TB Report.[43] and it would be lower for patients failing or not able to take an optimal traditional regimen. This trial provides an opportunity to treat these high-need patients with three active drugs, for which there is no or minimal pre-existing resistance, in a very closely controlled and monitored clinical trial setting with the opportunity to define the optimal dosing scheme for linezolid. Participants will be monitored closely and regular reviews of safety and efficacy will be made by the Data Safety Monitoring Committee (DSMC). Preliminary results of the ongoing Nix-TB trial from patients with XDR-TB and who are failing or intolerant to treatment of MDR-TB demonstrate that this regimen has the potential to give relapse-free cure of XDR-TB with a simple regimen in a much shorter period of time than currently required by the available drugs used in the best standard of care. Preclinical studies of this regimen in a murine model of infection demonstrated relapse free cure of MTB in half the time (3 vs 6 months) required by standard HRZ therapy. Clinical studies of linezolid alone and pretomanid and bedaquiline alone and in combination have demonstrated activity against TB infection.

These three drugs have not been used in combination in humans prior to the Nix-TB trial, and thus their combined toxicity profile is emerging. The greatest risks of key concern for participants in this trial from linezolid are from the adverse events of myelosuppression and peripheral and optic neuropathy. Participants will be closely monitored with full blood counts, vision examinations, and screening for peripheral neuropathy. The investigator may interrupt dosing of either linezolid or linezolid with pretomanid and bedaquiline if adverse events of concern develop, and a resumption of the drugs, with linezolid at the same or at a lower dose, may be made cautiously. Participants will be under close surveillance for hepatotoxicity, as that risk for pretomanid and bedaquiline is not yet well characterized.

Overall the benefit-risk balance justifies evaluating the B-Pa-L regimen in this study, with the cautious surveillance in place, to treat patients with XDR-TB who have few options for a successful outcome.

3 Trial Objectives

3.1 Primary Objectives

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.

4 Trial Design

4.1 Summary of Trial Design

This is a Phase 3, multi-center, partially-blinded, randomized clinical trial conducted in 4 treatment groups. Participants, 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 180 XDR-TB and Pre-XDR/MDR intolerant or non-responsive participants who meet all of the inclusion criteria and none of the exclusion criteria, aged 14 and over, will be randomized to receive one of the 4 active treatment arms. Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive voice and web response system (IXRS) which will utilize a randomization system using stratification with a random element to allocate participants evenly across the arms by HIV status and type of TB after they have given written, informed consent and met all eligibility criteria.

Each participant will receive 26 weeks of treatment. If participant's sputum sample is culture positive between the 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 with and approved by the Sponsor Medical Monitor before implementation. Participants will be followed for 78 weeks after end of treatment.

4.2 Treatment Plan: Schedule of Assessments

- **Screening Period-** Screening Visit up to 14 days prior to Treatment
- **Treatment Period-** Day 1 to Week 26. Additional visits every 3 weeks until last dose when dosing extended due to pauses or positive culture at Week 16
- **Follow-up Period-** 4 Week post end of treatment follow-up Visit to 78 Week post end of treatment follow-up Visit

Refer to:

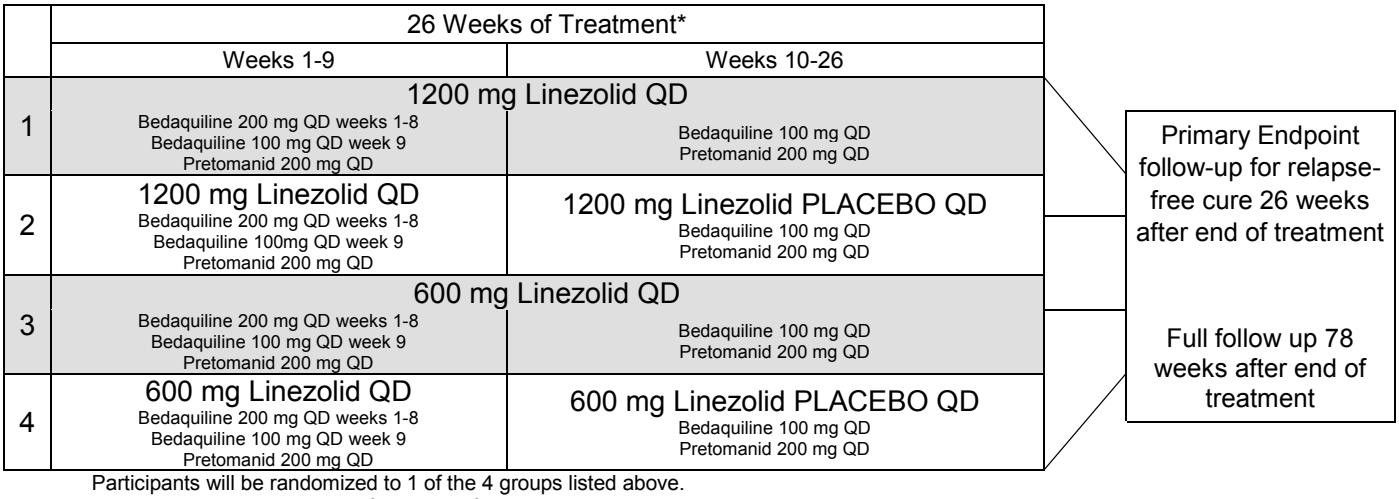
- Trial Flow Chart (Section 1.2) for the timing of all procedures and laboratory samples to done at each visit.
- Trial Procedures (Section 7) for details regarding specific procedures or laboratory tests.

Participants will receive oral daily dosing. They will be randomized to one of the following arms:

Table 8: Treatment Groups

	Treatment Group	No of Participants
1	Linezolid 1200 mg daily for 26 weeks • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks.	• 30 XDR-TB • Up to 15 Pre-XDR or MDR intolerant/non-responsive
2	Linezolid 1200 mg daily for 9 weeks followed by linezolid placebo for 17 weeks • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks.	• 30 XDR-TB • Up to 15 Pre-XDR or MDR intolerant/non-responsive
3	Linezolid 600 mg daily for 26 weeks • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks.	• 30 XDR-TB • Up to 15 Pre-XDR or MDR intolerant/non-responsive
4	Linezolid 600 mg daily for 9 weeks followed by linezolid placebo for 17 weeks • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks.	• 30 XDR-TB • Up to 15 Pre-XDR or MDR intolerant/non-responsive

Figure 4: Trial Schematic



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

5 Trial Population

Participants must meet all inclusion and no exclusion criteria within the screening period. Re-testing for laboratory or ECG parameters is allowed within the 14-day screening period. Sponsor may consider replacement of late screen failure and un-assessable (as detailed in the statistical analysis plan) participants.

5.1 Inclusion Criteria

Participants are required to meet all of the following inclusion criteria during the screening period in order to be randomized.

1. Provide written, informed consent prior to all trial-related procedures (including any additional consent required for participants considered as minors per applicable regulatory authority or ethics committee).
2. Willingness and ability to attend scheduled follow-up visits and undergo study assessments.
3. HIV testing (if an HIV test was performed within 1 month prior to screening, it should not be repeated as long as a documented result can be provided [ELISA and/or Western Blot and/or Electro-Chemiluminescence]. If HIV status is a confirmed known positive, repeated HIV test is not needed if ELISA and/or Western Blot and/or Electro-Chemiluminescence documentation of presence of HIV infection is available.
4. Male or female, aged 14 years or older.

<u>Disease Characteristics:</u>

5. Participants with one of the following pulmonary TB conditions:
    a. XDR-TB with
        i. A documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and:
        ii. documented resistance to rifamycins, a fluoroquinolone **AND** an injectable during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid);
    b. Pre-XDR-TB with
        i. A documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based molecular test within 3 months prior to or at screening and;
        ii. documented resistance to rifamycins, and to a fluoroquinolone **OR** an injectable during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid);
    c. MDR-TB with
        i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected results within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and;
        ii. documented resistance to rifamycins during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid) and;
        iii. with documented non-response to treatment with the best available regimen for 6 months or more prior to enrolment who in the opinion of the Investigator have been adherent to treatment and will be adherent to study regimen.
    d. MDR-TB with
        i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB

confirmed in sputum based on molecular test within 3 months prior to or at screening and:

ii. documented resistance to rifamycins during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid) and;

iii. who are unable to continue second line drug regimen due to a documented intolerance to:
   a. PAS, ethionamide, aminoglycosides or fluoroquinolones or ;
   b. Current treatment not listed above that renders participant eligible for the study in the Investigator's opinion.

6. Chest X-Ray within 6 months prior to or at screening, obtained and read locally by investigator or designee with results consistent with pulmonary TB in the opinion of the Investigator.

Contraception:

7. Be of non-childbearing potential **or** using effective methods of birth control, as defined below:

Non-childbearing potential:

a. Participant - not heterosexually active or practices sexual abstinence; or
b. Female participant or male participant's female sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or
c. Male participant or female participant's male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening.

Effective birth control methods:

a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or
b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female participant;
c. Male participant's female sexual partner: Double barrier method or hormone based contraceptives or an intra-uterine device for the female partner.

And are willing to continue practicing birth control methods throughout treatment and for 6 months (female participants) and 12 weeks (male participants) after the last dose of study medication.

> **Note:** Hormone based contraception alone may not be reliable when taking IMP; therefore, hormone-based contraceptives alone cannot be used by female participants to prevent pregnancy.

5.2 Exclusion Criteria

Participants will be excluded from participation if they meet any of the following criteria during the screening period:

Medical History and Concurrent Conditions

1. Any condition in the Investigator's opinion (i.e., an unstable disease such as uncontrolled diabetes or cardiomyopathy, extra-pulmonary TB requiring extended treatment, cancer that could affect survival through the protocol-specified follow up period), where participation in the trial would compromise the well-being of participant or prevent, limit or confound protocol specified assessments.
2. Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
3. In the judgment of the Investigator, the participant is not expected to survive for more than 6 months.
4. Karnofsky score < 60 at screening.
5. History of allergy or known hypersensitivity to any of the trial Investigational Medicinal Products or related substances.
6. Body mass index (BMI) < 17 kg/m^2
7. TB infection with historic DST or MIC results with values suggesting likely resistance to pretomanid, delamanid, linezolid or bedaquiline; the Sponsor Medical Monitor must be consulted to help interpret any available historic results.
8. Participants who, upon the evaluation of their pulmonary disease, are expected to require a surgical procedure.
9. Having participated in other clinical studies with dosing of investigational agents within 8 weeks prior to screening or currently enrolled in an investigational study that includes treatment with medicinal agents. Participants who are participating in observational studies or who are in a follow up period of a trial that included drug therapy may be considered for inclusion.
10. Participants with any of the following at Screening:
    - QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with and approved by the Sponsor Medical Monitor before enrolment. (Per measurements and reading done from screening central ECG.)
    - Heart failure
    - A personal or family history of congenital QT prolongation
    - A history of or known, untreated, ongoing hypothyroidism
    - A history of or ongoing bradyarrhythmia
    - A history of Torsade de Pointe
11. Females who have a positive pregnancy test at Screening or already known to be pregnant, breast-feeding, or planning to conceive a child during the study or within 6 months of cessation of treatment. Males planning to conceive a child during the study or within 6 months of cessation of treatment.
12. A peripheral neuropathy of Grade 3 or 4, according to DMID (Appendix 2). Or, participants with a Grade 1 or 2 neuropathy which is likely to progress/worsen over the course of the study, in the opinion of the Investigator.

Previous and Concomitant Therapy

13. Known (during screening) requirement for future Concomitant (during treatment) use of any prohibited and/or avoided medications noted in section 5.3.

14. Prior use of Monoamine Oxidase Inhibitors (MAOIs) within 2 weeks of randomization.
15. Prior use of serotonergic antidepressants within 3 days of randomization if Investigator foresees potential risks for serotonin syndrome when combined with linezolid.
16. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP.
17. Participants with newly diagnosed tuberculosis and HIV that require initiation of appropriate HIV therapy before participant has received at least 2 weeks of an anti-tuberculosis regimen.
18. HIV infected participants with planned continued use of zidovudine, stavudine or didanosine. The antiretroviral therapy (ART) booster cobicistat should not be used. Please reference restrictions Section 5.3.3 Antiretroviral Therapy, for guidance on ART treatment during the treatment period.

Diagnostic and Laboratory Abnormalities

19. Participants with any of the following toxicities at Screening (labs may be repeated during screening period) as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November 2007):

    a. Viral load >1000 copies/mL (Unless newly diagnosed HIV and not yet on ART who otherwise qualify for participation);
    b. CD4+ count < 100 cells/µL (HIV positive participants);
    c. Serum potassium less than the lower limit of normal for the laboratory;
    d. Hemoglobin < 9.0 g/dL or < 90 g/L;
    e. Platelets <100,000/mm^3 or < 100 x 10^9/L;
    f. Absolute neutrophil count (ANC) < 1500/ mm^3 or < 1.5 x 10^9/L;
    g. Aspartate aminotransferase (AST)
        - Grade 3 or greater (≥ 3.0 x ULN) to be excluded;
        - Results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor
    h. Alanine aminotransferase
        - Grade 3 or greater (≥ 3.0 x ULN) to be excluded;
        - Results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor medical monitor;
    i. Total bilirubin
        - greater than 1.5 x ULN to be excluded;
        - 1-1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor
    j. Direct bilirubin
        - Greater than ULN to be excluded
    k. Serum creatinine level greater than 1.5 times upper limit of normal
    l. Albumin <3.0 g/dl or < 30 g/L

All inclusion and no exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the Investigator has reason to suspect that there might be a health problem (other than TB), enrolment should only be considered after discussing the case with the Sponsor Medical Monitor.

No protocol waivers will be granted by the TB Alliance.

5.3 Restrictions

5.3.1 Prior and Concomitant Medications and Other Treatments

Concomitant medications should be kept to a minimum during the treatment period of the trial. However, if concomitant medications are necessary for the participant's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator. For any concomitant medications given as a treatment for a new condition or a worsening of an existing condition occurring after signing of the Informed Consent Form, the condition must be documented on the Adverse Event pages of the electronic Case Report Form (eCRF).

The prescribing information for all concomitant medication should be consulted and reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected to prevent any potentially serious and/or life-threatening drug interactions.

The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:

- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.
- Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)

The following concomitant medications should be avoided during the treatment period and during the 14 days after treatment completion to avoid possible drug interactions with the IMP. Use of any of the following must be discussed and approved by the Sponsor Medical Monitor prior to use:

- Concomitant use of any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).
- Treatment with fluoroquinolones (as they are known prolong QTc), are strongly discouraged in the trial. They should only be used to treat intercurrent non-TB infections and if the benefit of treatment outweighs the risk of prolonged QTc.
- Concomitant use of any drug known to induce significant myelosuppression
- The systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolids such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 3 consecutive days;
- The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone.
- Concomitant use of serotonergic antidepressants should be avoided if possible as participants on these agents and linezolid are at risk for serotonin syndrome.

- Caution should be used in treating diabetic patients receiving insulin or oral hypoglycemic agents as cases have been reported of hypoglycemic reactions when patients on these agents have been treated with linezolid.

The following concomitant medications which are known to be hepatotoxic should be avoided as much as possible during screening and throughout the treatment period. If there are concerns about the co-administration of hepatoxic drugs, discussion with the Sponsor Medical Monitor is encouraged (including but not limited to acetaminophen/paracetamol, acetazolamide, allopurinol, amiodarone, amitriptyline, amoxicillin, amprenavir, atorvastatin, augmentin/co-amoxiclav, azathioprine, baclofen, bumetanide, captopril, carbamazepine, celecoxib, chlorpromazine, chlorpromazine, clindamycin, clopidogrel, contraceptive pill, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).

5.3.2 Recommendations for Concomitant use of Anti-Malarials

The following treatments for malaria are recommended for concomitant use with the IMP, should it be necessary:

- Proguanil/atovaquone or
- Artesunate plus sulfadoxine-pyrimethamine

These recommendations are based on the potential for QT prolongation by bedaquiline and many anti-malarials. Due to the extended half-life of bedaquiline commencing anti-malarial treatment containing drugs that could prolong the QT interval, shortly after discontinuing bedaquiline, is not recommended.

5.3.3 Antiretroviral Therapy

For HIV infected participants, to avoid potentiating known key toxicities of linezolid (neuropathy and myelosuppression), the following antiretroviral therapies should not be used during the treatment period: zidovudine, stavudine, didanosine.

The ART booster cobicistat should not be used.

Only the following types of antiretroviral therapy (ART) are permissible during administration of regimens:

- Nevirapine based regimen consisting of NVP in combination with any two NRTIs TDF/ABC and FTC/3TC.
- Lopinavir/ritonavir based regimen consisting of lopinavir/ritonavir in combination with any two NRTIs TDF/ABC and FTC/3TC.
- Integrase inhibitor (e.g., dolutegravir) in combination with TDF/ABC and FTC/3TC.

- In patients who have viral load suppressed on efavirenz at the time of screening, their ART can be changed to rilpivirine in combination with TDF/ABC and FTC/3TC. If possible, the same nucleoside backbone should be used.

The investigator must assess the risks and benefits of these antiretroviral regimens in the context of co-infection with TB acknowledging the following caveats:

- Triple NRTI is generally not considered optimal chronic ART;
- Nevirapine based regimens are associated with higher ART failure in participants having or known to have previously had a viral load more than or equal to 100,000/ mL.

5.3.4 Other Restrictions

Large quantities of foods or beverages with high tyramine content should be avoided while taking linezolid. Quantities of tyramine consumed should be less than 100mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavour, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5mg tyramine per 1 teaspoon). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.

Alcohol should be avoided while on IMP, especially in participants with impaired hepatic function.

5.4 Trial Discontinuation and Visits

5.4.1 Treatment Discontinuation and Early Withdrawal

A participant must be withdrawn from the trial due to the following;

- Pregnancy (unless female post visit for end of treatment/early withdrawal from treatment);
- Investigator considers it for safety reasons in the best interest of the participant that he/she be discontinued, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment.
- At the specific request of the Sponsor or termination of the trial by Sponsor;
- Lost to follow-up
- In the opinion of the investigator, fails to comply with the protocol, including non-compliance to IMP.

Participants may be withdrawn from the trial based on the following. The specific situation should be discussed with the Medical Monitor before withdrawing the patient.

  - Myco testing results from baseline (Screening through Week 4) indicate sensitivity to rifamycins;
  - Myco testing results from baseline (Screening through Week 4) with MICs that indicate likely resistance to bedaquiline, pretomanid or linezolid;

All participants who discontinue trial treatment (but have not withdrawn consent) and received at least one dose of IMP will be requested to return for an early withdrawal visit and applicable safety Follow Up visits, as per flow chart (Section 1.2).

A participant may discontinue from the trial at any time at his/her request (withdrawal of consent) or may be withdrawn at any time at the discretion of the investigator for safety,

behavioral compliance or administrative issues. When a participant withdraws consent from the trial, no additional follow-up visits will be performed.

5.4.2 Early Withdrawal Follow-up

In case of early withdrawal during the treatment or follow-up period, all efforts shall be made to complete the Early Withdrawal assessments.

Once a participant has been withdrawn early from the trial, they will be requested to attend follow-up visits as described in Table 9:

Table 9: Follow-up Visits Required for Early Withdrawal Participants

Treatment Duration at EW visit	Ophthalmology Examination at EW[a]	Ophthalmology Examination 12 week Post treatment follow-up visit[a]	26 Week Post Treatment Follow-up Visit	78 Week Post Treatment Follow-up Visit
≤ 14 days	NA	NA	NA	NA
15 days to ≤ 12 weeks	NA	Required	Required	Required
> 12 weeks	Required	Required	Required, if not already performed	Required

a. If an additional visit is required for an ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 12 weeks after the EWD visit date.

The 26 and 78 week post treatment follow-up visits will be performed to collect SAE information (including verification of survival) and participant reported TB outcome information. This visit may be telephonic, a home or a site visit.

5.4.3 Unscheduled Visits

Any visit which is conducted in addition to those required by the Synopsis Flow Chart and Procedures, should be considered unscheduled regardless of the reason for the visit. The assessments which are undertaken as part of an Unscheduled visit should be as clinically indicated.

The following situation/s require an unscheduled visit/s:

- If cultures of both spot sputum samples are contaminated *at the following visits*, or if necessary, in order to help define a participant's outcome status/assess culture status during follow-up, the participant should return for an unscheduled visit(s) to give additional samples or to document the participant is not able to produce sputum:
    - End of treatment visit
    - Week 26 post treatment follow-up visit
    - Post treatment follow-up visits from week 8 through week 65 (in addition to week 26 follow-up)
    - End of Follow-up Period (week 78 post treatment completion visit)

- Early Withdrawal (if applicable).

- At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, and to determine whether the participant has:
  - At least two sequential negative sputum culture results; or
  - At least two sequential positive sputum culture results; or
  - Has been unable to produce sputum after documentation of at least two negative sputum cultures with no intervening positive and are clinically asymptomatic.

If they **do not** fall into one of the above categories, site should continue to collect sputum samples x 2 (one early morning and one spot at the research site or 2 spots samples at least 30 minutes apart, under the coaching and observation of the trial staff) at a minimum of 7 days or more apart until they fall into one of the above categories.

5.4.4 Lost to Follow-up

Every reasonable attempt must be made to minimise Lost-to-Follow-up (LTFU) participants. A minimum of three contact attempts (telephonic/home visit) will be made for participants who do not arrive for their scheduled trial visits. If these attempts are unsuccessful the participant will be considered LTFU. All attempts to contact the participant must be clearly documented in the participant's source documents.

5.4.5 Early Withdrawal due to TB

Ultimately it is the investigator's decision whether a participant should discontinue treatment due to a concern that the participant has symptomatic worsening TB and/or bacteriological failure/relapse.

Discontinuation is usually not indicated by a single positive culture. Should a participant have a single positive culture result after being negative, the investigator is to evaluate whether the participant has signs and symptoms suggestive of active inadequately treated TB and whether it is in the participant's best interest that he/she be discontinued. Prior to discontinuation of a participant due to TB, the investigator must discuss the participant with the Sponsor Medical Monitor, unless the investigator cannot contact the Sponsor Medical Monitor and considers that discontinuation must occur immediately due to immediate safety concerns with respect to the participant.

If the Investigator decides to discontinue trial treatment for a participant due to TB, additional sputum samples may need to be collected in order to ensure the participant's outcome status may be determined, details noted in trial flowchart (Section 1.2).

All Early Withdrawal participants who are confirmed sputum positive (at least two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These participants will be referred to specialists who treat XDR-TB, pre-XDR TB or MDR-TB as applicable.

5.5 Participant Progress Definitions

Status	Treatment	Follow-Up
Screen Failure	Participants from whom informed consent is obtained and is documented in writing (i.e., participant signs an informed consent form) but who is not randomized	
Completed Treatment / Completed FU*	Participants who complete the full course of IMP	Participants who complete all follow-up visits
Completed Treatment / Discontinued FU	Participants who complete the full course of IMP	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)
Completed Treatment / Lost to Follow-Up	Participants who complete the full course of IMP	Participants who are unable to be contacted on or before their final visit
Discontinued Treatment / Completed FU	Participants who discontinue treatment prior to completion of the protocol-defined treatment course	Participants who complete all applicable follow-up visits
Discontinued Treatment / Discontinued FU**	Participants who discontinue treatment prior to completion of the protocol-defined treatment course	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)
Lost to Follow-Up	Participants who are unable to be contacted on or before their final treatment visit and it cannot be confirmed whether treatment was completed	

* Note that this includes treatment failures who complete all applicable follow-up visits

** Early Withdrawal

5.6 Trial Stopping Rules

There are no trial specific stopping rules.

The trial or parts of the trial can be stopped by the Sponsor on advice from the Data Safety and Monitoring Committee (DSMC) after their review of applicable trial data. In addition, the Sponsor has the right to stop the trial or a specific Investigational Site at any time, although this should only occur after consultation between involved parties. Should this occur, the local and central Ethics Committee/Institutional review Board (EC/IRB) and Regulatory Authorities will be informed. Should the Trial/Investigational Site be closed prematurely, all trial materials (except documentation that has to remain stored at the Investigational Site) will be returned to the Sponsor or vendor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Participants currently on treatment will receive an appropriate regimen and all participants will be referred to a unit specializing in the treatment of XDR-TB, Pre-XDR-TB or MDR-TB as applicable.

6 Treatment

6.1 IMP Administration

Treatment will be administered orally, once daily, with a full glass of water and a meal in the dosing schemes (treatment arms) outlined in Table 9. The study drug regimen should be initiated as specified below regardless of whether participant has received any of the allowed

prior exposure of bedaquiline or linezolid (up to 14 days), including a loading dose of bedaquiline. The Pharmacy Manual should be referenced for further details.

Table 10: Investigational Medicinal Product Details

Treatment Group	Active and Placebo
Linezolid 1200 mg daily for 26 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. • 2 linezolid 600 mg active tablets once daily for 26 weeks • 1/2 (one half) placebo linezolid tablet once daily for 26 weeks
Linezolid 1200 mg daily for 9 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. **Weeks 1-9** • 2 linezolid 600 mg active tablets once daily for 9 weeks • ½ (one half) placebo linezolid tablet once daily for 9 weeks **Weeks 10-26** • 2 placebo linezolid tablets once daily for 17 weeks • ½ (one half) placebo linezolid tablet once daily for 17 weeks
Linezolid 600 mg daily for 26 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. • 1 linezolid 600 mg active tablet once daily for 26 weeks • 1 placebo linezolid tablet once daily for 26 weeks • ½ (one half) placebo linezolid tablet once daily for 26 weeks
Linezolid 600 mg daily for 9 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. **Weeks 1-9** • 1 linezolid 600 mg active tablet once daily for 9 weeks • 1 placebo linezolid tablet for 9 weeks • ½ (one half) placebo linezolid tablet once daily for 9 weeks **Weeks 10-26** • 2 placebo linezolidtablets once daily for 17 weeks • ½ (one half) placebo linezolid tablet once daily for 17 weeks

6.2 Participant Compliance

During site clinic visits or hospitalization, the IMP will be administered by the Investigator/designated site personnel. During the study, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how IMP is to be taken. When possible, participants will be checked for IMP compliance by the Investigators or trial personnel/National TB Treatment Program personnel via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the participant has swallowed the IMP). Additionally, participant cards/bottles will be checked for unused tablets at each visit during the treatment period

6.3 Treatment Modification(s)

All treatment modifications should be discussed with the Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation.

In the event of linezolid specific toxicities, the following should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol (8.3):

- **Blinded** one step reductions (maximum 2 steps) in the dose of linezolid managed by the IXRS as per instructions in pharmacy manual and/or IXRS user manual
  - 1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or;
  - 600 mg QD to 300 mg QD, 300mg QD to placebo).
- Temporary pause of linezolid
- Permanent discontinuation of linezolid.
- Participants who have a linezolid reduction can go back to a higher dose (1 step or 2 steps) post discussion with and approval by the Sponsor Medical Monitor.

Participants experiencing suspected drug related toxicities due to other drugs in the regimen (B-Pa), the full regimen may be halted for up to 35 consecutive days.

Interruptions/pauses of the full regimen must not exceed 8 weeks (56 days) cumulatively.

If participant's sample is culture positive between the week 16 and week 26 treatment visits and their clinical condition suggests they may have an ongoing TB infection, Investigator may consider the option to extend the treatment to which the participant is randomized 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 with and approved by the Sponsor Medical Monitor before implementation.

When treatment extended to 39 weeks, pauses of the full regimen must not exceed 13 weeks (91 days) cumulatively.

When the total of missed dosing days of the prescribed regimen and/or pauses is greater than 7 days, the same number of missed doses should be dispensed/treatment extended to make up for the total missed doses.

At no time should the participant be treated with a single agent.

Every effort should be made for participants to receive a total of at least 9 weeks of linezolid, even if pauses are required.

6.4 IMP Packaging and Labelling

The complete formulations of the IMP bedaquiline and pretomanid are found in the respective Investigator Brochures[5,6]. The complete formulations of linezolid are found in the Package Inserts[23,24,26].

The IMP will be packaged as follows:

- Bedaquiline: Bottles containing:
  - 200 mg QD dose- 28 tablets- bedaquiline 100 mg
  - 100mg QD dose- 14 tablets- bedaquiline 100 mg
- Pretomanid: Blister card containing 14 tablets- pretomanid 200 mg
- Linezolid: Blister Card containing 7 days of dosing as follows:
  - 1200 mg QD Dose
    - 2 blister strips of 7 tablets each (14 tablets) containing active linezolid 600 mg
    - 1 blister strip of 7 half tablets containing placebo linezolid
  - 600 mg QD Dose:
    - 1 blister strip of 7 tablets containing active linezolid 600 mg
    - 1 blister strip of 7 tablets containing placebo linezolid
    - 1 blister strip of 7 half tablets containing placebo linezolid
  - 300 mg Dose (for reductions):
    - 2 blister strips of 7 tablets each (14 tablets) containing placebo linezolid
    - 1 blister strip of 7 half tablets containing active linezolid 300 mg
  - Placebo Linezolid Dose:
    - 2 blister strips of 7 tablets each (14 tablets) containing placebo linezolid
    - 1 blister strip of 7 half tablets containing placebo linezolid

The packaging of each bottle/blister card will be labelled with, at a minimum, the following information:

- Name of Sponsor.
- Name of medication.
- Dosage, quantity and method of administration for bedaquiline and pretomanid.
- Potential dosage, quantity and method of administration for linezolid.
- Reference/Lot Number.
- The statement “For Clinical Trial Use Only”.
- Space for completion of Name of Investigator and Site Number.
- MedID: medication identification number
- Storage conditions.
- Period of Use.
- The statement “Keep out of reach of children”.
- Expiry Date.
- Directions for use.
- Space for completion of participant number and visit/date dispensed.

6.5 Method of Treatment Assignment

Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive web/voice response system (IXRS) which will utilize a randomization system using stratification with a random element to allocate participants evenly across the arms by HIV status and type of TB. Information & directions will be provided to each site via the IXRS user manual.

6.6 Blinding and Procedures for Breaking the Blind

The blind for a participant must not be broken by the site or sponsor except in the case of a medical emergency, where treatment of a participant is influenced by the knowledge of what dose and duration of linezolid the participant is receiving. The investigator should discuss breaking the blind with the Sponsor Medical Monitor (or designee) prior to breaking the blind unless knowledge of treatment arm is required urgently for a safety concern. The Sponsor Medical Monitor should be informed of the blind break within 24 hours if not discussed prior. IXRS will be programmed with blind-breaking instructions, described in the user manual. The Sponsor reserves the right to break the blind to fulfil any regulatory requirements regarding reporting of SAEs. If a participant is unblinded, they are not required to be withdrawn from the study.

There will be three unblinded analyses which will contain results by linezolid treatment group in aggregate (see section 9.3). The first analysis will be after all participants have completed 26 weeks of treatment and here sites, participants, and Sponsor staff will not be unblinded to individual linezolid treatment information. A limited number of statisticians will have access to individual linezolid treatment assignments.

The blind for all individual participants will be broken for the primary endpoint analysis (the second unblinded analysis) once all clinical data and outcome parameters have been captured, no more data queries are pending, and the statistical analysis plan has been finalized. The third analysis will occur when all participants have completed 78 weeks of follow-up after end of treatment.

6.7 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions as per details on IMP labelling, have been maintained during transit for all trial treatment received and any discrepancies are reported and resolved before use of the trial treatment.

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

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for trial treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Upon completion or termination of the trial, all unused and/or partially used IMPs must either be returned to Sponsor (or designated vendor) who will arrange for destruction or destroyed at site as agreed by Sponsor after final accountability has been confirmed.

The Investigator/designee will immediately inform the Sponsor of any quality issues arising with respect to the trial medication. The Sponsor will take whatever action is required should such a situation arise.

Further guidance and information for the handling, storage, accountability and final disposition of unused trial treatment are provided in the pharmacy manual.

7 Trial Variables and Procedures

The trial flowchart in Section (1.2) should be referenced for timing and sequence of assessments.

7.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected:

- Written informed consent.
- Visit dates
- Participant disposition
- Demography (date of birth, race and gender)
- Inclusion and exclusion criteria
- Clinically significant medical and treatment history (including past and current TB diagnosis, alcohol use and smoking)
- Screening coached spot sputum samples:
    - Smear microscopy for acid-fast bacilli.
    - Gene Xpert, Hain Assay MTBDRplus or equivalent to determine MTB complex and rifamycin resistance.
- Urine pregnancy test: women of child-bearing potential only, whether they are sexually active or not.
- Serology: HIV,CD4 count and viral load.
    - If an HIV test was performed within 1 month prior to trial start, it should not be repeated as long as documentation of results can be provided (ELISA and/or Western Blot and/or Electro-Chemiluminescence).
    - Where required by regulatory authorities or ethics committees:
        - Separate approval for this to be performed will be obtained from participants in the written informed consent process.
    - prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the participant, HIV counselling provided to the participant by the study site should be clearly documented in the participant's medical records/source. Participants have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the participant's medical records/source.
- Karnofsky score (Appendix 4).
- Chest X-Ray: A Chest X-Ray digital image will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor; this process will be documented in the Radiology Manual. The Investigator is responsible for review and analysis for participant inclusion.
- Method of birth control: male and female participants and their partners.
- IMP details: randomization
- IMP compliance and actual dosing
- Concomitant medications

7.2 Efficacy Variables and Procedures

Two spot sputum samples are collected, one early morning brought from home or collected in the hospital ward and one spot collected at the research site under the coaching and observation of the trial staff or, if no early morning sample was provided, 2 samples collected on site at least 30 minutes apart. The Mycobacteriology sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start.

The following analyses will be performed:

- Liquid culture (MGIT), to detect presence or absence of MTB and obtain the time to positivity (TTP) followed by a speciation test when applicable, to confirm MTB.

Using these observed variables, the following derived variables will be assessed for evaluation of the efficacy endpoints:

- Bacteriologic failure/relapse;
- Time to Sputum Culture Conversion;
- Number of participants with Sputum Culture Conversion.

Every effort is to be made to collect sputum samples. However, in general, the inability to produce sputum is treated as being equivalent to having a negative culture (favorable) result. A participant who never achieves culture negative status due to inability to produce sputum, but has completed 26 week /78 week post treatment completion follow-up and is without clinical or biological evidence of relapse, will be considered to have a favorable outcome.

TB Symptoms Profile:

- The TB Symptoms Profile (found in the Subject Questionnaires Guideline) will record participants' ratings of the severity of common TB symptoms.

Patient Reported Health Status Variables and Procedures:

- The Patient Reported Health Status variables will be collected at the time points described in the trial flow chart. Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire (found in the Subject Questionnaires Guideline). This descriptive system consists of five health-related quality of life dimensions, each of which will be recorded using five levels of severity. Methodology: The Patient Reported Health Status methodology and requirements will be described in a separate document/guideline which will be provided prior to the trial start.

7.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the trial flow chart and assessed for evaluation of the safety endpoints:

- Laboratory parameters. The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
    - Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count),

  - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO_2, creatine phosphokinase (CPK).
  - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis.
- 12-lead Electrocardiogram (ECG):
  - Investigator assessment: normal, abnormal.
  - Central cardiologist assessment: heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.
  - Methodology:
    - Timing and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start;
    - Participants should be lying down (recumbent) for at least 5 minutes prior to each 12-lead ECG evaluation;
    - ECGs are to be recorded for 10 seconds;
    - All ECGs are to be performed in single.
    - ECGs should be done before any labs when both included in a visit)
    - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch).

- Vital signs:
  - Vital Signs, including weight (should be done before any labs)
  - Systolic and diastolic blood pressure (mmHg) to be measured supine (after 5 minutes of rest) using an appropriately sized cuff, and using the same type of sphygmomanometer, if possible by the same observer, at each relevant visit.
  - Heart rate (bpm).
  - Respiratory rate (breaths per minute)
  - Axillary body temperature (°C).
- Physical examination:
  - Height is measured at screening only.
  - Full (complete) and limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded.
  - Weight (kg) (in light clothing and with no shoes).
  - Using the observed variables weight and height, calculated body mass index (BMI) will be derived.

- Ophthalmology slit lamp examination. To be done by an Ophthalmologist trained on AREDS2 assessment. The ophthalmology slit lamp methodology and requirements will be described in a separate document, the Ophthalmology Guideline. The following analyses will be performed: AREDS2 opacity typing and grading.
- Ophthalmic examination. The ophthalmic examinations can be performed by any trained study staff. The screening exams must be done by the trained site study staff AND an Ophthalmologist. Methodology and requirements will be detailed in the Ophthalmology Guideline.
  - Ophthalmology History (Screening only);

  - Visual Acuity Test – Corrected. Distance Vision;
  - Color Vision Assessment.
- Adverse events.
- Brief peripheral neuropathy screen (found in the Subject Questionnaires Guideline) will record ratings.
- Investigator assessment:
  Principal Investigator to review participant status at specified visits in flow chart including any time Investigator determines that participant fulfills criteria for primary outcome of treatment failure. Investigator to assess whether TB treatment is considered a "success" or "failure". If considered a failure, should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration.

7.4 PK Variables and Procedures

Plasma concentrations from sparse sampling (see Synopsis Flowchart 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, and linezolid to further evaluate the effects of covariates on model parameters in this trial population. PK data from the current trial may be combined with prior data (e.g., from the NiX-TB trial) to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{trough}, C_{max}, AUC_{τ}, C_{mean}, and $T_{>MIC}$) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

7.5 Mycobacteriology Characterization Variable and Procedures

The following Mycobacterial Characterization variables will be collected:

Positive Culture (for MTB) from:

- Day 1 or if Day 1 is not available, first positive between Screening through Week 4;
- If consent granted, and when applicable, Pre-screening culture/isolate to be sub cultured and shipped and/or tested:
  - At the study lab if/when samples could support inclusion in the trial
  - To the study/central lab for relevant participants/with no baseline (positive cultures from screening through Week 4)
- When applicable, 1st positive for MTB at/after week 16 for participant not responding to therapy and/or 1st positive during follow-up for potential new infection.

The MTB isolates will be processed at the central lab(s) for:

- MIC against bedaquiline, pretomanid and linezolid;
- Drug Susceptibility Testing in liquid culture for rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide and second line TB drugs including but not limited to fluoroquinolones, and injectables;
- Genotyping.

The MTB isolates will be processed at the central lab(s) for: Positive MTB at/after end of treatment: Hain MTBDR*plus* and HainMTBR*sl*

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

Any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a trial treatment whether or not considered related to trial treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a trial treatment, whether or not related to the trial treatment.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening (any event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization; In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity; the term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect; or
- Is a medically important event.

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. A "suspected transmission of infectious agent by a medicinal product" is also considered a serious adverse event under the SAE criterion "Other medically important condition".

8.1.3 Attribution/Causality

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor/designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

Table 11: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An adverse event, which is not related to the use of the drug.
Unlikely	An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.
Possible	An adverse event, which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
Probable	An adverse event, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by dechallenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

8.1.4 Severity

Table 12: Definitions for Adverse Event Severity Gradings

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.

