## **16.1** Trial Information

#### 16.1.1 Protocol and Protocol Amendments

- NC-007 Protocol, Version 1.0, 23FEB2017
- NC-007 Protocol Amendment, Version 1.0, RUS/BEL, 28FEB2017
- NC-007 Protocol Amendment, Version 1.0, RUS, 15NOV2017
- NC-007 Protocol, Version 2.0, 13JUN2018
- NC-007 Protocol Amendment Summary of Changes, 13JUN2018
- NC-007 Protocol Amendment, Version 2.0, RUS, 13JUN2018
- NC-007 Protocol Amendment, Version 1.0, MDA, 13JUN2018
- NC-007 Protocol Amendment, Version 2.0 Summary of Changes, 10MAR2020
- NC-007 Protocol, Version 3.0, 10MAR2020
- NC-007 Protocol Amendment, Version 2.0, MDA, 10MAR2020
- NC-007 Protocol Amendment, Version 3.0, RUS, 18MAR2020





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





#### **PROTOCOL SIGNATURE PAGE**

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

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

Protocol Date: 22FEB2017

Protocol Name: ZeNix

SPONSOR

I agree to the terms of this trial protocol.

Signature of Senior Medical Officer

0

Date

#### LEAD INVESTIGATOR

Daniel Everitt. MD

Printed Name

40 Wall Street, 24th Floor New York, NY 10005 Phone 646-616-8671 email: daniel.everitt@tballiance.org

I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations.

Signatúre

Froncesca Conrolu

Printed Name

201 e

Date

CONFIDENTIAL Page 2 of 99





## PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

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

Protocol Date: 22FEB2017 Protocol Name: ZeNix

I hereby confirm that I have read the above protocol and agree to conduct this clinical trial as outlined in the above protocol. I will provide copies of the protocol and access to all the information required to conduct the clinical trial according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature

Printed Name

Date

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#### 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	Al anine aminoTransferase
AREDS2	Age Related Eve Disease Scale 2
ART	Anti-Retroviral Therapy
AST	ASpartate aminoTransferase
AT	AminoTransferase
	Area Under Curve over a dosing interval
	Rodaquilino
	Bedy Mean Index
DIVII	body Mass muex
upini DNO	Deals per minute
BPINS	Bhei Penpheral Neuropathy Scale
CK(-MB)	Creatine Kinase(-MB isoenzyme)
C <sub>(max), (min)</sub>	plasma Concentration (maximum), (minimum)
	Carbon diOxide
CPK	Creatine PhosphoKinase
CS	Clinically Significant
Ctrough	plasma Concentration <sub>trough</sub>
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-Glutamvl Transferase
GMR	Geometric Mean Ratio
H	Isoniazid
hERG	Human <i>Ether-à-go-go</i> Related Gene
HIV	Human Immunodeficiency Virus
HR7F	Isoniazid Rifampicin Pyrazinamide Ethambutol
ICF	Informed Consent Form

IMPInvestigational Medicinal ProductIRBInstitutional Review BoardIUATLDInternational Union Against Tuberculosis and Lung Disea	
IRB Institutional Review Board IUATLD International Union Against Tuberculosis and Lung Disea	
IUATLD International Union Against Tuberculosis and Lung Disea	
	se
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	
ma/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	
OD Once Daily	
R Rifampicin	
S Streptomycin	
SAF Serious Adverse Event	
SAP Statistical Analysis Plan	
SIRE Streptomycin Isoniazid Rifampicin Ethambutol	
SOC System Organ Class	
TB Tuberculosis	
TBI serum Total Bil irubin	
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	
LII N Lipper Limit of Normal	
WBC White Blood Cell	
WHO World Health Organization	
WHO World Health Organization XDR-TB eXtensively Drug Resistant Tuberculosis	
<ul><li>WHO World Health Organization</li><li>XDR-TB eXtensively Drug Resistant Tuberculosis</li><li>ug(/dl) micrograms (per deciliter)</li></ul>	

## 1 Synopsis

## 1.1 Synopsis Summary

Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished	bedaguiline (B), pretomanid (Pa) and linezolid (L)
Products:	
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.
	Dertisinents will have a severaging period of up to 0 days and will be readersized.
	to receive one of the 4 active treatment arms. Derticipants will be randomized
	to nee 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-1B participants are randomized. Sponsor may consider replacement
	of late screen failure and un-assessable (as detailed in the statistical analysis
Tost product Doso and	The test product will be supplied as:
Mode of Administration	he bodaguiling 100 mg tablets
mode of Administration.	protomonid 200 mg tablets
	<ul> <li>pretornanid 200 mg tablets</li> <li>linezolid (scored) 600 mg tablets</li> </ul>
	<ul> <li>Illezolid (scoled) 000 mg tablets</li> <li>placeba lipozolid (scored) 600 mg tablets</li> </ul>
	<ul> <li>placebo illezolid (scoled) 600 mg lablets</li> <li>linezolid helf tablet (pro out) 200 mg</li> </ul>
	<ul> <li>Illiezoliu hali tablet (pie-cut) 500 mg</li> <li>nlaesolo linozolid half tablet (pro out) 200 mg</li> </ul>
	placebo linezolid nali tablet (pre-cut) 300 mg
	Linezolid treatment will be supplied as 2 rows of full tablets and one row of
	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
	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.
	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 class of water and