Grade	Severity Rating	Definition
GRADE 4	Potentially Life-Threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

See Appendix 2 for full DMID Toxicity Tables. Above ratings should be used to estimate the grade for abnormalities NOT found elsewhere in the Toxicity Tables.

8.2 Reporting

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

All AEs will be collected from the signing of the ICF until the 78-week post treatment follow-up visit at the time points specified in the Flowchart (Section 1.2) and recorded in the case report from (CRF). The exception is early withdrawal participants who will only have SAEs collected from the time of their early withdrawal through the 78-week post treatment visit.

Medical occurrences that begin after obtaining informed consent will be recorded as adverse events. If an adverse event started before signing of the informed consent, but is ongoing at trial start, it should be recorded as medical history. If the pre-existing medical occurrence worsens during the trial, and adverse event will be recorded.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of the information becoming known to the Investigator, as noted in the SAE reporting guidelines. The investigator will submit any updated SAE data to the Sponsor within 24 hours of information becoming known to the investigator.

The Sponsor/investigator/designee will inform Regulatory Authorities and/or IEC/IRB of all SAEs in accordance with local requirements and ICH guidelines for GCP.

The Sponsor/designee will forward Safety Notification letters to the Investigator for submission to the IEC/IRB.

Investigators are not obligated to actively seek AE or SAE information in participants who have completed the trial. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be reasonably related to the trial treatment or trial participation, the investigator must promptly notify the Sponsor, IEC/IRB and regulatory authorities on an expedited basis in accordance with local requirements and ICH guidelines for GCP.

8.2.1 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- Until the end of the follow-up period; and
- Until all queries on these AEs have been resolved.

Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In these cases, follow-up will be the responsibility of the treating physician. If there is uncertainty, Investigator can discuss appropriate follow-up with the Sponsor Medical Monitor.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. Investigator should contact Sponsor/designee to discuss appropriate medical follow-up if consultation required.

If a participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide Sponsor/representative with a copy of any post-mortem findings including histopathology.

New or updated information on an SAE will be recorded in the originally completed CRF and submitted to Sponsor within 24 hours of the information becoming known per SAE reporting guidelines.

8.2.2 Clinical Laboratory Adverse Events

Changes in the results of the Clinical Laboratory assessment results which the Investigator feels are clinically significant will be reported as adverse events. It is the Investigators' responsibility to review the results of all laboratory tests as they become available. This review must be documented by the Investigators' dated signature on the laboratory report. For each abnormal laboratory test result, the Investigator needs to ascertain and document if this is a clinically significant change from baseline for that individual participant. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is determined by the Investigator to be a clinically significant change from baseline for that participant, it is considered to be an adverse event.

8.2.3 Disease under Study

Symptoms of the disease under trial (Pulmonary Tuberculosis) experienced by the participant while on the trial will be assessed by the Investigator. If the symptom has:

- worsened while the participant is in the trial; and
- the Investigator assesses it as clinically significant;

it will be recorded as an adverse event.

If there is:

- no change; and
- the Investigator assesses the symptom as due to the participant's TB; and
- not clinically significant;

it will not be recorded as an AE and this will be noted in the participant's source documentation.

All TB related symptoms that meet SAE criteria will be recorded and reported as a SAE.

8.2.4 Overdose

Overdose of IMP experienced by the participant while on the trial, will be assessed by the Investigator to determine whether the overdose led to an Adverse Event, including if the taking of the suspect medicine led to suicidal intention and subsequent overdose of the suspect medicine, or other medication. In this case it will be recorded as an adverse event. If it does not lead to an Adverse Event, it will not be recorded as an AE and this will be noted in the participant's source documentation.

8.2.5 Drug Interaction

If the Investigator becomes aware that the participant has experienced a drug interaction which has resulted in an adverse event, it will be recorded as an adverse event.

8.2.6 Pregnancy

The Investigator will immediately notify the Sponsor of any pregnancy that is discovered during IMP administration or which started during IMP administration. Pregnancy forms will be completed for all pregnancies reported during the clinical trial, as defined below. In addition, the Investigator will report to the Sponsor follow up information regarding the outcome of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for 6 months.

All women of childbearing potential will be instructed to contact the Investigator immediately if they suspect they might be pregnant (for example, missed or late menses) for the following time-periods:

- During the trial
- Within 6 months after last dose of IMP

If pregnancy is suspected while the participant is receiving IMP, the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner and the participant withdrawn from the trial. Protocol-required procedures for trial discontinuation and follow up will be performed unless contraindicated by the pregnancy.

Pregnancy reporting **will follow the same time lines for a SAE** (see above). Instructions and forms will be provided separately. SAE reporting will also occur if the pregnancy outcome is a congenital anomaly. This will follow the reporting procedures described above for SAE reporting.

8.3 Monitoring for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in preclinical toxicity studies Investigator's Brochures[5,6] and Package Inserts.[23,24,25,26] Please reference section 6.3 Treatment Modifications, which notes that all treatment modifications should be discussed with Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern. The Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation.

AEs still ongoing at the end of treatment in the trial will be followed until satisfactory clinical resolution or stabilization or until the end of the follow-up period and until all queries on these AEs have been resolved. Grade 3 and grade 4 laboratory abnormalities and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization. Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In

these cases follow-up will be the responsibility of the treating physician. If there is uncertainty, Investigator can discuss appropriate follow-up with the Sponsor Medical Monitor.

Note: For Grade 3 or 4 laboratory toxicities, participants should have a confirmatory measurement within 48 hours where possible. The recommendations for managing participants below assumes the laboratory abnormalities of concern have been confirmed.

8.3.1 Neurological

Participants with co-administration of a serotonergic agent, including anti-depressants, should be monitored closely for signs of serotonin syndrome. The Investigator should determine whether the full regimen or the concomitant agent should be discontinued for those who experience signs or symptoms of serotonin syndrome such as cognitive dysfunction, hyperrexia, hyperreflexia and incoordination.

Linezolid and/or the full regimen should be paused for participants experiencing a seizure. The Sponsor Medical Monitor should be contacted to review details and discuss whether linezolid or full regimen should be resumed.

8.3.2 ALT, AST and Alkaline Phosphatase elevations:

The Investigator should refer to Appendix 5 – Liver Toxicity Management and to the ZeNix Hepatotoxicity Management Guideline to appropriately manage the participant for clinically significant elevations of AST, ALT or Alkaline Phosphatase.

8.3.3 Lipase

Grade 3 (> 2.0 to ≤ 5.0 x ULN) or Grade 4 (> 5.0 x ULN):

Contact Sponsor Medical Monitor to review. Participants with confirmed Grade 3 or 4 elevations of lipase, Investigator should consider pausing the full regimen, pending further evaluation.

8.3.4 Musculoskeletal System and Cardiac Muscle

Myalgia

Grade 2 (muscle tenderness at site other than sites of injection and/or venipuncture or with moderate impairment of activity) or Grade 3 (severe muscle tenderness with marked impairment of activity) or Grade 4 (frank myonecrosis):

Participants with Grade 2 signs and symptoms should be followed closely. Participants with Grade 3 or 4 signs and symptoms should be discussed with the Sponsor Medical Monitor to consider pausing trial medication, pending further evaluation.

CPK

For participants having elevations in CPK of potential clinical concern, the Investigator should check the CK-MB subunit, if high, consider pausing regimen and discuss with Sponsor Medical Monitor.

8.3.5 Cardiac Rhythm Disturbances

Cardiac rhythm disturbances that are Grade 3 (recurrent, persistent, symptomatic arrhythmia requiring treatment) or Grade 4 (unstable dysrhythmia requiring treatment):

Participants should be monitored closely. The Investigator should discuss with the Sponsor Medical Monitor to consider pausing the full regimen, pending further evaluation.

QTc prolongation

If QTcF is equal to or greater than 500 msec, the ECG should be repeated and serum electrolytes should be evaluated. If the second ECG also has a QTcF of > 500 msec, the Sponsor Medical Monitor should be consulted to consider pausing the full regimen, pending further evaluation.

New left bundle branch block (LBBB) or Mobitz type 2 or complete heart block. Recordings with artifacts that interfere with the interpretation of the ECG should be repeated to confirm the findings. If the finding is from the centralized ECG machine reading the result is to be checked and confirmed by the Investigator. If this is confirmed by the Investigator, dosing is to be paused until the reading has been confirmed by the central cardiologist and the participant is to be treated per the Investigator's clinical judgment. If it is confirmed by the central cardiologist, the participant is to be withdrawn from the full regimen.

8.3.6 Monitoring Linezolid Toxicities

The following are guidelines for decisions to pause, reduce and to resume linezolid in response to the onset and resolution of known linezolid-specific toxicities. These are guidelines, and decisions must be made in the context of the entire clinical status of the participant. While the investigator may need to urgently interrupt dosing for potentially life threatening symptoms or laboratory findings, the Medical Monitor should be contacted and informed of any changes in dose within 24 hours. Questions should be raised to the Sponsor's Medical Monitor if the decision is not clear.

8.3.6.1 **Myelosuppression**

The hematologic parameters of hemoglobin and counts of Neutrophils and platelets are variable from measurement to measurement. While decreases in any of these may be caused by linezolid toxicity, decreases of concern should be evaluated in the context of the participant's full clinical status and alternate explanations. Guidelines below are for situations of concern when it is considered likely that linezolid has caused the decrease.

Anemia

- Consider pausing linezolid if hemoglobin falls below 8 gm/dL or 80g/L (Grade 3) and significantly below baseline, or if hemoglobin falls > 25% of baseline. If it is clear that the anemia was caused by linezolid, consider resuming linezolid at half the dose when hemoglobin improves and linezolid is resumed.

Leukopenia

- Consider pausing linezolid if the Absolute Neutrophil Count (ANC) falls below 750/mm3 or 0.75 x 10^9/L (Grade 3) and significantly below baseline. Ideally confirm with a repeat test before making further decisions as ANCs can have diurnal and other variability. If it is clear that the leukopenia was caused by linezolid, consider resuming linezolid at half the dose when ANC improves and linezolid is resumed.

Thrombocytopenia

- Consider pausing linezolid if platelets fall below 50,000/mm3 or 50 x 10^9/L (Grade 3) and significantly below baseline. Ideally confirm with a repeat test before making further decisions. If it is clear that the thrombocytopenia was caused by linezolid, consider resuming linezolid at half the dose when platelets improves and linezolid is resumed.

8.3.6.2 Peripheral Neuropathy

The decision to reduce the dose, or to pause linezolid until symptoms improve is a judgment based on changes in signs and symptoms identified by the investigator and informed by discussion with the trial participant. As general guidance, consider pausing and/or reducing linezolid when the grade of a neuropathy sign or symptom increases by a grade to grade two or greater. If it is clear that linezolid caused the neuropathy, consider resuming linezolid at half the dose, when the neuropathy improves.

8.3.6.3 Optic Neuropathy

A participant with visual symptoms of concern or change in visual acuity of 2 lines or more or change in color vision of more than one plate should be referred to the site ophthalmologist for evaluation with a retinal examination. Any changes as assessed by the ophthalmologist that raise concern that an optic neuropathy may be developing should be discussed with the medical monitor and linezolid should be paused. If a likely or definite optic neuropathy is confirmed, linezolid should be permanently discontinued.

8.3.6.4 Lactic Acidosis

Lactic acidosis as a toxicity of linezolid should be considered if participants have gastrointestinal symptoms that are not explained by other more common causes of their symptoms. Such participants should have lactate measured and, as indicated, a full evaluation of pH and bicarbonate. Note that lactate should not be measured in participants who have no symptoms of concern, as elevated asymptomatic lactate may be common and it is difficult to interpret the clinical relevance of this. Also evaluate whether any concomitant medications, such as anti-retroviral therapies, may be associated with lactic acidosis and consider pausing them until the acidosis resolves. Consider pausing linezolid if a patient has GI symptoms and acidosis likely to be secondary to linezolid toxicity that is not otherwise explained.

8.4 Safety Monitoring by Data Monitoring Committee

A DSMC will be appointed for the trial. The primary responsibility of the DSMC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial participants by monitoring participant safety, assess participant 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 trial 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.

9 Statistical Analysis

The statistical analysis plan (SAP), which will contain details of the analyses specified in this section, will be written and signed off prior to first patient randomized.

9.1 Analysis Population

The primary analysis population will include both XDR and non-XDR (pre-XDR and MDR intolerant and non-responsive TB) participants (up to 45 per arm). A secondary analysis will be restricted to the XDR participants only (30 per arm).

A modified intent-to-treat (mITT) and a per-protocol (PP) analysis for each arm and analysis population will be conducted. The mITT will be considered the primary analysis and will include all those in the ITT analysis with additional specific exclusions detailed in the statistical analysis plan (SAP).

Other analyses will be performed (for sensitivity) including a full intent-to-treat (ITT) analysis with no exclusions, and an analysis excluding only those who were later found to be ineligible at baseline (based on data collected prior to randomization).

The Safety analysis population will include data from all randomized participants who received at least one dose of IMP.

Full details of all the analysis populations will be defined in the SAP.

9.2 Sample Size

The objective of this trial 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. In order to fulfil this objective, it is planned to randomize 30 XDR-TB participants per treatment group and up to 15 pre-XDR and/or MDR intolerant/non-responsive -TB participants 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.

There will not be a standard-of-care control group. A 50% treatment success rate was chosen as the target, because it is above the entire range of the historical control for cure of XDR-TB and because a cure rate of 50% in XDR, pre-XDR or MDR-TB treatment intolerant/failures with a shortened, simplified, all oral, inexpensive and safer regimen would clearly represent an important therapeutic advancement. A standard-of-care control group cannot reasonably be included in the trial for several reasons. 1) Given that the regimens being tested contain B and L, these drugs would need to be excluded from the control group. However, they are beginning to be used increasingly in XDR-TB, despite lack of firm evidence, but with positive anecdotal reports. Asking patients in the control group to avoid these medications could present an ethical issue. 2) The success rate of standard-of-care treatment for XDR-TB, particularly without B and L (see below), and the risk and difficulty of its administration contrast markedly with the early findings of B-L-Pa in the Nix-TB trial. It is unlikely that patients would sign informed consent to receive standard-of-care treatment if there is an alternative, but even if they do there remains an ethical issue of comparing such a disadvantaged treatment with such an advantaged treatment. 3) The scientific validity of comparing a 12-month endpoint (B-L-Pa) with a 30- or 36-month endpoint (standard of care) would represent a significant challenge.

9.3 Interim Analyses

No formal interim analyses are planned. However, there will be three planned unblinded analyses which will contain results by linezolid treatment group in aggregate as described below. The first analysis will be done after all participants have completed 26 weeks of treatment. The analysis will be on treatment safety events (mainly the specific toxicities described in section 8.3) and time to culture conversion (on treatment). The sites, participants, and Sponsor staff will not be unblinded to individual linezolid treatment information. A limited number of statisticians will have access to individual linezolid treatment assignments.

The blind for all individual participants will be broken for the primary endpoint analysis (the second unblinded analysis) once all clinical data and outcome parameters for the primary endpoint have been captured, no more data queries are pending, and the statistical analysis plan has been updated accordingly.

There will be three database locks for the three planned unblinded data analyses generated for this trial:

1. When all participants have completed 26 weeks of treatment
2. When all participants have completed 26 weeks of follow-up after end of treatment.
3. When all participants have completed 78 weeks of follow-up from after end of treatment.

9.4 Primary and Secondary Endpoint Analysis

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT). A 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) 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.

9.5 Safety and Tolerability Analysis

- The incidence of all-cause mortality will be summarized.

- All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by Preferred Term within each MedDRA System Organ Class (SOC).
- Treatment-emergent adverse events (TEAEs) are defined as AEs which started at or after the first administration of IMP and includes those events started prior to the first administration of IMP but which worsened after the first intake. Adverse events starting after the last administration of IMP until the last scheduled visit/assessment/measurement will be regarded as treatment-emergent.
- The incidence of the following events will be summarized for further medical analysis:
    - Incidence of TEAEs;
    - Incidence of TEAEs by Severity;
    - Incidence of TEAEs by DMID toxicity grade;
    - Incidence of Drug-Related TEAEs;
    - Incidence of Serious TEAEs;
    - Incidence of TEAEs Leading to Early Withdrawal;
    - Incidence of TEAEs leading to Death.
- Cardiovascular Safety: 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. These will be presented as descriptive analyses, and no inferential tests will be carried out.
    - Post-baseline QT/QTc intervals will be classified into the following categories:
        - QT/QTc < 450 msec
        - 450 msec $\leq$ QT/QTc < 480 msec
        - 480 msec $\leq$ QT/QTc < 500 msec
        - QT/QTc $\geq$ 500 msec
    - QTc changes from baseline will be classified into the following categories:
        - increase < 30 msec,
        - 30 msec and < 60 msec, and
        - increase $\geq$ 60 msec.
    - Frequency counts will be used to summarize the number of participants at each time point according to the above categories.
    - ECG results will be classified as normal or abnormal (investigator assessment) and summarized using frequency counts by dose group and time of collection.
- Ophthalmology: Descriptive statistics, including changes from baseline, will be summarized and listed by participant for ophthalmology slit lamp examination (age related eye disease study 2 [AREDS2] lens opacity classification and grading). Categorical data for lens opacity will be summarized in a frequency table for the right and left eye, respectively.

- Visual acuity and color vision: Descriptive statistics, including changes from baseline, will be summarized and listed by participant for both Visual Acuity and Color Assessments. Categorical data for changes in visual acuity and color vision from baseline will be summarized in a frequency table for the right and left eye, respectively.

- Descriptive statistics of neuropathy data derived from Brief Peripheral Neuropathy Screen. Categorical data for observed signs and symptoms of neuropathy will be summarized in frequency tables, including changes in signs and symptoms from baseline.

- Other safety variables: Laboratory Parameters, Physical Examination, Vital signs (see Appendix 3), Concomitant medication, ophthalmic examination and peripheral neuropathy. Descriptive summary statistics will be presented. The incidence of liver related laboratory abnormalities will be explored.

9.6 Pharmacokinetics

For each analyte and each scheduled sampling time/window, the plasma concentration will be summarized by descriptive statistics including the mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and geometric CV (%).

In addition, mean and/or median concentration-versus-time graphs will be provided, with error bars and/or scatter plots as appropriate.

Plasma concentrations from sparse sampling will be used to update population pharmacokinetic (PopPK) models for bedaquiline and its M2 metabolite, pretomanid, and linezolid to further evaluate the effects of covariates on model parameters in this study trial population, and to derive individual exposure metrics for use in exposure-response analyses. PK data from the current trial may be combined with prior data (e.g., from the NiX-TB trial) to enhance this population PK analysis. Detailed plans for the PopPK analysis will be outlined in a separate modeling plan, and results will be reported in separate modeling report.

9.7 Pharmacokinetics/Pharmacodynamics

For each analyte, the PopPK model will be used to derive individual exposure metrics such as steady-state Ctrough, Cmax, AUCτ, and time-above-minimum-inhibitory-concentration (T>MIC), or alternative individual summaries of these metrics over the treatment period to account for dose adjustments and interruptions as appropriate. Relationships between such exposure metrics and efficacy and safety endpoints will be explored graphically and by model-based analyses as appropriate. Planning details and results will be included in the separate modeling plan and report.

10 Records Management

10.1 Data Collection

All relevant CRF/eCRF pages will be completed for each participant who receives any amount of IMP, depending on visits attended. For screening failure participants specific eCRF pages will be completed as described in the eCRF Completion Guidelines. For participants who are prematurely withdrawn, all the visits the participant attended including withdrawal and follow-up visits need to be completed.

10.2 Source Documents

Source documents are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents will include, but are not limited to, progress notes, in-Patient hospital records, electronic data, screening logs, and recorded data from automated instruments.

All source documents pertaining to this trial will be maintained by the Investigators. The Investigator has to permit trial related monitoring, audits, Independent Ethics Committee/Institutional Review Board (IEC/IRB) review and regulatory inspections providing authorized personnel direct access to source documents, including documents required to confirm inclusion/exclusion and relevant in-Patient records while participants is on trial treatment.

10.3 File Management at the Trial Centre

It is the responsibility of the Investigators to ensure that the trial center files are maintained in accordance with International Good Clinical Practice Guidelines and the ethical principles that have their origin in the Declaration of Helsinki.

10.4 Records Retention at the Trial Centre

The Investigator is obliged to retain records and data from the trial for safety reasons and for audit and inspection subsequent to trial completion. The essential documents should be retained for not less than 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. Investigator should notify Sponsor/designees prior to destroying any records pertaining to the trial.

11 Quality Control and Assurance

11.1 Site Procedures

The Investigator undertakes to perform the clinical trial in accordance with this protocol, local regulations, ICH GCP, and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator undertakes to complete the CRFs according to the Sponsor's requirements, in a timely, accurate and legible manner. CRF entries will be verifiable to source documentation other than the CRF.

Site Standard Operating Procedures, where available will be adhered to for all clinical and bioanalytical activities relevant to the quality of the trial. Participant compliance will be monitored throughout the trial.

The Investigator will sign and date any analysis results (e.g., laboratory, ECG, etc.) to verify that the results have been reviewed.

The Investigator may appoint other sub-investigators to assist with the trial. However, the Investigator maintains responsibility for the trial and will supervise the sub-investigators. Written IEC/IRB approval of the trial will be obtained prior to involvement in the trial.

The Investigator will ensure that all site personnel are adequately trained in GCP, local regulations, the protocol, IBs/package inserts and all trial procedures and requirements

11.2 Monitoring

The Investigator is responsible for the validity of all data collected at the clinical site and must accept the various monitoring procedures employed by the Sponsor. The purpose of monitoring is to verify that the rights and well-being of human participants are protected; that trial data are accurate, complete and verifiable with source data; and that the trial is conducted in compliance with the protocol, ICH GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

Monitors assigned by the Sponsor will conduct regular site visits before, during and after the trial for the purpose of monitoring various aspects of the trial, and to assure appropriate conduct of the trial in accordance with ICH GCP. Visits will take place usually within a predetermined interval, but this may vary during the course of the trial. The Investigator and site staff will allow the trial monitor and authorized representatives of the Sponsor to (1) inspect all CRFs, written informed consent documents and corresponding source documents (e.g., original medical records), patient records and laboratory raw data, site SOPs (where applicable), training records, facilities and other trial related systems/processes, and (2) access clinical supplies, dispensing and storage areas. The Investigator and site staff should also (1) agree to assist with monitoring activities if requested and (2) provide adequate time and space for monitoring visits.

The monitor will query any missing, confusing, spurious, or otherwise ambiguous data with the Investigator. All queries should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor's signature and Investigator or designee's confirmation signature.

11.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Monitoring Plan requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to Sponsor/designee. Protocol deviations must be sent to the local IRB and Health Authority, per their guidelines. The site PI/all study staff is responsible for knowing and adhering to their IRB and Health Authority (as required) requirements.

11.4 Auditing

For the purpose of compliance with ICH GCP and regulatory agency guidelines, it may be necessary for Sponsor-authorized Quality Assurance personnel and/or authorized personnel from an external regulatory agency to conduct an audit or inspection of the investigational site. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy and consistency, and to assure that studies are in accordance with the guidelines. Having the highest quality data from studies is an essential aspect of drug development.

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by ICH GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source

documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The auditors or inspectors may also review site SOPs (where applicable), training records, site facilities and other trial related systems/processes.

In the event of the site being notified of a Regulatory Inspection, the Sponsor will help with preparation. It is essential that the Sponsor be notified of the inspection as soon as possible.

12 Ethics and Regulatory

12.1 Basic Principles

This research will be carried out in accordance with ICH GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

12.2 Independent Ethics Committee/Institutional Review Board (IEC/IRB) Review

The protocol and required trial related documents will be reviewed by the sites respective IEC/IRB. The trial will not start until the IEC/IRB has approved the protocol, written informed consent, any written information to be provided to the participant or any modification thereof, plus any other trial related documents required for review. The IEC/IRB shall be constituted and shall operate in accordance with International ICH GCP, the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will maintain an accurate and complete record of all submissions made to, and responses from the IRB/IEC. The records should be filed in the Investigator's Trial File, and copies will be sent to the Sponsor.

12.3 Regulatory Authorities

The Regulatory Authorities will receive the protocol, amendments, reports on SAEs, and the Integrated Clinical Trial Report according to national regulations. As required by local legislation, written approval will be obtained from the Regulatory Authorities prior to commencement of the trial and implementation of e.g. amendments as applicable.

12.4 Informed Consent

Written informed consent will be obtained from all participants (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment procedures) are performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The Investigators have both ethical and legal responsibility to ensure that each participant being considered for inclusion in this trial is given a full explanation of the protocol. Participants must be informed that their participation is voluntary. The investigator or his/her representative will explain the nature of the trial to the participant or his/her legally authorized representative and answer all questions regarding the trial. This shall be documented on a written informed consent form that shall be approved by the same IEC/IRB responsible for approval of this protocol. Each

informed consent form shall include the elements required by the ICH GCP and must adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The trial will be included and updated in the appropriate Country registry and referenced in the ICF.

Once the appropriate essential information has been provided to the participant and fully explained by the Investigators (or qualified designees) and it is felt that the participant understands the implications of participating, the IEC/IRB approved written informed consent form will be signed and dated by both the participant and the person obtaining consent (Investigators or designees), and by any other parties required by the IEC/IRB. Ongoing participants must be re-consented to the most current version of the ICF(s) during their participation in the trial.

The original signed informed consent form will be kept with the trial records and a copy of signed informed consent form will be provided to the participant or the participant's legally authorized representative. Another copy of the signed informed consent form and a source document identifying the trial and recording the dates of participation will be placed in the participant's medical record.

The monitor will inspect the original completed consent form(s) for all participants

12.5 Confidentiality

All site staff, the Sponsor, and any Sponsor representatives will preserve the confidentiality of all participants taking part in the trial, in accordance with ICH GCP, applicable local legislation/regulations. Subject to the requirement for source data verification by the trial personnel by reference to the participant's notes, confidentiality of all participant identities will be maintained. Unique identifiers will be used on the CRF and in all trial correspondence, as permitted. No material bearing a participant's name will be kept on file by the Sponsor. The written informed consent will contain a clause granting permission for review of the participants' source data by the Sponsor or designees.

13 Publication Policy

The definition of publication for this purpose is any public presentation of the data emerging from this trial.

All unpublished information given to the Investigator by the Sponsor shall not be published or disclosed to a third party, other than to the responsible IEC/IRB, within the understanding of the confidentiality of their nature, without the prior written consent of the Sponsor.

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors. [30]

Because the Study is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the Study must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy.
Specifically, (a) all peer-reviewed published research relating to the Study must be submitted for

publication by TB Alliance through the Chronos Open Access Publishing Service established by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy.

14 Protocol Amendment Policy

Any change to the protocol will be effected by means of a protocol amendment. Any changes which affect participant safety or welfare will be submitted to the IEC/IRB and Regulatory Authorities prior to implementation. The Investigator, IEC/IRB, and Sponsor must agree on all amendments. No amendment will be implemented until approved by the relevant Authorities and/or IEC/IRB and signed by all required parties. Exceptions to this are when the Investigator considers that the participant's safety is compromised.

Protocol amendments detailing minor administrative changes should be submitted by the Investigator to the IEC/IRB and Regulatory Authorities, either for notification purposes or approval as appropriate.

15 Sponsor, Financial Aspects, Insurance and Indemnity

The trial Sponsor is the Global Alliance for TB Drug Development (TB Alliance). The TB Alliance is a not for profit, product development partnership accelerating the discovery and development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies for those HIV-TB participants currently on such therapies, and improve treatment of latent infection.

The TB Alliance works with public and private partners worldwide. It is committed to ensuring that approved new regimens are affordable, adopted and available to those who need them.

The TB Alliance operates with funding mainly from the Bill & Melinda Gates Foundation, the Netherlands Ministry of Foreign Affairs (DGIS), the United Kingdom Department for International Development (DFID), and the United States Agency for International Development (USAID).

The participants will not receive any incentives for their involvement in the trial. The Sponsor has made provision to reimburse the participants for out-of-pocket expenses such as travelling to and from the trial site and other miscellaneous costs as a result of their trial participation.

The Sponsor certifies that it has liability insurance coverage for itself and will provide an associated certificate upon request. The insurance does not relieve the Investigators of the obligation to maintain their own liability insurance as required by applicable law. The Sponsor does not assume any obligation for the medical treatment of other injuries and illnesses.

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Appendix 1: The IUATLD Scale

The IUATLD scale proposes five groups for reporting the results of reading smears for acid fast bacilli. They should be recorded as follows:

FINDING	RECORDING
No acid-fast bacilli found in at least 100 fields	negative
1 to 9 acid-fast bacilli per 100 fields	exact figure/100/scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

Reference: The Public Health Service National Tuberculosis Reference Laboratory and the National Laboratory Network. Minimum Requirements, Role and Operation in a Low-Income Country. International Union Against Tuberculosis and Lung Disease 1998.

Appendix 2: Division of Microbiology and Infectious Disease (DMID) Toxicity Table

Source: U.S. National Institute of Allergy and Infectious Diseases, DMID, November 2007 (Draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of Patients in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 /mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures

Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day

Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent ; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatienttreatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient - no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	Subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25- 50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Appendix 3: Cardiovascular Safety

Vital Signs

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs Parameter			
	Pulse	DBP	SBP	RR
Abnormalities on actual values				
"Abnormally low"	≤ 50 bpm	≤ 50 mmHg	≤ 90 mm Hg	<12 Breaths per minute
"Grade 1 or mild"	-	> 90 mmHg-<100 mmHg	> 140 mmHg-<160 mmHg	17-20 Breaths per minute
"Grade 2 or moderate"	-	≥ 100 mmHg-<110 mmHg	≥ 160 mmHg-<180 mmHg	21-25 Breaths per minute
"Grade 3 or severe"	-	≥ 110 mmHg	≥ 180 mmHg	>25 Breaths per minute
"Abnormally high or Grade 4"	≥ 120 bpm	-	-	Intubation

Appendix 4: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Description		%
Able to carry on normal activity and to work; no special care needed.	Normal no complaints; no evidence of disease.	100
	Able to carry on normal activity; minor signs or symptoms of disease.	90
	Normal activity with effort; some signs or symptoms of disease.	80
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	Cares for self; unable to carry on normal activity or to do active work.	70
	Requires occasional assistance, but is able to care for most of his personal needs.	60
	Requires considerable assistance and frequent medical care.	50
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	Disabled; requires special care and assistance.	40
	Severely disabled; hospital admission is indicated although death not imminent.	30
	Very sick; hospital admission necessary; active supportive treatment necessary.	20
	Moribund; fatal processes progressing rapidly.	10
	Dead	0

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109[22].

Appendix 5: Liver Toxicity Management

Standard anti-TB chemotherapy is known to cause derangement of liver function tests in a substantial number of patients. In many cases this will be asymptomatic and self-limiting. In some cases, severe hepatitis and even fulminant liver failure and death can occur.

In pre-marketing clinical trials of new drugs and regimens it is especially important to identify and carefully manage any trial participants who are at risk of progression to serious liver injury. The observation of altered liver function to a degree that has a high risk of progressing to liver failure has been referred to informally as Hy's Law;[31,39]; this reflects that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
2. Among trial participants showing such aminotransferase (AT) elevations, often with ATs much greater than 3x ULN, one or more also show elevation of serum total bilirubin (TBL) to >2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase (ALP)).
3. No other reason can be found to explain the combination of increased AT and total bilirubin level (TBL), such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

During the trial, liver function will be monitored regularly with clinical assessment and blood tests in study participants and this will assist in follow up laboratory measurements that can document either resolution of abnormalities or signal the potential for drug-induced liver injury (DILI). In a clinical trial of new drugs and combinations it is especially important for investigators to follow closely any participants who have evidence of hepatic inflammation or potential toxicity. The following procedure describes the management of deranged liver function tests in study participants.

Procedure

Blood tests for liver function will be taken routinely at screening (Day -14 to -1) and at the specific time points designated in the protocol, and at Early Withdrawal. If at any other visit the clinician suspects derangement of liver function, e.g. the participant describes nausea and vomiting, right upper abdominal pain or is jaundiced, blood should be taken for liver function tests and the participant comprehensively assessed for evidence of hepatitis or hepatic impairment and any potentially contributing causes.

Suspected liver toxicity (or elevated liver enzymes detected in the absence of symptoms) must be taken seriously and detailed guidance will be provided in a separate document "ZeNix Hepatotoxicity Management Guideline". Investigators should refer to this document as a guide to management in cases of suspected or proven liver toxicity. Importantly, the trial Medical Monitor is available to provide further assistance if there is any uncertainty or additional questions.

The laboratory source (print-out of any results) should be stored alongside or transcribed into the clinical source document. Each abnormal value should be marked as clinically significant (CS) or non-clinically significant (NCS); the assessment of significance is at the discretion of the investigator. All clinically significant abnormal results must be recorded as Adverse Events in the eCRF and graded clinically as per the DMID adult toxicity table grading, (Appendix 2). Assessments and decision making for elevations in aminotransferase values or bilirubin of various levels of concern are detailed below:

Elevated liver enzymes considered of clinical significance, but not accompanied by other signs and symptoms, should be reported as an adverse event and should usually be recorded as elevated liver enzymes. If the term "hepatitis" is used, the Safety Data Manager will question the site for additional evidence to support the diagnosis, such as clinical signs and serological or biopsy data. While a liver biopsy is not required to make a diagnosis of hepatitis, the term "hepatitis" should be reserved in most instances for cases where there is supportive evidence beyond a liver enzyme abnormality. However, if the investigator will confirm the diagnosis of hepatitis just on the basis of clinical signs and laboratory values the diagnosis will be accepted. Should other symptoms or signs be present, these should also be recorded as adverse events.

Restarting Medication

Liver function tests that are improving should be repeated regularly, such as every 3 days for the first week then once a week until they return to near baseline values for the participant. Manage the participant symptomatically as required using medications that are not potentially hepatotoxic. Infection control issues must be carefully managed whilst TB medications are being withheld, especially if the participant is still culture positive for acid fast bacilli.

If medication has been temporarily stopped, once the liver function values have decreased substantially a decision must be made about further TB management. This will be dependent on the clinical context and a decision must be made in discussion with the Sponsor Medical Monitor. Treatment can only be restarted if the trial Medical Monitor is in agreement with the plan. In all cases treatment should be recommenced under close supervision for any evidence of recurrent liver function abnormalities.

If there is a further significant elevation of hepatic enzymes or bilirubin or symptoms of clinical concern after resumption of study medication, the study medication should be withdrawn permanently. Participants who permanently discontinue study medication should be managed as clinically indicated according to local National TB Programme guidelines. The Sponsor Medical Monitor can be contacted for further advice when referring to the National Treatment Program.

The trial Medical Monitor is available to assist the Investigators in both the management of liver toxicity and decisions regarding the holding or re-introduction of trial medication. Investigators must involve the Medical Monitor in any decisions regarding medication hold or re-start, and there should always be a low threshold for contacting the Medical Monitor in cases of elevated liver enzymes.

Refer to ZeNix Hepatotoxicity Management Guideline for further details.

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Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

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Protocol Number	NC-007-(B-Pa-L)
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).
Drug(s)/Combination(s):	Bedaquiline (B), pretomanid (Pa) and linezolid (L)
Initial Protocol Version/Date:	1.0/23 February, 2017
Protocol Name:	ZeNix

TABLES

FIGURES

Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	ABaCavir
ADR	Adverse Drug Reactions
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	ALanine aminoTransferase
AREDS2	Age Related Eye Disease Scale 2
ART	Anti-Retroviral Therapy
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
C	Clofazimine
CFU	Colony Forming Units
CK(-MB)	Creatine Kinase(-MB isoenzyme)
$C_{(max),\ (min)}$	plasma Concentration (maximum), (minimum)
CO_2	Carbon diOxide
CPK	Creatine PhosphoKinase
CS	Clinically Significant
C_{trough}	plasma $Concentration_{trough}$
CYP3A4	Cytochrome P450 3A4
DMID	Division of Microbiology and Infection Disease
DNA	DeoxyriboNucleic Acid
DOH	Department of Health
DILI	Drug Induced Liver Injury
DSMC	Data Safety Monitoring Committee
DST	Drug Sensitivity Testing
E	Ethambutol
EBA	Early Bacteriocidal Activity
EC	Ethics Committee
ECG	ElectroCardioGram
EFV	EFaVirenz
(e)CRF	(electronic) Case Report Form
FQ	FluoroQuinolone
FTC	Emtricitabine
GI	GastroIntestinal
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMR	Geometric Mean Ratio
H	Isoniazid
hERG	Human *Ether-à-go-go* Related Gene
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
ICF	Informed Consent Form

ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUATLD	International Union Against Tuberculosis and Lung Disease
IWRS	Interactive Web Randomization System
kg	kilogram
L	Linezolid
LLN	Lower Limit of Normal
LPV	LoPinaVir
M	Moxifloxacin
MAO(I)	MonoAmine Oxidase (Inhibitor)
MBD	Minimum Bactericidal Dose
MIC	Minimum Inhibitory Concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi Drug Resistant Tuberculosis
mg/dl	milligrams per decilitre
MGIT	Mycobacterial Growth Inhibiting Tube
mITT	Modified Intent To Treat
ms	millisecond
NCS	Not Clinically Significant
NEJM	New England Journal of Medicine
NVP	NeViraPine
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NRTI	(Triple) Nucleosidase Reverse Transcriptase Inhibitor
Pa	Pretomanid
PD	PharmacoDynamic
PP	Per Protocol
PK	PharmacoKinetic
PR	PR interval
QD	Once Daily
R	Rifampicin
S	Streptomycin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIRE	Streptomycin Isoniazid Rifampicin Ethambutol
SOC	System Organ Class
TB	Tuberculosis
TBL	serum Total BiLirubin
TDF	Tenofovir
TEAE	Treatment Emergent Adverse Events
T>MIC	Time above minimum inhibitory concentration
t.i.w.	three times a week
(BA) TTP	(Bacteriocidal Activity) Time To Positivity
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
XDR-TB	eXtensively Drug Resistant Tuberculosis
µg(/dl)	micrograms (per deciliter)
Z	pyraZinamide

1 Synopsis

1.1 Synopsis Summary

Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished Products:	bedaquiline (B), pretomanid (Pa) and linezolid (L)
Protocol Number/Title:	NC-007: 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)
Treatment Indication:	Pulmonary XDR-TB, pre-XDR-TB, and treatment intolerant or non-responsive MDR-TB
Trial Objective:	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.
Trial Design:	A phase 3, multi-center, partially-blinded, randomized clinical trial in four parallel treatment groups. 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 4 active treatment arms. Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive web response system (IWRS) which will utilize a dynamic randomization system using minimization with a random element to allocate participants evenly across the arms by HIV status and type of TB. Each participant will receive 26 weeks of treatment. If participant's week 16 sample remains culture positive, 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.
Patient Population:	A total of up to 180 participants: 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. Enrollment will stop when 120 XDR-TB participants are randomized. Sponsor may consider replacement of late screen failure and un-assessable (as detailed in the statistical analysis plan) participants.
Test product, Dose and Mode of Administration:	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 • placebo linezolid half tablet (pre-cut) 300 mg 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 arms):

Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished Products:	bedaquiline (B), pretomanid (Pa) and linezolid (L)
	Participants will receive the following: • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks plus; • Linezolid- participants will be randomly assigned to receive one of the following four linezolid treatment doses and durations: 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 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 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 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 Treatment Modifications: The above treatment schemes may require modification due to toxicities as noted below. All dose modifications should be discussed with the Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation In the event of linezolid specific toxicities, the following should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol. Every effort should be made for participants to receive a total of 9 weeks of linezolid, even if pauses are required: • Blinded one step reductions (maximum 3 steps) in the dose of linezolid (1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or 300mg QD to placebo) managed by the IWRS as per instructions in pharmacy manual and/or IWRS user manual.

Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished Products:	bedaquiline (B), pretomanid (Pa) and linezolid (L)
	• Temporary pause of linezolid due to a linezolid-specific toxicity should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol. • Permanent discontinuation of linezolid. For participants experiencing suspected drug related toxicities due to other drugs in the regimen (B-Pa), the full regimen may be halted for up to 35 consecutive days. Interruptions/pauses of all Investigational Medicinal Product (IMP) must not exceed 8 weeks (56 days) cumulatively. If participant's week 16 sample remains culture positive, Investigator may consider option to extend current treatment to 39 weeks, in consultation with the Sponsor Medical Monitor. When treatment is extended due to a positive culture at week 16, interruptions/pauses of all IMP must not exceed 13 weeks (91 days) cumulatively. At no time should the participant be treated with a single agent.

Criteria for Evaluation:

Primary Endpoint:

Incidence of bacteriologic failure or relapse or clinical failure through follow up until 26 weeks after the end of treatment.

Abbreviated Definitions, full definitions will be described in the Statistical Analysis Plan (SAP):

- Bacteriologic failure: During the treatment period, failure to attain or maintain culture conversion to negative.
- Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status, with culture conversion to positive status with a strain of *Mycobacterium tuberculosis* (MTB) genetically identical to the infecting strain at baseline.
- Clinical failure: A change from protocol-specified TB treatment to a new regimen before end of protocol specified treatment due to treatment failure, retreatment for TB during follow up, or TB-related death.

Note:

- Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.
- Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit.

Further details of definitions to be provided in the SAP.

Secondary Endpoints:

- Incidence of bacteriologic failure or relapse or clinical failure through follow up until 78 weeks after the end of treatment.
- Time to sputum culture conversion to negative status through the treatment period.
- Proportion of participants with sputum culture conversion to negative status at weeks 4, 6, 8, 12, 16 and end of treatment.
- Change from baseline TB symptoms.
- Change from baseline in Patient Reported Health Status.
- Change from baseline weight.

Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished Products:	bedaquiline (B), pretomanid (Pa) and linezolid (L)

Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD):
Plasma concentrations of bedaquiline and its M2, pretomanid and linezolid from sparse sampling (see Table 1.2) will be measured and used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, and linezolid to further evaluate the effects of covariates on model parameters in this study population. PK data from the current trial may be combined with prior data (e.g., from the NiX-TB trial) to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{trough}, C_{max}, AUC_{T}, C_{mean}, and T>MIC) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

Safety and Tolerability:
These data will be presented as descriptive analyses, and no inferential tests will be carried out.

- All-cause mortality.
- Incidence of Treatment Emergent Adverse Events (TEAEs) will be presented 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.
- Descriptive statistics of ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2]) lens opacity classification and grading). Categorical data for lens opacity will be summarized in a frequency table for the right and left eye, respectively, including 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.

Mycobacteriology:
Sputum samples will be obtained at all scheduled visits. The following tests will be performed.

- Smear microscopy for acid-fast bacilli (AFB);
- Liquid Culture (MGIT), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP);
- GeneXpert, Hain Genotype MTBDR*plus* or an alternative molecular to confirm MTB and rifamycin resistance.
- Minimum Inhibitory concentration (MIC) of bedaquiline, pretomanid and linezolid;
- Drug Susceptibility Testing (DST) in liquid culture for rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide and second line TB drugs including fluoroquinolones and injectable;
- Genotyping.

Details on the testing and the collection and timing of samples are in sections 1.2 and 7.1.2.

Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished Products:	bedaquiline (B), pretomanid (Pa) and linezolid (L)

Statistical Methods:
A general description of the statistical methods planned for the primary efficacy outcome is outlined below. Specific details will be provided in the SAP.

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT). We will evaluate the hypothesis, separately for each of the experimental B-Pa-L treatment arms, that the incidence of bacteriologic and clinical cure at 26 weeks after the end of therapy is greater than 50%.

The incidence will be estimated from the binomial proportion for participants with success criteria based on the lower bound of the confidence interval for this proportion being greater than 50%.

There will not be a standard-of-care control group. A 50% treatment success rate was chosen as the target, because it is above the entire range of the historical control for cure of XDR-TB and because a cure rate of 50% in XDR, pre-XDR or MDR-TB treatment intolerant/failures with a shortened, simplified, all oral, inexpensive and safer regimen would clearly represent an important therapeutic advancement.

The primary analysis population will include both XDR and non-XDR participants (up to 45 per arm). A secondary analysis will be restricted to the XDR participants only (30 per arm). 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.

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 6 months) with the L1200 2 months 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.

Both a Modified Intent to Treat (mITT) and a Per Protocol (PP) analysis for each arm will be conducted. No formal statistical pairwise comparisons between the arms will be performed.

Trial Duration:
~3.5 Years (An enrolment period of at least 18 months plus 9 days pre-treatment plus 6 month treatment period plus 18 months post treatment follow-up).

1.2 Synopsis Flowchart

Period	Screening[a]	Treatment																	Visits every 3 weeks if extended due to IMP pause or culture (+) at week 16[b]	End of OR Early Withdrawal from Treatment[c]	Post Treatment Follow-up							
Time of Visit	Up to 9 days prior to Treatment	Day 1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 23			4 weeks	8 weeks	12 weeks	26 weeks	39 weeks	52 weeks	65 weeks	78 weeks
Visit Window[q]	N/A	+/- 3 days									+/- 5 days						+/- 7 days		Post last dose IMP +7 days	+/- 14 days							
Informed Consent	X																										
Demography	X																										
Med/Trtmnt/Smoking History	X																										
Inclusion/Exclusion[d]	X	X																									
Randomization		X																									
Karnofsky Assessment	X																										
HIV Status[e]	X																										
CD4 Count and Viral Load[f]	X																		X								
Chest X-Ray[g]	X																		X								
Urine Pregnancy Test[h]	X	X								X				X					X								
TB Symptoms Profile	X									X				X					X				X		X		X
Patient Reported Health Status	X									X				X					X				X		X		X
Slit Lamp Exam[i]	X																		X[i]			X					
Ophthalmic Exam[j]	X					X				X		X		X		X		X	X	X							
Vital Signs	X	X	X	X		X		X		X		X		X		X		X	X			X	X	X	X	X	X
Single 12-LeadECG[k]	X	X	X			X				X				X					X			X	X	X	X	X	X
Limited Physical Exam[l]			X	X		X		X		X		X		X		X		X				X	X	X	X	X	X
Full Physical Exam	X	X																	X								
Laboratory Safety Tests (includes Full Blood Count)[m]	X	X	X	X	X	X		X		X		X		X		X	X	X	X								
Full Blood Count							X		X		X		X		X												
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication/Compliance[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
PK Sampling[o]		X		X						X		X				X			X[o]								
Early Morning & Spot Sputum[r]	X	X	X	X	X	X		X		X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Peripheral Neuropathy Assessment	X					X				X		X		X		X	X	X	X			X	X		X		X
Investigator Assessment[p]																							X				X

GENERAL: Vital signs, ECGs and blood draws are to be performed pre-dosing unless otherwise specified. Vital signs and/or ECGs should be done prior to blood draws (safety and PK) on days with those assessments.

a. **Screening:** Screening assessments can occur on different days within nine days prior to Day 1 dosing. If a participant fails screening, a full re-screen may occur at a later date post discussion with Medical Monitor. All screening procedures must be repeated at re-screen visit, with the exception of the slit lamp examination, which can be used from a previous screening if within 8 weeks of anticipated randomization.
b. **Visit Schedule:** If the duration of treatment is extended due to dose pauses (e.g., takes participant 35 weeks to complete 26 weeks of treatment) or positive week 16 culture, unscheduled visits should be added every 3 weeks (+/- 7 days). End of treatment visit (final treatment visit) should be done within 7 days **AFTER** the last dose of IMP.
    1. If participant completes treatment at week 26, end of treatment visit should be done within 7 days after last dose of week 26.
    2. If participant completes 26 weeks of therapy at week 33 due to pauses, visits can be done at weeks 26, 29 and 33 (3 weeks from week 29 plus 7-day window). The week 33 visit would be the end of treatment visit and should be completed within 7 days after last dose.
    3. If participant completes treatment at week 39 due to post treatment extension related to positive culture at week 16, visits can be completed at weeks 26, 29, 32, 35 and 39 (3 weeks plus 7-day window), visit at week 39 would be the end of treatment visit.
    4. Follow-up visits should be scheduled based on timing of end of treatment/early withdrawal from treatment (e.g., 4-week follow-up to be scheduled 4 weeks after last dose of IMP).
c. **Follow-up Visits Early Withdrawal Participants:** Once a participant has been discontinued from treatment, they will be **required to attend an Early Withdrawal visit.** If participant:
    1. Received/took $\leq$ 14 doses, no additional follow-up visits are required.
    2. Received 15 or more doses, follow-up after end of treatment at week 12, week 26 (if not already performed) and week 78 are required. The week 12 visit will only require the ophthalmologic exams. The week 26 and 78 follow-up visits will be to collect Serious Adverse Event (SAE) information (including verification of survival) and patient reported TB outcome information only and may be telephonic, a home or a site visit. This includes participants who are *withdrawn from the trial due to meeting the treatment failure endpoint*. Participant may need to return for visits to collect sputum samples to determine outcome status as per section “r”.
d. **Inclusion/Exclusion:** to be confirmed at screening and prior to randomization.
e. **HIV testing:** If HIV status is a confirmed known positive, repeated HIV test is not needed provided documentation is available. If HIV status is unknown or suspected negative, HIV test should be requested. If an ELISA and/or Western Blot based HIV test was performed within 1 month prior to screening, it should not be repeated as long as documentation of testing method and negative results can be provided.
f. **CD4 count and viral load:** For all HIV-positive participants. Viral load and CD4 at screening, CD4 only at end of treatment or early withdrawal.
g. **Chest X-Ray:** A chest x-ray (digital image) within one month prior to screening, will be obtained and read locally by Investigator or designee. Digital images will be provided to Sponsor, this process will be described in a separate document, the Radiology Manual.
h. **Urine Pregnancy:** Women of child-bearing potential only, whether they are sexually active or not.
i. **Slit-Lamp Exam:** Slit Lamp examination will be performed by an Ophthalmologist with AREDS2 training:
    1. For participants who receive $\leq$ 14 doses of IMP, exam at: Screening only.
    2. For participants who receive 15 days to $\leq$ 12 weeks of treatment, exams at: Screening and the 12-week follow-up visit.

3. Participants who complete > 12 weeks of treatment exams at: Screening, End of Treatment or Early Withdrawal and the 12-week follow-up.

j. **Ophthalmic Exam:** to include Ophthalmologic Medical history at Screening; All exams to include Visual Acuity (distance testing) and Colour Vision assessment. Can be done by any trained study staff throughout study. Screening exam must be done by Ophthalmologist in addition to trained study staff that will perform exams throughout the study.

k. **Single 12-Lead ECG:** To every extent possible, should be performed at approximately the same time of day (+/- 1 hours) and in the same fed/fasted state throughout the trial (e.g. 4 hours after lunch). Central ECG analysis will be performed.

l. **Physical Exam:** Limited Physical exams should include weight and a gross neurological, pulmonary, cardiovascular and abdominal exam.

m. **Safety Laboratory Assessments**: The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
   1. Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count).
   2. Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO2, creatine phosphokinase (CPK).
   3. Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator.
   4. Urine Drug Screen: Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at **Screening only.** Investigator to utilize to determine whether participant meets Exclusion criteria 2. Positive results will not automatically exclude participant from the trial.

n. **Study Medication/Compliance:** Study medication administration will be supervised per local site practice to assure compliance to regimen.

o. **PK Sampling:** Specific PK blood draws as follows:
   1. Day 1; pre-dose (within 2 hours prior to dosing)
   2. Week 2: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose
   3. Week 8: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose
   4. Week 12: pre-dose (within 2 hours prior to dosing)
   5. Week 20 or at early withdrawal if prior to week 20: pre-dose (within 2 hours prior to dosing) and 2–3 hours post-dose

   When participant is discharged and seen as an outpatient, site should make every effort to collect 6-8 hour samples at weeks 8 and when operationally and logistically feasible.

p. Investigator Assessment: Principal Investigator to review participant status and assess whether TB treatment at current visit is considered a “success” or “failure”. If considered a failure, should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration. To be completed at 26 and 78 week post treatment follow-up visits and at any time Investigator determines that participant fulfills criteria for outcome of treatment failure.

q. **Visit Windows:** the windows noted on the flowchart for timing of visit also apply to timing ***within a visit***. **For example**, procedures that are difficult to schedule such as ophthalmology exams, should be scheduled within +/- 3 days of scheduled visit from Day 1 to Week 8 or +/- 14 days within scheduled visit at the week 12 post treatment follow-up visit. Sites should make every effort to ensure all other procedures should be done on the same day when possible.

r. Sputum Sampling:

Visit	Sample		Tests					
	EMS*	Spot	AFB Smear microscopy	MGIT culture, speciation	Molecular testing	MIC: B, Pa, L	Liquid DST	Genotyping
Screening (Day -9 to -1)		●●	S	S	S			
Baseline (Day 1) *or screen - wk4 if baseline negative or contaminated*	●	●		S		C	C	C
All Visits Post Baseline	●	●		S				
Positive for MTB at/after EoT	●			S	S	C	C	C

C – Central laboratory (specialized facility)
S – Study Laboratory (facility that receives samples directly from site)

SPUTUM SAMPLES GENERAL: If EMS is not available, site should make every attempt to collect two spot samples at least 30 minutes apart.

BASELINE: If available, site will request pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be subcultured and shipped to the study lab from the applicable lab for relevant participants with no positive cultures from screening through week 4 (with consent). Samples should be stored according to the applicable lab procedures until shipment to the designated study lab. Included with each shipment will be a copy of the applicable lab reports and all participant identifying information redacted and a completed shipment inventory form with appropriate participant trial identifiers. Details on how samples will be packed and shipped will be provided in the lab manual.

POSITIVE MTB AT/AFTER END OF TREATMENT: Only one isolate (preferably from EMS) should be shipped. Second isolate may be requested if first is contaminated.

MOLECULAR TESTING:

- At Screening: GeneXpert, Hain MTBDR*plus* or equivalent to determine MTB complex and R resistance.
- Positive MTB at/after end of treatment: Hain MTBDR*plus* and HainMTBR*sl*

LIQUID DST: for SIRE, Z and second line anti-TB drugs, including but not limited to FQ and injectables.

STORAGE: MTB isolates from all positive cultures to be stored at the study laboratory until trial closure for the applicable study tests. The extracted MTB DNA from the applicable baseline and follow-up isolates will also be stored at the central lab for potential further work to validate new assay tools for 5 years after trial closure.

CENTRAL LAB: Results from testing at Central myco lab (MIC, DST and genotyping) will not routinely be provided to sites. In the event of participant relapse/failure, Sponsor will provide available results to the site in order to inform appropriate participant treatment.

UNSCHEDULED VISITS: If cultures of both spot sputum samples are contaminated *at the following visits*, or if necessary in order to help define a participant's outcome status/assess culture status during follow-up, the participant should return for an unscheduled visit(s) to give additional samples or to document the participant is not able to produce sputum:

- End of treatment visit;
- Week 26 post treatment follow-up visit;
- Post treatment follow-up visits from week 8 through week 65 (in addition to week 26 follow-up);
- End of Follow-up Period (week 78 post treatment completion visit);
- Early Withdrawal (if applicable).

<u>At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, need to confirm whether the participant has:</u>

- At least two sequential negative sputum culture results; or
- At least two sequential positive sputum culture results; or
- Has been unable to produce sputum after documentation of at least two negative sputum cultures with no intervening positive and are clinically asymptomatic.

If they **do not** fall into one of these categories, site should continue to collect sputum samples x 2 (one Early Morning and one Spot at the research site or 2 spots samples at least 30 minutes apart, under the coaching and observation of the trial staff) at a minimum of 7 days or more apart until they fall into one of the above categories.

If in any of the above scenarios the Investigator is unsure of the outcome, the Investigator must contact the Sponsor Medical Monitor to discuss and agree on how the patient is to be handled.

2 Introduction and Rationale

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in many countries. TB is now the world's leading infectious disease killer and is responsible for more deaths than HIV.[43] 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.

Outcomes of treatment for XDR-TB using the best available treatments have traditionally been very poor. The best treatment historically has been to use available second line drugs individually tailored based on drug susceptibility testing in an inpatient setting to assure adherence with treatment lasting from 24 months to much longer for patients without culture conversion. The most detailed report using this approach with long term follow-up prior to the use of linezolid, bedaquiline or delamanid in regimens has come from South Africa, where the HIV co-infection rate among patients with XDR-TB ranges from 40 to 70%. A cohort study of 107 patients with XDR-TB found cure or completion of therapy at 24 months to be 16%, with 46% having died.[28] In another report from South Africa of 114 patients with XDR-TB, 22% completed treatment successfully.[21] The largest evaluation of treatment outcomes was noted in the WHO 2014 annual tuberculosis report of 1269 patients in 40 countries, where 22% of patients with XDR-TB completed treatment successfully and 35% died.[42] A meta-analysis of 397 patients with XDR-TB from 31 centers, with HIV coinfection <10%, reported 32% treatment success.[17] Reports of the outcome of XDR-TB treatment from Peru (43 patients, 42% treatment success)[2] and Ukraine (114 patients, 22% treatment success)[11] have been similar. Based on these reports, the success of traditionally available drug therapies for treating XDR-TB infection is substantially less than 50% and in the most detailed and largest reports is less than 25%.

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. Experience recently published from the C209 uncontrolled study of bedaquiline given on a background of multiple drugs notes that the subset of 38 patients with XDR-TB had rates of sputum culture conversion to negative of 62.2%.[29] However, in this study only one patient with XDR-TB was co-infected with HIV. All participants were required to have Mycobacterium tuberculosis (MTB) isolates susceptible to at least 3 drugs at enrolment, and patients had a median of only 5.4 months of treatment-free follow-up. This study added bedaquiline for 6 months to a background regimen of many drugs given for 18 months or longer.

While treatment success for MDR-TB is better than for XDR-TB, overall success in treating MDR-TB is still approximately 50% according to the World Health Organization 2015 Global TB Report.[43] This report presented that overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, 10% failed treatment, and for 8% there was no outcome information.

With such poor historical outcomes for patients with XDR-TB and with the complexity, expense and toxicity of treatments for all forms of drug resistant TB, novel drug combinations are desperately needed to improve treatment outcomes. Linezolid was identified in a small study as

a potentially efficacious drug in patients with XDR-TB when added to a failing regimen[9] and this drug has increasingly been added to complex regimens to treat patients with MDR-TB.

With the current availability of three drugs for which there is little, if any, pre-existing resistance among strains of 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. Mice infected with MTB had relapse-free cures with 3 months of treatment with a B-Pa-L regimen. While it is not known whether that treatment duration will translate to humans, it is hypothesized in the design of the ongoing Nix-TB clinical study that patients with pulmonary XDR-TB may have relapse-free cure after as little as 6 months' treatment with the B-Pa-L regimen. Therefore, since 2015, the TB Alliance has sponsored a study with a 6 month treatment duration with the B-Pa-L regimen in participants with XDR-TB or MDR TB not responsive to or intolerant to therapy (the Nix-TB study).[1]

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 includes daily injections for a minimum of 6 months. The NC-007 trial takes this regimen into a randomized Phase 3 trial to optimize the dosing scheme for linezolid and the benefit relative to risk, and to expand the patient population to include individuals with pre-XDR TB.

The information presented below first details the trial rationale, then key preclinical information and human efficacy and safety information for each of the drugs in the regimen and then presents preclinical and clinical data to support the combination of these drugs in a regimen to treat patients with XDR, pre-XDR and MDR treatment intolerant/failure-TB.

2.1 Trial Rationale

2.1.1 Trial Design Rationale

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.

2.1.2 Trial Drug Rationale

2.1.2.1 Bedaquiline

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this study bedaquiline will be administered as 200 mg daily for 8 weeks, followed by 100 mg daily for the remaining 18 weeks or 30 weeks if treatment is extended. This daily dosing scheme will allow more convenient dosing that should ultimately enhance patient adherence and may allow the formulation of fixed dose combinations with other drugs. This daily dosing regimen is supported by safety and efficacy demonstrated in the NC-005 study that administered bedaquiline 200 mg daily over 8 weeks, and

by pharmacokinetic modelling and simulation of the daily dosing scheme. This supportive information is detailed below.

The NC-005 study allows the efficacy and safety to be compared for treatment arms that dosed bedaquiline at the currently registered dose and at 200 mg daily for the 8 weeks of the trial. Briefly, Study NC-005 evaluated a regimen in patients with drug susceptible pulmonary TB given bedaquiline with pretomanid and pyrazinamide over an 8 week period. One arm was to enroll 60 patients who were to be given this regimen with bedaquiline dosed as approved for marketing (referred to as the B (loading dose/t.i.w.) PaZ arm), and another 60 patients were to be enrolled who would be given the regimen with bedaquiline dosed at 200 mg daily (referred to as the B (200mg) PaZ arm). Another group of patients with DS TB were randomized to treatment with standard HRZE therapy. Patients with MDR-TB were given the regimen with bedaquiline dosed at 200 mg daily in addition to moxifloxacin (referred to as the B (200 mg) MPaZ MDR-TB arm). The primary endpoint was The Bactericidal Activity (BATTP (0-56)) as determined by the rate of change in time to sputum culture positivity (TTP) over 8 weeks of treatment in the Mycobacterial Growth Indicator Tube system, represented by the model-fitted log (TTP) results as calculated by the regression of the observed log (TTP) results over time. The assessments of safety and tolerability included the incidence of Treatment Emergent Adverse Events (TEAEs) presented by severity (DMID Grade), by drug relatedness and seriousness, and for those leading to early withdrawal and leading to death, by group. In addition, quantitative and qualitative clinical laboratory result measurements were evaluated, including group summaries of observed values and changes from baseline. Pharmacokinetics for all participants included pre-dose samples on 9 days during and one day following dosing with the regimen. Fifteen PK Sub-study participants in each treatment arm had in addition intense PK sampling on Days 14 and 56.

<u>Efficacy of bedaquiline 200 mg daily dose vs the marketed dosing scheme over 8 weeks</u>

In the efficacy analysis of the NC-005 trial, based on liquid media collected from overnight sputum samples, the B(200 mg)MPaZ MDR-TB treatment group showed the highest bactericidal activity over the 8-week treatment period, followed by that of B(200 mg)PaZ, B(loading dose/t.i.w.)PaZ and then HRZE. It appears clear that the daily dosing regimen for bedaquiline provided at least as good a result in the primary efficacy analysis as the registered dosing scheme for bedaquiline.

<u>Safety of bedaquiline 200 mg daily dose vs the marketed dosing scheme</u>

Adverse events, including serious adverse events and Grade III/IV adverse events were similar among groups. In particular, the mean change from baseline in the corrected QTc intervals was numerically less in the participants given bedaquiline daily than in the participants given bedaquiline with the labelled dosing scheme. Measures of potential hepatic toxicity, including participants with greater than 3 fold or 10 fold elevations in aminotransferase levels, were numerically greater in participants given the labelled dosing scheme than subjects given daily doses of bedaquiline.

<u>Pharmacokinetics of bedaquiline 200 mg daily dose vs the marketed dosing scheme</u>

A population PK model published by McLeay in 2014 was used with PK data from Study NC-005 to simulate the expected bedaquiline exposures when dosed at 200 mg daily followed by 100 mg daily for the remainder of the study in comparison to the labelled dosing scheme with bedaquiline administered for 6 months.[14] The key findings from the simulations of the proposed dosing

scheme for NC-007 of bedaquiline administered 200 mg daily over 8 weeks followed by 100 mg daily for an additional 16 weeks are:

- The exposures of the proposed dosing scheme (C_{max}, $_{mean}$ or $_{trough}$) are not expected to exceed the exposures associated with the labelled scheme on Day 14 at the end of the 400 mg daily dose. With the labelled dosing scheme, the highest exposures are on Day 14 at the end of the 400 mg daily loading dose.
- The average daily exposures with the proposed dosing scheme over 6 months are within (or not substantially different from) the range of exposures over 6 months of the labelled dosing scheme.
- The cumulative exposure, in terms of AUC over time, is similar between the proposed dosing scheme and the labelled scheme

2.1.3 Pretomanid

Pretomanid has demonstrated good microbicidal activity at the 200mg daily dose as monotherapy in studies PA-824-CL-007 and PA-824-CL-010, in combination with either bedaquiline or pyrazinamide over 14 days in the early bacteriocidal activity (EBA) Study NC-001-(B-M-Pa-Z), in combination with either bedaquiline and/or pyrazinamide and/or clofazimine over 14 days in the EBA Study NC-003-(B-C-Pa-Z), and in combination with bedaquiline and linezolid over 6 months in the Nix-TB study. In the EBA Study PA-824-CL-010 the 100mg dose demonstrated similar microbicidal activity to the 150 and the 200mg daily dose over 14 days. The Phase 2 trial NC-002-(M-Pa-Z) evaluated this regimen at doses of pretomanid of both 100 mg and 200 mg relative to the HRZE control. In this trial the efficacy results were similar between participants treated with 100 mg/day and 200 mg/day of pretomanid in the regimen, although for the primary endpoint, reduction in colony forming units of MTB from sputum, only the 200 mg/day dose group was statistically significantly better than the group randomized to standard HRZE therapy. Safety was also similar between the groups, although the 200 mg/day group had more grade 2 adverse events than either the 100 mg/day group or the HRZE control group. Because sterilizing relapse-free cure of TB in patients with XDR-TB may ultimately require a regimen with higher drug exposures, the 200mg dose was chosen for evaluation in the Nix-TB study of the B-Pa-L regimen. The manageable toxicity of the regimen and very encouraging efficacy in the Nix-TB trial support taking the 200 mg dose of pretomanid forward in the NC-007 trial.

2.1.4 Linezolid

The standard dose of linezolid for a multitude of indications is 400mg or 600mg BID. Doses of linezolid used to treat pulmonary TB in reported observational trials and case series range from 300 mg to 1200 mg per day over periods of up to 20 months of treatment. While the development of adverse events is generally higher with higher doses, the adverse events often ameliorate with a reduction of the dose or discontinuation of drug for several weeks and then reintroduction at a lower dose. No controlled trials have clearly identified differences in anti-TB effect across a range of doses over long term treatment of TB.

In this trial, each arm will vary the linezolid dosing to identify the optimal ratio of efficacy to adverse events as noted below. The 4 arms, to which participants will be randomly assigned in a blinded manner, are:

- Linezolid 1200 mg orally once daily for 26 weeks, with the ability to interrupt or reduce the dose if needed based on toxicity.
- Linezolid 1200 mg orally once daily for the first 9 weeks, with the ability to interrupt or reduce the dose if needed based on toxicity.
- Linezolid 600 mg orally once daily for 26 weeks, with the ability to interrupt or reduce the dose if needed based on toxicity.
- Linezolid 600 mg orally once daily for the first 9 weeks, with the ability to interrupt or reduce the dose if needed based on toxicity.

These dosing schemes for linezolid are chosen based on clinical experience in the Nix-TB trial, the company's linezolid early bactericidal activity (EBA) study findings in the Lin CL-001 study, and preclinical data in the mouse model of infection. While the EBA study showed that a modestly greater bactericidal effect over 14 days at the highest 1200 mg daily dose (see further details below in Section 2.2.3), this dose appears to be associated in the Nix-TB trial and in published literature with a greater incidence of unwanted neuropathic and myelosuppressive effects than the 600 mg daily dose. While a full 6 months of linezolid therapy in the regimen may give greater culture conversion and avoid relapse, the mouse model found that linezolid dosing of only 1 or 2 months, when B and Pa were given continuously for a total of 3 months, maximized relapse-free cure; in other words, similar to pyrazinamide in the present first line HRZE therapy, more than 2 months of linezolid when combined with B and Pa does not increase relapse-free cure in the mouse model. Thus, the 4 treatment arms in this study will give randomized comparative information about the optimal duration and dose of linezolid in the regimen relative to efficacy and toxicity.

The decision to give linezolid as a single daily dose is based on the results of the linezolid EBA study that showed over 14 days that similar bactericidal activity was noted whether the drug was given as a single daily dose or divided in to 2 doses. A single daily dose will ultimately enhance patient adherence and will reduce the total time the drug concentration is greater than the calculated concentration associated with mitochondrial toxicity (which we hypothesize to be the likely mechanism for the toxicities of peripheral neuropathy and myelosuppression).

2.2 Agents to be Studied

2.2.1 Bedaquiline

Bedaquiline is being developed as part of combination therapies for pulmonary TB due to MDR-TB and approved in 2012 in the USA under the provisions of accelerated approval regulations. Bedaquiline received conditional Marketing Authorization in the EU in 2014 and is approved in over 40 countries (EU countries counted individually). The approved indication may vary per country. Bedaquiline is marketed under the trade name SIRTURO™. Bedaquiline has a novel mechanism of action as it specifically inhibits mycobacterial ATP synthase, an enzyme that is essential for the generation of energy in MTB The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.

In the placebo-controlled Phase 2b study C208 conducted in newly-diagnosed patients with sputum smear-positive pulmonary MDR-TB (including pre-XDR-TB), the addition of bedaquiline to a preferred background regimen of MDR-TB treatment resulted in a decreased time to culture conversion and improved culture conversion rates compared to placebo. Median time to culture conversion according to the primary analysis method was 83 days for the bedaquiline group

compared to 125 days for the placebo group (p<0.0001; hazard ratio, 95% CI: 2.44 [1.57; 3.80]). The proportion of patients in the mITT population with sputum culture conversion after 24 weeks of treatment with bedaquiline or placebo in combination with background regimen (with patients who discontinued considered as non-responders), was 52/66 (78.8%) in the bedaquiline group and 38/66 (57.6%) in the placebo group. Durability of response seen in the bedaquiline treatment group was supported by the results at Week 120. The proportion of responders (with patients who discontinued considered as non-responders) at Week 120 was 41/66 (62.1%) in the bedaquiline group and 29/66 (43.9%) in the placebo group.

In the Phase 2b, open-label study C209, conducted in 233 patients with sputum smear positive pulmonary MDR-TB, the median time to sputum culture conversion excluding patients with DS-TB and those that did not have a positive sputum culture at screening and/or baseline (mITT; 205 patients), was 57 days. At Week 24, 163 of 205 (79.5%) patients responded to bedaquiline treatment as determined by sputum culture conversion rates. Conversion rates at Week 24 were highest (87.1%; 81/93) in patients with MDR-TB resistant to only RMP and INH, 77.3% (34/44) in pre-XDR-TB patients and lowest (54.1%; 20/37) in XDR-TB patients.

The average terminal half-life of bedaquiline, is about 5.5 months. After reaching C_{max}, however, there is initially a fairly rapid reduction in plasma bedaquiline concentrations over the dosing interval (with an estimated half-life of about 13 hours). Four weeks after ceasing bedaquiline intake, the mean bedaquiline concentrations were reduced by approximately 40% compared to the end of the bedaquiline treatment period in the C208 study. Administration of bedaquiline with food increased the relative bioavailability by about 2-fold compared to administration under fasted conditions. It is therefore recommended to take bedaquiline with food to enhance its oral bioavailability.

CYP3A4 is the major CYP isoenzyme involved *in vitro* in the metabolism of bedaquiline. Drug-drug interaction (DDI) studies have showed reduced exposure to bedaquiline during combination with a strong or moderate inducer of CYP3A4 metabolism (i.e., rifampicin) and increased exposure during combination with a strong or moderate inhibitor of CYP3A4 metabolism (i.e., ketoconazole). Potential drug interactions with anti-retroviral drugs have been evaluated in three studies. In an interaction study of single-dose bedaquiline and multiple-dose Lopinavir/ritonavir, exposure (AUC) to bedaquiline was increased by 22% (90% CI: 11-34). Co-administration of single-dose bedaquiline and multiple-dose nevaripine did not result in clinically relevant changes in the exposure to bedaquiline. Co-administration of a single dose of bedaquiline and multiple-dose efavirenz (EFV) resulted in approximately a 20% decrease in the AUC_{inf} of bedaquiline with no alteration in the C_{max}. Modeling based on the data from this DDI study predicts average steady-state concentrations of bedaquiline and M2 to be reduced by 52% with chronic co-administration of bedaquiline and EFV.[5]

Safety of Bedaquiline

The Investigator's Brochure for bedaquiline provides detailed safety information.[5]

Data were used from 14 completed clinical studies to identify Adverse Drug Reactions (ADRs) according to the ICH guideline entitled, E6: Good Clinical Practice, Consolidated Guideline (ICH, 1996): "…all noxious and unintended responses to a medicinal product related to any dose should

be considered adverse drug reactions. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out."

The ADRs were identified from the pooled safety database of reported AEs in the Phase 2b clinical studies with bedaquiline, based upon a systematic well-documented approach and are presented for study C208 below in Table 1. None of the ADRs reported in the controlled studies during the Investigational Treatment phase were considered serious.

Table 1: ADRs C208 Stage 1 and Stage 2

Adverse Drug Reactions (ADRs) in the Controlled Studies (C208 Stage 1 and Stage 2) During the Investigational Treatment Phase			
ADR (Grouped term), n (%)	**Frequency**	**Any BDQ N=102**	**Any Placebo N=105**
Nervous system disorders			
Headache	Very Common	24 (23.5)	12 (11.4)
Dizziness	Very Common	13 (12.7)	12 (11.4)
Cardiac disorders			
ECG QT prolonged	Common	3 (2.9)	4 (3.8)
Gastrointestinal disorders			
Nausea	Very Common	36 (35.3)	27 (25.7)
Vomiting	Very Common	21 (20.6)	24 (22.9)
Diarrhea	Common	6 (5.9)	12 (11.4)
Hepatobiliary disorders			
Transaminases increased[a]	Common	7 (6.9)	1 (1.0)
Musculoskeletal and connective tissue disorders			
Arthralgia	Very Common	30 (29.4)	21 (20.0)
Myalgia	Common	6 (5.9)	7 (6.7)

a. Different AE preferred terms (i.e., transaminases increased, aspartate aminotransferase [AST] increased, alanine aminotransferase [ALT] increased, hepatic enzyme increased, and hepatic function abnormal) contribute to this ADR, while for the other ADRs the ADR is the preferred term.

Of note, 13 deaths occurred in the C208 Stage 2 study: 10 subjects (12.7%) in the bedaquiline group and 3 subjects (3.7%) in the placebo group experienced an SAE leading to death. One death (alcohol poisoning) occurred during administration of bedaquiline. The median time to death for the remaining 9 subjects was 344 days after last intake of bedaquiline. One of the 10 deaths in the bedaquiline treatment group and 1 of the 3 deaths in the placebo group occurred after the Week 120 window. In the bedaquiline group, the most common cause of death as reported by the investigator was TB or TB-related illness (5 subjects). For all deaths due to TB, the subject’s last microbiological outcome was either failure to convert or relapse. The causes of death in the remaining bedaquiline subjects varied. The investigator considered all the SAEs leading to death not or doubtfully related to bedaquiline/placebo. The imbalance in deaths is unexplained. In addition, no discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, or severity of disease was observed.

During clinical studies with bedaquiline a prolongation of QTc interval on the ECG was observed. Consequently, bedaquiline treatment initiation is not recommended in patients with, personal or

family history of prolonged QT intervals, or additional risk factors for Torsades de Pointes. Detailed criteria are noted in Section 5.2,5.2 Exclusion Criteria.

Increases in transaminases were seen in clinical studies during administration of bedaquiline in combination with a background regimen. Based on a review confirmed by an external hepatologist, it was concluded that bedaquiline has a signal for liver injury manifested by increases in AST and to a lesser extent ALT. Transaminase elevations are not unexpected given the number of other hepatotoxic drugs in the background regimens in clinical trials based on the publication by Keshavjee, which describes a 16.5% incidence of hepatotoxicity during MDR-TB treatment. [7]

2.2.2 Pretomanid

As detailed in the Investigator's Brochure[6], pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazo-oxazines, which possess significant anti-tuberculosis activity and a unique mechanism of action[35]. Pretomanid demonstrated *in vitro* activity against both DS- and MDR-TB[10], and *in vivo* activity in a mouse model of tuberculosis[10, 35].

2.2.2.1 Pharmacology

2.2.2.1.1 Key in Vitro Evaluation of Pretomanid Bactericidal Activity

Non-clinical in vitro studies demonstrated that pretomanid was active against actively growing drug-sensitive and drug-resistant MTB strains as well as against non-replicating MTB The minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive MTB isolates *in vitro* was shown to be similar to the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of MTB with MIC values ranging from 0.03 to 0.53 µg/mL. The Investigator's Brochure contains further information on *in vitro* bactericidal activity. [6]

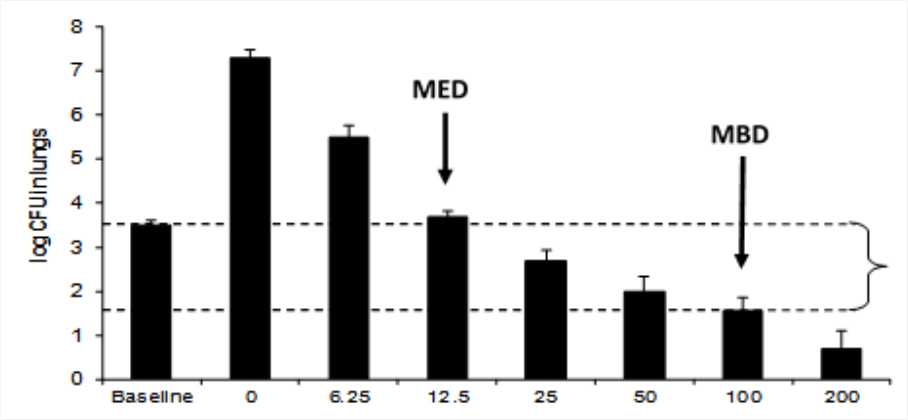
Although not thoroughly elucidated at this time, pretomanid has a novel mechanism of action that appears to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reduction of pretomanid by a deazaflavin (F420)-dependent nitroreductase has been shown to be associated with generation of reactive nitrogen species, including nitric oxide (NO), [33] although the exact target(s) of the reactive nitrogen species are not known. Transcriptional profiling studies also suggest that pretomanid affects both cell wall biosynthesis and the respiratory complex of MTB.[12,13]

2.2.2.1.2 Key Non-Clinical Studies of Pretomanid

The activity of pretomanid as a single agent or as part of a multi-drug combination regimen has been examined in a number of mouse studies.[18,19,20,36,40] In a mouse model of established TB, the activity of various doses of pretomanid (given once daily, 5 days/week, for 1 month), initiated 22 days after inhalation infection with H37Rv MTB is shown in Figure 1. In this model, the minimum effective dose (MED) for pretomanid, defined as the lowest dose able to prevent the development of gross lung lesions and splenomegaly, was 12.5 mg/kg/day, while the minimum bactericidal dose (MBD), defined as the lowest dose able to reduce lung colony forming units (CFU) by 99%, was 100 mg/kg/day. Moreover, in these experiments, the activity of pretomanid at 100 mg/kg was comparable to the activity of isoniazid at 25 mg/kg.