Name of	Global Alliance for TB Drug Development
Sponsor/Company	had a willing (D) materia (Da) and line wallid (L)
Products:	bedaquiline (B), pretomanid (Pa) and linezolid (L)
Floducis.	Participants will receive the following:
	Farticipants will receive the following.
	• bedaquinite 200 mg once daily for 8 weeks their 100 mg once daily for 18 weeks plus:
	<ul> <li>pretomanid 200 mg once daily for 26 weeks plus:</li> </ul>
	<ul> <li>pretomania 200 mg once dany for 20 weeks plus,</li> <li>Linozolid, participante will be randomly assigned to receive one of the</li> </ul>
	Ellezono- participants will be randomly assigned to receive one of the following four line zolid treatment desea 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
	2 linezolid 600 mg active tablets once daily for 9 weeks
	<ul> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> </ul>
	Weeks 10-26
	<ul> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> </ul>
	• 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 dally for 26 weeks
	Linezolid 600 mg daily for 9 weeks
	Weeks 1-9
	<ul> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> </ul>
	1 placebo linezolid 600 mg tablet for 9 weeks
	1 placebo linezolid 300 mg half tablet once daily for 9 weeks
	Weeks 10-26
	<ul> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> </ul>
	• 1 placebo linezolid 300 mg half tablet once daily for 17 weeks
	Ireatment 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 line relid encoding to visiting the following should be say it and
	In the event of linezolia specific toxicities, the following should be considered
	and implemented per guidance in the monitoring and safety for specific
	rocaive a total of 0 wooks of line rolid, even if neuross are required:
	Plinded one stop reductions (maximum 2 stops) in the does of line reductions
	(1200 mg OD to 600 mg OD 600 mg OD to 300 mg OD or 300 mg OD to
	nlacebo) managed by the IWRS as per instructions in pharmacy manual
	and/or IWRS user manual.

Name of	Clobal Alliance for TR Drug Development
	Gibbal Allance for TB Drug Development
Sponsor/Company	
Name of Finished	bedaguiline (B), pretomanid (Pa) and linezolid (L)
Products:	
	<ul> <li>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.</li> <li>Permanent discontinuation of linezolid.</li> </ul>
	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	Global Alliance for TB Drug Development								
Sponsor/Company									
Name of Finished bedaquiline (B), pretomanid (Pa) and linezolid (L)									
Products:									
Pharmacokinetics (PK) and	Pharmacokinetics/Pharmacodynamics (PK/PD):								
Plasma concentrations of be	edaquiline and its M2, pretomanid and linezolid_from sparse sampling (see Table								
1.2) will be measured and us	sed 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	e 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.,									
Ctrough, Cmax, AUC, Cmean, 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 7.2.

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

#### **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 <sup>a</sup>	a Treatment S				y m	Post Treatment Folic					)w-I	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	Visits every 3 weeks if extended due t IMP pause or culture (+) at week 16 <sup>b</sup>	End of OR Ear Withdrawal frc Treatment <sup>c</sup>	4 weeks	8 weeks	12 weeks	26 weeks	39 weeks	52 weeks	65 weeks	78 weeks
Visit Window <sup>q</sup>	N/A		T	T	+/	/- 3 d	ays	1					+/- 5	5 days	S			+/- 7 days	Post last dose IMP +7 days			+/-	- 14	l da	ys		
Informed Consent	Х																										
Demography	Х																										
Med/Trtmnt/Smoking History	Х																										
Inclusion/Exclusion <sup>d</sup>	Х	Х																									
Randomization		Х																									
Karnofsky Assessment	Х																				1 1					ļ	
HIV Status <sup>e</sup>	Х																										
CD4 Count and Viral Load <sup>f</sup>	Х																		Х								
Chest X-Ray <sup>g</sup>	Х																		Х								
Urine Pregnancy Test <sup>h</sup>	Х	Х								Х				Х					Х								
TB Symptoms Profile	Х									Х				Х					Х				Х		Х		Х
Patient Reported Health Status	Х									Х				Х					Х				Х		Х		Х
Slit Lamp Exam <sup>i</sup>	Х				1			1											Xi			Х					
Ophthalmic Exam <sup>j</sup>	Х				1	Х		1		Х		Х		Х		Х		Х	Х	Х							
Vital Signs	Х	Х	Х	Х	1	Х		Х		Х		Х		Х		Х		Х	Х			Х	Х	Х	Х	Х	Х
Single 12-LeadECG <sup>k</sup>	Х	Х	Х		1	Х		1		Х				Х					Х							$\neg$	
Limited Physical Exam <sup>1</sup>			Х	Х		Х		Х		Х		Х		Х		Х		Х				Х	Х	Х	Х	X	Х
Full Physical Exam	Х	Х																	Х	1		, I					
Laboratory Safety Tests (includes Full Blood Count) <sup>m</sup>	х	х	х	х	х	х		х		х		х		х		х	х	х	х								
Full Blood Count							Х		Х		Х		Х		Х												
Con Meds	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Adverse Events	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Study Medication/Compliance <sup>n</sup>		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х							$\neg$	
PK Sampling <sup>o</sup>		Х		Х	1		1	1		Х	1	Х			1	Х	1		Xo								
Early Morning & Spot Sputum <sup>r</sup>	Х	Х	Х	X	X	Х	1	X		X	X	Х		Х		X	Х	Х	Х	X	Х	X	Х	Х	х	Х	Х
Peripheral Neuropathy							1				1											$\overline{}$				÷	
Assessment	X					X	1			X		X		X		X	X	X	Х			Х	Х		X		X
Investigator Assessment <sup>p</sup>					1		1	1									1						Х			-	Х

# 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 < 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.
  - For participants who receive 15 days to < 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.
- I. **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).
  - 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:

	San	nple	Tests									
Visit	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		С	С	С				
All Visits Post Baseline	•	•		S								
Positive for MTB at/after EoT				S	S	С	С	С				

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*s*/

**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).

At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, need to confirm 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 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.<sup>(43)</sup> 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.<sup>(28)</sup> In another report from South Africa of 114 patients with XDR-TB, 22% completed treatment successfully.<sup>(21)</sup> 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.<sup>(42)</sup> A meta-analysis of 397 patients with XDR-TB from 31 centers, with HIV coinfection <10%, reported 32% treatment success.<sup>(17)</sup> Reports of the outcome of XDR-TB treatment from Peru (43 patients, 42% treatment success)<sup>(2)</sup> and Ukraine (114 patients, 22% treatment success)<sup>(11)</sup> 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%.<sup>(29)</sup> 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.<sup>(43)</sup> 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<sup>(9)</sup> 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).<sup>(1)</sup>

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 bedaguiline 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 bedaguiline 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.

#### Efficacy of bedaquiline 200 mg daily dose vs the marketed dosing scheme over 8 weeks

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.

#### Safety of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.

#### Pharmacokinetics of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.<sup>(14)</sup> 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<sub>max</sub>, 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 bedaguiline 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 relapsefree 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<sup>TM</sup>. 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. Drugdrug 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 multipledose efavirenz (EFV) resulted in approximately a 20% decrease in the AUC<sub>inf</sub> of bedaquiline with no alteration in the C<sub>max</sub>. Modeling based on the data from this DDI study predicts average steadystate concentrations of bedaquiline and M2 to be reduced by 52% with chronic co-administration of bedaquiline and EFV.<sup>(5)</sup>

#### Safety of Bedaquiline

The Investigator's Brochure for bedaquiline provides detailed safety information.<sup>5</sup>

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.

Adverse Drug Reactions (ADRs) in the Controlled Studies (C208 Stage 1 and Stage 2)										
ADR (Grouped term), n (%) Frequency N=102 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	a Common 6 (5.9) 12 (11									
Hepatobiliary disorders										
Transaminases increased <sup>a</sup>	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)							

#### Table 1: ADRs C208 Stage 1 and Stage 2

<sup>a.</sup> 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.<sup>(7)</sup>

## 2.2.2 Pretomanid

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

#### 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,  $\leq 0.015$  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. <sup>(6)</sup>

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), <sup>(33)</sup> 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.<sup>(12,13)</sup>

#### 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.<sup>(18,19,20,36,40)</sup> 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.<sup>(6)</sup>

## 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  $\geq$ 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  $\geq$ 100 mg/kg/day, and early deaths occurred at doses  $\geq$ 500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at  $\geq$ 450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at  $\leq$ 30 mg/kg/day in rats and  $\leq$ 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.

<u>Drug interaction with midazolam:</u> 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<sub>0-t</sub>), and area under the curve extrapolated to infinity (AUC<sub>0-inf</sub>). The C<sub>max</sub> 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<sub>max</sub>) and half-life (t<sub>1/2</sub>) 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<sub>0-24h</sub>) was 0.65, and the GMR for the trough concentration (C<sub>min</sub>) 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 PKevaluable participants, the GMR for C<sub>max</sub> was 0.87, for AUC<sub>0-24h</sub> was 0.83, and for C<sub>min</sub> 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<sub>max</sub>, AUC<sub>0-24h</sub>, and C<sub>min</sub> 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<sub>0-24h</sub>), 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 <sup>(4)</sup> (Figure 2).