Figure 1: Log10 CFU Counts in Lungs

After One Month of Daily Treatment with the Indicated Dose (in mg/kg) of Pretomanid



Arrows denote the minimum effective dose (MED) and minimum bactericidal dose (MBD).

2.2.2.2 Non-Clinical Toxicology and Safety

Pretomanid has been evaluated in an ICH recommended battery of safety pharmacology studies, in repeat-dose toxicity studies in rats (2 to 26 weeks) and cynomolgus monkeys (7 days to 9 months), in 8 genotoxicity studies, and in fertility and teratology studies in rats and rabbits.

In the repeat-dose toxicity studies, the lowest no-observed adverse effect level (NOAELs) was 10 mg/kg/day in a 26-week study in rats, 50 mg/kg/day in a 13-week study in monkeys and <25 mg/kg/day (based on findings of thickening of the GI tract at all doses) in a 9-month study in monkeys. The major findings in safety and toxicity studies are listed below in Table 2 and are detailed in the Investigator's Brochure.[6]

Table 2: Key findings of Pretomanid in Safety and Toxicity Studies

Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behaviour at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
Testicular toxicity Although rat and rabbit embryonic development studies indicate no effects of PA-824 on fetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose

toxicology studies and a Segment I fertility study. In this fertility study, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower dose not associated with testicular atrophy. A detailed study in sexually mature male monkeys demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing.

Cataracts

Cataracts developed in rats with prolonged daily administration of pretomanid at doses ≥100 mg/kg/day. In one 13-week study in monkeys, cataracts did develop at 450/300 mg/kg/day, but only by the end of a 13-week recovery period. In a second 13-week study in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.

hERG inhibition and QT prolongation

Altered ventricular repolarisation due to inhibition of hERG-mediated potassium current and manifested on the electrocardiogram (ECG) as a prolonged QT interval corrected for heart rate (QTc). Pretomanid inhibited hERG current with IC50 values of approximately 6.2 µg/mL. Following a single pretomanid dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Co-administration of pretomanid with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at pretomanid doses of ≥150 mg/kg/day.

2.2.2.3 Clinical Background Information

Pretomanid has been evaluated in 8 single- and multi-dose Phase 1 studies with healthy adult male and female subjects, with 163 subjects receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 7 days. These Phase 1 studies have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid. Two additional Phase 1 studies sponsored by the NIH included a Thorough QT study and a study of drug interactions among pretomanid, efavirenz and ritonavir/lopinavir. Further details of the studies are in the Investigator's Brochure.

2.2.2.3.1 Pharmacokinetics

Several Phase 1 studies have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid and have demonstrated that pretomanid has a half-life of approximately 18 hours, which supports daily dosing, and an effect of food with the 200 mg dose that increases total exposure by 88%. Interaction studies with midazolam, efavirenz and ritonavir/lopinavir demonstrate effects that are not likely to be clinically significant.

Drug interaction with midazolam: Study CL-006 was an open-label, fixed-sequence drug-drug interaction study to evaluate the effects of multiple-dose administration of pretomanid on the PK of midazolam, a sensitive probe substrate and representative compound for drugs metabolised

by CYP3A enzymes. Dosing with pretomanid at 400 mg/day for 14 days (to steady state) had minimal effect on the PK of midazolam and its 1-hydroxy metabolite as assessed by measurement of the Day 17: Day 1 ratios of maximum concentration (C_{max}), area under the curve to the last available time point (AUC_{0-t}), and area under the curve extrapolated to infinity (AUC_{0-inf}). The C_{max} and AUC values for midazolam after co-administration with pretomanid were approximately 85% of those observed after treatment with midazolam alone. Furthermore, midazolam and 1-hydroxy midazolam time to maximum concentration (T_{max}) and half-life ($t_{1/2}$) values were not different in the presence or absence of pretomanid. Therefore, 14 days' dosing with 400 mg/day pretomanid does not appear to significantly inhibit CYP3A4 in humans.

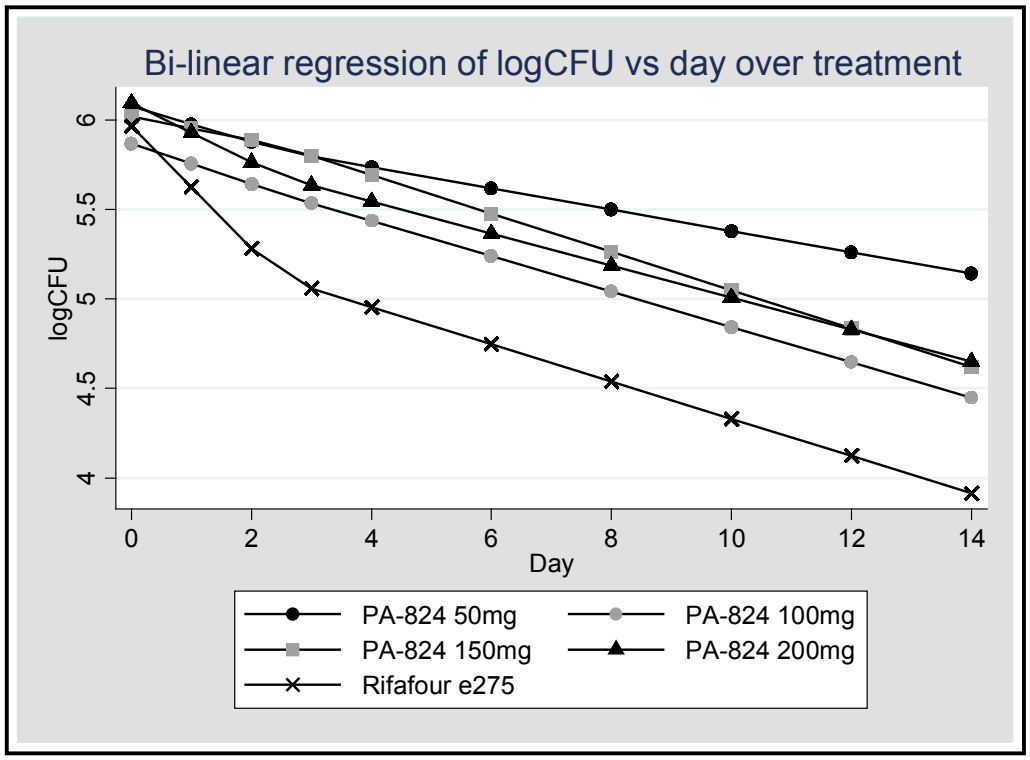
Drug interaction with efavirenz, ritonavir/lopinavir, and rifampicin: The US NIH sponsored this drug interaction study with rifampicin, a known hepatic enzyme inducer, and with the antiretroviral drugs efavirenz and ritonavir/lopinavir (LPV/r) in healthy subjects. Participants in Arm 1 were randomised to Sequence 1 (pretomanid 200 mg once daily for 7 days, two-week washout period, efavirenz (EFV) 600 mg once daily for 14 days, then both drugs for 7 days) or Sequence 2 (Treatment 1B: EFV, then EFV + pretomanid, washout, and pretomanid). Results indicate that comparing pretomanid given with EFV versus pretomanid alone in 16 participants, the geometric mean ratio (GMR) for the maximum concentration (C_{max}) was 0.71, the GMR for the 24-hour area under the time-concentration curve (AUC_{0-24h}) was 0.65, and the GMR for the trough concentration (C_{min}) was 0.54. Concentrations of EFV when given with pretomanid versus given alone were similar. Participants in Arm 2 were randomised to Sequence 1 (pretomanid 200 mg once daily for 7 days, then a 2-week washout period, then LPV/r 400/100 mg twice daily for 14 days, then LPV/r + pretomanid together for 7 days) or Sequence 2 (LPV/r, then LPV/r + pretomanid, washout, then pretomanid alone). Comparing pretomanid + LPV/r versus pretomanid alone from 16 PK-evaluable participants, the GMR for C_{max} was 0.87, for AUC_{0-24h} was 0.83, and for C_{min} was 0.78. In Arm 3, participants received pretomanid for 7 days, then rifampicin 600 mg for 7 days, then pretomanid + rifampicin together for 7 days. Comparing pretomanid + rifampicin versus pretomanid alone from 16 PK-evaluable participants, the GMR for C_{max}, AUC_{0-24h}, and C_{min} were 0.47, 0.34, and 0.15, respectively.

In conclusion, compared to pretomanid alone, plasma pretomanid values (based on geometric mean ratios) for maximum concentration (C_{max}), area under the concentration-time curve (AUC_{0-24h}), and trough concentration (C_{min}) were reduced 28%, 35%, and 46% with efavirenz; 13%, 17%, and 21% with LPV/r; and 53%, 66%, and 85% with rifampin, respectively.

2.2.2.3.2 Pretomanid Clinical Efficacy

The first two Phase 2 studies to evaluate the early bactericidal effect (EBA) of pretomanid oral monotherapy (50 to 1200 mg/day for 14 days) examined the dose-response for pretomanid in participants with newly diagnosed pulmonary TB infection. The first study (CL-007) demonstrated good EBA, but all doses in this study (200 to 1200 mg/day) had the same activity. The second study (CL-010) evaluated a lower dose range (50 to 200 mg/day) and the maximum effect on EBA was seen at a dose of 100 mg/day over 14 days [4] (Figure 2).

Figure 2: Mean log Colony Forming Unit Values over Time Study CL-010



CFU = colony-forming unit; PA-824 = pretomanid

* Day 0 = (Day -2 + Day -1)/2 = baseline measurement

Pretomanid has been evaluated in patients with TB as monotherapy for a maximum duration of 14 days, the longest considered acceptable for a TB patient to be treated in a clinical trial with a single drug. Studies of Pretomanid for both 14 days and for up to 6 months, in combination with either bedaquiline and/or linezolid, are described below in Section 2.3.2.

2.2.2.3.3 Pretomanid Clinical Safety

The pretomanid Investigator's Brochure[6] provides detailed safety information.

Across the 16 clinical studies with pretomanid completed to date, a total of 649 participants have been exposed to pretomanid, including 289 healthy subjects across the 10 Phase 1 studies and 360 participants with newly diagnosed smear positive pulmonary TB across 5 Phase 2 studies. Among the 289 healthy Subjects, 174 received exposure to a single dose of pretomanid ranging from 50 to 1500 mg and 115 received exposures to repeated daily doses of pretomanid (50 to 1000 mg) for up to 14 days. The 360 participants with newly diagnosed smear positive pulmonary TB were exposed to pretomanid either as a single agent at daily doses of 50 to 1200 mg for 14 days or in combination with other anti-TB agents (bedaquiline, moxifloxacin, pyrazinamide, linezolid and/or clofazimine) at a dose of 100 mg or 200 mg for up to 26 weeks. The overall safety profile determined from the clinical studies completed to date indicates pretomanid

is well tolerated in healthy adults and in TB patients when administered alone and in combination with moxifloxacin, pyrazinamide, bedaquiline and clofazimine.

Pretomanid is an investigational drug and there is limited experience in humans; the safety database is being developed and investigators should be vigilant to any adverse events noted in clinical trials. Across these studies, the most common side effects or AEs associated with pretomanid exposure include:

- Headache
- Stomach discomfort (nausea, vomiting, flatulence, and/or diarrhea)
- Skin and subcutaneous tissue disorders

The only adverse drug reaction identified in clinical studies completed to date as likely caused by pretomanid is blood creatinine increased. A study of the effects of repeat doses of pretomanid in healthy volunteers determined that the drug does not adversely affect glomerular filtration rate, effective renal plasma flow or filtration fraction and the elevations in serum creatinine reverse.

The following parameters will be followed with particular care in the Phase 3 development program:

- Hepatic Safety – Specific guidelines are included in the protocol to assure close surveillance and careful management of participants who have elevations in aminotransferases and/or bilirubin. Serious liver injury, including death in 3 participants taking a combination of pretomanid, pyrazinamide and moxifloxacin, has occurred during clinical studies and the risk of liver injury may be higher for participants taking a combination of PA-824 and pyrazinamide than it is for the standard HRZE treatment. Therefore, close monitoring of liver function is required for participants who are administered PA-824, especially when combined with pyrazinamide. Administration of the regimen of PaMZ has been associated with death in 3 participants associated with hepatic injury. Furthermore, the HRZE control regimen, and both pyrazinamide and moxifloxacin, has been associated with drug induced liver injury and in rare cases hepatic necrosis. Consequently, hepatic safety will be under close surveillance in all clinical studies.

- Ophthalmologic Evaluations – while the detailed examinations in Phase 2 have not raised concern for humans, ophthalmologic examinations, with slit lamp exam and grading of lens opacities, will continue in all human studies that involve exposure to pretomanid longer than 14 days. These examinations will be conducted at baseline, near the end of the dosing period and 3 months after the end of study drug exposure. These examinations are to follow up on the finding of cataracts in rats exposed to pretomanid in clinical studies.

- Cardiovascular Safety – All participants will have ECGs taken at baseline and at multiple time points during the study. Although the Thorough QT Study in healthy subjects found that pretomanid did not increase corrected QT intervals in a clinically meaningful way and did not add to the known effect of moxifloxacin, the ECGs will be carefully monitored during Phase 3. All ECGs will be interpreted and conduction intervals will be confirmed by a central cardiology service.

- Central Nervous System Safety –While pretomanid alone or combined in various regimens has been well tolerated overall, one participant in Study NC-002 of the Pa-M-Z regimen had a seizure without any prior seizure history, and some animals in toxicology studies have had seizures at high drug exposures. Consequently, close surveillance will be made of participants in the Phase 3 study for seizures or any central nervous system adverse events of potential concern.

Of note, preclinical toxicology studies found that rats, but not primates, had testicular toxicity when treated with pretomanid. Clinical evaluations of potential testicular toxicity in Phase 2 studies have evaluated over 300 participants exposed to pretomanid over 2-6 months with evaluations of testosterone, LH, or Inhibin B (2 studies) or FSH values (3 studies) at baseline and after daily dosing of regimens containing pretomanid in various combinations with moxifloxacin, pyrazinamide and bedaquiline. A review of data from the 3 studies by an independent reproductive endocrine expert concluded that, based on the hormone evaluations to date, there is no evidence that PA-824 is a testicular toxicant in men at the doses and exposure times evaluated.

2.2.3 Linezolid

Linezolid is a synthetic antibacterial agent of the oxazolidanone class approved in many countries around the world for drug-resistant, gram-positive bacterial infections, including gram positive organisms such as *Staphylococcus aureus*, coagulase negative *Staphlococcus* and *Enterococcal* infections. The recommended dose for these infections is 600 mg twice daily for up to 28 days of therapy.[23,24,26] Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism.[8] Resistance of MTB to linezolid is rare, as this drug has not been widely used to treat tuberculosis. In a recent study using linezolid to treat patients with XDR-TB in Korea, none of 41 patients had resistance to linezolid at baseline.[9]

Preclinical *in vitro* data shows linezolid is active against MTB, including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1 µg/mL.[38] Recent studies of the bactericidal and sterilizing activity of linezolid in a mouse model of MTB infection have demonstrated linezolid alone causes marked reductions in lung colony forming units (CFUs) from mice following 1-3 months of therapy.[36] (Table 3, below)

Table 3: Murine Lung CFU counts during Treatment with Linezolid

Monotherapy versus Standard Therapy

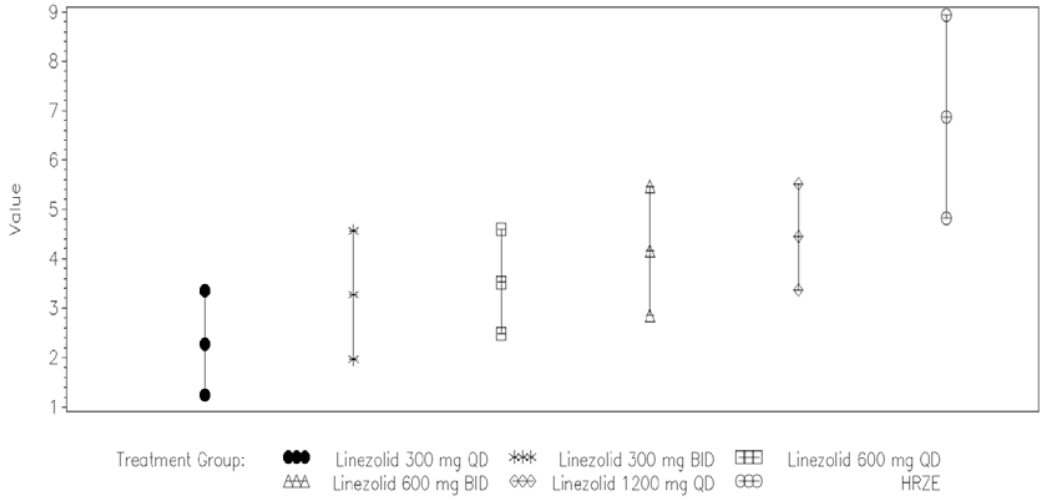
	Mean lung log_{10} CFU count (± S.D.) at:			
Regimen	**D0**	**Month 1**	**Month 2**	**Month 3**
Untreated	6.17 ± 0.27	6.47 ± 0.06		
2RHZ/4RH		3.47 ± 0.37	1.59 ± 0.25	0.50 ± 0.51
L		4.97 ± 0.26		

In recent years linezolid has been used to treat patients with MDR[28] and XDR-TB, although there have been no fully controlled trials of linezolid in a regimen for this indication. The World Health Organization management guidelines place linezolid in Group 5 ("Agents with unclear role in treatment of drug resistant-TB") in their groups of drugs to treat MDR-TB.[41] Over the past 10 years small retrospective observational studies have reported good results when linezolid has been added to failing regimens for patients with MDR-TB.[9, 27, 34] The most compelling recent evidence linezolid may be of benefit to patients with XDR-TB was reported by Lee and colleagues from a study in S. Korea.[9] Forty-one patients who had sputum culture–positive XDR-TB and who had not had a response to any available chemotherapeutic option during the previous 6 months were randomized to start linezolid at 600 mg daily or to delay therapy with linezolid at 600 mg daily for 2 months without changing their failing background regimen. After confirmed sputum-smear conversion, or at 4 months, patients underwent a second randomization to continued linezolid therapy at a dose of 600 mg per day or 300 mg per day for at least an additional 18 months. Thirty four of 39 (87%) of the patients had a negative sputum culture within 6 months after linezolid had been added to their drug regimen. As of the cutoff date prior to publication, of the 38 patients who received linezolid, 17 were still receiving the treatment per protocol, and 13 had completed treatment, including 6 with no relapse during the treatment period, 4 with no relapse at the 6-month follow-up, and 3 with no relapse at the 12-month follow-up (end of study).

While the standard dose of linezolid for short term use for severe bacterial infections is 600 mg bid, some clinicians and clinical trials using linezolid as Group 5 therapy to treat TB use only 300 mg or 600 mg daily due to concerns about toxicity developing when used over a period of months (see below for a review of linezolid toxicity).[9] However, there are no data to indicate what dose of linezolid is required or optimal to effectively treat TB infection. Consequently, TB Alliance has recently conducted and completed an Early Bactericidal Activity trial to evaluate the use of linezolid over 14 days in patients with newly diagnosed DS Pulmonary TB in dosing schedules including 300 mg daily, 300 mg bid, 600 mg daily, 600 mg bid, 1200 mg daily, and HRZE at standard doses daily. Preliminary unpublished in-house results using Bayesian mixed effects modelling have noted that there is a bactericidal effect of linezolid over 14 days that is substantial, but less than for the full HRZE regimen. There is little difference between daily or twice daily dosing of the same total daily dose of drug, and there is a dose-response relationship between total daily dose and daily reductions in either total CFU counts on solid culture or increases in Time to Positivity in liquid culture (a decreased load of MTB is associated with an increase in Time to Positivity). Point estimates of the log of the daily increase in Time to Positivity over 14 days ranged from 2.278 for Linezolid 300 mg QD to 4.446 for linezolid 1200 mg QD, with the estimate of 6.860 for HRZE for reference.

Figure 3: Mean Early Bactericidal Activity Time to Positivity, Days 0 to 14, Study Lin CL-001

Bayesian Nonlinear Mixed Effects Regression Model: Posterior Estimates and 95% Bayesian Confidence Intervals



HRZE = isoniazid, rifampin, pyrazinamide, and ethambutol

2.2.3.1 Linezolid Clinical Safety

Linezolid is currently marketed globally for a variety of acute infectious diseases and has been studied for the treatment of XDR-TB in several recent trials.[3,9] The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label.[23,24,26] Of note, the approved indication for linezolid is for administration up to 28 days.

Warnings and Precautions

- Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g., phenelzine, isocarboxazid) or within 2 weeks of taking any such product.

- Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression or those with a chronic infection who have received previous or concomitant antibiotic therapy.

- Lactic acidosis has been reported with the use of linezolid. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent

nausea or vomiting, unexplained acidosis, or low bicarbonate level while receiving linezolid should receive immediate medical evaluation.

- Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Where administration of linezolid and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).

- Peripheral and optic neuropathy has been reported in patients treated with linezolid, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with linezolid for less than 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. Visual function should be monitored in all patients taking linezolid for extended periods and in all patients reporting new visual symptoms regardless of length of therapy with linezolid. If peripheral or optic neuropathy occurs, the continued use of linezolid in these patients should be weighed against the potential risks. Additional information on the neuropathies reported in recent studies of linezolid administered over prolonged periods to patients with TB infection is presented above in Section 2.2.3.2.3.2

- Convulsions have been reported in patients when treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported.

- Postmarketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid, a reversible, nonselective MAO inhibitor. Some MAO inhibitors have been associated with hypoglycemic episodes in diabetic patients receiving insulin or hypoglycemic agents. While a causal relationship between linezolid and hypoglycemia has not been established, diabetic patients should be cautioned of potential hypoglycemic reactions when treated with linezolid.

In addition, the linezolid product label notes that there was an excess of abnormal liver function tests in comparator-controlled trials. These abnormalities were noted in 0.4% of linezolid treated patients in trials of skin and skin structure infections vs in 0.2% of clarithromycin treated patients, and in 1.6% of patients treated with linezolid versus 0.8% of patients with other treatments in trials of all other infections.

Adverse events of linezolid long term therapy for Tuberculosis have been described in several literature reports. The most complete review is a meta-analysis by Cox which noted the proportion of adverse events necessitating treatment discontinuation was significantly different by dose: 29.49% (95%CI 3.24–55.74) for ⩽600 mg daily vs. 60.75% (95%CI 42.69–78.81) for >600 mg daily (P = 0.05). [3]

In a trial reported by Lee et al in S Korea[9], seven of 41 participants had myelosuppression, including anemia and neutropenia, primarily within the first 5 months, and only one participant withdrew due to anemia. Six had clinically significant myelosuppression: 5 in 0-4 months and 1 in 4-8 months, with 0 in 8-12 months.

Peripheral and Optic Neuropathy:

The linezolid product label notes these adverse events have been " *reported in patients, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual function should be monitored in all patients taking ZVYOX for extended periods (≥3 months) and in all patients reporting new visual symptoms, regardless of length of therapy*.[26]

In Lee, NEJM, 2012[9], the publication's Supplemental Table 3 notes that 21 patients had clinically significant peripheral neuropathy spread over 12 months: 5 in months 0-4, 10 in months 4-8 and 5 in months 8-12 (time of onset not noted for one). Participants who developed any peripheral neuropathy had their dosing of linezolid interrupted, generally for several weeks, and then resumed at the lower dose of 300 mg/day (C. Barry, personal communication). None of the participants withdrew from the study based on peripheral neuropathies. At baseline, patients received visual acuity testing, contrast sensitivity and color vision tests. Seven cases were observed as having potential effects on vision; only two of 38 patients withdrew from study due to optic neuropathy. For clinically significant optic neuropathy, one had this at 0-4 months, 2 at 4-8 months and 3 at months 8-12. Except for the 2 participants who withdrew from the study, the others resumed linezolid at the 300 mg dose after a hiatus of several weeks of treatment and completed the study with resolution of their visual acuity changes (C. Barry, personal communication).

In the Schecter California Department of Health (DOH) review[32], peripheral neuropathy developed in 5 of 30 patients (no standardized monitoring), but only one withdrew from linezolid therapy. One patient developed visual loss secondary to optic neuropathy after 10 months of linezolid therapy, but vision returned to normal 3-4 weeks after discontinuation.

In Park, 2006[27], two patients of eight in the case series developed optic neuropathy after 8-9 month and had linezolid discontinued; these patients also had peripheral neuropathy. After linezolid treatment was stopped, the optic neuropathy fully resolved after 2-3 months. A total of 4 patients developed peripheral neuropathy at 4, 5, 8, 11 months; in the patients with optic neuropathy who stopped treatment, the peripheral neuropathic symptoms continued or improved only marginally.

In Singla, 2012[34], two of 29 patients treated with linezolid, 600 mg daily over 12 months, stopped the drug because of peripheral neuritis (one patient) and optic neuritis (one patient). The time course of these adverse events was not noted.

2.3 Regimens to be Studied

The regimen included in this study (B-Pa-L) has been selected based on the performance of the regimen in non-clinical pharmacology studies and on the combination of bedaquiline and pretomanid with other drugs in clinical studies NC-001 and NC-003. In addition, improved treatment outcomes in XDR patients with the addition of linezolid to existing therapy provide support for combining linezolid with other drugs that have no pre-existing resistance. Preliminary results from the ongoing Nix-TB clinical study demonstrate the encouraging potential of this regimen.

This regimen has the potential to treat drug resistant strains of tuberculosis. This is an oral regimen, removing the need for injectables as part of drug resistant treatment, and is also projected to be markedly less expensive than current XDR-TB therapy. Treatment duration is anticipated to be shorter than current regimens for drug resistant TB, based on findings in mouse models of infection and the fact that all participants will be treated with three active drugs against TB for which there is no expected resistance.

The key data supporting the use of the B-L-Pa regimen are described below.

2.3.1 Non-Clinical Studies

In the murine model of TB, addition of bedaquiline to HRZ results in accelerated clearance of MTB [5,36] when compared to HRZ alone. While the combination of bedaquiline and pretomanid in the murine model of TB in initial studies appeared somewhat antagonistic relative to bedaquiline alone, it was as active as the triple combination of HRZ[15] and in a subsequent study it was more active in the mouse model than HRZ.[16] Thus a novel regimen with bedaquiline plus pretomanid core could be effective in the treatment of MDR-TB by providing two novel drugs for which there is no known pre-existing resistance.

Recent studies of the bactericidal and sterilising activity of linezolid in an animal model where mice were given high dose aerosol MTB infection have demonstrated that linezolid alone and in combination with bedaquiline and pretomanid causes marked reductions in lung CFUs from mice following 1 to 3 months of therapy (Table 4 below). Additionally, all mice treated daily with bedaquiline, pretomanid and linezolid (B-L-Pa) were cured of the infection after 3 months of therapy as evidenced by no MTB cultured from lungs when mice were sacrificed 3 months after the completion of therapy that lasted 3 months or more (Table 4, below). This is in contrast to the 5-6 months required in previous studies to cure all mice when treated with the standard of care isoniazid, rifampicin and pyrazinamide (HRZ; note that typically ethambutol is not used in the mouse model of infection). Additional mouse studies were performed to determine whether shorter durations of linezolid, with continuation of the other drugs, would result in relapse-free cure in the mouse (Table 4 below). Treatment with linezolid for only the first 4 to 8 weeks of a 3-month treatment also resulted in relapse-free cure when lungs from the mice were cultured 3 months after the completion of therapy.[37]

Table 4: Murine Relapse Data

Impact of Linezolid Treatment Duration on Lung Colony Forming Unit Counts Assessed during Treatment and Proportion of Mice Relapsing after Treatment Completion

	Proportion of mice relapsing after treatment for:	
Regimen	**2 months**	**3 months**
2RHZ/RH*		8/14 **(57%)**
BPa		3/14 **(21%)**
3BPaL **	6/15 **(40%)**	0/15#† **(0%)**
2BPaL/1BPa***		0/15#† **(0%)**
1BPaL/2BPa	9/15 **(60%)**	0/15#† **(0%)**

#p = 0.11 vs. BPa; †p≤ 0.001 vs. RHZ
*2RHZ/RH means 2 months on the full regimen and a third month on only RH
**3BPaL means 3 months on the full regimen
***2BPaL/1BPa means 2 months on the full regimen and a third month on only BPa
****1BPaL/2Bpa means 1 month on the full regimen and a third month on only BPa
B – bedaquiline, H-isoniazid, L-linezolid, Pa-pretomanid, R-rifampicin, Z-pyrazinamide

In conclusion, linezolid increases the sterilising activity of the bedaquiline-pretomanid combination; no MTB could be cultured from the lungs of mice 3 months after cessation of 3 months of treatment with the combination, in contrast to MTB cultured from 13 of 15 mice treated with the standard 2RHZ/4RH regimen over 3 months. In addition, limiting the duration of linezolid to the first month of treatment does not affect linezolid's contribution to the sterilising activity of the regimen in the preclinical mouse study.

Prior to the use of pretomanid in combination with bedaquiline in clinical study NC-001, a preclinical cardiovascular safety pharmacology study was conducted in unrestrained beagle dogs with both drugs to explore the potential for additive effects on QT prolongation induced by the combination. Results indicate that administration of 100 mg/kg bedaquiline daily for 7 days causes a small increase in QTc interval by Day 6 in some animals that is not influenced by the addition of 100 mg/kg pretomanid on Day 7. The effect of pretomanid dosing alone on QT interval appeared to be due to discomfort related to the subcutaneous route of administration and not related to the plasma exposure.

2.3.2 Clinical Studies of Pretomanid in a Regimen with Bedaquiline and/or Linezolid

2.3.2.1 Clinical Study NC-001

Study NC-001 was a partially double-blind, randomized, parallel group study in adult male and female participants with newly diagnosed, uncomplicated, smear-positive, pulmonary TB. A total of 85 participants met study eligibility criteria and were randomly assigned to one of the six treatment groups. All study treatments were given once daily for 14 days. Substantial EBA activity

was demonstrated across participants in all arms of the study and the daily reductions in cultured colony counts per mL of sputum are presented in Table 5 below.

Table 5: Summary Statistics for $EBA_{CFU(0-14)}$

Derived Using Bi-Linear Regression, Study NC-001

Treatment Group	N	Daily Mean (SD) $EBA_{CFU(0-14)}$
Pretomanid + pyrazinamide + moxifloxacin	13	0.23 (0.128)
Pretomanid + pyrazinamide	14	0.15 (0.040)
Pretomanid + bedaquiline	15[a]	0.11 (0.050)
Bedaquiline alone	14	0.07 (0.068)
Bedaquiline + pyrazinamide	15	0.13 (0.102)
Rifafour e-275	10	0.14 (0.094)

There were no Serious Adverse Events from the study among participants treated with pretomanid and bedaquiline. Three participants in a bedaquiline-containing treatment arm were withdrawn: one participant on the bedaquiline only arm for a Grade 3 ALT and Gamma-Glutamyl Transferase (GGT) elevation (although the elevation occurred prior to the first dose of study medication), one on a bedaquiline plus pyrazinamide (weight banded) arm for a Grade 3 ALT and AST elevation, and one on a pretomanid and bedaquiline arm for to a Grade 3 ALT elevation.

2.3.2.2 Clinical Study NC-003

Efficacy

In the 14 day EBA study NC-003 two monotherapy and four different combinations of bedaquiline, pretomanid, pyrazinamide and clofazimine were evaluated in DS-TB participants. Fifteen participants were randomized into 7 treatment arms: C, Z, B-Pa-Z-C, B-Pa-Z, B-Pa-C, B-Z-C, and HRZE control. This study demonstrated no EBA for the clofazimine monotherapy arm and modest EBA for the pyrazinamide monotherapy arm. However, all of the experimental regimens demonstrated EBA. In general, adding clofazimine to the various agents resulted in either no increase in EBA, or a decrease when compared to a similar regimen that did not include clofazimine. In this study, the experimental regimen with the best EBA was B-Pa-Z which demonstrated a rate of decrease in both $\log_{CFU}$ and $\log_{TTP}$ that was at least as good as the HRZE control. The daily $\log_{CFU}$ results are presented in Table 6. Similar results were found when TTP was used to calculate the bactericidal activity over 14 days ($BA_{(0-14)}$).

Table 6: NC-003 Efficacy Results: Daily BAlog$_{CFU(0-14)}$

Arm	logCFU
BPaZC	.124
BPaZ	.180
BPaC	.086
BZC	.098
Z	.036
C	-.025
Rifafour®	.152

Safety

Generally, the regimens in this study were well tolerated. Table 7 provides a list of the overall safety findings. The only SAE experienced in the study was in a participant in the clofazimine monotherapy arm. Otherwise, the rates of treatment emergent AEs (TEAEs) were similar across the treatment arms. One participant in the B-Pa-Z arm was withdrawn from the study due an adverse event of increased liver function tests (alanine aminotransferase (ALT), AST and GGT).

Table 7: NC-003 Safety Data

	BPaZC	BPaZ	BPaC	BZC	Z	C	HRZE	Total
N	15	15	15	15	15	15	15	105
Participants with:								
TEAEs	11	9	8	10	10	9	8	65
TEAEs leading to death:								
Serious TEAEs						1		1
TEAES leading to early withdrawal		1						1
TEAEs leading to discontinuation of study drug		1						1
Drug-related TEAES	8	5	7	3	5	6	5	39
Serious, drug-related TEAEs								
Grade III AEs		2	1	2		1		6
Grade IV AEs		1	1					2
Grade II/IV AEs		2	1	2		1		6

QT Prolongation

Because bedaquiline and clofazimine are both known to prolong the QT interval, intensive ECG monitoring was included in the study endpoints. The mean change from baseline in QTcB and QTcF tended to be larger at 5 hours than at 10 hours post-dose in the (B-Pa-Z-C) arm and in the (B-Pa-C) arm. No QTcB or QTcF ≥500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of ≥60 ms in QTcB was reported for 2 participants in the (B-Pa-C) arm and for 1 participant in the clofazimine alone arm. An increase from baseline to Visit 5 and subsequent

visits of ≥60 msec in QTcF was reported for 4 participants in the (B-Pa-C) arm and for 1 participant in the clofazimine alone arm. For both QTcB and QTcF, the (B-Pa-Z-C) arm and the (B-Pa-C) arm showed the largest increase from baseline. Clofazimine will not be used in any treatment arms in the NC-007 study.

2.3.2.3 The Nix-TB Study

The NiX-TB Study is an ongoing open-label study assessing the safety and efficacy of bedaquiline plus linezolid plus pretomanid in participants with pulmonary infection of either XDR-TB or treatment intolerant/non-responsive MDR-TB. The study regimen includes: bedaquiline 400 mg once daily for 2 weeks then 200 mg 3 times per week plus pretomanid 200 mg once daily plus linezolid 600 mg twice daily amended (22 Jan 2016 protocol) to 1200 mg once daily. Treatment duration is 6 months, although if participants are still culture positive at month 4, there is the option to extend treatment to 9 months or withdraw. The primary endpoint is the incidence of bacteriologic failure or relapse or clinical failure through follow-up until 6 months after the end of treatment. Secondary Endpoints include: incidence of bacteriologic failure or relapse or clinical failure through follow-up until 24 months after the end of treatment as a confirmatory analysis, time to sputum culture conversion to negative status through the treatment period, and the proportion of participants with sputum culture conversion to negative status at 4, 6, 8, 12, 16 and end of treatment. In addition, linezolid dosing (actual) and efficacy will be explored and changes from baseline will be evaluated for TB symptoms, Patient Reported Health Status, body weight, and measures of safety.

Efficacy Experience to Date:

Sixty-nine participants have been enrolled as of February 1, 2017, at 2 sites in South Africa. Forty-nine percent of the participants are HIV positive, 79% have XDR-TB and 21% have MDR intolerant or resistant to prior therapy. Forty have completed the 6 months of therapy with the drug regimen and 31 have been followed to the primary endpoint at 6 months after treatment. All surviving patients were culture negative by 4 months, with 74% negative at 8 wks. As of February 1, 2017, there has been 1 microbiological relapse during follow up after drug therapy and 1 participant has had a new infection during follow-up with Drug Sensitive TB. This study will continue to enrol participants until the NC-007 study is initiated.

Safety of the B-Pa-L Regimen in the Nix-TB Study: As of December 2016, four participants have died in the study. The causes of death have varied and include: 2 with multi-organ disseminated TB who died within the first 5 weeks of therapy, 1 who had a gastrointestinal bleed and 1 with multi-organ failure and disseminated TB on autopsy. No deaths or SAEs have been caused by hepatic injury. No participants have been withdrawn from the study except for the 4 who died. The expected linezolid toxicities of peripheral neuropathy and myelosuppression were common but manageable. Seventy-one percent of participants had at least one linezolid dose pause (22% of all participants due to myelosuppression and 28% due to peripheral neuropathy), during the 6 months of treatment. One had peak ALT and AST > 3 X ULN and total bili > 2X ULN, but these improved and treatment restarted without a recurrence. There were 7 cases of grade 3 or 4 transaminitis and all resolved and allowed the study regimen to be continued. There were no cases of optic neuritis. While participants have required close surveillance for signs and

symptoms of neuropathies and bone marrow suppression, these toxicities have been manageable.