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<sup>(6)</sup> 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.<sup>(23,24,26)</sup> Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism.<sup>(8)</sup> 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.<sup>(9)</sup>

Preclinical *in vitro* data shows linezolid is active against MTB, including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1  $\mu$ g/mL.<sup>(38)</sup> 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.<sup>(36)</sup> (Table 3, below)

#### Table 3: Murine Lung CFU counts during Treatment with Linezolid

•	•											
	Mean lung log₁₀ CFU count (± S.D.) at:											
Regimen	D0	Month 1	Month 2	Month 3								
Untreated	6.17 <u>+</u> 0.27	6.47 <u>+</u> 0.06										
2RHZ/4R H		3.47 <u>+</u> 0.37	1.59 <u>+</u> 0.25	0.50 <u>+</u> 0.51								
L		4.97 <u>+</u> 0.26										

Monotherapy versus Standard Therapy

In recent years linezolid has been used to treat patients with MDR<sup>(28)</sup> 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.<sup>(41)</sup> 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.<sup>(9, 27, 34)</sup> 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.<sup>(9)</sup> 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 sputumsmear 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).<sup>(9)</sup> 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.<sup>(3,9)</sup> The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label.<sup>(23,24,26)</sup> 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.
- 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  $\leq 600$  mg daily vs. 60.75% (95%CI 42.69–78.81) for >600 mg daily (P = 0.05).<sup>(3)</sup>

In a trial reported by Lee et al in S Korea<sup>(9)</sup>, seven of 41 participants had myelosuppression, including anemia and neutropenia, <u>primarily within the first 5 months</u>, 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 ( $\geq$ 3 months) and in all patients reporting new visual symptoms, regardless of length of therapy.<sup>(26)</sup>

In Lee, NEJM, 2012<sup>(9)</sup>, 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<sup>(32)</sup>, 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<sup>(27)</sup>, 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<sup>(34)</sup>, 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 <sup>(5,36)</sup> 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<sup>(15)</sup> and in a subsequent study it was more active in the mouse model than HRZ.<sup>(16)</sup> 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.<sup>(37)</sup>

#### 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 <b>(57%)</b>		
BPa		3/14 <b>(21%)</b>		
3BPaL **	6/15 <b>(40%)</b>	0/15# <del>†</del> <b>(0%)</b>		
2BPaL/1BPa***		0/15# <del>†</del> <b>(0%)</b>		
1BPaL/2BPa	9/15 <b>(60%)</b>	0/15# <del>†</del> <b>(0%)</b>		

#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<sub>CFU(0-14)</sub>

Treatment Group	Ν	Daily Mean (SD) EBA <sub>CFU(0-14)</sub>
Pretomanid + pyrazinamide + moxifloxacin	13	0.23 (0.128)
Pretomanid + pyrazinamide	14	0.15 (0.040)
Pretomanid + bedaquiline	15ª	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)

Derived Using Bi-Linear Regression, Study NC-001

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<sub>CFU</sub> and log<sub>TTP</sub> that was at least as good as the HRZE control. The daily log<sub>CFU</sub> results are presented in Table 6. Similar results were found when TTP was used to calculate the bactericidal activity over 14 days (BA<sub>(0-14)</sub>).

#### Table 6: NC-003 Efficacy Results: Daily BAlog<sub>CFU(0-14)</sub>

Arm	logCFU
BPaZC	.124
BPaZ	.180
BPaC	.086
BZC	.098
Z	.036
С	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

	BPaZ C	BPaZ	BPa C	BZC	Z	С	HRZ E	Total
Ν	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  $\geq$ 500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of  $\geq$ 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  $\geq$ 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 failer through the 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. Fortynine 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.

<u>Safety of the B-Pa-L Regimen in the Nix-TB Study</u>: 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<sup>(28)</sup>. 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.<sup>(43)</sup> 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	<ul> <li><u>Linezolid 1200 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
2	<ul> <li>Linezolid 1200 mg daily for 9 weeks followed by linezolid placebo for <u>17 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
3	<ul> <li><u>Linezolid 600 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
4	<ul> <li>Linezolid 600 mg daily for 9 weeks followed by linezolid placebo for <u>17 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>

# 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. Retesting 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.

#### Disease Characteristics:

- 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
    - 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<sup>2</sup>
- 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.

#### Previous and Concomitant Therapy

- 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<sup>3</sup>;
  - 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
  - I. 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 noncompliance 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.

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

## 5.5 Participant Progress Definitions

\* 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 Deta	ails
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Treatment Group	Active and Placebo
<u>Linezolid 1200 mg</u> <u>daily for 26 weeks</u>	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> </ul>
<u>Linezolid 1200 mg</u> daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>
<u>Linezolid 600 mg</u> daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> </ul>
<u>Linezolid 600 mg</u> daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 600 mg tablets once daily for 17 weeks</li> </ul>

## 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 300 mg 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<sup>(5,6)</sup>. The complete formulations of linezolid are found in the Package Inserts<sup>(23,24,26)</sup>.