2.4 Overall Benefit/Risk Assessment

The recent report of the long term outcome of patients with XDR-TB treated in S. Africa highlighted the very poor prognosis for patients with this disease. After 60 months of follow up 73% of 107 patients had died and only 11% had a favourable outcome[28]. These patients have infection with MTB resistant to many/most of the available drugs to treat tuberculosis. Patients with XDR-TB have limited treatment options due to their resistance profile, and the drugs that are typically used in Standard of Care have many side effects, some are administered as injectables and have poor treatment outcomes in XDR-TB. Similarly, patients with Pre-XDR-TB and patients with MDR-TB who are failing or are intolerant to treatment have traditionally poor outcomes and are a challenge to treat. While treatment success for MDR-TB is better than for XDR-TB, overall success in treating MDR-TB is still approximately 50% according to the World Health Organization 2015 Global TB Report.[43] and it would be lower for patients failing or not able to take an optimal traditional regimen. This trial provides an opportunity to treat these high-need patients with three active drugs, for which there is no or minimal pre-existing resistance, in a very closely controlled and monitored clinical trial setting with the opportunity to define the optimal dosing scheme for linezolid. Participants will be monitored closely and regular reviews of safety and efficacy will be made by the Data Safety Monitoring Committee (DSMC). Preliminary results of the ongoing Nix-TB trial from patients with XDR-TB and who are failing or intolerant to treatment of MDR-TB demonstrate that this regimen has the potential to give relapse-free cure of XDR-TB with a simple regimen in a much shorter period of time than currently required by the available drugs used in the best standard of care. Preclinical studies of this regimen in a murine model of infection demonstrated relapse free cure of MTB in half the time (3 vs 6 months) required by standard HRZ therapy. Clinical studies of linezolid alone and pretomanid and bedaquiline alone and in combination have demonstrated activity against TB infection.

These three drugs have not been used in combination in humans prior to the Nix-TB trial, and thus their combined toxicity profile is emerging. The greatest risks of key concern for participants in this trial from linezolid are from the adverse events of myelosuppression and peripheral and optic neuropathy. Participants will be closely monitored with full blood counts, vision examinations, and screening for peripheral neuropathy. The investigator may interrupt dosing of either linezolid or linezolid with pretomanid and bedaquiline if adverse events of concern develop, and a resumption of the drugs, with linezolid at the same or at a lower dose, may be made cautiously. Participants will be under close surveillance for hepatotoxicity, as that risk for pretomanid and bedaquiline is not yet well characterized.

Overall the benefit-risk balance justifies evaluating the B-Pa-L regimen in this study, with the cautious surveillance in place, to treat patients with XDR-TB who have few options for a successful outcome.

3 Trial Objectives

3.1 Primary Objectives

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.

4 Trial Design

4.1 Summary of Trial Design

This is a Phase 3, multi-center, partially-blinded, randomized clinical trial conducted in 4 treatment groups. Participants, 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 intolerant or non-responsive participants who meet all of the inclusion criteria and none of the exclusion criteria, aged 14 and over, will be randomized to receive one of the 4 active treatment arms. Enrolment will stop when 120 XDR-TB participants are randomized. Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive web response system (IWRS) which will utilize a dynamic randomization system using minimization with a random element to allocate participants evenly across the arms by HIV status and type of TB after they have given written, informed consent and met all eligibility criteria.

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

4.2 Treatment Plan: Schedule of Assessments

- **Screening Period** (Screening Visit up to 9 days prior to Treatment)
- **Treatment Period** (Day 1 to Week 26. Additional visits every 3 weeks until last dose when dosing extended due to pauses or positive culture at Week 16
- **Follow-up Period** (4 Week post end of treatment follow-up Visit to 78 Week post end of treatment follow-up Visit)

Refer to:

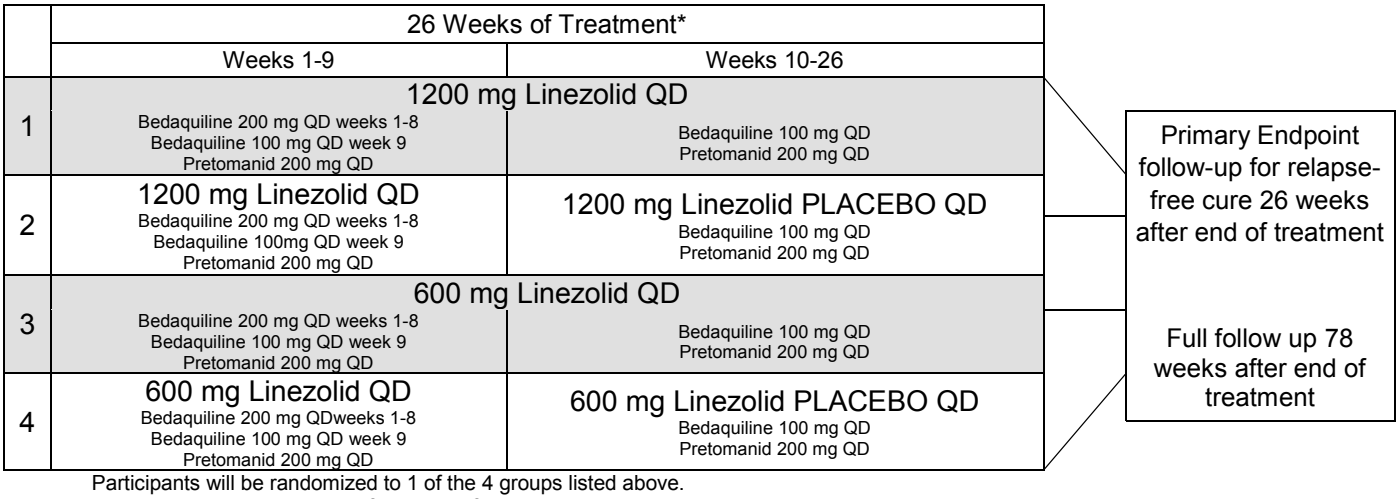
- Trial Flow Chart (Section 1.2) for the timing of all procedures and laboratory samples to done at each visit.
- Trial Procedures (Section 7) for details regarding specific procedures or laboratory tests.

Participants will receive oral daily dosing. They will be randomized to one of the following arms:

Table 8: Treatment Groups

	Treatment Group	No of Participants
1	Linezolid 1200 mg daily for 26 weeks • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks.	• 30 XDR-TB • Up to 15 Pre-XDR or MDR intolerant/non-responsive
2	Linezolid 1200 mg daily for 9 weeks followed by linezolid placebo for 17 weeks • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks.	• 30 XDR-TB • Up to 15 Pre-XDR or MDR intolerant/non-responsive
3	Linezolid 600 mg daily for 26 weeks • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks.	• 30 XDR-TB • Up to 15 Pre-XDR or MDR intolerant/non-responsive
4	Linezolid 600 mg daily for 9 weeks followed by linezolid placebo for 17 weeks • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks.	• 30 XDR-TB • Up to 15 Pre-XDR or MDR intolerant/non-responsive

Figure 4: Trial Schematic



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

5 Trial Population

Participant must meet all inclusion and no exclusion criteria within the screening period. Re-testing for laboratory or ECG parameters is allowed within the 9-day screening period. Sponsor may consider replacement of late screen failure and un-assessable (as detailed in the statistical analysis plan) participants.

5.1 Inclusion Criteria

Participants are required to meet all of the following inclusion criteria during the screening period in order to be randomized.

1. Provide written, informed consent prior to all trial-related procedures (including any additional consent required for participants considered as minors per applicable regulatory authority or ethics committee).
2. Willingness and ability to attend scheduled follow-up visits and undergo study assessments
3. HIV testing (if an HIV test was performed within 1 month prior to screening, it should not be repeated as long as documentation can be provided [ELISA and/or Western Blot]. If HIV status is a confirmed known positive, repeated HIV test is not needed provided documentation is available.
4. Male or female, aged 14 years or older.

<u>Disease Characteristics:</u>

5. Participants with one of the following pulmonary TB conditions:
    a. XDR-TB with
        i. A documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and:
        ii. historical documented resistance to isoniazid, rifamycins, a fluoroquinolone **AND** an injectable during the current TB diagnosis/disease course;
    b. Pre-XDR-TB with
        i. A documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based molecular test within 3 months prior to or at screening and;
        ii. historical documented resistance to isoniazid, rifamycins, and to a fluoroquinolone **OR** an injectable during the current TB diagnosis/disease course.
    c. MDR-TB with
        i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected results within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and;
        ii. historical documented resistance to isoniazid and rifamycins during the current TB diagnosis/disease course;
        iii. with documented non-response to treatment with the best available regimen for 6 months or more prior to enrolment who in the opinion of the Investigator have been adherent to treatment and will be adherent to study regimen.
    d. MDR-TB with
        i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and:
        ii. historical documented resistance to isoniazid and rifamycins during the current TB diagnosis/disease course and;

iii. who are unable to continue second line drug regimen due to a documented intolerance to:
   a. PAS, ethionamide, aminoglycosides or fluoroquinolones or ;
   b. Current treatment not listed above that renders participant eligible for the study in the Investigator's opinion.

6. Chest X-Ray within one month prior to screening, obtained and read locally by investigator or designee with results consistent with pulmonary TB in the opinion of the Investigator.

Contraception:

7. Be of non-childbearing potential or using effective methods of birth control, as defined below:

Non-childbearing potential:

a. Participant - not heterosexually active or practices sexual abstinence; or
b. Female participant/sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or
c. Male participant/sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to Screening.

Effective birth control methods:

A double contraceptive method should be used as follows:

a. Double barrier method which can include any 2 of the following: a male condom, diaphragm, cervical cap, or female condom (male and female condoms should not be used together); or
b. Barrier method (one of the above) combined with hormone-based contraceptives or an intra-uterine device for the female participant/partner;

And are willing to continue practicing birth control methods throughout treatment and for 6 months (both male and female participants) after the last dose of study medication.

> **Note:** Hormone based contraception alone may not be reliable when taking IMP; therefore, hormone based contraceptives alone cannot be used by female participants or female partners of male participants to prevent pregnancy.

5.2 Exclusion Criteria

Participants will be excluded from participation if they meet any of the following criteria during the screening period:

Medical History and Concurrent Conditions

1. Any condition in the Investigator's opinion (i.e., an unstable disease such as uncontrolled diabetes or cardiomyopathy, extra-pulmonary TB requiring extended treatment, cancer that could affect survival through the protocol-specified follow up period), where participation in the trial would compromise the well-being of participant or prevent, limit or confound protocol specified assessments.

2. Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
3. In the judgment of the Investigator, the patient is not expected to survive for more than 6 months.
4. Karnofsky score < 60 at screening.
5. History of allergy or known hypersensitivity to any of the trial Investigational Medicinal Products or related substances.
6. Body mass index (BMI) < 17 kg/m^2
7. TB infection with known resistance to pretomanid, delamanid, linezolid or bedaquiline.
8. Participants who, upon the evaluation of their pulmonary disease, are expected to require a surgical procedure.
9. Having participated in other clinical studies with dosing of investigational agents within 8 weeks prior to screening or currently enrolled in an investigational study that includes treatment with medicinal agents. Participants who are participating in observational studies or who are in a follow up period of a trial that included drug therapy may be considered for inclusion.
10. Participants with any of the following at Screening:
    - QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with the Sponsor Medical Monitor before enrolment.
    - Heart failure
    - A personal or family history of congenital QT prolongation
    - A history of or known, untreated, ongoing hypothyroidism
    - A history of or ongoing bradyarrhythmia
    - A history of Torsade de Pointe
11. Females who have a positive pregnancy test at Screening or already known to be pregnant, breast-feeding, or planning to conceive a child during the study or within 6 months of cessation of treatment. Males planning to conceive a child during the study or within 6 months of cessation of treatment.
12. A peripheral neuropathy of Grade 3 or 4, according to DMID (Appendix 2). Or, participants with a Grade 1 or 2 neuropathy which is likely to progress/worsen over the course of the study, in the opinion of the Investigator.

<u>Previous and Concomitant Therapy</u>

13. Concomitant use of Monoamine Oxidase Inhibitors (MAOIs) or prior use within 2 weeks of randomization.
14. Concomitant use of serotonergic antidepressants or prior use within 3 days of randomization if Investigator foresees potential risks for serotonin syndrome when combined with linezolid.
15. Concomitant use of any drug known to prolong QTc interval (including, but not limited to, amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, fluoroquinolones, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).
16. Concomitant use of any drug known to induce myelosuppression.

17. Concomitant use of any drugs or substances known to be strong inhibitors or inducers of cytochrome P450 enzymes (including but not limited to efavirenz, quinidine, tyramine, ketoconazole, fluconazole, testosterone, quinine, gestodene, metyrapone, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafylline, cimetidine, dextromethorphan). Exceptions may include use of lopinavir/ritonavir regimen as noted in section 5.3.3.
18. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP.
19. Participants with an existing TB diagnosis (a diagnosis made > 4 weeks prior to screening) and HIV co-infection, must have been on an ART for at least 4 weeks prior to screening.
20. Participants with newly diagnosed tuberculosis and HIV may be enrolled provided that appropriate HIV therapy will not be initiated until participant has received at least 2 weeks of study medication.
21. HIV infected participants: the following antiretroviral therapies should not be used: zidovudine, stavudine, didanosine. The antiretroviral therapy (ART) booster cobicistat should not be used. Please reference restrictions Section 5.3.3 Antiretroviral Therapy, for guidance on ART treatment during the treatment period.

Diagnostic and Laboratory Abnormalities

22. Participants with any of the following toxicities at Screening (labs may be repeated during screening period) as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November 2007):

    a. Viral load >1000 IU/ml (Unless newly diagnosed HIV and not yet on ART who otherwise qualify for participation);
    b. CD4+ count < 100 cells/μL (HIV positive participants);
    c. Serum potassium less than the lower limit of normal for the laboratory;
    d. Hemoglobin < 9.0 g/dL;
    e. Platelets <100,000/mm^3;
    f. Absolute neutrophil count (ANC) < 1500/ mm^3;
    g. Aspartate aminotransferase (AST)
        - Grade 3 or greater (≥ 3.0 x ULN) to be excluded;
        - Results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor
    h. Alanine aminotransferase
        - Grade 3 or greater (≥ 3.0 x ULN) to be excluded;
        - Results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor medical monitor;
    i. Total bilirubin
        - greater than 1.5 x ULN to be excluded;
        - 1-1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor
    j. Direct bilirubin
        - Greater than ULN to be excluded
    k. Serum creatinine level greater than 1.5 times upper limit of normal
    l. Albumin <3.0 mg/dl

All inclusion and no exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the Investigator has reason to suspect that there might be a health problem (other than TB), enrolment should only be considered after discussing the case with the sponsor medical monitor.

5.3 Restrictions

5.3.1 Prior and Concomitant Medications and Other Treatments

Concomitant medications should be kept to a minimum during the treatment period of the trial. However, if concomitant medications are considered to be necessary for the participant's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the investigator. For any concomitant medications given as a treatment for a new condition or a worsening of an existing condition occurring after signing of the informed consent form, the condition must be documented on the Adverse Event pages of the electronic Case Report Form (eCRF).

The prescribing information for all concomitant medication should be consulted and reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected in order to prevent any potentially serious and/or life-threatening drug interactions.

The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:

- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.
- Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)
- Concomitant use of any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).
- Treatment with fluoroquinolones (as they are known prolong QTc), are strongly discouraged in the trial. They should only be used to treat intercurrent non-TB infections and if the benefit of treatment outweighs the risk of prolonged QTc.
- Concomitant use of any drug known to induce myelosuppression.
- The systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolids such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 3 consecutive days;
- The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone.

Concomitant use of serotonergic antidepressants should be avoided if possible as participants on these agents and linezolid are at risk for serotonin syndrome.

Caution should be used in treating diabetic patients receiving insulin or oral hypoglycemic agents as cases have been reported of hypoglycemic reactions when patients on these agents have been treated with linezolid.

Any drug known to be hepatotoxic should be avoided as much as possible during screening and throughout the treatment period (including but not limited to acetaminophen/paracetamol, acetazolamide, allopurinol, amiodarone, amitriptyline, amoxicillin, amprenavir, atorvastatin, augmentin/co-amoxiclav, azathioprine, baclofen, bumetanide, captopril, carbamazepine, celecoxib, chlorpromazine, chlorpromazine, clindamycin, clopidogrel, contraceptive pill, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).

5.3.2 Recommendations for Concomitant use of Anti-Malarials

The following treatments for malaria are recommended for concomitant use with the IMP, should it be necessary:

- Proguanil/atovaquone or
- Artesunate plus sulfadoxine-pyrimethamine

These recommendations are based on the potential for QT prolongation by bedaquiline and many anti-malarials. Due to the extended half-life of bedaquiline commencing anti-malarial treatment containing drugs that could prolong the QT interval, shortly after discontinuing bedaquiline, is not recommended.

5.3.3 Antiretroviral Therapy

For HIV infected participants, to avoid potentiating known key toxicities of linezolid (neuropathy and myelosuppression), the following antiretroviral therapies should not be used during the treatment period: zidovudine, stavudine, didanosine. The ART booster cobicistat should not be used.

Only the following types of antiretroviral therapy (ART) are permissible during administration of regimens:

- Nevirapine based regimen consisting of NVP in combination with any two NRTIs TDF/ABC and FTC/3TC.
- Lopinavir/ritonavir based regimen consisting of lopinavir/ritonavir in combination with any two NRTIs TDF/ABC and FTC/3TC.
- Integrase inhibitor (e.g., dolutegravir) in combination with TDF/ABC and FTC/3TC.
- In patients who have viral load suppressed on efavirenz at the time of screening, their ART can be changed to rilpivirine in combination with TDF/ABC and FTC/3TC. If possible, the same nucleoside backbone should be used.

The investigator must assess the risks and benefits of these antiretroviral regimens in the context of co-infection with TB acknowledging the following caveats:

- Triple NRTI is generally not considered optimal chronic ART;
- Nevirapine based regimens are associated with higher ART failure in participants having or known to have previously had a viral load more than or equal to 100,000/ mL.

5.3.4 Other Restrictions

Large quantities of foods or beverages with high tyramine content should be avoided while taking linezolid. Quantities of tyramine consumed should be less than 100mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavour, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5mg tyramine per 1 teaspoon). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.

Alcohol should be avoided while on IMP, especially in patients with impaired hepatic function.

5.4 Discontinuation from Treatment/Trial

The following may result in the discontinuation of trial treatment;

- Pregnancy;
- Investigator considers it for safety reasons in the best interest of the participant that he/she be discontinued. This could include, but is not limited to:
    - Adverse event(s);
    - Myco testing results from baseline (Screening through Week 4) indicate sensitivity to isoniazid and/or rifamycins;
    - Myco testing results from baseline (Screening through Week 4) indicate resistance to bedaquiline, pretomanid or linezolid;
    - In the opinion of the investigator, fails to comply with the protocol, including non-compliance to IMP.

All participants who discontinue trial treatment (but have not withdrawn consent) and received at least one dose of IMP will be requested to return for an early withdrawal visit and applicable safety Follow Up visits, as per flow chart (Section 1.2).

In the event of the following, participants will be and/or are considered discontinued from the trial and no additional follow-up visits are required:

- Withdrawal of informed consent;
- Lost to follow-up;
- Termination of the trial by the sponsor.

A participant may discontinue from the trial at any time at his/her request (withdrawal of consent).

Discontinuation from treatment due to TB

Ultimately it is the investigator's decision whether a participant should discontinue treatment due to a concern that the participant has symptomatic worsening TB and/or bacteriological failure/relapse.

Discontinuation is usually not indicated by a single positive culture. Should a participant have a single positive culture result after being negative, the investigator is to evaluate whether the participant has signs and symptoms suggestive of active inadequately treated TB and whether it is in the participant's best interest that he/she be discontinued. Prior to discontinuation of a participant due to TB, the investigator must discuss the participant with the sponsor medical monitor, unless the investigator cannot contact the sponsor medical monitor and considers that discontinuation must occur immediately due to immediate safety concerns with respect to the participant.

If the investigator decides to discontinue trial treatment for a participant due to TB, additional sputum samples may need to be collected in order to ensure the participant's outcome status may be determined, details noted in trial flowchart (Section 1.2).

All Early Withdrawal participants who are confirmed sputum positive (at least two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These participants will be referred to specialists who treat XDR-TB, pre-XDR TB or MDR-TB as applicable.

5.5 Participant Progress Definitions

Status	Treatment	Follow-Up
Screen Failure	Participants from whom informed consent is obtained and is documented in writing (i.e., participant signs an informed consent form) but who is not randomized	
Completed Treatment / Completed FU*	Participants who complete the full course of IMP	Participants who complete all follow-up visits
Completed Treatment / Discontinued FU	Participants who complete the full course of IMP	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)
Completed Treatment / Lost to Follow-Up	Participants who complete the full course of IMP	Participants who are unable to be contacted on or before their final visit
Discontinued Treatment / Completed FU	Participants who discontinue treatment prior to completion of the protocol-defined treatment course	Participants who complete all applicable follow-up visits
Discontinued Treatment / Discontinued FU**	Participants who discontinue treatment prior to completion of the protocol-defined treatment course	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)
Lost to Follow-Up	Participants who are unable to be contacted on or before their final treatment visit and it cannot be confirmed whether treatment was completed	

* Note that this includes treatment failures who complete all applicable follow-up visits

** Early Withdrawal

5.6 Trial Stopping Rules

There are no trial specific stopping rules.

The trial or parts of the trial can be stopped by the Sponsor on advice from the Data Safety and Monitoring Committee (DSMC) after their review of applicable trial data. In addition, the Sponsor has the right to stop the trial or a specific Investigational Site at any time, although this should only occur after consultation between involved parties. Should this occur, the local and central Ethics Committee/Institutional review Board (EC/IRB) and Regulatory Authorities will be informed. Should the Trial/Investigational Site be closed prematurely, all trial materials (except documentation that has to remain stored at the Investigational Site) will be returned to the Sponsor or vendor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Participants currently on treatment will receive an appropriate regimen and all participants will be referred to a unit specializing in the treatment of XDR-TB, Pre-XDR-TB or MDR-TB as applicable.

6 Treatment

6.1 IMP Administration

Treatment will be administered orally, once daily, with a full glass of water and a meal in the dosing schemes (treatment arms) outlined in Table 9. The study drug regimen should be initiated as specified below regardless of whether participant has received any of the allowed prior exposure of bedaquiline or linezolid (up to 14 days), including a loading dose of bedaquiline. The Pharmacy Manual should be referenced for further details.

Table 9: Investigational Medicinal Product Details

Treatment Group	Active and Placebo
Linezolid 1200 mg daily for 26 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. • 2 linezolid 600 mg active tablets once daily for 26 weeks • 1 placebo linezolid 600 mg tablet once daily for 26 weeks
Linezolid 1200 mg daily for 9 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 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
Linezolid 600 mg daily for 26 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once 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
Linezolid 600 mg daily for 9 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 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

6.2 Participant Compliance

During site clinic visits or hospitalization, the IMP will be administered by the Investigator/designated site personnel. During the study, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how IMP is to be taken. When possible, participants will be checked for IMP compliance by the Investigators or trial personnel/National TB Treatment Program personnel via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the participant has swallowed the IMP). Additionally, participant cards will be checked for unused tablets in the blisters.

6.3 Treatment Modification(s)

All dose modifications should be discussed with the Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern; the

Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation.

In the event of linezolid specific toxicities, the following should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol:

- Blinded one step reductions (maximum 3 steps) in the dose of linezolid (1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or 300mg QD to placebo) managed by the IWRS as per instructions in pharmacy manual and/or IWRS user manual.
- Temporary pause of linezolid due to a linezolid-specific toxicity should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol.
- Permanent discontinuation of linezolid.

Participants experiencing suspected drug related toxicities due to other drugs in the regimen (B-Pa), the full regimen may be halted for up to 35 consecutive days.

Pauses of the full regimen must not exceed 8 weeks (56 days) cumulatively.

If participant's week 16 sample remains culture positive, Investigator may consider option to extend current treatment to 39 weeks, in consultation with the Sponsor Medical Monitor. When treatment extended due to a positive culture at week 16, pauses of the full regimen must not exceed 13 weeks (91 days) cumulatively.

When total of missed dosing days and/or pauses is greater than 7 days, additional make-up doses should be dispensed/treatment extended.

At no time should the participant be treated with a single agent.

6.4 IMP Packaging and Labelling

The complete formulations of the IMP bedaquiline and pretomanid are found in the respective Investigator Brochures[5,6]. The complete formulations of linezolid are found in the Package Inserts[23,24,26].

The IMP will be packaged as follows:

- Bedaquiline: Bottles containing:
  - 200 mg QD dose- 28 tablets- bedaquiline 100 mg
  - 100mg QD dose- 14 tablets- bedaquiline 100 mg
- Pretomanid: Blister card containing 14 tablets- pretomanid 200 mg
- Linezolid: Blister Card containing 7 days of dosing as follows:
  - 1200 mg QD Dose
    - 2 blister strips of 7 tablets each (14 tablets) containing **active linezolid 600 mg**
    - 1 blister strip of 7 half tablets containing **placebo linezolid 300 mg**
  - 600 mg QD Dose:
    - 1 blister strip of 7 tablets containing **active linezolid 600 mg**
    - 1 blister strip of 7 tablets containing **placebo linezolid 600 mg**
    - 1 blister strip of 7 half tablets containing **placebo linezolid 300 mg**
  - 300 mg Dose (for reductions): 1 row of 7 active 600 mg tablets for 7 days of dosing

        - 2 blister strips of 7 tablets each (14 tablets) containing **placebo linezolid 600 mg**
        - 1 blister strip of 7 half tablets containing **active linezolid 300 mg**
    - Placebo Linezolid Dose: 2 rows of 7 placebo 600 mg tablets for 7 days of dosing
        - 2 blister strips of 7 tablets each (14 tablets) containing **placebo linezolid 600 mg**
        - 1 blister strip of 7 half tablets containing **placebo linezolid 300 mg**

The packaging of each bottle/blister card will be labelled with, at a minimum, the following information:

- Name, address and telephone number of Sponsor.
- Name of medication.
- Dosage, quantity and method of administration for bedaquiline and pretomanid.
- Potential dosage, quantity and method of administration for linezolid.
- Reference/Lot Number.
- The statement “For Clinical Trial Use Only”.
- Space for completion of Name of Investigator and Site Number.
- MedID: medication identification number
- Storage conditions.
- Period of Use.
- The statement “Keep out of reach of children”.
- Expiry Date.
- Directions for use.
  Space for completion of participant number and visit/date dispensed.

6.5 Method of Treatment Assignment

Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive web response system (IWRS) which will utilize a dynamic randomization system using minimization with a random element to allocate participants evenly across the arms by HIV status and type of TB. Information & directions will be provided to each site via the IWRS user manual.

6.6 Blinding and Procedures for Breaking the Blind

The blind must not be broken except in the case of a medical emergency, where treatment of the participant is influenced by the knowledge of what dose and duration of linezolid the participant is receiving. It is requested that the Investigator make every effort to contact the Sponsors 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 SAEs.

In the absence of any medical emergencies requiring a blind break, the blind for all participants 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.

6.7 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions as per details on IMP labelling, have been maintained during transit for all trial treatment received and any discrepancies are reported and resolved before use of the trial treatment.

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

The investigator, institution, or the head of the medical institution (where applicable) is responsible for trial treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Upon completion or termination of the trial, all unused and/or partially used IMPs must either be returned to Sponsor (or designated vendor) who will arrange for destruction or destroyed at site as agreed by sponsor after final accountability has been confirmed,

The Investigator/designee will immediately inform the sponsor of any quality issues arising with respect to the trial medication. The sponsor will take whatever action is required should such a situation arise.

Further guidance and information for the handling, storage, accountability and final disposition of unused trial treatment are provided in the pharmacy manual.

7 Trial Variables and Procedures

The trial flowchart in Section (1.2) should be referenced for timing and sequence of assessments.

7.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected:

- Written Informed Consent.
- Visit Dates
- Participant Disposition
- Demography (date of birth, race and gender)
- Inclusion and Exclusion criteria
- Clinically significant medical and treatment history (including past and current TB diagnosis and smoking)
- Screening Coached Spot Sputum Sample:
    - Smear microscopy for acid-fast bacilli.
    - Gene Xpert, Hain Assay MTBDRplus or equivalent to determine MTB complex and rifamycin resistance.
- Urine pregnancy test: women of child-bearing potential only, whether they are sexually active or not.
- Serology: HIV and CD4 count.
    - If an HIV test was performed within 1 month prior to trial start, it should not be repeated as long as documentation of results can be provided (ELISA and/or Western Blot).

    - Where required by regulatory authorities or ethics committees:
        - Separate approval for this to be performed will be obtained from participants in the written informed consent process.
    - prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the participant, HIV counselling provided to the participant by the study site should be clearly documented in the participant's medical records/source. Participants have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the participant's medical records/source.
- Karnofsky Score (Appendix 4).
- Chest X-Ray: A Chest X-Ray digital image will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor; this process will be documented in the Radiology Manual. The Investigator is responsible for review and analysis for participant inclusion.
- Method of Birth Control: Male and Female participants and their partners.
- IMP Details: Randomization
- IMP Compliance/Actual Dosing

7.2 Efficacy Variables and Procedures

Two Spot Sputum Samples are collected, one Early Morning brought from home or collected in the hospital ward and one spot collected at the research site under the coaching and observation of the trial staff or, if no early morning sample was provided, 2 samples collected on site at least 30 minutes apart. The Mycobacteriology sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start.

The following analyses will be performed:

- Liquid culture (MGIT), to detect presence or absence of MTB and obtain the time to positivity (TTP) followed by a speciation test when applicable, to confirm MTB.

Using these observed variables, the following derived variables will be assessed for evaluation of the efficacy endpoints:

- Bacteriologic failure/relapse;
- Time to Sputum Culture Conversion;
- Number of participants with Sputum Culture Conversion.

Every effort is to be made to collect sputum samples. However, in general, the inability to produce sputum is treated as being equivalent to having a negative culture (favorable) result. A participant who never achieves culture negative status due to inability to produce sputum, but has completed 26 week /78 week post treatment completion follow-up and is without clinical or biological evidence of relapse, will be considered to have a favorable outcome.

TB Symptoms Profile:

- The TB Symptoms Profile (Appendix 7) will record participants' ratings of the severity of common TB symptoms.

Patient Reported Health Status Variables and Procedures:

- The Patient Reported Health Status variables will be collected at the time points described in the trial flow chart. Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire (Appendix 5). This descriptive system consists of five health-related quality of life dimensions, each of which will be recorded using five levels of severity. Methodology: The Patient Reported Health Status methodology and requirements will be described in a separate document/guideline which will be provided prior to the trial start.

7.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the trial flow chart and assessed for evaluation of the safety endpoints:

- Laboratory parameters. The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
    - Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count),
    - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO_2, creatine phosphokinase (CPK).
    - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator.
- 12-lead Electrocardiogram (ECG):
    - Investigator Assessment: Normal, Abnormal.
    - Central Cardiologist Assessment: Heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.
    - Methodology:
        - Timing and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start;
        - Participants should be lying down (recumbent) for at least 5 minutes prior to each 12-lead ECG evaluation;
        - ECGs are to be recorded for 10 seconds;
        - All ECGs are to be performed in single.
        - ECGs should be done before any labs when both included in a visit)
        - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch).
- Vital signs:
    - Vital Signs, including weight (should be done before any labs)
    - Systolic and diastolic blood pressure (mmHg) to be measured supine (after 5 minutes of rest) using an appropriately sized cuff, and using the same type of sphygmomanometer, if possible by the same observer, at each relevant visit.
    - Heart rate (bpm).

  - Respiratory rate (breaths per minute)
  - Axillary body temperature (°C).
- Physical Examination:
  - Height is measured at screening only.
  - Full (complete) and Limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded.
  - Weight (kg) (in light clothing and with no shoes).
  - Using the observed variables weight and height, calculated body mass index (BMI) will be derived.

- Ophthalmology Slit Lamp Examination. To be done by an Ophthalmologist trained on AREDS2 assessment. The ophthalmology slit lamp methodology and requirements will be described in a separate document, the Ophthalmology Guideline. The following analyses will be performed: AREDS2 opacity typing and grading.
- Ophthalmic Examination. The ophthalmic examinations can be performed by any trained study staff. The screening exams must be done by the trained study staff AND an Ophthalmologist. Methodology and requirements will be detailed in the Ophthalmology Guideline.
  - Ophthalmology History (Screening only);
  - Visual Acuity Test – Corrected. Distance Vision;
  - Color Vision Assessment.
- Adverse Events.
- Brief Peripheral Neuropathy Screen (Appendix 6) will record ratings.
- Investigator Assessment:
  Principal Investigator to review participant status at specified visits in flow chart including any time Investigator determines that participant fulfills criteria for primary outcome of treatment failure. Investigator to assess whether TB treatment is considered a “success” or “failure”. If considered a failure, should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration.

7.4 PK Variables and Procedures

Plasma concentrations from sparse sampling (see Synopsis Flowchart 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, and linezolid to further evaluate the effects of covariates on model parameters in this study population. PK data from the current trial may be combined with prior data (e.g., from the NiX-TB trial) to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{trough}, C_{max}, AUC_{τ}, C_{mean}, and $T_{>MIC}$) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

7.5 Mycobacteriology Characterization Variable and Procedures

The following Mycobacterial Characterization variables will be collected:

Positive Culture (for MTB) from:

- Day 1 or if Day 1 is not available, first positive between screening through Week 4;
- Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be subcultured and shipped to the central from the applicable lab for relevant participants/with no positive cultures from screening through week 4 and appropriate consent
- When applicable, end of treatment or visits with positive cultures during post-treatment follow-up.

The MTB isolates will be processed at the central lab(s) for:

- MIC against bedaquiline, pretomanid and linezolid;
- Drug Susceptibility Testing in liquid culture for rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide and second line TB drugs including but not limited to fluoroquinolones, and injectables;
- Genotyping.

The MTB isolates will be processed at the central lab(s) for: Positive MTB at/after end of treatment: Hain MTBDR*plus* and HainMTBR*sl*

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

Any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a trial treatment whether or not considered related to trial treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a trial treatment, whether or not related to the trial treatment.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening (any event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization; In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity; the term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect; or
- Is a medically important event.

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. A "suspected transmission of infectious agent by a medicinal product" is also considered a serious adverse event under the SAE criterion "Other medically important condition".

8.1.3 Attribution/Causality

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor/designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

Table 10: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An adverse event, which is not related to the use of the drug.
Unlikely	An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.
Possible	An adverse event, which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
Probable	An adverse event, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by dechallenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

8.1.4 Severity

Table 11: Definitions for Adverse Event Severity Gradings

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-Threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

See Appendix 2 for full DMID Toxicity Tables. Above ratings should be used to estimate the grade for abnormalities NOT found elsewhere in the Toxicity Tables.

8.2 Reporting

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

All AEs will be collected from the signing of the ICF until the 78-week post treatment follow-up visit at the time points specified in the Flowchart (Section 1.2) and recorded in the case report from (CRF). The exception is early withdrawal participants who will only have SAEs collected from the time of their early withdrawal through the 78-week post treatment visit.

Medical occurrences that begin after obtaining informed consent will be recorded as adverse events. If an adverse event started before signing of the informed consent, but is ongoing at trial start, it should be recorded as medical history. If the pre-existing medical occurrence worsens during the study, and adverse event will be recorded.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours of the information becoming known to the Investigator, as noted in the SAE reporting guidelines. The investigator will submit any updated SAE data to the sponsor within 24 hours of information becoming known to the investigator.

The sponsor/investigator/designee will inform Regulatory Authorities and/or IEC/IRB of all SAEs in accordance with local requirements and ICH guidelines for GCP.

The sponsor/designee will forward Safety Notification letters to the Investigator for submission to the IEC/IRB.

Investigators are not obligated to actively seek AE or SAE information in former trial participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be reasonably related to

the trial treatment or trial participation, the investigator must promptly notify the sponsor, IEC/IRB and regulatory authorities on an expedited basis in accordance with local requirements and ICH guidelines for GCP.

8.2.1 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- Until the end of the follow-up period; and
- Until all queries on these AEs have been resolved.

Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In these cases follow-up will be the responsibility of the treating physician. However, this will have to be agreed upon with the Sponsor Medical Monitor.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. Investigator should contact sponsor/designee to discuss appropriate medical follow-up if consultation required.

If a participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide sponsor/representative with a copy of any post-mortem findings including histopathology.

New or updated information on an SAE will be recorded in the originally completed CRF and submitted to sponsor within 24 hours of the information becoming known per SAE reporting guidelines.

8.2.2 Clinical Laboratory Adverse Events

Changes in the results of the Clinical Laboratory assessment results which the Investigator feels are clinically significant will be reported as adverse events. It is the Investigators' responsibility to review the results of all laboratory tests as they become available. This review must be documented by the Investigators' dated signature on the laboratory report. For each abnormal laboratory test result, the Investigator needs to ascertain and document if this is a clinically significant change from baseline for that individual participant. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is determined by the Investigator to be a clinically significant change from baseline for that participant, it is considered to be an adverse event.

8.2.3 Disease under Study

Symptoms of the disease under trial (Pulmonary Tuberculosis) experienced by the participant while on the trial will be assessed by the Investigator. If the symptom has:

- worsened while the participant is in the trial; and
- the Investigator assesses it as clinically significant;

it will be recorded as an adverse event.

If there is:

- no change; and
- the Investigator assesses the symptom as due to the participant's TB; and
- not clinically significant;

it will not be recorded as an AE and this will be noted in the participant's source documentation.

All TB related symptoms that meet SAE criteria will be recorded and reported as a SAE.

8.2.4 Overdose

Overdose of IMP experienced by the participant while on the trial, will be assessed by the Investigator to determine whether the overdose led to an Adverse Event, including if the taking of the suspect medicine led to suicidal intention and subsequent overdose of the suspect medicine, or other medication. In this case it will be recorded as an adverse event. If it does not lead to an Adverse Event, it will not be recorded as an AE and this will be noted in the participant's source documentation.

8.2.5 Drug Interaction

If the Investigator becomes aware that the participant has experienced a drug interaction which has resulted in an adverse event, it will be recorded as an adverse event.

8.2.6 Pregnancy

The Investigator will immediately notify the sponsor of any pregnancy that is discovered during IMP administration or which started during IMP administration. Pregnancy forms will be completed for all pregnancies reported during the clinical trial, as defined below. In addition, the Investigator will report to the sponsor follow up information regarding the outcome of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for 6 months.

All women of childbearing potential will be instructed to contact the Investigator immediately if they suspect they might be pregnant (for example, missed or late menses) for the following time-periods:

- During the trial
- Within 6 months after last dose of IMP

If pregnancy is suspected while the participant is receiving IMP, the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner and the participant withdrawn from the trial. Protocol-required procedures for trial discontinuation and follow up will be performed unless contraindicated by the pregnancy.

Pregnancy reporting **will follow the same time lines for a SAE** (see above). Instructions and forms will be provided separately. SAE reporting will also occur if the pregnancy outcome is a congenital anomaly. This will follow the reporting procedures described above for SAE reporting.

8.3 Monitoring for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in preclinical toxicity studies Investigator's Brochures[5,6] and Package Inserts.[23,24,25,26]

AEs still ongoing at the end of treatment in the trial will be followed until satisfactory clinical resolution or stabilization or until the end of the follow-up period and until all queries on these AEs have been resolved. Grade 3 and grade 4 laboratory abnormalities and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.

Note: For Grade 3 or 4 laboratory toxicities, participants should have a confirmatory measurement within 48 hours where possible. The recommendations for managing participants below assumes the laboratory abnormalities of concern have been confirmed.

8.3.1 Neurological

Participants with co-administration of a serotonergic agent, including anti-depressants, should be monitored closely for signs of serotonin syndrome. The Investigator should determine whether the full regimen or the concomitant agent should be discontinued for those who experience signs or symptoms of serotonin syndrome such as cognitive dysfunction, hyperrexia, hyperreflexia and incoordination.

Linezolid and/or the full regimen should be paused for participants experiencing a seizure. The Sponsor Medical Monitor should be contacted to review details and discuss whether linezolid or full regimen should be resumed.

8.3.2 ALT, AST and Alkaline Phosphatase elevations:

The Investigator should refer to Appendix 8 – Liver Toxicity Management to appropriately manage the participant for clinically significant elevations of AST, ALT or Alkaline Phosphatase.

8.3.3 Lipase

Grade 3 (> 2.0 to ≤ 5.0 x ULN) or Grade 4 (> 5.0 x ULN):

Contact Sponsor Medical Monitor to review. Participants with confirmed Grade 3 or 4 elevations of lipase, Investigator should consider pausing the full regimen, pending further evaluation.

8.3.4 Musculoskeletal System and Cardiac Muscle

Myalgia

Grade 2 (muscle tenderness at site other than sites of injection and/or venipuncture or with moderate impairment of activity) or Grade 3 (severe muscle tenderness with marked impairment of activity) or Grade 4 (frank myonecrosis):

Participants with Grade 2 signs and symptoms should be followed closely. Participants with Grade 3 or 4 signs and symptoms should be discussed with the Sponsor Medical Monitor to consider pausing study medication, pending further evaluation.

CPK

For participants having elevations in CPK of potential clinical concern, the Investigator should check the CK-MB subunit, if high, consider pausing regimen and discuss with Sponsor Medical Monitor.

8.3.5 Cardiac Rhythm Disturbances

Cardiac rhythm disturbances that are Grade 3 (recurrent, persistent, symptomatic arrhythmia requiring treatment) or Grade 4 (unstable dysrhythmia requiring treatment):

Participants should be monitored closely. The Investigator should discuss with the Sponsor Medical Monitor to consider pausing the full regimen, pending further evaluation.

QTc prolongation

If QTcF is equal to or greater than 500 msec, the ECG should be repeated and serum electrolytes should be evaluated. If the second ECG also has a QTcF of > 500 msec, the Sponsor Medical Monitor should be consulted to consider pausing the full regimen, pending further evaluation.

New left bundle branch block (LBBB) or Mobitz type 2 or complete heart block. Recordings with artifacts that interfere with the interpretation of the ECG should be repeated to confirm the findings. If the finding is from the centralized ECG machine reading the result is to be checked and confirmed by the Investigator. If this is confirmed by the Investigator, dosing is to be paused until the reading has been confirmed by the central cardiologist and the participant is to be treated per the Investigator's clinical judgment. If it is confirmed by the central cardiologist, the participant is to be withdrawn from the full regimen

Monitoring Linezolid Toxicities

The following are guidelines for decisions to pause, reduce and to resume linezolid in response to the onset and resolution of known linezolid-specific toxicities. These are guidelines, and decisions must be made in the context of the entire clinical status of the participant. While the investigator may need to urgently interrupt dosing for potentially life threatening symptoms or laboratory findings, the Medical Monitor should be contacted and informed of any changes in dose within 24 hours. Questions should be raised to the Sponsor's Medical Monitor if the decision is not clear.

8.3.6 Myelosuppression

The hematologic parameters of hemoglobin and counts of Neutrophils and platelets are variable from measurement to measurement. While decreases in any of these may be caused by linezolid toxicity, decreases of concern should be evaluated in the context of the participant's full clinical status and alternate explanations. Guidelines below are for situations of concern when it is considered likely that linezolid has caused the decrease.

Anemia

- Consider pausing linezolid if hemoglobin falls below 8 gm/dL (Grade 3) and significantly below baseline, or if hemoglobin falls > 25% of baseline. If it is clear that the anemia was caused by linezolid, consider resuming linezolid at half the dose when hemoglobin improves and linezolid is resumed.

Leukopenia

- Consider pausing linezolid if the Absolute Neutrophil Count (ANC) falls below 750/mm3 (Grade 3) and significantly below baseline. Ideally confirm with a repeat test before making further decisions as ANCs can have diurnal and other variability. If it is clear that the leukopenia was caused by linezolid, consider resuming linezolid at half the dose when ANC improves and linezolid is resumed.

Thrombocytopenia

- Consider pausing linezolid if platelets fall below 50,000/mm3 (Grade 3) and significantly below baseline. Ideally confirm with a repeat test before making further decisions. If it is clear that the thrombocytopenia was caused by linezolid, consider resuming linezolid at half the dose when platelets improves and linezolid is resumed.

8.3.7 Peripheral Neuropathy

The decision to reduce the dose, or to pause linezolid until symptoms improve is a judgment based on changes in signs and symptoms identified by the investigator and informed by discussion with the trial participant. As general guidance, consider pausing and/or reducing linezolid when the grade of a neuropathy sign or symptom increases by a grade to grade two or greater. If it is clear that linezolid caused the neuropathy, consider resuming linezolid at half the dose, when the neuropathy improves.

8.3.8 Optic Neuropathy

A participant with visual symptoms of concern or change in visual acuity of 2 lines or more or change in color vision of more than one plate should be referred to the site ophthalmologist for evaluation with a retinal examination. Any changes as assessed by the ophthalmologist that raise concern that an optic neuropathy may be developing should be discussed with the medical monitor and linezolid should be paused. If a likely or definite optic neuropathy is confirmed, linezolid should be permanently discontinued.

8.3.9 Lactic Acidosis

Lactic acidosis as a toxicity of linezolid should be considered if participants have gastrointestinal symptoms that are not explained by other more common causes of their symptoms. Such participants should have lactate measured and, as indicated, a full evaluation of pH and bicarbonate. Note that lactate should not be measured in participants who have no symptoms of concern, as elevated asymptomatic lactate may be common and it is difficult to interpret the clinical relevance of this. Also evaluate whether any concomitant medications, such as anti-retroviral therapies, may be associated with lactic acidosis and consider pausing them until the acidosis resolves. Consider pausing linezolid if a patient has GI symptoms and acidosis likely to be secondary to linezolid toxicity that is not otherwise explained.

8.4 Safety Monitoring by Data 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 participants by monitoring participant safety, assess participant 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.

9 Statistical Analysis

The statistical analysis plan (SAP), which will contain details of the analyses specified in this section, will be written and signed off prior to first patient randomized.

9.1 Analysis Population

The primary analysis population will include both XDR and non-XDR (pre-XDR and MDR intolerant and non-responsive TB) participants (up to 45 per arm). A secondary analysis will be restricted to the XDR participants only (30 per arm).

A modified intent-to-treat (mITT) and a per-protocol (PP) analysis for each arm and analysis population will be conducted. The mITT will be considered the primary analysis and will include all those in the ITT analysis with additional specific exclusions detailed in the statistical analysis plan (SAP).

Other analyses will be performed (for sensitivity) including a full intent-to-treat (ITT) analysis with no exclusions, and an analysis excluding only those who were later found to be ineligible at baseline (based on data collected prior to randomization).

The Safety analysis population will include data from all randomized participants who received at least one dose of IMP.

Full details of all the analysis populations will be defined in the SAP.

9.2 Sample Size

The objective of this trial 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. In order to fulfil this objective, it is planned to randomize 30 XDR-TB participants per treatment group and up to 15 pre-XDR and/or MDR intolerant/non-responsive -TB participants 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.

There will not be a standard-of-care control group. A 50% treatment success rate was chosen as the target, because it is above the entire range of the historical control for cure of XDR-TB and because a cure rate of 50% in XDR, pre-XDR or MDR-TB treatment intolerant/failures with a shortened, simplified, all oral, inexpensive and safer regimen would clearly represent an important therapeutic advancement. A standard-of-care control group cannot reasonably be included in the trial for several reasons. 1) Given that the regimens being tested contain B and L, these drugs would need to be excluded from the control group. However, they are beginning to be used increasingly in XDR-TB, despite lack of firm evidence, but with positive anecdotal reports. Asking patients in the control group to avoid these medications could present an ethical issue. 2) The success rate of standard-of-care treatment for XDR-TB, particularly without B and L (see below), and the risk and difficulty of its administration contrast markedly with the early findings of B-L-Pa in the Nix-TB trial. It is unlikely that patients would sign informed consent to receive standard-of-care treatment if there is an alternative, but even if they do there remains an ethical issue of comparing such a disadvantaged treatment with such an advantaged treatment. 3) The scientific validity of comparing a 12-month endpoint (B-L-Pa) with a 30- or 36-month endpoint (standard of care) would represent a significant challenge.

9.3 Interim Analyses

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 participant has completed 26 weeks of follow-up after end of treatment).

There will be either two database locks, data analyses and trial reports generated for this trial:

1. When all participants have completed 26 weeks of follow-up after end of treatment.

2. When all participants have completed 78 weeks of follow-up from after end of treatment.

9.4 Primary and Secondary Endpoint Analysis

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT). A 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) 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.

9.5 Safety and Tolerability Analysis

- The incidence of all-cause mortality will be summarized.

- All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by Preferred Term within each MedDRA System Organ Class (SOC).

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

- The incidence of the following events will be summarized for further medical analysis:

    - Incidence of TEAEs;
    - Incidence of TEAEs by Severity;
    - Incidence of TEAEs by DMID toxicity grade;
    - Incidence of Drug-Related TEAEs;
    - Incidence of Serious TEAEs;

  - Incidence of TEAEs Leading to Early Withdrawal;
  - Incidence of TEAEs leading to Death.

- Cardiovascular Safety: 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. These will be presented as descriptive analyses, and no inferential tests will be carried out.
  - 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,
    - 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.
  - ECG results will be classified as normal or abnormal (investigator assessment) and summarized using frequency counts by dose group and time of collection.
- Ophthalmology: Descriptive statistics, including changes from baseline, will be summarized and listed by participant for ophthalmology slit lamp examination (age related eye disease study 2 [AREDS2] lens opacity classification and grading). Categorical data for lens opacity will be summarized in a frequency table for the right and left eye, respectively.
- Visual acuity and color vision: Descriptive statistics, including changes from baseline, will be summarized and listed by participant for both Visual Acuity and Color Assessments. Categorical data for changes in visual acuity and color vision from baseline will be summarized in a frequency table for the right and left eye, respectively.
- Descriptive statistics of neuropathy data derived from Brief Peripheral Neuropathy Screen. Categorical data for observed signs and symptoms of neuropathy will be summarized in frequency tables, including changes in signs and symptoms from baseline.
- Other safety variables: Laboratory Parameters, Physical Examination, Vital signs (see Appendix 3), Concomitant medication, ophthalmic examination and peripheral neuropathy. Descriptive summary statistics will be presented. The incidence of liver related laboratory abnormalities will be explored.

9.6 Pharmacokinetics

For each analyte and each scheduled sampling time/window, the plasma concentration will be summarized by descriptive statistics including the mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and geometric CV (%).

In addition, mean and/or median concentration-versus-time graphs will be provided, with error bars and/or scatter plots as appropriate.

Plasma concentrations from sparse sampling will be used to update population pharmacokinetic (PopPK) models for bedaquiline and its M2 metabolite, pretomanid, and linezolid to further evaluate the effects of covariates on model parameters in this study population, and to derive individual exposure metrics for use in exposure-response analyses. PK data from the current trial may be combined with prior data (e.g., from the NiX-TB trial) to enhance this population PK analysis. Detailed plans for the PopPK analysis will be outlined in a separate modeling plan, and results will be reported in separate modeling report.

9.7 Pharmacokinetics/Pharmacodynamics

For each analyte, the PopPK model will be used to derive individual exposure metrics such as steady-state Ctrough, Cmax, AUC_{τ}, and time-above-minimum-inhibitory-concentration (T>MIC), or alternative individual summaries of these metrics over the treatment period to account for dose adjustments and interruptions as appropriate. Relationships between such exposure metrics and efficacy and safety endpoints will be explored graphically and by model-based analyses as appropriate. Planning details and results will be included in the separate modeling plan and report.

10 Records Management

10.1 Data Collection

All relevant CRF/eCRF pages will be completed for each participant who receives any amount of IMP, depending on visits attended. For screening failure participants specific eCRF pages will be completed as described in the eCRF Completion Guidelines. For participants who are prematurely withdrawn, all the visits the participant attended including withdrawal and follow-up visits need to be completed.

10.2 Source Documents

Source documents are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents will include, but are not limited to, progress notes, in-Patient hospital records, electronic data, screening logs, and recorded data from automated instruments.

All source documents pertaining to this trial will be maintained by the Investigators. The Investigator has to permit trial related monitoring, audits, Independent Ethics Committee/Institutional Review Board (IEC/IRB) review and regulatory inspections providing authorized personnel direct access to source documents, including documents required to confirm inclusion/exclusion and relevant in-Patient records while participants is on trial treatment.

10.3 File Management at the Trial Centre

It is the responsibility of the Investigators to ensure that the trial center files are maintained in accordance with International Good Clinical Practice Guidelines and the ethical principles that have their origin in the Declaration of Helsinki.

10.4 Records Retention at the Trial Centre

The Investigator is obliged to retain records and data from the trial for safety reasons and for audit and inspection subsequent to trial completion. The essential documents should be retained for

not less than 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. Investigator should notify sponsor/designees prior to destroying any records pertaining to the trial.

11 Quality Control and Assurance

11.1 Site Procedures

The Investigator undertakes to perform the clinical trial in accordance with this protocol, local regulations, International GCP, and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator undertakes to complete the CRFs according to the Sponsor's requirements, in a timely, accurate and legible manner. CRF entries will be verifiable to source documentation other than the CRF.

Site Standard Operating Procedures will be adhered to for all clinical and bioanalytical activities relevant to the quality of the trial. Participant compliance will be monitored throughout the trial.

The Investigator will sign and date any analysis results (e.g., laboratory, ECG, etc.) to verify that the results have been reviewed.

The Investigator may appoint other sub-investigators to assist with the trial. However, the Investigator maintains responsibility for the trial and will supervise the sub-investigators. Written IEC/IRB approval of the trial will be obtained prior to involvement in the trial.

The Investigator will ensure that all site personnel are adequately trained in GCP, local regulations, the protocol, IBs/package inserts and all trial procedures and requirements

11.2 Monitoring

The Investigator is responsible for the validity of all data collected at the clinical site and must accept the various monitoring procedures employed by the Sponsor. The purpose of monitoring is to verify that the rights and well-being of human participants are protected; that trial data are accurate, complete and verifiable with source data; and that the trial is conducted in compliance with the protocol, International GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

Monitors assigned by the Sponsor will conduct regular site visits before, during and after the trial for the purpose of monitoring various aspects of the trial, and to assure appropriate conduct of the trial in accordance with ICH GCP. Visits will take place usually within a predetermined interval, but this may vary during the course of the trial. The Investigator and site staff will allow the trial monitor and authorized representatives of the Sponsor to (1) inspect all CRFs, written informed consent documents and corresponding source documents (e.g., original medical records), patient records and laboratory raw data, site SOPs, training records, facilities and other trial related systems/processes, and (2) access clinical supplies, dispensing and storage areas. The Investigator and site staff should also (1) agree to assist with monitoring activities if requested and (2) provide adequate time and space for monitoring visits.

The monitor will query any missing, confusing, spurious, or otherwise ambiguous data with the Investigator. All queries should be resolved in a timely manner. A monitoring log will be

maintained recording each visit, the reason for the visit, the monitor's signature and Investigator or designee's confirmation signature.

11.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Monitoring Plan requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to Sponsor/designee. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

11.4 Auditing

For the purpose of compliance with International GCP and regulatory agency guidelines, it may be necessary for Sponsor-authorized Quality Assurance personnel and/or authorized personnel from an external regulatory agency to conduct an audit or inspection of the investigational site. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy and consistency, and to assure that studies are in accordance with the guidelines. Having the highest quality data from studies is an essential aspect of drug development.

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The auditors or inspectors may also review site SOPs, training records, site facilities and other trial related systems/processes.

In the event of the site being notified of a Regulatory Inspection, the Sponsor will help with preparation. It is essential that the Sponsor be notified of the inspection as soon as possible.

12 Ethics and Regulatory

12.1 Basic Principles

This research will be carried out in accordance with International GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

12.2 Independent Ethics Committee/Institutional Review Board (IEC/IRB) Review

The protocol and required trial related documents will be reviewed by the sites respective IEC/IRB. The trial will not start until the IEC/IRB has approved the protocol, written informed consent, any written information to be provided to the participant or any modification thereof, plus any other trial related documents required for review. The IEC/IRB shall be constituted and shall operate in accordance with International GCP, the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will maintain an accurate and complete record of all submissions made to, and responses from the IRB/IEC. The records should be filed in the Investigator's Trial File, and copies will be sent to the Sponsor.

12.3 Regulatory Authorities

The Regulatory Authorities will receive the protocol, amendments, reports on SAEs, and the Integrated Clinical Trial Report according to national regulations. As required by local legislation, written approval will be obtained from the Regulatory Authorities prior to commencement of the trial and implementation of e.g. amendments as applicable.

12.4 Informed Consent

Written informed consent will be obtained from all participants (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment procedures) are performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The Investigators have both ethical and legal responsibility to ensure that each participant being considered for inclusion in this trial is given a full explanation of the protocol. Participants must be informed that their participation is voluntary The investigator or his/her representative will explain the nature of the trial to the participant or his/her legally authorized representative and answer all questions regarding the trial. This shall be documented on a written informed consent form that shall be approved by the same IEC/IRB responsible for approval of this protocol. Each informed consent form shall include the elements required by the international GCP and must adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The trial will be included and updated in the appropriate Country registry and referenced in the ICF.

Once the appropriate essential information has been provided to the participant and fully explained by the Investigators (or qualified designees) and it is felt that the participant understands the implications of participating, the IEC/IRB approved written informed consent form will be signed and dated by both the participant and the person obtaining consent (Investigators or designees), and by any other parties required by the IEC/IRB. Ongoing participants must be re-consented to the most current version of the ICF(s) during their participation in the trial.

The original signed informed consent form will be kept with the trial records and a copy of signed informed consent form will be provided to the participant or the participant's legally authorized representative. Another copy of the signed informed consent form and a source document identifying the trial and recording the dates of participation will be placed in the participant's medical record.

The monitor will inspect the original completed consent form(s) for all participants

12.5 Confidentiality

All site staff, the Sponsor, and any sponsor representatives will preserve the confidentiality of all participants taking part in the trial, in accordance with International GCP, applicable local legislation/regulations. Subject to the requirement for source data verification by the trial personnel by reference to the participant's notes, confidentiality of all participant identities will be maintained. Unique identifiers will be used on the CRF and in all trial correspondence, as

permitted. No material bearing a participant's name will be kept on file by the Sponsor. The written informed consent will contain a clause granting permission for review of the participants' source data by the sponsor or designees.

13 Publication Policy

The definition of publication for this purpose is any public presentation of the data emerging from this trial.

All unpublished information given to the Investigator by the Sponsor shall not be published or disclosed to a third party, other than to the responsible IEC/IRB, within the understanding of the confidentiality of their nature, without the prior written consent of the Sponsor.

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors. [30]

Because the Study is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the Study must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy. Specifically, (a) all peer-reviewed published research relating to the Study must be submitted for publication by TB Alliance through the Chronos Open Access Publishing Service established by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy.

14 Protocol Amendment Policy

Any change to the protocol will be effected by means of a protocol amendment. Any changes which affect participant safety or welfare will be submitted to the IEC/IRB and Regulatory Authorities prior to implementation. The Investigator, IEC/IRB, and Sponsor must agree on all amendments. No amendment will be implemented until approved by the relevant Authorities and/or IEC/IRB and signed by all required parties. Exceptions to this are when the Investigator considers that the participant's safety is compromised.

Protocol amendments detailing minor administrative changes should be submitted by the Investigator to the IEC/IRB and Regulatory Authorities, either for notification purposes or approval as appropriate.

15 Sponsor, Financial Aspects, Insurance and Indemnity

The trial sponsor is the Global Alliance for TB Drug Development (TB Alliance). The TB Alliance is a not for profit, product development partnership accelerating the discovery and development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies for those HIV-TB participants currently on such therapies, and improve treatment of latent infection.

The TB Alliance works with public and private partners worldwide. It is committed to ensuring that approved new regimens are affordable, adopted and available to those who need them.

The TB Alliance operates with funding mainly from the Bill & Melinda Gates Foundation, the Netherlands Ministry of Foreign Affairs (DGIS), the United Kingdom Department for International Development (DFID), and the United States Agency for International Development (USAID).

The participants will not receive any incentives for their involvement in the trial. The sponsor has made provision to reimburse the participants for out-of-pocket expenses such as travelling to and from the trial site and other miscellaneous costs as a result of their trial participation.

The sponsor certifies that it has liability insurance coverage for itself and will provide an associated certificate upon request. The insurance does not relieve the Investigators of the obligation to maintain their own liability insurance as required by applicable law. The sponsor does not assume any obligation for the medical treatment of other injuries and illnesses.

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Appendix 1: The IUATLD Scale

The IUATLD scale proposes five groups for reporting the results of reading smears for acid fast bacilli. They should be recorded as follows:

FINDING	RECORDING
No acid-fast bacilli found in at least 100 fields	negative
1 to 9 acid-fast bacilli per 100 fields	exact figure/100/scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

Reference: The Public Health Service National Tuberculosis Reference Laboratory and the National Laboratory Network. Minimum Requirements, Role and Operation in a Low-Income Country. International Union Against Tuberculosis and Lung Disease 1998.

Appendix 2: Division of Microbiology and Infectious Disease (DMID) Toxicity Table

Source: U.S. National Institute of Allergy and Infectious Diseases, DMID, November 2007 (Draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of Patients in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 /mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures

Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day

Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent ; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatienttreatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient - no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	Subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25- 50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Appendix 3: Cardiovascular Safety

Vital Signs

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs Parameter			
	Pulse	DBP	SBP	RR
Abnormalities on actual values				
"Abnormally low"	≤ 50 bpm	≤ 50 mmHg	≤ 90 mm Hg	<12 Breaths per minute
"Grade 1 or mild"	-	> 90 mmHg-<100 mmHg	> 140 mmHg-<160 mmHg	17-20 Breaths per minute
"Grade 2 or moderate"	-	≥ 100 mmHg-<110 mmHg	≥ 160 mmHg-<180 mmHg	21-25 Breaths per minute
"Grade 3 or severe"	-	≥ 110 mmHg	≥ 180 mmHg	>25 Breaths per minute
"Abnormally high or Grade 4"	≥ 120 bpm	-	-	Intubation

Appendix 4: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Descrip
Able to carry on normal activity and to work; no special care needed.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109[22].

Appendix 5: EQ-5D-5L Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

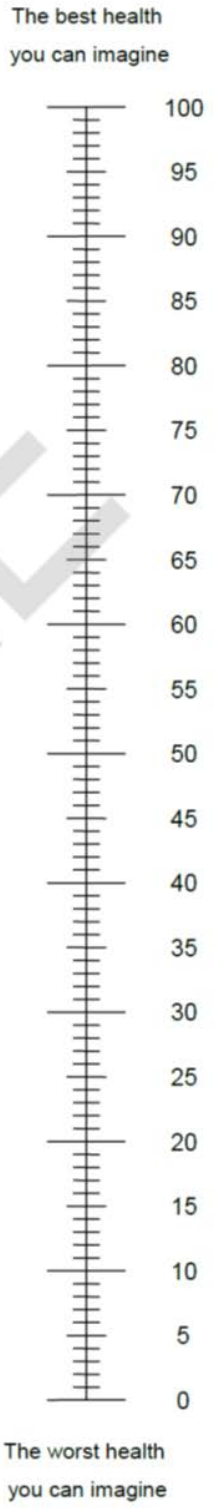
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6: Brief Peripheral Neuropathy Screening

BRIEF PERIPHERAL NEUROPATHY SCREEN

Patient Initials				Patient ID								
1. Visit (Circle One)	During Treatment	Screening	Week 4	Week 8	Week 12	Week 16	Week 20	Week 23				
	Post Treatment	12 Week		26 Weeks		52 Weeks		78 Weeks				
	Other	End of or Early Withdrawal from Treatment				Unscheduled For new onset or worsening peripheral neuropathy OR treatment extension (+ culture or interruptions)						
2. Date of Assessment		D	D	M	M	M	Y	Y	Y	Y		

INTERFERENCE WITH WALKING OR SLEEPING

3. In the last two weeks, have pain, aching or burning in your feet interfered with your walking or sleeping? (Check one)									Y	N
3a.	*If **YES**, ask the patient to rate the level of interference (1 to 10) to his walking or sleeping caused by this pain, ache or burning (circle one).*									
	Minimal			**Modest**				**Severe**		
	01	02	03	04	05	06	07	08	09	10

SUBJECT ELICITED SYMPTOMS

- *Using the faces below, ask the patient to rate the severity of the symptoms for the questions 4, 5, 6 on a scale of 1 (mild) to 10 (severe) for both feet. If the severity is different between the left and right foot, record the severity of the most affected foot.*
- *Enter a score for each symptom.*
- *If a symptom has been present in the past, but not since the last visit, enter '00 – Currently Absent'*
- *If a symptom has never been present, enter '11 – Always Been Normal'*

					
00 Very Happy, No Symptoms	**02** Just a little bit	**04** A little more	**06** Even more	**08** A whole lot	**10** Worst

During the last 14 days, have you experienced:		Severity	
	4. Pain, aching or burning in feet or legs?		
	5. "Pins and needles" in feet or legs?		
	6. Numbness (lack of feeling) in feet or legs?		

19-Jan-17 version

BRIEF PERIPHERAL NEUROPATHY SCREEN

Patient Initials				Patient ID									

PERCEPTION OF VIBRATION

- *Press the ends of a 128 Hz tuning fork together so the sides touch and let go. Place the vibrating tuning fork on the bony prominence on the patient's wrist to be sure that they can recognize the vibration or "buzzing" quality of the tuning fork.*
- *Again, press the ends of the tuning fork hard enough so that the sides touch and let go. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of the great toe and begin counting the seconds. Instruct the Subject to tell you when they stop feeling the vibration or "buzzing".*
- *Repeat for the great toe on the other foot*

Vibration Perception Grade Scale:
0 – Vibration felt for >10 seconds (normal)
1 – Vibration felt for 6-10 seconds (mild loss)
*2 – Vibration felt for 5 seconds or less (moderate loss)**
*3 – No feeling of vibration (severe loss)**
*9 – Unable to evaluate or did not assess**

	Right	Left
7. Measured vibration grade of great toe DIP joint		

DEEP TENDON REFLEXES

- *The examiner uses one hand to press upward on the ball of the foot, dorsiflexing the Subject's ankle to 90 degrees. Using the reflex hammer (preferably long handled), the examiner strikes the Achilles tendon.*
- *The tendon reflex is felt by the examiner's hand as plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck.*
- *Repeat for ankle on other leg*

Ankle reflex grade scale:
0 – Absent
1 – Hypoactive
2 – Normal deep tendon reflexes
3 – hyperactive deep tendon reflexes ***(e.g. with prominent spread of toes)***
4 – clonus
9 – unable to evaluate or did not assess

	Right	Left
8. Measured ankle reflex grade		

COMMENTS

Name of Person Completing Form										Name of Clinician (if required)									
Signature of Person Completing Form										Signature of Clinician (if required)									
Date	D	D	M	M	M	Y	Y	Y	Y	Date	D	D	M	M	M	Y	Y	Y	Y

Appendix 7: Tuberculosis Symptoms Profile

TUBERCULOSIS SYMPTOM PROFILE (V3)

This questionnaire asks about symptoms that patients with tuberculosis may or may not experience.

Please read each symptom carefully and think about your experience **during the past 7 days** when you make your response. Then tick (☑) one box for each symptom.

If you **did not** experience the symptom **during the past 7 days**, please tick (☑) "None" for that symptom.

If you **did** experience the symptom **during the past 7 days**, please tick (☑) whether the intensity of the symptom you experienced was "Mild", "Moderate" or "Severe".

TB Symptom	**Rate your experience of each symptom over the past 7 days.**			
Feeling feverish	☐ None	☐ Mild	☐ Moderate	☐ Severe
Feeling chills	☐ None	☐ Mild	☐ Moderate	☐ Severe
Excessive sweating	☐ None	☐ Mild	☐ Moderate	☐ Severe
Shortness of breath	☐ None	☐ Mild	☐ Moderate	☐ Severe
Chest pain	☐ None	☐ Mild	☐ Moderate	☐ Severe
Feeling unwell	☐ None	☐ Mild	☐ Moderate	☐ Severe
Tiredness/weakness	☐ None	☐ Mild	☐ Moderate	☐ Severe
Cough	☐ None	☐ Mild	☐ Moderate	☐ Severe
Coughing up mucus	☐ None	☐ Mild	☐ Moderate	☐ Severe
Coughing up blood	☐ None	☐ Mild	☐ Moderate	☐ Severe

During the past 7 days, how would you rate your appetite?

☐ Good ☐ Fair ☐ Poor

Approved, Issued Date 09-Apr-2012

Appendix 8: Liver Toxicity Management

Standard anti-TB chemotherapy is known to cause derangement of liver function tests in a substantial number of patients. In many cases this will be asymptomatic and self-limiting. In some cases, severe hepatitis and even fulminant liver failure and death can occur.

In pre-marketing clinical trials of new drugs and regimens it is especially important to identify and carefully manage any trial participants who are at risk of progression to serious liver injury. The observation of altered liver function to a degree that has a high risk of progressing to liver failure has been referred to informally as Hy's Law;[31,39]; this reflects that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
2. Among trial participants showing such aminotransferase (AT) elevations, often with ATs much greater than 3x ULN, one or more also show elevation of serum total bilirubin (TBL) to >2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase (ALP)).
3. No other reason can be found to explain the combination of increased AT and total bilirubin level (TBL), such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

During the trial, liver function will be monitored regularly with clinical assessment and blood tests in study participants and this will assist in follow up laboratory measurements that can document either resolution of abnormalities or signal the potential for drug-induced liver injury (DILI). In a clinical trial of new drugs and combinations it is especially important for investigators to follow closely any participants who have evidence of hepatic inflammation or potential toxicity. The following procedure describes the management of deranged liver function tests in study participants.

Procedure

Blood tests for liver function will be taken routinely at screening (Day -9 to -1) and at the specific time points designated in the protocol, and at Early Withdrawal. If at any other visit the clinician suspects derangement of liver function, e.g. the participant describes nausea and vomiting, right upper abdominal pain or is jaundiced, blood should be taken for liver function tests and the participant comprehensively assessed for evidence of hepatitis or hepatic impairment and any potentially contributing causes.

Suspected liver toxicity (or elevated liver enzymes detected in the absence of symptoms) must be taken seriously and detailed guidance will be provided in a separate document "NC-007 Study Management of Hepatotoxicity Guideline". Investigators should refer to this document as a guide to management in cases of suspected or proven liver toxicity. Importantly, the trial Medical Monitor is available to provide further assistance if there is any uncertainty or additional questions.

The laboratory source (print-out of any results) should be stored alongside or transcribed into the clinical source document. Each abnormal value should be marked as clinically significant (CS) or non-clinically significant (NCS); the assessment of significance is at the discretion of the

investigator. All clinically significant abnormal results must be recorded as Adverse Events in the eCRF and graded clinically as per the DMID adult toxicity table grading, (Appendix 2). Assessments and decision making for elevations in aminotransferase values or bilirubin of various levels of concern are detailed below:

Elevated liver enzymes considered of clinical significance, but not accompanied by other signs and symptoms, should be reported as an adverse event and should usually be recorded as elevated liver enzymes. If the term "hepatitis" is used, the Safety Data Manager will question the site for additional evidence to support the diagnosis, such as clinical signs and serological or biopsy data. While a liver biopsy is not required to make a diagnosis of hepatitis, the term "hepatitis" should be reserved in most instances for cases where there is supportive evidence beyond a liver enzyme abnormality. However, if the investigator will confirm the diagnosis of hepatitis just on the basis of clinical signs and laboratory values the diagnosis will be accepted. Should other symptoms or signs be present, these should also be recorded as adverse events.

Restarting Medication

Liver function tests that are improving should be repeated regularly, such as every 3 days for the first week then once a week until they return to near baseline values for the participant. Manage the participant symptomatically as required using medications that are not potentially hepatotoxic. Infection control issues must be carefully managed whilst TB medications are being withheld, especially if the participant is still culture positive for acid fast bacilli.

If medication has been temporarily stopped, once the liver function values have decreased substantially a decision must be made about further TB management. This will be dependent on the clinical context and a decision must be made in discussion with the sponsor medical monitor. Treatment can only be restarted if the trial Medical Monitor is in agreement with the plan. In all cases treatment should be recommenced under close supervision for any evidence of recurrent liver function abnormalities.

If there is a further significant elevation of hepatic enzymes or bilirubin or symptoms of clinical concern after resumption of study medication, the study medication should be withdrawn permanently. Participants who permanently discontinue study medication should be managed as clinically indicated according to local National TB Programme guidelines. The sponsor medical monitor can be contacted for further advice when referring to the National Treatment Program.

The trial Medical Monitor is available to assist the Investigators in both the management of liver toxicity and decisions regarding the holding or re-introduction of trial medication. Investigators must involve the Medical Monitor in any decisions regarding medication hold or re-start, and there should always be a low threshold for contacting the Medical Monitor in cases of elevated liver enzymes.

Protocol Amendment Template

Protocol Name / Number: ZeNix/ NC-007-(B-Pa-L)

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).