The IMP will be packaged as follows:

- Bedaquiline: Bottles containing:
  - o 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:
  - o 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
  - o 300 mg Dose (for reductions): 1 row of 7 active 600 mg tablets for 7 days of dosing

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- 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 <u>4</u>).
- 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 <u>7</u>) 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 <u>5</u>). 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<sub>2</sub>, 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 <u>6</u>) 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<sub>T</sub>,  $C_{mean}$ , 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.

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).

 Table 10:
 Adverse Events Attribution/Causality Ratings

## 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  $\frac{2}{2}$  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 nonleading 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.

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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 timeperiods:

- 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 <u>will follow the same time lines for a SAE</u> (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<sup>(5,6)</sup> and Package Inserts.<sup>(23,24,25,26)</sup>

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  $\leq$  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.

## СРК

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-ofcare 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</p>
    - 480 msec < QT/QTc < 500 msec</p>
    - QT/QTc > 500 msec
  - o QTc changes from baseline will be classified into the following categories:
    - increase < 30 msec,</li>
    - 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 <u>3</u>), 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, AUCT, 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. <sup>(30)</sup>

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 described from Policy as 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

<u>Source:</u> 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 <sub>x</sub> = 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 <sup>3</sup>	750-999/mm <sup>3</sup>	500-749/mm <sup>3</sup>	<500/mm <sup>3</sup>		
Platelets	75,000- 99,999/mm <sup>3</sup>	50,000- 74,999/mm <sup>3</sup>	20,000- 49,999/mm <sup>3</sup>	<20,000/mm <sup>3</sup>		
WBCs	11,000-13,000/ mm <sup>3</sup>	13,000-15,000 /mm <sup>3</sup>	15,000- 30,000/mm <sup>3</sup>	>30,000 or <1,000 /mm <sup>3</sup>		
% 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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; outpatienttreatm ent 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% FEV₁ of peak flow	requires treatment; normalizes with bronchodilator; FEV <sub>1</sub> 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV <sub>1</sub> 25% - 50% of peak flow; or retractions present	cyanosis: FEV <sub>1</sub> < 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 v	alues								
"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	%			
	Normal no complaints; no evidence of disease.	100			
Able to carry on normal activity and to work; no special care	Able to carry on normal activity; minor signs or symptoms of disease.	90			
needed.	Normal activity with effort; some signs or symptoms of disease.	80			
Unable to work; able to live at	Cares for self; unable to carry on normal activity or to do active work.	70			
home and care for most personal needs; varying amount of	Requires occasional assistance, but is able to care for most of his personal needs.				
assistance needed.	Requires considerable assistance and frequent medical care.	50			
	Disabled; requires special care and assistance.	40			
Unable to care for self; requires	Severely disabled; hospital admission is indicated although death not imminent.	30			
hospital care; disease may be	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<sup>(22)</sup>.

# 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	
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	F.
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	

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			- units	BRIE	FPER	IPHER			ROPATH	Y	SCRE	EN				
Patier	nt Initials				Patient	ID										
		Durin	g Trea	tment	Scree	ening	We 4	ek	Week 8	ľ	Week 12	v	Week 16		eek 20	Week 23
1. V	isit Sircle One)	Post	Treatm	ent	12	Week		2	6 Weeks	-		52 We	eks		78 V	Veeks
		Other	r		End of or Early Withdrawal Uns from Treatment For new onset or worse treatment extension						Unsc or worsen xtension (	cheduled ning peripheral neuropathy OR n (+ culture or interruptions)				
2. D	ate of Ass	essme	nt		D D M M Y Y							Υ	Y			
0	11			INTE	RFERE		ITH \	NAL	KING OF	l SL	EEPI	NG				
3. Ir W	alking or s	/o wee leeping	sks, nav g? (Ch	ve pain ieck on	, aching e)	or burnin	g in y	our 1	eet interre	rea	with yo	bur		Y		Ν
	If YES, ache o	ask th r burni	e patie ng (circ	ent to ra cle one	ate the le ).	vel of inte	erfere	ence	(1 to 10) to	o his	walkii	ng or s	leeping	r cau	sed by	r this pain,
3a.		Mi	inimal					Мо	dest					Se	vere	
	01	(	02 03 04			04	0	5	06		07	(	98	0	)9	10
					SUE	JECT E	LICI	TED	SYMPTO	DMS	5	•				
:	severity Enter a If a sym If a sym	of the score i ptom h ptom h	most a for each has bee has nev	offected h symp en pres ver bee	I foot. otom. ent in the n presen	e past, bu	it not 11 - 7	sinc Alwaj	e the last v vs Been No	risit, orma	enter al'	00 - 00'		y Ab	sent'	200
(,	٣ ا		100	, 						)				600	5	
	00		02	2		04			06			08	;			10
Ver No S	ry Happy, Symptoms	J	lust a li	ittle bit	A	little mor	e		Even more	e		A who	le lot		W	/orst
		-			-									_		Severity
					4. Pair	n, aching	or bu	Irnin	g in feet or	legs	s?					
you e	ig the last experience	14 day d:	ys, nav	/e	5. "Pin	is and ne	edles	" in f	eet or legs	?						
					6. Nun	6. Numbness (lack of feeling) in feet or legs?										
																-