Reasons for Protocol Amendment:

1	**Change** of screening period from up to 9 to up to 14 days to provide sites with adequate time for assessments (In section 1.1 Synopsis Summary, 1.2 Synopsis Flowchart and 4.2 Treatment Plan: Schedule of Assessments, 5. Trial Population.)
2	**Removed** limitation of 60 non-XDR participants/requirement for 120 XDR participants. Enrollment to include 180 participants who are either XDR, pre-XDR or MDR intolerant or non-responsive. (In section 1.1 Synopsis summary and 4.1 Summary of Trial Design)
3	**Updated** randomization details**,** specifically abbreviation of phone/web system utilized (changed IWRS to IXRS) and "minimization" to "stratification". (In section 1.1 Synopsis Summary, 4.1 Summary of Trial Design, and 6.5 Method of Treatment Assignment)
4	**Clarified** scenarios and timing of culture positive results for consideration of treatment extensions from "week 16" to "between week 16 and week 26" (In section 1.1 Synopsis Summary, 1.2 of Synopsis Flowchart, and 4.1 Summary of Trial Design)
5	**Clarified** language throughout the protocol to specify when Sponsor Medical Monitor's approval vs. notification required (In section 1.1 Synopsis, 4.1 Summary of Trial Design, 5.2 Exclusion Criteria, 5.4 Trial Discontinuation and Visits, 5.3.1 Prior and Concomitant Medications and Other Treatments, 6.3 Treatment Modification(s), 6.6 Blinding and Procedures for Breaking the Blind, 8.2.1 Follow up of AE, and 8.3 Monitoring for Specific Toxicities)
6	**Clarified** descriptions of regimen and dosing instructions to note linezolid 600 mg full or half tablets and placebo full or half tablets vs. 300 mg half tablet or linezolid 300 or 600 mg placebo. (In section 1.1 Synopsis Summary, 6.1 IMP Administration, and 6.4 IMP Packaging and Labelling)
7	**Clarified** treatment modifications to note 2 step (vs. 3 step) blinded decreases, and ability to raise linezolid dose back up to starting level, specifics on when for make-up dosing required (when missed more than 7 days) and deleted (when repetitive) or moved wording. (In section 1.1 Synopsis Summary and 6.3 Treatment Modification[s])

8	**Clarified** primary endpoint timing in definition, from “through follow up until 26 weeks” to “at 26 weeks” after the end of treatment (In section 1.1 Synopsis Summary)
9	**Updated** Safety endpoint for ophthalmology slit lamp exams to include “observed” (In section 1.1 Synopsis Summary)
10	**Addition** of ophthalmology exams at treatment week 23 and follow-up week 12 to ensure appropriate safety monitoring (In section 1.2 Synopsis Flowchart, and section 5.4 Trial Discontinuation and Visits)
11	**Addition** of assessments required when patients withdraw during post treatment follow-up, which will be the same assessments required for week 78 post treatment follow-up visit. (In section 1.2 Synopsis Flowchart, and 5.4.2 Early Withdrawal Follow-up)
12	**Clarified** visit scheduling for understanding. Referenced treatment modification for treatment extension scenarios, removed repeated text, and provided clear examples. (In section 6.3 Treatment Modification[s])
13	**Updated and added** details on HIV testing to clarify that historical documented results must be from ELISA, Western blot or electrochemiluminescence (added). Added allowance for repeated HIV testing when results indeterminate. (In section 1.2 Synopsis Flowchart, and 5.1 Inclusion Criteria)
14	**Clarified** requirement for CD4 and viral load testing for HIV positive participants, noted that CD4 testing should be done if patient is an early withdrawal during treatment period.
15	**Change** of acceptable chest x-ray results from 1 month prior to screening to 6 months prior to or at screening (In section 1.2 Synopsis Flowchart, and 5.1 Inclusion Criteria)
16	**Clarified** ECG testing to note that central reading of screening to be used for eligibility. (In section 1.2 Synopsis Flowchart)
17	**Added** sentence to note that height is only collected as part of full physical exam at screening (In section 1.2 Synopsis Flowchart)
18	**Addition** of Gamma Glutamyl Transferase (GGT) test to screening labs and instructions on additional testing for liver toxicity management to safety laboratory section. Removed note that follow-up microscopy will be done at discretion of Investigator as will be done automatically for all abnormal results. (In section 1.2 Synopsis Flowchart)
19	**Clarified** language regarding PK sampling timing, including instructions for sampling when full regimen or linezolid paused or when linezolid is reduced. Included language regarding recoding of dates and times of previous 2 doses of IMP. (In section 1.2 Synopsis Flowchart)
20	**Updated** Sputum Sampling details: **Clarified** and detailed testing on sputum vs. isolate in table (In section 1.2 Synopsis Flowchart) **Addition** of details on extended DST to inform patient treatment at appropriate labs (In section 1.2 Synopsis Flowchart)

	Clarified timing of tests, detailing requirements for testing on first positive samples at/after week 16 (addition) for extension or at/after end of treatment for potential new infections (In section 1.2 Synopsis Flowchart and 7.5 Mycobacteriology Characterization and Variable and Procedures) **Clarified** use of pre-screening, adding scenario to support testing for inclusion into the trial. (In section 1.2 Synopsis Flowchart) **Removed** details on handling of pre-screening samples. (In section 1.2 Synopsis Flowchart and 7.5 Mycobacteriology Characterization and Variable and Procedures) **Moved** wording on isolate testing (EMS preference and scenarios for requesting second isolate) to footnote under table (In section 1.2 Synopsis Flowchart) **Clarified** that cultures should be stored (In section 1.2 Synopsis Flowchart) **Clarified** testing done at Central lab to describe scenarios for paired genotyping to determine relapse/reinfection (In section 1.2 Synopsis Flowchart) **Moved** details on unscheduled visits to section 5.4.3
21	**Removal** of Isoniazid (INH) resistance as an inclusion criteria (In section 5.1 Inclusion Criteria, section 5.4 Discontinuation from Treatment/Trial) **Clarified** requirements for documented resistance to make it clear that testing done at screening can be used for inclusion into trial (In section 5.1 Inclusion Criteria)
22	**Updated** Contraception inclusion criteria to align clarify differences between female participants and male participant's female partners (In section 5.1 Inclusion Criteria) **Changed** required period for male participants to practice birth control methods from 6 months to 12 weeks to align with guidance in IB (In section 5.1 Inclusion Criteria) **Removed** "female partners of male participants" in note about hormone based contraception as female partners not taking IMP (In section 5.1 Inclusion Criteria)
23	**Clarified** exclusion based on resistance to study IMP to specific historic DST or MIC results and added wording to consult Sponsor Medical Monitor (In section 5.2 Exclusion Criteria)
24	**Updated** Previous and Concomitant Therapy exclusion section to: Reference restriction section (and **removal** of the detailed examples) for exclusion of patients who have planned use of those medications (In section 5.2 Exclusion Criteria and section 5.3 Restrictions)

	Removed exclusion criteria for participants with existing TB diagnosis and HIV coinfection to have been on ARTs for at least 4 weeks prior to screening as not necessary, as suppressed viral load and minimum CD4 count indicates that the participant's HIV is controlled (In section 5.2 Exclusion Criteria) **Changed** requirement for participants with newly diagnosed TB and HIV for receipt of at least 2 weeks of an anti-tuberculosis regimen instead of study medication as many participants are already on TB medications when screened for trial (In section 5.2 Exclusion Criteria)
25	**Addition** of laboratory units utilized by the central lab and **correction** of units for viral load and Albumin (In section 5.2 Exclusion Criteria)
26	**Addition** of wording to note that no protocol waivers will be granted by the TB Alliance (In section 5.2 Exclusion Criteria)
27	**Updated** Concomitant therapy restrictions to distinguish medications that are strictly prohibited, must be discussed and approved prior to use or should be avoided with option to contact the Sponsor Medical Monitor to discuss. (Section 5.3 Restrictions)
28	**Updated** Discontinuation from Treatment/Trial section: **Clarified** when participant "must" be withdrawn vs. "may" be withdrawn post discussion with Sponsor Medical Monitor (In section 5.4.1 Treatment Discontinuation and Early Withdrawal) **Clarified** that withdrawal for pregnancy not relevant post treatment completion trial (In section 5.4.1 Treatment Discontinuation and Early Withdrawal) **Clarified** withdrawal for safety reasons to include concerns of symptomatic TB (failure/relapse) (In section 5.4.1 Treatment Discontinuation and Early Withdrawal) **Clarified** withdraw at anytime at discretion of Investigator for safety, administrative, or compliance reasons (In section 5.4.1 Treatment Discontinuation and Early Withdrawal) **Added** wording that clarified no follow-up visits will be performed when a participant withdraws consent (In section 5.4.1 Treatment Discontinuation and Early Withdrawal) **Added** section to clarify what visits/assessments are done post early withdrawal (In section 5.4.2 Early Withdrawal Follow-up) **Moved** section on unscheduled visits/assessments are done post early withdrawal (In section 5.4.3 Unscheduled Visits) **Removed** wording from unscheduled visit section that instructed investigator to contact medical monitor to discuss outcome status scenarios (In section 5.4.4 Early Withdrawal due to TB)
29	**Clarified** that cards and bottles will be checked for unused tablets at each treatment visit (In section 6.2 Participant Compliance)

30	**Updated** IMP package labeling requirements to reflect the same information as the updated label, removal of sponsor address and phone number (In section 6.4 IMP Packaging and Labelling)
31	**Addition** of wording to note that patients are not required to be withdrawn if their treatment blind is broken (In section 6.6 Blinding and Procedures for Breaking the Blind)
32	**Addition** of alcohol use to clinically significant medical and treatment history (In section 7.1 Demographic and Background Variables and Procedures)
33	**Addition** of viral load and electrochemiluminescence as example of HIV test (In section 7.1 Demographic and Background Variables and Procedures)
34	**Addition of** concomitant medications (In section 7.1 Demographic and Background Variables and Procedures)
35	**Removed** appendices and references to appendices for EQ-5D-5L, BPNS and TB Symptoms profiles and referenced the ZeNix Subject Questionnaires Guideline, for the current forms. (In section 7.2 Efficacy Variable and Procedures, 7.3 Safety and Tolerability of Assessments, 7.5 Mycobacteriology Characterization Variable and Procedures)
36	**Addition** of reference to Liver Toxicity Management Guideline (In section 8.3.2 ALT, AST, and Alkaline Phosphatase Elevation)
37	**Addition** of reference to health authority, where applicable for protocol deviation reporting (In Section 11.3 Protocol Deviations)
38	Administrative changes, including spelling, grammar and format changes have been applied to the entire document. Refer to the 'tracked changes' for details of changes made

#	Section	Previous Text Version 1.0, dated 23-Feb-17	Amended Text Version 2.0, dated 13-Jun-18 ~~Additional text - bold font. Deleted text – strike-through.~~	Reason for Change Insert reason # from table above
1	1.1 Synopsis Summary	Participants will have a screening period of up to 9 days and will be randomized to receive one of the 4 active treatment arms. Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive web response system (IWRS) which will utilize a dynamic randomization system using minimization with a random element to allocate participants evenly across the arms by HIV status and type of TB.	Participants will have a screening period of up to 14 days and will be randomized to receive one of the 4 active treatment arms. Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive voice and web response system (IXRS) which will utilize a randomization system using stratification with a random element to allocate participants evenly across the arms by HIV status and type of TB.	1,3,4, and 5

		Each participant will receive 26 weeks of treatment. If participant's week 16 sample remains culture positive, 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.	Each participant will receive 26 weeks of treatment 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 with and approved by the Sponsor Medical Monitor before implementation. Participants will be followed for 78 weeks after end of treatment.	
2	1.1 Synopsis Summary	A total of up to 180 participants: 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. Enrollment will stop when 120 XDR-TB participants are randomized. Sponsor may consider replacement of late screen failure and un-assessable (as detailed in the statistical analysis plan) participants.	A total of up to 180 participants male and female, aged 14 and over. Sponsor may consider replacement of late screen failure and un-assessable (as detailed in the statistical analysis plan) participants.	2
3	1.1 Synopsis Summary	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 • placebo linezolid half tablet (pre-cut) 300 mg 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 arms): <u>Participants will receive the following:</u> • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks plus; • Linezolid- participants will be randomly assigned to receive one of the following four linezolid treatment doses and durations:	The regimen will be supplied as the following: Product / Tablet Strength / Abbreviation Bedaquiline / 100 mg / (B) Pretomanid / 200 mg / (Pa) Linezolid (scored) / 600 mg / (L) Placebo Linezolid (scored) / placebo / (L) Linezolid 600 mg half tablet (pre-cut) / 300 mg / (L) Placebo linezolid 600 mg half tablet (pre-cut) / placebo / (L) Linezolid treatment will be supplied as 2 rows of full tablets (active or placebo) and one row of half-tablets (active or placebo) to allow for all possible dosing options while maintaining the blind. <u>Instructions for Dosing:</u>	6

		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 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 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 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	Treatment will be administered orally, once daily, with a full glass of water and a meal in the following dosing schemes (treatment arms): Participants will receive the following: • bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus; • pretomanid 200 mg once daily for 26 weeks plus; • Linezolid- participants will be randomly assigned to receive one of the following four blinded linezolid treatment doses and durations: Linezolid 1200 mg daily for 26 weeks • 2 linezolid 600 mg active tablets once daily for 26 weeks • ½ (one half) placebo linezolid tablet once daily for 26 weeks Linezolid 1200 mg daily for 9 weeks Weeks 1-9 • 2 linezolid 600 mg active tablets once daily for 9 weeks • ½ (one half) placebo linezolid tablet once daily for 9 weeks Weeks 10-26 • 2 placebo linezolid tablets once daily for 17 weeks • ½ (one half) placebo linezolid tablet once daily for 17 weeks Linezolid 600 mg daily for 26 weeks • 1 linezolid 600 mg active tablet once daily for 26 weeks • 1 placebo linezolid tablet once daily for 26 weeks • ½ (one half) placebo linezolid tablet once daily for 26 weeks Linezolid 600 mg daily for 9 weeks Weeks 1-9 • 1 linezolid 600 mg active tablet once daily for 9 weeks • 1 placebo linezolid tablet for 9 weeks • ½ (one half) placebo linezolid tablet once daily for 9 weeks Weeks 10-26 • 2 placebo linezolid tablets once daily for 17 weeks	

			• ½ (one half) placebo linezolid tablet once daily for 17 weeks <u>Linezolid 600 mg daily for 9 weeks</u> Weeks 1-9 • 1 linezolid 600 mg active tablet once daily for 9 weeks • 1 placebo linezolid tablet for 9 weeks • ½ (one half) placebo linezolid tablet once daily for 17 weeks Weeks 10-26 • 2 placebo linezolid tablets once daily for 17 weeks • ½ (one half) placebo linezolid tablet once daily for 17 weeks	

4	1.1 Synopsis Summary	**<u>Treatment Modifications:</u>**
		
		The above treatment schemes may require modification due to toxicities as noted below. All dose modifications should be discussed with the Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation
		
		In the event of linezolid specific toxicities, the following should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol. Every effort should be made for participants to receive a total of 9 weeks of linezolid, even if pauses are required:
		• Blinded one step reductions (maximum 3 steps) in the dose of linezolid (1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or 300mg QD to placebo) managed by the IWRS as per instructions in pharmacy manual and/or IWRS user manual.
		• Temporary pause of linezolid due to a linezolid-specific toxicity should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol.
		• Permanent discontinuation of linezolid.
		
		For participants experiencing suspected drug related toxicities due to other drugs in the regimen (B-Pa), the full regimen may be halted for up to 35 consecutive days.
			<u>Treatment Modifications:</u>
			
			The above treatment schemes may require modification due to toxicities as noted below. All dose modifications should be discussed with the Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation
			
			In the event of linezolid specific toxicities, the following should be considered and implemented per guidance in the monitoring and safety for specific toxicities section (8.3) of protocol:
			
			• **Blinded** one step reductions (maximum 2 steps) in the dose of linezolid managed by the IXRS as per instructions in pharmacy manual and/or IXRS user manual.
			  ○ 1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or
			  ○ 600 mg QD to 300 mg QD, 300mg QD to placebo
			• Temporary pause of linezolid.
			• Permanent discontinuation of linezolid.
			• Participants who have a linezolid reduction can go back to a higher dose (1 step or 2 steps) post discussion with and approval by Sponsor Medical Monitor.
				7

		Interruptions/pauses of all Investigational Medicinal Product (IMP) must not exceed 8 weeks (56 days) cumulatively. If participant's week 16 sample remains culture positive, Investigator may consider option to extend current treatment to 39 weeks, in consultation with the Sponsor Medical Monitor. When treatment is extended due to a positive culture at week 16, interruptions/pauses of all IMP must not exceed 13 weeks (91 days) cumulatively. At no time should the participant be treated with a single agent.	For participants experiencing suspected drug related toxicities due to other drugs in the regimen (B-Pa), the full regimen may be halted for up to 35 consecutive days. Interruptions/pauses of all Investigational Medicinal Product (IMP) must not exceed 8 weeks (56 days) cumulatively. When treatment is extended to 39 weeks, interruptions/pauses of all IMP must not exceed 13 weeks (91 days) cumulatively. When the total of missed dosing days of the prescribed regimen and/or pauses is greater than 7 days, the same number of missed doses should be dispensed/treatment extended to make up for the total missed doses. At no time should the participant be treated with a single agent. Every effort should be made for participants to receive a total of 9 weeks of linezolid, even if pauses are required	
5	1.1 Synopsis Summary	<u>Primary Endpoint:</u> Incidence of bacteriologic failure or relapse or clinical failure through follow up until 26 weeks after the end of treatment.	<u>Primary Endpoint:</u> Incidence of bacteriologic failure or relapse, or clinical failure at 26 weeks after the end of treatment.	8
6	1.1 Synopsis Summary	• Descriptive statistics of ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2]) lens opacity classification and grading). Categorical data for lens opacity will be summarized in a frequency table for the right and left eye, respectively, including change from baseline.	• Descriptive statistics of ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2]) lens opacity classification and grading). Categorical data for lens opacity will be summarized in a frequency table for the right and left eye, respectively, including observed and change from baseline	9
7	1.1 Synopsis Summary	**Trial Duration:** ~3.5 Years (An enrolment period of at least 18 months plus 9 days pre-treatment plus 6 month treatment period plus 18 months post treatment follow-up).	**Trial Duration:** ~3.5 Years (An enrolment period of at least 18 months plus 14 days pre-treatment plus 6 months treatment period plus 18 months post treatment follow-up).	1
8	1.2 Synopsis Flowchart	*Captured in synopsis flowchart/table under time of visits, screening:* **Up to 9 days prior to Treatment**	*Captured in synopsis flowchart/table under time of visits, screening:* **Up to 14 days prior to first dose**	1

9	1.2 Synopsis Flowchart	*Captured in synopsis flowchart/*table (after week 23 treatment): Visits every 3 weeks if extended due to IMP pause or culture (+) at week 16	*Captured in synopsis flowchart/table (after week 23 treatment):* Visits every 3 weeks if extended**.**	12
10	1.2 Synopsis Flowchart	*Captured in flowchart/table:* Ophthalmic exams are performed during screening, treatment week 4, week 8, week 12, week 16m week 20 visits every 3 weeks if extended, end of OR Early withdrawal from treatment, and post treatment follow-up week 4.	*Captured in flowchart/table*: Ophthalmic exams are marked as performed during screening, treatment week 4, week 8, week 12, week 16, week 20, week 23, visits every 3 weeks if extended, end of OR Early withdrawal from treatment, post treatment follow-up week 4, and follow-up week 12.	10
11	1.2 Synopsis Flowchart	1.2 Synopsis Flowchart: *Captured in flowchart/table: Post Treatment Follow-up* 78 weeks	1.2 Synopsis Flowchart: *Captured in flowchart/table: Post Treatment Follow-up* 78 weeks/EW	11
12	1.2 Synopsis Flowchart	a. **Screening:** Screening assessments can occur on different days within nine days prior to Day 1 dosing. If a participant fails screening, a full re-screen may occur at a later date post discussion with Medical Monitor. All screening procedures must be repeated at re-screen visit, with the exception of the slit lamp examination, which can be used from a previous screening if within 8 weeks of anticipated randomization.	a. **Screening:** Screening assessments can occur on different days within 14 days prior to Day 1 dosing (randomization). If a participant fails screening, a full re-screen may occur at a later date. All screening procedures must be repeated at re-screen visit, with the exception of the slit lamp examination, which can be used from a previous screening if within 8 weeks of anticipated randomization.	1 and 5
13	1.2 Synopsis Flowchart	b. **Visit Schedule:** If the duration of treatment is extended due to dose pauses (e.g., takes participant 35 weeks to complete 26 weeks of treatment) or positive week 16 culture, unscheduled visits should be added every 3 weeks (+/- 7 days). End of treatment visit (final treatment visit) should be done within 7 days AFTER the last dose of IMP. 1. If participant completes treatment at week 26, end of treatment visit should be done within 7 days after last dose of week 26. 2. If participant completes 26 weeks of therapy at week 33 due to pauses, visits can be done at weeks 26, 29 and 33 (3 weeks from week 29 plus 7-day window). The week 33 visit would be the end of treatment visit and should be completed within 7 days after last dose. 3. If participant completes treatment at week 39 due to post treatment extension related to positive culture at week 16, visits can be completed at weeks 26, 29, 32, 35 and 39 (3	b. **Visit Schedule:** If the duration of treatment is extended (see section 6.3, Treatment Modifications for details), unscheduled visits should be added every 3 weeks (+/- 7 days). 1. End of treatment visit (final treatment visit) should be done within 7 days AFTER the last dose of IMP. 2. If participant completes 26 weeks of therapy at week 33 due to full regimen pauses, an EXAMPLE of visit scheduling would be weeks 26, 29 and 33 (3 weeks from week 29 plus 7-day window). In this scenario, the week 33 visit would be the end of treatment visit and should be completed within 7 days after last dose. 3. If participant completes treatment at week 39 due to treatment extension, an example of visit scheduling would be visits at weeks 26, 29, 32, 35 and 39/End of treatment (3 weeks plus 7-day window). 4. Follow-up visits should be scheduled based on timing of end of last dose of IMP (e.g., 4-week	12

		weeks plus 7-day window), visit at week 39 would be the end of treatment visit. 4. Follow-up visits should be scheduled based on timing of end of treatment/early withdrawal from treatment (e.g., 4-week follow-up to be scheduled 4 weeks after last dose of IMP).	follow-up to be scheduled 4 weeks after last dose of IMP).	
14	1.2 Synopsis Flowchart	c. **Follow-up Visits Early Withdrawal Participants**: Once a participant has been discontinued from treatment, they will be **required to attend an Early Withdrawal visit**. If participant: 1. Received/took ≤ 14 doses, no additional follow-up visits are required. 2. Received 15 or more doses, follow-up after end of treatment at week 12, week 26 (if not already performed) and week 78 are required. The week 12 visit will only require the ophthalmologic exams. The week 26 and 78 follow-up visits will be to collect Serious Adverse Event (SAE) information (including verification of survival) and patient reported TB outcome information only and may be telephonic, a home or a site visit. This includes participants who are *withdrawn from the trial due to meeting the treatment failure endpoint*. Participant may need to return for visits to collect sputum samples to determine outcome status as per section "r".	c. **Follow-up Visits Early Withdrawal Participants: Once** a participant has been discontinued, they will be **required to attend an Early Withdrawal visit**. If participant: 1. Received/took ≤ 14 doses, no additional follow-up visits are required. 2. Received 15 or more doses and is withdrawn during treatment, follow-up after end of treatment/EW visit at week 12, week 26 (if not already performed) and week 78 are required. The follow-up week 12 visit will only require the ophthalmologic exams. The week 26 and 78 follow-up visits will be to collect Serious Adverse Event (SAE) information (including verification of survival) and patient reported TB outcome information only and may be telephonic, a home or a site visit. This includes participants who are *withdrawn from the trial due to meeting the treatment failure endpoint*. Participant may need to return for visits to collect sputum samples to determine outcome status. 3. For participants who are withdrawn during post treatment follow-up, site should perform study procedures required for week 78 post treatment follow-up visit. If participant will not return for visit, site should obtain information on SAE and patient reported TB outcome as noted above in no 2.	11
15	1.2 Synopsis Flowchart	e. **HIV testing:** If HIV status is a confirmed known positive, repeated HIV test is not needed provided that a documented HIV test result (ELISA, Western Blot or Electro-Chemiluminescence) is available. If HIV status is unknown or suspected negative, HIV test will be requested. If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated if documentation of testing method and negative HIV results can be provided. Repeated	e. **HIV testing:** If HIV status is a confirmed known positive, repeated HIV test is not needed provided that a documented HIV test result (ELISA, Western Blot or Electro-Chemiluminescence) is available. If HIV status is unknown or suspected negative, HIV test will be requested. If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated if documentation of testing method and negative HIV results can be provided. Repeated HIV testing,	13

		HIV testing, during the Screening period is permitted for indeterminate HIV results.	during the Screening period is permitted for indeterminate HIV results.	
16	1.2 Synopsis Flowchart	f. **CD4 count and viral load:** For all HIV-positive participants, viral load and CD4 at screening, CD4 only tested at end of treatment or early withdrawal.	f. **CD4 count and viral load:** Required for all HIV-positive participants. Viral load and CD4 required at screening, CD4 will be tested at end of treatment or early withdrawal from treatment visit.	14
17	1.2 Synopsis Flowchart	g. **Chest X-Ray:** A chest x-ray (digital image) within one month prior to screening, will be obtained and read locally by Investigator or designee. Digital images will be provided to Sponsor, this process will be described in a separate document, the Radiology Manual.	g. **Chest X-Ray:** A chest x-ray (digital image) within 6 months one month prior to or at screening, will be obtained and read locally by Investigator or designee. Digital images will be provided to Sponsor, this process will be described in a separate document, the Radiology Manual	15
18	1.2 Synopsis Flowchart	k. **Single 12-Lead ECG**: To every extent possible, should be performed at approximately the same time of day (+/- 1 hours) and in the same fed/fasted state throughout the trial (e.g. 4 hours after lunch). Central ECG analysis will be performed.	k. **Single 12-Lead ECG:** When possible, should be performed at approximately the same time of day (+/- 1 hours) and in the same fed/fasted state throughout the trial (e.g. 4 hours after lunch). Central ECG analysis will be performed. Central reading of screening results will be used to determine eligibility.	16
19	1. 2 Synopsis Flowchart	l. **Physical Exam:** Limited Physical exams should include weight and a gross neurological, pulmonary, cardiovascular and abdominal exam.	l. **Physical Exam:** Limited Physical exams should include weight and a gross neurological, pulmonary, cardiovascular and abdominal exam. Height will only be collected as part of full exam at screening.	17
20	1.2 Synopsis Flowchart	**m. Safety Laboratory Assessments:** The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed: 1. Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count). 2. Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO2, creatine phosphokinase (CPK). 3. Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium,	**m. Safety Laboratory Assessments/Urine Drug Screen**: The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed: • Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count). • Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose,	18

		urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator. 4. Urine Drug Screen: Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at Screening only. Investigator to utilize to determine whether participant meets Exclusion criteria 5. Positive results will not automatically exclude participant from the trial.	bicarbonate/CO2, creatine phosphokinase (CPK). GGT will be done at screening. • When managing participants with elevated liver enzymes at an unscheduled visit, the Investigator can request additional tests, in addition to the repeated LFT [e.g. Gamma Glutamyl Transferase, screening for hepatitis A, B, C; to assist in ruling out other causes of abnormal liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection). • Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis. • Urine Drug Screen: Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at Screening only. Investigator to utilize to determine whether participant meets Exclusion criteria 2. Positive results will not automatically exclude participant from the trial.	
21	1.2 Synopsis Flowchart	**o. PK Sampling:** Specific PK blood draws as follows: 1. Day 1; pre-dose (within 2 hours prior to dosing) 2. Week 2: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose 3. Week 8: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose 4. Week 12: pre-dose (within 2 hours prior to dosing) 5. Week 20 or at early withdrawal if prior to week 20: pre-dose (within 2 hours prior to dosing) and 2–3 hours post-dose. When participant is discharged and seen as an outpatient, site should make every effort to collect 6-8 hour samples at weeks 8 and when operationally and logistically feasible. If dosing of any component of the regimen has been paused, and no dose of some component is given on the scheduled day of sampling, then defer the sampling until the dosing of all components has been resumed, even if some component is at a different dose level, and bring the ~~patient~~ back for sampling on an unscheduled visit when all	**o. PK Sampling:** The dates and times of the two doses of IMP taken prior to all pre-dose PK samples will be collected in the eCRF. Specific PK blood draws will be obtained as follows **(pre-dose to be done after ECGs):** 1. Day 1; pre-dose (within 2 hours prior to dosing) 2. Week 2: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose 3. Week 8: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose 4. Week 12: pre-dose (within 2 hours prior to dosing) 5. Week 20 or at early withdrawal if prior to week 20: pre-dose (within 2 hours prior to dosing) and 2–3 hours post-dose • When participant is discharged and seen as an outpatient, site should make every effort to collect 6-8	19

<table>
<tr>
<td></td>
<td></td>
<td>components are administered. If the site has permanently discontinued linezolid due to toxicity, sampling should be done on a day when the bedaquiline and pretomanid are dosed.</td>
<td>hour sample at week 8 when operationally and logistically feasible.
• Hospitalization information (e.g. discharge date) will be collected in the eCRF.
• If the full regimen or linezolid is paused, PK sampling should be delayed until full regimen or linezolid are resumed.
• PK sampling should be completed even if the participant's linezolid dose has been lowered or Linezolid has been permanently discontinued.
• Sites may bring participant back at a scheduled or unscheduled visit (can occur outside of visit windows) to collect PKs to ensure draw is done when IMP is administered.</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>1.2 Synopsis Flowchart</td>
<td>
r. Sputum Sampling:
<table>
<tr><th rowspan="2">Visit</th><th colspan="2">Sample</th><th colspan="6">Tests</th></tr>
<tr><th>EMS*</th><th>Spot</th><th>AFB Smear microscopy</th><th>MGIT culture, speciation</th><th>Molecular testing</th><th>MIC: B, Pa, L</th><th>Liquid DST</th><th>Genotyping</th></tr>
<tr><td>Screening (Day -9 to -1)</td><td></td><td>●●</td><td>S</td><td>S</td><td>S</td><td></td><td></td><td></td></tr>
<tr><td>Baseline (Day 1) or screen - wk4 if baseline negative or contaminated</td><td>●</td><td>●</td><td></td><td>S</td><td></td><td>C</td><td>C</td><td>C</td></tr>
<tr><td>All Visits Post Baseline</td><td>●</td><td>●</td><td></td><td>S</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Positive for MTB at/after EoT</td><td colspan="2">●</td><td></td><td>S</td><td>S</td><td>C</td><td>C</td><td>C</td></tr>
</table>
C – Central laboratory (specialized facility)
S – Study Laboratory (facility that receives samples directly from site)

SPUTUM SAMPLES GENERAL: If EMS is not available, site should make every attempt to collect two spot samples at least 30 minutes apart.

BASELINE: If available, site will request pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to
</td>
<td>
r. Sputum Sampling:
<table>
<tr><th rowspan="2">Visit</th><th colspan="3">Sample</th><th colspan="8">Tests</th></tr>
<tr><th>EMS</th><th>SPOT</th><th>ISOLATE*</th><th>AFB Smear microscopy</th><th>MGIT culture, speciation</th><th>Molecular testing</th><th>MIC: B, Pa, L</th><th>MGIT DST</th><th>Genotyping</th><th>Extended DST (paired with baseline isolate)</th></tr>
<tr><td>Screening (Day -14 to -1)</td><td></td><td>●
●</td><td></td><td>S</td><td>S</td><td>S</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Baseline (Day 1) or 1st positive between screening and wk4 if Day 1 negative or contaminated</td><td></td><td></td><td>●</td><td></td><td></td><td></td><td>C</td><td>C</td><td>C</td><td>L (when applicable, with isolate below)</td></tr>
<tr><td>All Visits Post Screening</td><td>●</td><td>●</td><td></td><td></td><td>S</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1st positive for MTB at/after week 16 for participant not responding to therapy and/or 1st positive during follow-up for potential new infection</td><td></td><td></td><td>●</td><td></td><td></td><td>S</td><td>C</td><td>C</td><td>C</td><td>L</td></tr>
</table>
C – Central Mycobacteriology Laboratory (specialized facility)
S – Study Mycobacteriology Laboratory (facility that receives sputum samples directly from site)

L – Lab (as applicable per Country) that performs extended DST beyond panel at Central lab
*Preferably from EMS Sample when available. Alternate isolate can be requested if initial one is contaminated, or the test needs to be repeated.
</td>
<td>5 and 20</td>
</tr>
</table>

		be subcultured and shipped to the study lab from the applicable lab for relevant participants with no positive cultures from screening through week 4 (with consent). Samples should be stored according to the applicable lab procedures until shipment to the designated study lab. Included with each shipment will be a copy of the applicable lab reports and all participant identifying information redacted and a completed shipment inventory form with appropriate participant trial identifiers. Details on how samples will be packed and shipped will be provided in the lab manual. **POSITIVE MTB AT/AFTER END OF TREATMENT**: Only one isolate (preferably from EMS) should be shipped. Second isolate may be requested if first is contaminated. **MOLECULAR TESTING**: • At Screening: GeneXpert, Hain MTBDR*plus* or equivalent to determine MTB complex and R resistance. • Positive MTB at/after end of treatment: Hain MTBDR*plus* and HainMTBR*sl* **LIQUID DST**: for SIRE, Z and second line anti-TB drugs, including but not limited to FQ and injectables. **STORAGE**: MTB isolates from all positive cultures to be stored at the study laboratory until trial closure for the applicable study tests. The extracted MTB DNA from the applicable baseline and follow-up isolates will also be stored at the central lab for potential further work to validate new assay tools for 5 years after trial closure. **CENTRAL LAB**: Results from testing at Central myco lab (MIC, DST and genotyping) will not routinely be provided to sites. In the event of participant relapse/failure, Sponsor will provide available results to the site in order to inform appropriate participant treatment. **UNSCHEDULED VISITS**: If cultures of both spot sputum samples are contaminated *at the following visits*, or if necessary in order to help define a participant's outcome status/assess culture status during follow-up, the participant should return for an unscheduled visit(s) to give additional samples or to document the participant is not able to produce sputum:	**SPUTUM SAMPLES GENERAL**: If EMS (early morning sputum) is not available, site should make every attempt to collect two spot samples at least 30 minutes apart. **PRE-SCREENING SAMPLES**: If consent granted by participant, and when applicable, site can request pre-screening culture/isolate/DNA from current TB diagnosis/disease course to be sub-cultured and shipped and/or tested: • at the study lab if/when those samples could support inclusion in trial. • at the study/central lab for relevant participants with no baseline (no positive cultures from screening through week 4). **MOLECULAR TESTING**: • At Screening: GeneXpert, Hain MTBDR*plus* or equivalent to determine MTB complex and Rifampicin resistance. • Positive MTB at/after week 16: Hain MTBDR*plus* and HainMTBR*sl* **LIQUID DST**: for SIRE, Z and second line anti-TB drugs, including but not limited to fluoroquinolones and injectables. **STORAGE: MTB** isolates from all positive cultures to be stored at the study laboratory until trial closure for the applicable study tests. The cultures as well as the extracted MTB DNA from the applicable baseline and follow-up isolates will also be stored at the central lab for potential further work to validate new assay tools for 5 years after trial closure. **CENTRAL LAB**: Results from testing at central lab (MIC, DST and genotyping) will not routinely be provided to sites. In the event that results are necessary to determine appropriate participant treatment, Sponsor will provide available drug susceptibility results to the site. Genotyping will be performed on paired DNA extracts to determine if the participant was a relapse or reinfection (See SAP for details).	

		• End of treatment visit; • Week 26 post treatment follow-up visit; • Post treatment follow-up visits from week 8 through week 65 (in addition to week 26 follow-up); • End of Follow-up Period (week 78 post treatment completion visit); • Early Withdrawal (if applicable). <u>At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, need to confirm whether the participant has:</u> • At least two sequential negative sputum culture results; or • At least two sequential positive sputum culture results; or • Has been unable to produce sputum after documentation of at least two negative sputum cultures with no intervening positive and are clinically asymptomatic. If they do not fall into one of these categories, site should continue to collect sputum samples x 2 (one Early Morning and one Spot at the research site or 2 spots samples at least 30 minutes apart, under the coaching and observation of the trial staff) at a minimum of 7 days or more apart until they fall into one of the above categories. If in any of the above scenarios the Investigator is unsure of the outcome, the Investigator must contact the Sponsor Medical Monitor to discuss and agree on how the patient is to be handled.	**EXTENDED DST TESTING:** Paired isolates from baseline and at/after week 16 should be shipped to a relevant lab (as applicable/available per Country) for DST extending beyond the panel of drugs tested at the central lab. Extended results will be provided to the site to inform appropriate participant treatment.	
23	4.1 Summary of Trial Design	Enrolment will stop when 120 XDR-TB participants are randomized. Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive web response system (IXRS) which will utilize a dynamic randomization system using minimization with a random element to allocate participants evenly across the arms by HIV status and type of TB after they have given written, informed consent and met all eligibility criteria.	Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive voice and web response system (IXRS) which will utilize a randomization system using stratification with a random element to allocate participants evenly across the arms by HIV status and type of TB after they have given written, informed consent and met all eligibility criteria.	2
24	4.1 Summary of Trial Design	Each participant will receive 26 weeks of treatment. If participant's week 16 sample remains culture positive, Investigator may consider option to extend current treatment to 39 weeks, in consultation with the Sponsor	Each participant will receive 26 weeks of treatment. If participant's sputum sample is culture positive between the week 16 and week 26 treatment visits and their clinical condition suggests they may have	4 and 5

		Medical Monitor. Participants will be followed for 78 weeks after end of treatment.	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 with and approved by the Sponsor Medical Monitor before implementation. Participants will be followed for 78 weeks after end of treatment.	
25	5.1 Inclusion Criteria	3. HIV testing (if an HIV test was performed within 1 month prior to screening, it should not be repeated as long as documentation can be provided [ELISA and/or Western Blot]. If HIV status is a confirmed known positive, repeated HIV test is not needed provided documentation is available	3. HIV testing (if an HIV test was performed within 1 month prior to screening, it should not be repeated as long as a documented result can be provided [ELISA and/or Western Blot and/or Electro-Chemiluminescence]. If HIV status is a confirmed known positive, repeated HIV test is not needed if ELISA and/or Western Blot and/or Electro-Chemiluminescence documentation of positive is available.	13
26	5.1 Inclusion Criteria	5. Participants with one of the following pulmonary TB conditions: a. XDR-TB with i. A documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and: ii. historical documented resistance to isoniazid, rifamycins, a fluoroquinolone **AND** an injectable during the current TB diagnosis/disease course; b. Pre-XDR-TB with i. A documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based molecular test within 3 months prior to or at screening and; ii. historical documented resistance to isoniazid, rifamycins, and to a fluoroquinolone **OR** an injectable during the current TB diagnosis/disease course. c. MDR-TB with i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected results within	5. Participants with one of the following pulmonary TB conditions: a. XDR-TB with i. A documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and: ii. documented resistance to rifamycins, a fluoroquinolone **AND** an injectable during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid); b. Pre-XDR-TB with i. A documented culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to or at screening and; ii. documented resistance to rifamycins, and to a fluoroquinolone **OR** an injectable during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid); c. MDR-TB with	21

		3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and; ii. historical—documented resistance to isoniazid and rifamycins during the current TB diagnosis/disease course; iii. with documented non-response to treatment with the best available regimen for 6 months or more prior to enrolment who in the opinion of the Investigator have been adherent to treatment and will be adherent to study regimen. d. MDR-TB with i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and: ii. historical documented resistance to isoniazid and rifamycins during the current TB diagnosis/disease course and; iii. who are unable to continue second line drug regimen due to a documented intolerance to: a. PAS, ethionamide, aminoglycosides or fluoroquinolones or ; b. Current treatment not listed above that renders participant eligible for the study in the Investigator's opinion.	i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected results within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and; ii. documented resistance to rifamycins during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid) and; iii. with documented non-response to treatment with the best available regimen for 6 months or more prior to enrolment who in the opinion of the Investigator have been adherent to treatment and will be adherent to study regimen. d. MDR-TB with i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and: ii. documented resistance rifamycins during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid) and; iii. who are unable to continue second line drug regimen due to a documented intolerance to: a. PAS, ethionamide, aminoglycosides or fluoroquinolones or ; b. Current treatment not listed above that renders participant eligible for the study in the Investigator's opinion.	
27	5.1 Inclusion Criteria	Chest X-Ray within 1 months prior at screening, obtained and read locally by investigator or designee with results consistent with pulmonary TB in the opinion of the Investigator.	Chest X-Ray within 6 months prior to or at screening, obtained and read locally by investigator or designee with results consistent with pulmonary TB in the opinion of the Investigator.	15
28	5.1 Inclusion Criteria	Contraception: 7. Be of non-childbearing potential or using effective methods of birth control, as defined below:	Contraception: 7. Be of non-childbearing potential **or** using effective methods of birth control, as defined below:	22

		Non-childbearing potential: a. Participant - not heterosexually active or practices sexual abstinence; or b. Female participant/sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or c. Male participant/sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to Screening. **Effective birth control methods:** A double contraceptive method should be used as follows: a. Double barrier method which can include any 2 of the following: a male condom, diaphragm, cervical cap, or female condom (male and female condoms should not be used together); or b. Barrier method (one of the above) combined with hormone-based contraceptives or an intra-uterine device for the female participant/partner; And are willing to continue practicing birth control methods throughout treatment and for 6 months (both male and female participants~~)~~ after the last dose of study medication. **Note:** Hormone based contraception alone may not be reliable when taking IMP; therefore, hormone based contraceptives alone cannot be used by female participants or female partners of male participants to prevent pregnancy.	**Non-childbearing potential:** a. Participant - not heterosexually active or practices sexual abstinence; or b. Female participant or male participant's female sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or c. Male participant or female participant's male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening. **Effective birth control methods:** a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female participant; c. Male participant's female sexual partner: Double barrier method or hormone based contraceptives or an intra-uterine device for the female partner. And are willing to continue practicing birth control methods throughout treatment and for 6 months female participants and 12 weeks (male participants) after the last dose of study medication. **Note:** Hormone based contraception alone may not be reliable when taking IMP; therefore, hormone-based contraceptives alone cannot be used by female participants to prevent pregnancy.	
29	5.2 Exclusion Criteria	7. TB infection with known resistance to pretomanid, delamanid, linezolid or bedaquiline.	7. TB infection with historic DST or MIC results with values suggesting likely known resistance to pretomanid, delamanid, linezolid or bedaquiline; the Sponsor Medical Monitor should be consulted to help interpret any available historic results.	5 and 23

30	5.2 Exclusion Criteria	10. Participants with any of the following at Screening: • QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with the Sponsor Medical Monitor before enrolment. • Heart failure • A personal or family history of congenital QT prolongation • A history of or known, untreated, ongoing hypothyroidism • A history of or ongoing bradyarrhythmia • A history of Torsade de Pointe	10. Participants with any of the following at Screening: • QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with and approved by the Sponsor Medical Monitor before enrolment. (Per measurements and reading done from screening central ECG.) • Heart failure • A personal or family history of congenital QT prolongation • A history of or known, untreated, ongoing hypothyroidism • A history of or ongoing bradyarrhythmia • A history of Torsade de Pointe	5 and 16
31	5.2 Exclusion Criteria	<u>Previous and Concomitant Therapy</u> 13. Concomitant use of Monoamine Oxidase Inhibitors (MAOIs) or prior use within 2 weeks of randomization. 14. Concomitant use of serotonergic antidepressants or prior use within 3 days of randomization if Investigator foresees potential risks for serotonin syndrome when combined with linezolid. 15. Concomitant use of any drug known to prolong QTc interval (including, but not limited to, amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, fluoroquinolones, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). 16. Concomitant use of any drug known to induce myelosuppression. 17. Concomitant use of any drugs or substances known to be strong inhibitors or inducers of cytochrome P450 enzymes (including but not limited to efavirenz, quinidine, tyramine, ketoconazole, fluconazole, testosterone, quinine, gestodene, metyrapone, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafylline, cimetidine, dextromethorphan). Exceptions may include use of lopinavir/ritonavir regimen as noted in section 5.3.3. 18. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP. 19. Participants with an existing TB diagnosis (a diagnosis made > 4 weeks prior to screening) and HIV co-infection, must have been on an ART for at least 4 weeks prior to screening.	<u>Previous and Concomitant Therapy</u> 13. Known (during screening) requirement for future Concomitant (during treatment) use of any prohibited and/or avoided medications noted in section 5.3. 14. Prior use of Monoamine Oxidase Inhibitors (MAOIs) within 2 weeks of randomization. 15. Prior use of serotonergic antidepressants within 3 days of randomization if Investigator foresees potential risks for serotonin syndrome when combined with linezolid. 16. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP. 17. Participants with newly diagnosed tuberculosis and HIV that require initiation of appropriate HIV therapy before participant has received at least 2 weeks of an anti-tuberculosis regimen. 18. HIV infected participants with planned continued use of zidovudine, stavudine or didanosine. The antiretroviral therapy (ART) booster cobicistat should not be used. Please reference restrictions Section 5.3.3 Antiretroviral Therapy, for guidance on ART treatment during the treatment period.	24