# Appendix 6: Brief Peripheral Neuropathy Screening

19-Jan-17 version

		E	BRIEF	PERIPHER	ral n	EUROF	PATH	Y SCR	EEN			
Patient Initials			F	Patient ID								
	I I			PERCEP		of Vibf	RATIO	N				
<ul> <li>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.</li> <li>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".</li> <li>Repeat for the great toe on the other foot</li> <li><u>Vibration Perception Grade Scale:</u></li> <li>0 - Vibration felt for 510 seconds (mild loss)</li> <li>2 - Vibration felt for 5 seconds or less (moderate loss)*</li> <li>3 - No feeling of vibration (severe loss)*</li> <li>0 - Unsplit to given to seconds</li> </ul>												
9 – Una	ible to e	valuate (	or ala n	ot assess"			Pig	ht			ff	
7. Measured	7. Measured vibration grade of great toe DIP joint							in.		Le		
	_	_	_									_
<ul> <li>The exact degrees</li> <li>The tern from the</li> <li>Repeat</li> <li>Ankle m</li> <li>0 – Abs</li> <li>1 – Hyp</li> <li>2 – Nor</li> <li>3 – hyp</li> <li>4 – clor</li> <li>9 – una</li> </ul>	<ul> <li>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.</li> <li>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.</li> <li>Repeat for ankle on other leg         <ul> <li><u>Ankle reflex grade scale:</u></li> <li>0 – Absent</li> <li>1 – Hypoactive</li> <li>2 – Normal deep tendon reflexes</li> <li>3 – hyperactive deep tendon reflexes (e.g. with prominent spread of toes)</li> <li>4 – clonus</li> </ul> </li> </ul>								90 ay			
8. Measured an	kle refle	ex arade					Rig	ht		Le	ft	
					сомм	ENTS						

Name of Completin	Person ng For	n m							Name of C										
Signature Completir	e of Pe ng For	rson m								Signature o	of Clini	ician							
Date	D	D	Μ	М	М	Y	Υ	Y	Υ	Date	D	D	М	М	Μ	Υ	Υ	Υ	Υ

19-Jan-17 version

# 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  $(\square)$  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  $(\Box)$  whether the intensity of the symptom you experienced was "Mild", "Moderate" or "Severe".

	Rate your experience of each symptom over the past 7 days.								
Feeling feverish	□ None	D Mild	□ Moderate	Severe 2					
Feeling chills	□ None	□ Mild	□ Moderate	Severe					
Excessive sweating	□ None	Mild	□ Moderate	Severe					
Shortness of breath	□ None	D Mild	Moderate	Severe					
Chest pain	□ None	D Mild	□ Moderate	Severe					
Feeling unwell	□ None	D Mild	□ Moderate	Severe					
Tiredness/weakness	□ None	□ Mild	Moderate	Severe					
Cough	□ None	D Mild	□ Moderate	Severe					
Coughing up mucus	□ None	D Mild	□ Moderate	Severe					
	□ None	D Mild	□ Moderate	Severe					

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;<sup>(31,39)</sup>; 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.
- 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 <u>2</u>). 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 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 RUS/BEL 28 February, 2017
Protocol Name:	ZeNix





#### PROTOCOL SIGNATURE PAGE

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

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

Protocol Version and Date: 1.0 RUS/BEL 28 February, 2017

Protocol Name: ZeNix

#### SPONSOR

I agree to the terms of this trial protocol.

Signature of Senior Medical Officer

29 March 2017

Everitt mir) Printed Name

40 Wall Street, 24th Floor New York, NY 10005 Phone 646-616-8671 email: daniel.everitt@tballiance.org

Date

#### LEAD INVESTIGATOR

I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations.

nes

Signature

2017 Date

Francesca Convodu

CONFIDENTIAL Page 2 of 99





# PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

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

Protocol Version and Date: 1.0 RUS/BEL 28 February, 2017

Protocol Name: ZeNix

I hereby confirm that I have read the above protocol and agree to conduct this clinical trial as outlined in the above protocol. I will provide copies of the protocol and access to all the information required to conduct the clinical trial according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature

Printed Name

Date

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#### 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	Al anine aminoTransferase
AREDS2	Age Related Eve Disease Scale 2
ART	Anti-Retroviral Therapy
AST	
	AminoTransferase
	Area Under Curve over a desing interval
	Red onder Guive over a dosing interval
	Dedaquilline Deda Mass Jadax
DIVII	Body Mass Index
opm	
BPNS	Brief Peripheral Neuropathy Scale
C	
CFU	Colony Forming Units
CK(-MB)	Creatine Kinase(-MB isoenzyme)
C <sub>(max), (min)</sub>	plasma Concentration (maximum), (minimum)
CO <sub>2</sub>	Carbon diOxide
CPK	Creatine PhosphoKinase
CS	Clinically Significant
Ctrough	plasma Concentration <sub>trough</sub>
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
F	Ethambutol
FBA	Early Bacteriocidal Activity
FC	Ethics Committee
ECG	ElectroCardioGram
ECC FFV	FFaVirenz
	(electronic) Case Report Form
FO	EluoroQuinolone
	Emtricitabine
	CastroIntestinal
	Cood Clinical Practice
GCF	Commo Clutomyl Transforma
	Garmatria Maan Datia
GIVIR	
	Isuman Ether à re re Delated Care
NEKG	numan <i>Einer-a-go-go</i> Kelaieo 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
ka	kilogram
L	Linezolid
LLN	Lower Limit of Normal
LPV	LoPinaVir
Μ	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
MĞIT	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
ТВ	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
hđ(\ql)	micrograms (per deciliter)
Z	pyra∠ınamide

# 1 Synopsis

# 1.1 Synopsis Summary

Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished	bedaguiline (B), pretomanid (Pa) and linezolid (L)
Products:	
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
	overteen (IWPS) 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 18 and over. Enrollment will stop when
	120 XDR-IB participants are randomized. Sponsor may consider replacement
	of late screen failure and un-assessable (as detailed in the statistical analysis
Toot and ust Doos and	pian) participants.
Node of Administration	The test product will be supplied as:
Mode of Administration.	bedaquiline 100 mg tablets
	pretomania 200 mg tablets
	• linezolid (scored) 600 mg tablets
	placebo linezolid (scored) 600 mg tablets
	Inezolid 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 class of water and

Name of	Global Alliance for TB Drug Development					
Sponsor/Company	hadagwiling (D) protomonid (Da) and linegalid (L)					
Name of Finished	bedaquiline (B), pretomanid (Pa) and linezolid (L)					
Floducis.	Participants will receive the following:					
	<u>Participants will receive the following.</u>					
	• Decaduline 200 mg once daily for 8 weeks their 100 mg once daily for 18 weeks plus:					
	<ul> <li>pretomanid 200 mg once daily for 26 weeks plus:</li> </ul>					
	<ul> <li>Linezelid, participante will be randomly assigned to receive one of the</li> </ul>					
	<ul> <li>Elleving four linezolid treatment deeps and durations;</li> </ul>					
	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					
	<ul> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> </ul>					
	<ul> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> </ul>					
	Weeks 10-26					
	<ul> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> </ul>					
	<ul> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>					
	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					
	<ul> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> </ul>					
	Linezolid 600 mg daily for 9 weeks					
	Weeks 1-9					
	<ul> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> </ul>					
	<ul> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> </ul>					
	<ul> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> </ul>					
	Weeks 10.26					
	Weeks 10-20					
	• 2 placebo linezolid 600 mg tablets once daily for 17 weeks					
	• I placebo linezolid 500 mg hall 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 quidance 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 300 mg QD to					
	placebo) managed by the IWRS as per instructions in pharmacy manual					
	and/or IWRS user manual.					

Namo of	Clobal Alliance for TB Drug Development
	Global Alliance for TB Drug Development
Sponsor/Company	
Name of Finished	bedaguiline (B), pretomanid (Pa) and linezolid (L)
Products:	
	<ul> <li>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.</li> <li>Permanent discontinuation of linezolid.</li> </ul>
	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:

<u>Primary Endpoint:</u> Incidence of bacteriologic failure or rela

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	Global Alliance for TB Drug Development						
Sponsor/Company							
Name of Finished	bedaquiline (B), pretomanid (Pa) and linezolid (L)						
Products:							
Pharmacokinetics (PK) and	Pharmacokinetics/Pharmacodynamics (PK/PD):						
Plasma concentrations of be	edaquiline and its M2, pretomanid and linezolid_from sparse sampling (see Table						
1.2) will be measured and us	sed 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	e 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.,						
Ctrough, Cmax, AUC <sub>T</sub> , Cmean, a	nd 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 7.2.