		20. Participants with newly diagnosed tuberculosis and HIV may be enrolled provided that appropriate HIV therapy will not be initiated until participant has received at least 2 weeks of study medication. 21. HIV infected participants: the following antiretroviral therapies should not be used: zidovudine, stavudine, didanosine. The antiretroviral therapy (ART) booster cobicistat should not be used. Please reference restrictions Section 5.3.3 Antiretroviral Therapy, for guidance on ART treatment during the treatment period.		
32	5.2 Exclusion Criteria	<u>Diagnostic and Laboratory Abnormalities</u> 22. Participants with any of the following toxicities at Screening (labs may be repeated during screening period) as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November 2007): a. Viral load >1000 IU/ml (Unless newly diagnosed HIV and not yet on ART who otherwise qualify for participation); b. CD4+ count < 100 cells/µL (HIV positive participants); c. Serum potassium less than the lower limit of normal for the laboratory; d. Hemoglobin < 9.0 g/dL; e. Platelets <100,000/mm3; f. Absolute neutrophil count (ANC) < 1500/ mm3; g. Aspartate aminotransferase (AST) • Grade 3 or greater (> 3.0 x ULN) to be excluded; • Results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor h. Alanine aminotransferase • Grade 3 or greater (> 3.0 x ULN) to be excluded; • Results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor medical monitor; i. Total bilirubin • greater than 1.5 x ULN to be excluded; • 1-1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor j. Direct bilirubin • Greater than ULN to be excluded	<u>Diagnostic and Laboratory Abnormalities</u> 19. Participants with any of the following toxicities at Screening (labs may be repeated during screening period) as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November 2007): a. Viral load >1000 copies/mL (Unless newly diagnosed HIV and not yet on ART who otherwise qualify for participation); b. CD4+ count < 100 cells/µL (HIV positive participants); c. Serum potassium less than the lower limit of normal for the laboratory; d. Hemoglobin < 9.0 g/dL or < 90 g/L; e. Platelets <100,000/mm3 or < 100 x 10^9/L; f. Absolute neutrophil count (ANC) < 1500/ mm3 or < 1.5 x 10^9/L; g. Aspartate aminotransferase (AST) • Grade 3 or greater (> 3.0 x ULN) to be excluded; • Results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor h. Alanine aminotransferase • Grade 3 or greater (> 3.0 x ULN) to be excluded; • Results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor medical monitor; i. Total bilirubin • greater than 1.5 x ULN to be excluded; • 1-1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor j. Direct bilirubin • Greater than ULN to be excluded	25

		k. Serum creatinine level greater than 1.5 times upper limit of normal l. Albumin <3.0 mg/dl	k. Serum creatinine level greater than 1.5 times upper limit of normal l. Albumin <3.0 g/dl or < 30 g/L	
33	5.2 Exclusion Criteria		No protocol waivers will be granted by the TB Alliance.	26
34	5.3.1 Prior and Concomitant Medications and Other Treatments	The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP: • Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole. • Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid) • Concomitant use of any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). • Treatment with fluoroquinolones (as they are known prolong QTc), are strongly discouraged in the trial. They should only be used to treat intercurrent non-TB infections and if the benefit of treatment outweighs the risk of prolonged QTc. • Concomitant use of any drug known to induce myelosuppression. • The systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolids such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 3 consecutive days; • The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone.	The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion: • Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole. • Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid) The following concomitant medications should be avoided during the treatment period and during the 14 days after treatment completion to avoid possible drug interactions with the IMP. Use of any of the following must be discussed and approved by the Sponsor Medical Monitor prior to use: • Concomitant /use of any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). • Treatment with fluoroquinolones (as they are known prolong QTc), are strongly discouraged in the trial. They should only be used to treat intercurrent non-TB infections and if the benefit of treatment outweighs the risk of prolonged QTc.	5 and 27

		Concomitant use of serotonergic antidepressants should be avoided if possible as participants on these agents and linezolid are at risk for serotonin syndrome. Caution should be used in treating diabetic patients receiving insulin or oral hypoglycemic agents as cases have been reported of hypoglycemic reactions when patients on these agents have been treated with linezolid. Any drug known to be hepatotoxic should be avoided as much as possible during screening and throughout the treatment period (including but not limited to acetaminophen/paracetamol, acetazolamide, allopurinol, amiodarone, amitriptyline, amoxicillin, amprenavir, atorvastatin, augmentin/co-amoxiclav, azathioprine, baclofen, bumetanide, captopril, carbamazepine, celecoxib, chlorpromazine, chlorpromazine, clindamycin, clopidogrel, contraceptive pill, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).	• Concomitant use of any drug known to induce significant myelosuppression • The systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolids such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 3 consecutive days; • The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone. • Concomitant use of serotonergic antidepressants should be avoided if possible as participants on these agents and linezolid are at risk for serotonin syndrome. • Caution should be used in treating diabetic patients receiving insulin or oral hypoglycemic agents as cases have been reported of hypoglycemic reactions when patients on these agents have been treated with linezolid. The following concomitant medications which are known to be hepatotoxic should be avoided as much as possible during screening and throughout the treatment period. If there are concerns about the co-administration of hepatoxic drugs, discussion with the Sponsor Medical Monitor is encouraged (including but not limited to acetaminophen/paracetamol, acetazolamide, allopurinol, amiodarone, amitriptyline, amoxicillin, amprenavir, atorvastatin, augmentin/co-amoxiclav, azathioprine, baclofen, bumetanide, captopril, carbamazepine, celecoxib, chlorpromazine, chlorpromazine, clindamycin, clopidogrel, contraceptive pill, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin,	

			sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).	
35	5.4 Trial Discontinuation and Visits	5.4 Discontinuation from Treatment/Trial The following may result in the discontinuation of trial treatment; • Pregnancy; • Investigator considers it for safety reasons in the best interest of the participant that he/she be discontinued. This could include, but is not limited to: o Adverse event(s); o Myco testing results from baseline (Screening through Week 4) indicate sensitivity to isoniazid and/or rifamycins; o Myco testing results from baseline (Screening through Week 4) indicate resistance to bedaquiline, pretomanid or linezolid; o In the opinion of the investigator, fails to comply with the protocol, including non-compliance to IMP. All participants who discontinue trial treatment (but have not withdrawn consent) and received at least one dose of IMP will be requested to return for an early withdrawal visit and applicable safety Follow Up visits, as per flow chart (Section 1.2). In the event of the following, participants will be and/or are considered discontinued from the trial and no additional follow-up visits are required: • Withdrawal of informed consent; • Lost to follow-up; • Termination of the trial by the sponsor.	5.4 Trial Discontinuation and Visits 5.4.1 Treatment Discontinuation and Early Withdrawal A participant must be withdrawn from the trial due to the following; • Pregnancy;(unless female post visit for end of treatment/early withdrawal from treatment); • Investigator considers it for safety reasons in the best interest of the participant that he/she be discontinued, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment. • At the specific request of the sponsor or termination of the trial by Sponsor; • Lost to follow-up • In the opinion of the investigator, fails to comply with the protocol, including non-compliance to IMP. Participants may be withdrawn from the trial based on the following. The specific situation should be discussed with the Medical Monitor before withdrawing the patient. o Myco testing results from baseline (Screening through Week 4) indicate sensitivity to rifamycins; o Myco testing results from baseline (Screening through Week 4) with MICs that indicate likely resistance to bedaquiline, pretomanid or linezolid;	21 and 28

		A participant may discontinue from the trial at any time at his/her request (withdrawal of consent).	All participants who discontinue trial treatment (but have not withdrawn consent) and received at least one dose of IMP will be requested to return for an early withdrawal visit and applicable safety Follow Up visits, as per flow chart (Section 1.2). A participant may discontinue from the trial at any time at his/her request (withdrawal of consent) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral compliance or administrative issues. When a participant withdraws consent from the trial, no additional follow-up visits will be performed.	
36	5.4.2 Early Withdrawal Follow-up		**5.4.2 Early Withdrawal Follow-up** In case of early withdrawal during the treatment or follow-up period, all efforts shall be made to complete the Early Withdrawal assessments. Once a participant has been withdrawn early from the trial, they will be requested to attend follow-up visits as described in Table 9: **Table X: Follow-up Visits Required for Early Withdrawal Participants** **Treatment Duration at EW visit** / **Ophthalmology Examination at EW[a]** / **Ophthalmology Examination 12 week Post treatment follow-up visit[a]** / **26 Week Post Treatment Follow-up Visit** / **78 Week Post Treatment Follow-up Visit** **≤ 14 days** / NA / NA / NA / NA **15 days to ≤ 12 weeks** / NA / Required / Required / Required **> 12 weeks** / Required / Required / Required, if not already performed / Required a. If an additional visit is required for an ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 12 weeks after the EWD visit date. The 26 and 78 week post treatment follow-up visits will be performed to collect SAE information (including verification of survival) and participant reported TB outcome information. This visit may be telephonic, a home or a site visit.	10 and 28

37	5.4.3 Unscheduled Visits		**5.4.3 Unscheduled Visits** Any visit which is conducted in addition to those required by the Synopsis Flow Chart and Procedures, should be considered unscheduled regardless of the reason for the visit. The assessments which are undertaken as part of an Unscheduled visit should be as clinically indicated. The following situation/s require an unscheduled visit/s: • If cultures of both spot sputum samples are contaminated at the following visits, or if necessary in order to help define a participant's outcome status/assess culture status during follow-up, the participant should return for an unscheduled visit(s) to give additional samples or to document the participant is not able to produce sputum: • End of treatment visit; • Week 26 post treatment follow-up visit; • Post treatment follow-up visits from week 8 through week 65 (in addition to week 26 follow-up); • End of Follow-up Period (week 78 post treatment completion visit); • Early Withdrawal (if applicable). • At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, and to determine whether the participant has: • At least two sequential negative sputum culture results; or • At least two sequential positive sputum culture results; or • Has been unable to produce sputum after documentation of at least two negative sputum cultures with no intervening positive and are clinically asymptomatic. If they **do not** fall into one of the above categories, site should continue to collect sputum samples x 2 (one early morning and one spot at the research site or 2 spots samples at least 30 minutes apart, under the coaching and observation of the trial staff) at a	28

			minimum of 7 days or more apart until they fall into one of the above categories. **5.4.4 Lost to Follow-up** Every reasonable attempt must be made to minimise Lost-to-Follow-up (LTFU) participants. A minimum of three contact attempts (telephonic/home visit) will be made for participants who do not arrive for their scheduled trial visits. If these attempts are unsuccessful the participant will be considered LTFU. All attempts to contact the participant must be clearly documented in the participant's source documents	
38	5.4.4 Early Withdrawal due to TB	**Discontinuation from treatment due to TB**	**5.4.5 Early Withdrawal due to TB**	28
39	6.1 IMP Administration	Table 9: Investigational Medicinal Product Details	Table **10**: Investigational Medicinal Product Details	6

Treatment Group	Active and Placebo
Linezolid 1200 mg daily for 26 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. • 2 linezolid 600 mg active tablets once daily for 26 weeks • 1 placebo linezolid 600 mg tablet once daily for 26 weeks
Linezolid 1200 mg daily for 9 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 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
Linezolid 600 mg daily for 26 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once 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

Treatment Group	Active and Placebo
Linezolid 1200 mg daily for 26 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. • 2 linezolid 600 mg active tablets once daily for 26 weeks • ½ (one half) placebo linezolid tablet once daily for 26 weeks
Linezolid 1200 mg daily for 9 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. **Weeks 1-9** • 2 linezolid 600 mg active tablets once daily for 9 weeks • ½ (one half) placebo linezolid tablet once daily for 9 weeks **Weeks 10-26** • 2 placebo linezolid tablets once daily for 17 weeks • ½ (one half) placebo linezolid tablet once daily for 17 weeks
Linezolid 600 mg daily for 26 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. • 1 linezolid 600 mg active tablet once daily for 26 weeks • 1 placebo linezolid tablet once daily for 26 weeks

			• 1 placebo linezolid 300 mg half tablet once daily for 26 weeks		• ½ (one half) placebo linezolid tablet once daily for 26 weeks
		Linezolid 600 mg daily for 9 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 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	Linezolid 600 mg daily for 9 weeks	• 2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus; • 1 pretomanid 200 mg active tablet once daily for 26 weeks. **Weeks 1-9** • 1 linezolid 600 mg active tablet once daily for 9 weeks • 1 placebo linezolid tablet for 9 weeks • ½ (one half) placebo linezolid tablet once daily for 9 weeks **Weeks 10-26** • 2 placebo linezolid tablets once daily for 17 weeks • ½ (one half) placebo linezolid tablet once daily for 17 weeks
40	6.2 Participant Compliance	Additionally, participant cards will be checked for unused tablets in the blisters.		Additionally, participant cards/bottles will be checked for unused tablets at each visit during the treatment period.	29
41	6.3 Treatment Modification(s)	All dose modifications should be discussed with the Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation. All dose modifications should be discussed with the Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation. In the event of linezolid specific toxicities, the following should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol:		All treatment modifications should be discussed with the Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation. In the event of linezolid specific toxicities, the following should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol **(8.3)**: • Blinded one step reductions (maximum 2 steps) in the dose of linezolid managed by the IXRS as per instructions in pharmacy manual and/or IXRS user manual	4, 5, and 7

		• Blinded one step reductions (maximum 3 steps) in the dose of linezolid (1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or 300mg QD to placebo) managed by the IWRS as per instructions in pharmacy manual and/or IWRS user manual. • Temporary pause of linezolid due to a linezolid-specific toxicity should be considered and implemented per guidance in the monitoring and safety for specific toxicities section of protocol. • Permanent discontinuation of linezolid. Participants experiencing suspected drug related toxicities due to other drugs in the regimen (B-Pa), the full regimen may be halted for up to 35 consecutive days. Pauses of the full regimen must not exceed 8 weeks (56 days) cumulatively. If participant's week 16 sample remains culture positive, Investigator may consider option to extend current treatment to 39 weeks, in consultation with the Sponsor Medical Monitor. When treatment extended due to a positive culture at week 16, pauses of the full regimen must not exceed 13 weeks (91 days) cumulatively. When total of missed dosing days and/or pauses is greater than 7 days, additional make-up doses should be dispensed/treatment extended. At no time should the participant be treated with a single agent.	○ 1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or; ○ 600 mg QD to 300 mg QD, 300mg QD to placebo). • Temporary pause of linezolid • Permanent discontinuation of linezolid. • Participants who have a linezolid reduction can go back to a higher dose (1 step or 2 steps) post discussion with and approval by the Sponsor Medical Monitor. Participants experiencing suspected drug related toxicities due to other drugs in the regimen (B-Pa), the full regimen may be halted for up to 35 consecutive days. Interruptions/pauses of the full regimen must not exceed 8 weeks (56 days) cumulatively. If participant's sample is culture positive between the week 16 and week 26 treatment visits and their clinical condition suggests they may have an ingoing TB infection, Investigator may consider the option to extend treatment to which the participant is randomized 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 with and approved by the Sponsor Medical Monitor before implementation. When treatment extended to 39 weeks, pauses of the full regimen must not exceed 13 weeks (91 days) cumulatively. When the total of missed dosing days of the prescribed regimen and/or pauses is greater than 7 days, the same number of missed doses should be dispensed/treatment extended to make up for the total missed doses. At no time should the participant be treated with a single agent.	

			Every effort should be made for participants to receive a total of at least 9 weeks of linezolid, even if pauses are required.	

42	6.4 IMP Packaging and Labelling	The complete formulations of the IMP bedaquiline and pretomanid are found in the respective Investigator Brochures. The complete formulations of linezolid are found in the Package Inserts
		
		The IMP will be packaged as follows:
		
		• Bedaquiline: Bottles containing:
		  ○ 200 mg QD dose- 28 tablets- bedaquiline 100 mg
		  ○ 100mg QD dose- 14 tablets- bedaquiline 100 mg
		• Pretomanid: Blister card containing 14 tablets- pretomanid 200 mg
		• Linezolid: Blister Card containing 7 days of dosing as follows:
		  ○ 1200 mg QD Dose
		  ▪ 2 blister strips of 7 tablets each (14 tablets) containing active linezolid 600 mg
		  ▪ 1 blister strip of 7 half tablets containing placebo linezolid 300 mg
		  ○ 600 mg QD Dose:
		  ▪ 1 blister strip of 7 tablets containing active linezolid 600 mg
		  ▪ 1 blister strip of 7 tablets containing placebo linezolid 600 mg
		  ▪ 1 blister strip of 7 half tablets containing placebo linezolid 300 mg
		  ○ 300 mg Dose (for reductions): 1 row of 7 active 600 mg tablets for 7 days of dosing
		  ▪ 2 blister strips of 7 tablets each (14 tablets) containing placebo linezolid 600 mg
		  ▪ 1 blister strip of 7 half tablets containing active linezolid 300 mg
		  ○ Placebo Linezolid Dose: 2 rows of 7 placebo 600 mg tablets for 7 days of dosing
		  ▪ 2 blister strips of 7 tablets each (14 tablets) containing placebo linezolid 600 mg
			The complete formulations of the IMP bedaquiline and pretomanid are found in the respective Investigator Brochures. The complete formulations of linezolid are found in the Package Inserts.
			
			The IMP will be packaged as follows:
			
			• Bedaquiline: Bottles containing:
			  ○ 200 mg QD dose- 28 tablets- bedaquiline 100 mg
			  ○ 100mg QD dose- 14 tablets- bedaquiline 100 mg
			• Pretomanid: Blister card containing 14 tablets- pretomanid 200 mg
			• Linezolid: Blister Card containing 7 days of dosing as follows:
			  ○ 1200 mg QD Dose
			  ▪ 2 blister strips of 7 tablets each (14 tablets) containing active linezolid 600 mg
			  ▪ 1 blister strip of 7 half tablets containing placebo linezolid
			  ○ 600 mg QD Dose:
			  ▪ 1 blister strip of 7 tablets containing active linezolid 600 mg
			  ▪ 1 blister strip of 7 tablets containing placebo linezolid
			  ▪ 1 blister strip of 7 half tablets containing placebo linezolid
			  ○ 300 mg Dose (for reductions):
			  ▪ 2 blister strips of 7 tablets each (14 tablets) containing placebo linezolid
			  ▪ 1 blister strip of 7 half tablets containing active linezolid 300 mg
			  ○ Placebo Linezolid Dose:
			  ▪ 2 blister strips of 7 tablets each (14 tablets) containing placebo linezolid
				6

		▪ 1 blister strip of 7 half tablets containing placebo linezolid 300 mg	▪ 1 blister strip of 7 half tablets containing placebo linezolid	
43	6.4 IMP Packaging and Labelling	The packaging of each bottle/blister card will be labelled with, at a minimum, the following information: • Name, address and telephone number of Sponsor.	The packaging of each bottle/blister card will be labelled with, at a minimum, the following information: • Name of Sponsor.	30
44	6.5 Method of Treatment Assignment	Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive web response system (IWRS) which will utilize a dynamic randomization system using minimization with a random element to allocate participants evenly across the arms by HIV status and type of TB. Information & directions will be provided to each site via the IWRS user manual.	Participants will be randomized to one of the four regimens in a 1:1:1:1 ratio, using an interactive web/voice response system (IXRS) which will utilize a randomization system using stratification with a random element to allocate participants evenly across the arms by HIV status and type of TB. Information & directions will be provided to each site via the IXRS user manual.	3
45	6.6 Blinding and Procedures for Breaking the Blind	The blind must not be broken except in the case of a medical emergency, where treatment of the participant is influenced by the knowledge of what dose and duration of linezolid the participant is receiving. It is requested that the Investigator make every effort to contact the Sponsors 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 SAEs.	The blind must not be broken except in the case of a medical emergency, where treatment of the participant is influenced by the knowledge of what dose and duration of linezolid the participant is receiving. The investigator should discuss breaking the blind with the Sponsor Medical Monitor (or designee) prior to breaking the blind unless knowledge of treatment arm is required urgently for a safety concern. The Sponsor Medical Monitor should be informed of the blind break within 24 hours if not discussed prior. IXRS will be programmed with blind-breaking instructions, described in the user manual. The Sponsor reserves the right to break the blind to fulfil any regulatory requirements regarding reporting of SAEs. If a participant is unblinded they are not required to be withdrawn from the study.	31
46	7.1 Demographic and Background Variables	• Clinically significant medical and treatment history (including past and current TB diagnosis and smoking)	• Clinically significant medical and treatment history (including past and current TB diagnosis, alcohol use and smoking)	32
47	7.1 Demographic and Background Variables	• Serology: HIV and CD4 count.	• Serology: HIV, CD4 count and viral load. • If an HIV test was performed within 1 month prior to trial start, it should not be repeated as long as	33

		• If an HIV test was performed within 1 month prior to trial start, it should not be repeated as long as documentation of results can be provided (ELISA and/or Western Blot).	documentation of results can be provided (ELISA and/or Western Blot and/or Electro-Chemiluminescence).	
48	7.1 Demographic and Background Variables	*N/A- bullet point did not exist in version 1.0*	• Concomitant medications	34
49	7.2 Efficacy Variables and procedures	TB Symptoms Profile: • The TB Symptoms Profile (Appendix 7) will record participants' ratings of the severity of common TB symptoms. Patient Reported Health Status Variables and Procedures: • The Patient Reported Health Status variables will be collected at the time points described in the trial flow chart. Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire (Appendix 5). This descriptive system consists of five health-related quality of life dimensions, each of which will be recorded using five levels of severity. Methodology: The Patient Reported Health Status methodology and requirements will be described in a separate document/guideline which will be provided prior to the trial start.	TB Symptoms Profile: • The TB Symptoms Profile (found in the Subject Questionnaires Guideline) will record participants' ratings of the severity of common TB symptoms. Patient Reported Health Status Variables and Procedures: • The Patient Reported Health Status variables will be collected at the time points described in the trial flow chart. Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire (found in the Subject Questionnaires Guideline). This descriptive system consists of five health-related quality of life dimensions, each of which will be recorded using five levels of severity. Methodology: The Patient Reported Health Status methodology and requirements will be described in a separate document/guideline which will be provided prior to the trial start.	35
50	7.3 Safety and Tolerability Assessments	• Brief Peripheral Neuropathy Screen (Appendix 6) will record ratings.	• Brief peripheral neuropathy screen (found in the Subject Questionnaires Guideline) will record ratings.	35
51	7.5 Mycobacteriology Characterization Variable and Procedures	The following Mycobacterial Characterization variables will be collected: Positive Culture (for MTB) from: • Day 1 or if Day 1 is not available, first positive between screening through Week 4; • Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be subcultured and shipped to the central from the applicable lab for relevant participants/with no positive cultures from screening through week 4 and appropriate consent	The following Mycobacterial Characterization variables will be collected: Positive Culture (for MTB) from: • Day 1 or if Day 1 is not available, first positive between Screening through Week 4; • If consent granted, and when applicable, Pre-screening culture/isolate to be sub cultured and shipped and/or tested: o At the study lab if/when samples could support inclusion in the trial	35

		• When applicable, end of treatment or visits with positive cultures during post-treatment follow-up.	○ To the study/central lab for relevant participants/with no baseline (positive cultures from screening through Week 4) • When applicable, 1st positive for MTB at/after week 16 for participant not responding to therapy and/or 1st positive during follow-up for potential new infection.	
52	8.2.1 Follow up of Adverse Events	Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In these cases follow-up will be the responsibility of the treating physician. However, this will have to be agreed upon with the Sponsor Medical Monitor.	Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In these cases, follow-up will be the responsibility of the treating physician. If there is uncertainty, Investigator can discuss appropriate follow-up with the Sponsor Medical Monitor.	5
53	8.3 Monitoring for Specific Toxicities	Monitoring for specific toxicities is based upon target organs as defined in preclinical toxicity studies Investigator's Brochures and Package Inserts. AEs still ongoing at the end of treatment in the trial will be followed until satisfactory clinical resolution or stabilization or until the end of the follow-up period and until all queries on these AEs have been resolved. Grade 3 and grade 4 laboratory abnormalities and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.	Monitoring for specific toxicities is based upon target organs as defined in preclinical toxicity studies Investigator's Brochures(5,6) and Package Inserts.(24,25,26,27) Please reference section 6.3. Treatment Modifications, which notes that all treatment modifications should be discussed with Sponsor Medical Monitor prior to implementation, unless a pause or dose reduction is required urgently for a safety concern. The Medical Monitor should be informed within 24 hours of the change if not discussed prior to implementation. AEs still ongoing at the end of treatment in the trial will be followed until satisfactory clinical resolution or stabilization or until the end of the follow-up period and until all queries on these AEs have been resolved. Grade 3 and grade 4 laboratory abnormalities and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization. Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In these cases follow-up will be the responsibility of the treating physician. If there is uncertainty, Investigator can discuss appropriate follow-up with the Sponsor Medical Monitor.	5
54	8.3.2 ALT, AST and Alkaline Phosphatase elevations	The Investigator should refer to Appendix 8 – Liver Toxicity Management to appropriately manage the participant for clinically significant elevations of AST, ALT or Alkaline Phosphatase.	The Investigator should refer to Appendix 6 – Liver Toxicity Management and to the ZeNix Hepatotoxicity Management Guideline	36

			to appropriately manage the participant for clinically significant elevations of AST, ALT or Alkaline Phosphatase.	
55	11.3 Protocol Deviations	It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to Sponsor/designee. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.	It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to Sponsor/designee. Protocol deviations must be sent to the local IRB and Health Authority per their guidelines. The site PI/all study staff is responsible for knowing and adhering to their IRB and Health Authority (as required) requirements	37

TB ALLIANCE

Protocol Amendment or Administrative Change

Trial Number	Trial Name
NC-007	ZeNix

X Protocol Amendment Number 2.0, Dated 10/MAR/2020
☐ Protocol Administrative Change Number _ _, Dated _ _/_ _ _/_ _ _ _

Summary - Protocol section changed		Does amendment / administrative change affect any of the elements listed?	
		YES	NO
A	Purpose of trial	☐	X
B	Design of trial	☐	X
C	Informed consent	☐	X
D	Recruitment procedure	☐	X
E	Measures of efficacy	☐	X
F	Schedule of samples	☐	X
G	Addition or deletion of tests or measures	☐	X
H	Number of participants	☐	X
I	Age range of participants	☐	X
J	Inclusion criteria	☐	X
K	Exclusion criteria	☐	X
L	Safety monitoring	☐	X
M	Duration of exposure to the investigational medicinal product(s)	☐	X
N	Change of posology of the investigational medicinal product(s)	☐	X
O	Change of comparator	☐	X
P	Statistical analysis	X	☐

Protocol Amendment or Administrative Change

Reasons for Protocol Amendment or Administrative Change:

1	Addition of planned unblinded (in aggregate) Analysis Post 26 weeks of treatment completion
2	Updated timing of trial in synopsis
3	Updated TB Alliance logo on first page
4	
5	

#	Section	Previous Text Version 2.0, dated 13-Jun-18	Amended Text Version 3.0, dated 10-Mar-20 Additional text - bold font. Deleted text – strike-through.	Reason for Change Insert reason # from table above
1	Title Page	TB ALLIANCE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT	TB Alliance	3
2	Synopsis	~3.5 Years (An enrolment period of at least 18 months plus 14 days pre-treatment plus 6 months treatment period plus 18 months post treatment follow-up).	~~3.5~~ **4** Years (An enrolment period of ~~at least 18~~ **approximately 24** months plus 14 days pre-treatment plus 6 months treatment period plus 18 months post treatment follow-up).	2

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**Protocol Amendment
or Administrative Change**

3	6.6	The blind must not be broken except in the case of a medical emergency, where treatment of the participant is influenced by the knowledge of what dose and duration of linezolid the participant is receiving. The investigator should discuss breaking the blind with the Sponsor Medical Monitor (or designee) prior to breaking the blind unless knowledge of treatment arm is required urgently for a safety concern. The Sponsor Medical Monitor should be informed of the blind break within 24 hours if not discussed prior. IXRS will be programmed with blind-breaking instructions, described in the user manual. The Sponsor reserves the right to break the blind to fulfil any regulatory requirements regarding reporting of SAEs. If a participant is unblinded, they are not required to be withdrawn from the study. In the absence of any medical emergencies requiring a blind break, the blind for all participants 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.	The blind **for a participant** must not be broken **by the site or sponsor** except in the case of a medical emergency, where treatment of ~~the~~ **a** participant is influenced by the knowledge of what dose and duration of linezolid the participant is receiving. The investigator should discuss breaking the blind with the Sponsor Medical Monitor (or designee) prior to breaking the blind unless knowledge of treatment arm is required urgently for a safety concern. The Sponsor Medical Monitor should be informed of the blind break within 24 hours if not discussed prior. IXRS will be programmed with blind-breaking instructions, described in the user manual. The Sponsor reserves the right to break the blind to fulfil any regulatory requirements regarding reporting of SAEs. If a participant is unblinded, they are not required to be withdrawn from the study. ~~In the absence of any medical emergencies requiring a blind break, the blind for all participants 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.~~ **There will be three unblinded analyses which will contain results by linezolid treatment group in aggregate (see section 9.3). The first**	1

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**Protocol Amendment
or Administrative Change**

#	Section	Previous Text Version 2.0, dated 13-Jun-18	Amended Text Version 3.0, dated 10-Mar-20 Additional text - bold font. Deleted text – strike-through.	Reason for Change Insert reason # from table above
			analysis will be after all participants have completed 26 weeks of treatment and here sites, participants, and Sponsor staff will not be unblinded to individual linezolid treatment information. A limited number of statisticians will have access to individual linezolid treatment assignments. **The blind for all individual participants will be broken for the primary endpoint analysis (the second unblinded analysis) once all clinical data and outcome parameters have been captured, no more data queries are pending, and the statistical analysis plan has been finalized. The third analysis will occur when all participants have completed 78 weeks of follow-up after end of treatment.**	

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**Protocol Amendment
or Administrative Change**

4	9.3	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 participant has completed 26 weeks of follow-up after end of treatment). There will be two database locks, data analyses and trial reports generated for this trial: 1. When all participants have completed 26 weeks of follow-up after end of treatment. 2. When all participants have completed 78 weeks of follow-up from after end of treatment.	No formal interim analyses are planned. **However, there will be three planned unblinded analyses which will contain results by linezolid treatment group in aggregate as described below. The first analysis will be done after all participants have completed 26 weeks of treatment. The analysis will be on treatment safety events (mainly the specific toxicities described in section 8.3) and time to culture conversion (on treatment). The sites, participants, and Sponsor staff will not be unblinded to individual linezolid treatment information. A limited number of statisticians will have access to individual linezolid treatment assignments.** **The blind for all individual participants will be broken for the primary endpoint analysis (the second unblinded analysis) once all clinical data and outcome parameters for the primary endpoint have been captured, no more data queries are pending, and the statistical analysis plan has been updated accordingly.** ~~Primary analysis will be performed on the 26 week follow-up data (after end of treatment when the last randomized participant has completed 26 weeks of follow-up after end of treatment).~~	1

TB ALLIANCE

Protocol Amendment
or Administrative Change

#	Section	Previous Text Version 2.0, dated 13-Jun-18	Amended Text Version 3.0, dated 10-Mar-20 Additional text - bold font. Deleted text – strike-through.	Reason for Change Insert reason # from table above
			There will be ~~two~~ **three** database **locks for the three planned unblinded** data analyses ~~and trial reports~~ generated for this trial: 1. **When all participants have completed 26 weeks of treatment** ~~1.~~ **2.** When all participants have completed 26 weeks of follow-up after end of treatment. ~~2.~~ **3.** When all participants have completed 78 weeks of follow-up from after end of treatment.	

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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Author position:	Statistician, UCL
Author signature:	DocuSigned by: Signer Name: Stella Fabiane Signing Reason: I am the author of this document Signing Time: January 29, 2021 | 1:33 AM PST E763EB6C01F74696B5E745F2C4F19DEE
Date:	January 29, 2021 | 1:33 AM PST
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Approval position:	Vice President and Chief Medical Officer, TB Alliance
Approval signature:	DocuSigned by: Signer Name: Dan Everitt Signing Reason: I approve this document Signing Time: January 27, 2021 | 9:01 AM EST 32534894D9294A59B14B10FC37E90452
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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 participantscomplete 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 §8.3.1) 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 §2.1for 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 §**Error! Reference source not found.**) 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 §3.5), 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 §2.3.1.4) 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 §8.2.7).

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

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Electronic Record and Signature Disclosure: Accepted: 5/1/2018 9:27:51 AM ID: 72950d47-8d7f-4a28-adf2-3f2fb8898ab7		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

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	1/27/2021 8:59:48 AM
Certified Delivered	Security Checked	1/29/2021 4:32:47 AM
Signing Complete	Security Checked	1/29/2021 4:33:14 AM
Completed	Security Checked	1/29/2021 4:33:14 AM

Payment Events	Status	Timestamps

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You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
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To advise Global Alliance for TB Drug Development-Sub Account of your new e-mail address
To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to us at christi.baine@tballiance.org and in the body of such request you must state: your previous e-mail address, your new e-mail address. We do not require any other information from you to change your email address..
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Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will

have the right to withdraw your consent.

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MRC Clinical Trials Unit

ZeNix

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).

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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.

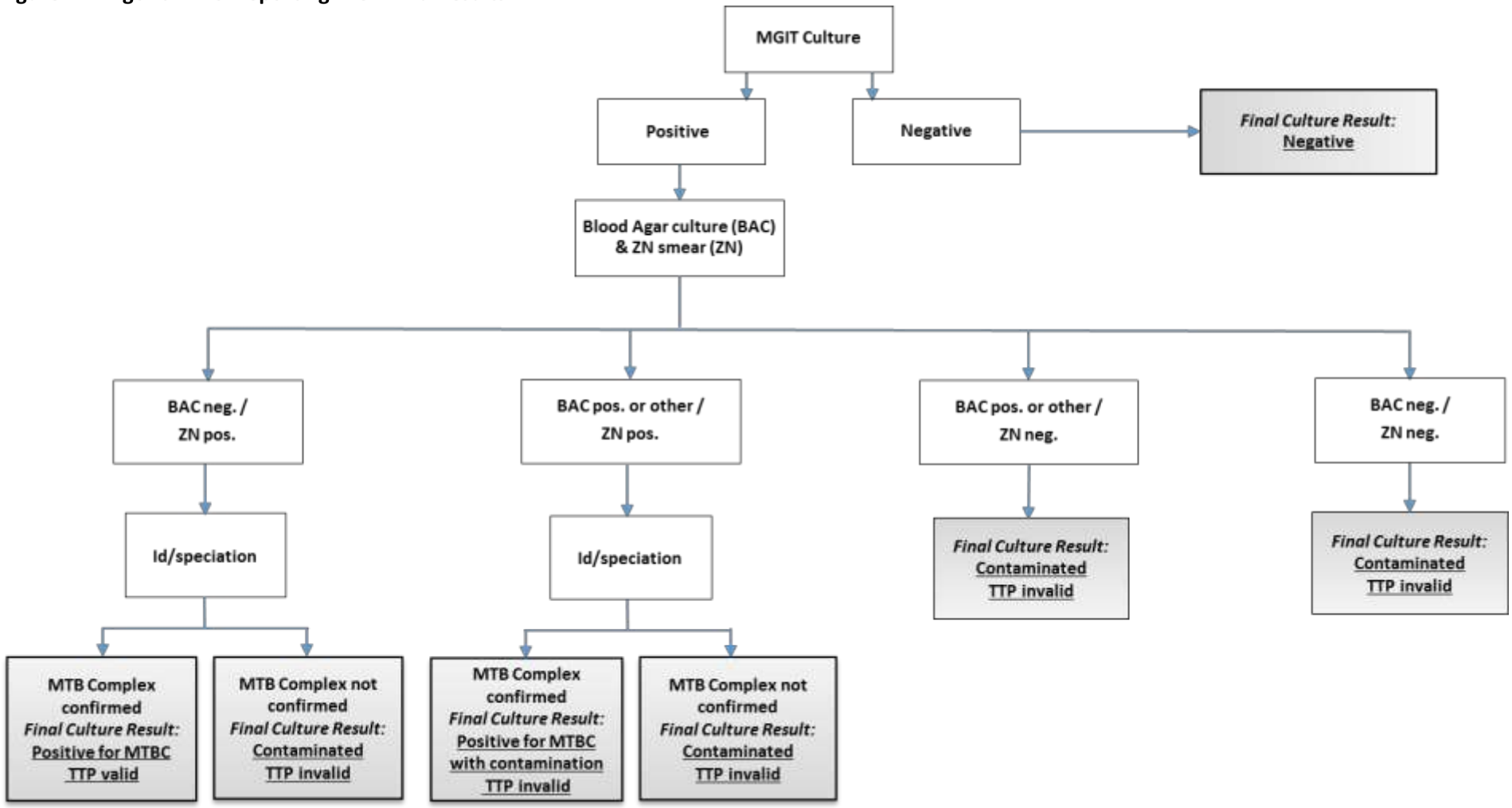
13 Reasons for treatment failure as determined by the local PI

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.

Summary of changes from ZeNix efficacy SAP v1.0 to v3.0

1. ADDITION: Incorporation of safety analyses and reordering of sections accordingly

2. ADDITION: Secondary Efficacy endpoints
   Analysis of change in BMI from baseline

3. MODIFICATION: Baseline period definition for patients who are never culture positive during the baseline period: day 1 through week 4

4. ADDITION: Safety population:
   "all randomized 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."

5. MODIFICATION: Long-term follow-up analyses corrected to 18 months after end of treatment

6. ADDITION: Week 26 analysis:
   "culture conversion status at week 26, 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."

7. ADDITION: Sub-group analysis:
   "primary endpoint on the MITT analysis population by baseline resistance to Bedaquiline"

8. ADDITION: Minimum Inhibitory Concentrations analyses:
   "Minimum Inhibitory Concentrations (MICs) for all three drugs will be tabulated separately. Baseline will be cross tabulated against all post-week 16 visits, for all patients that have them measured. For descriptive purposes only."