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

#### **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 <sup>a</sup>								Tre	atm	ent							to	ب ۳	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	Visits every 3 weeks if extended due IMP pause or culture (+) at week 16 <sup>b</sup>	End of OR Ear Withdrawal frc Treatment <sup>c</sup>	4 weeks	8 weeks	12 weeks	26 weeks	39 weeks	52 weeks	65 weeks	78 weeks
Visit Window <sup>q</sup>	N/A		T	T	+/	/- 3 d	lays	T					+/- 5	days	6			+/- 7 days	Post last dose IMP +7 days			+/-	- 14	l da	ys		
Informed Consent	Х																										
Demography	Х																										
Med/Trtmnt/Smoking History	Х																									1	
Inclusion/Exclusion <sup>d</sup>	Х	Х																								1	
Randomization		Х																								1	
Karnofsky Assessment	Х																				ĺ					1	
HIV Status <sup>e</sup>	Х																										
CD4 Count and Viral Load <sup>f</sup>	Х																		Х							1	
Chest X-Ray <sup>g</sup>	Х																		Х							1	
Urine Pregnancy Test <sup>h</sup>	Х	Х								Х				Х					Х							1	
TB Symptoms Profile	Х									Х				Х					Х				Х		Х	1	Х
Patient Reported Health Status	Х								1	Х				Х					Х				Х		Х	1	Х
Slit Lamp Exam <sup>i</sup>	Х								1										Xi			Х				1	
Ophthalmic Exam <sup>j</sup>	Х					Х			1	Х		Х		Х		Х		Х	Х	Х						1	
Vital Signs	Х	Х	Х	Х		Х		Х	1	Х		Х		Х		Х		Х	Х			Х	Х	Х	Х	Х	Х
Single 12-LeadECG <sup>k</sup>	Х	Х	Х			Х			1	Х				Х					Х							1	
Limited Physical Exam <sup>1</sup>			Х	Х		Х		Х		Х		Х		Х		Х	1	Х				Х	Х	Х	Х	X	X
Full Physical Exam	Х	Х															1		Х			, I					
Laboratory Safety Tests (includes Full Blood Count) <sup>m</sup>	х	х	х	х	х	х		х		х		х		х		х	х	х	Х								
Full Blood Count							Х		Х		Х		Х		Х											1	
Con Meds	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Adverse Events	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Study Medication/Compliance <sup>n</sup>		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х								
PK Sampling <sup>o</sup>		Х	1	Х	1	1	1	1	1	Х	1	Х	1	1		Х	İ –		X°		<u> </u>						
Early Morning & Spot Sputum	Х	Х	Х	Х	Х	Х		Х	1	X	X	Х		Х		X	Х	Х	Х	Х	Х	X	Х	Х	Х	Х	X
Peripheral Neuropathy								1	1												<u> </u>	$\overline{}$				<u> </u>	Ť.
Assessment	Х					X				X		X		X		X	X	Х	Х		i i	X	X		Х		X
Investigator Assessment <sup>p</sup>									1		1			1									Х				Х

# 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.
  - For participants who receive 15 days to < 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.
- I. **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).
  - 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:

	San	nple			Те	sts		
Visit	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		С	С	С
All Visits Post Baseline	•	•		S				
Positive for MTB at/after EoT				S	S	С	С	С

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*s*/

**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).

At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, need to confirm 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 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.<sup>(43)</sup> 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.<sup>(28)</sup> In another report from South Africa of 114 patients with XDR-TB, 22% completed treatment successfully.<sup>(21)</sup> 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.<sup>(42)</sup> A meta-analysis of 397 patients with XDR-TB from 31 centers, with HIV coinfection <10%, reported 32% treatment success.<sup>(17)</sup> Reports of the outcome of XDR-TB treatment from Peru (43 patients, 42% treatment success)<sup>(2)</sup> and Ukraine (114 patients, 22% treatment success)<sup>(11)</sup> 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%.<sup>(29)</sup> 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.<sup>(43)</sup> 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<sup>(9)</sup> 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).<sup>(1)</sup>

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 bedaguiline 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 bedaguiline 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.

#### Efficacy of bedaquiline 200 mg daily dose vs the marketed dosing scheme over 8 weeks

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.

#### Safety of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.

#### Pharmacokinetics of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.<sup>(14)</sup> 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<sub>max</sub>, 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 bedaguiline 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 relapsefree 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<sup>TM</sup>. 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. Drugdrug 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 multipledose efavirenz (EFV) resulted in approximately a 20% decrease in the AUC<sub>inf</sub> of bedaquiline with no alteration in the C<sub>max</sub>. Modeling based on the data from this DDI study predicts average steadystate concentrations of bedaquiline and M2 to be reduced by 52% with chronic co-administration of bedaquiline and EFV.<sup>(5)</sup>

#### Safety of Bedaquiline

The Investigator's Brochure for bedaquiline provides detailed safety information.<sup>5</sup>

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.

Advance Driver Departience (ADDa) in the Controlled Studies (C200 Store 1 and Store 2)								
During the Investigational Treatment Phase								
Dd			Any Placebo					
ADR (Grouped term), n (%)	Frequency	N=102	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 <sup>a</sup>	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)					

#### Table 1: ADRs C208 Stage 1 and Stage 2

<sup>a.</sup> 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.<sup>(7)</sup>

# 2.2.2 Pretomanid

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

#### 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,  $\leq 0.015$  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. <sup>(6)</sup>

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), <sup>(33)</sup> 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.<sup>(12,13)</sup>

#### 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.<sup>(18,19,20,36,40)</sup> 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.<sup>(6)</sup>

# 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  $\geq$ 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  $\geq$ 100 mg/kg/day, and early deaths occurred at doses  $\geq$ 500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at  $\geq$ 450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at  $\leq$ 30 mg/kg/day in rats and  $\leq$ 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.

<u>Drug interaction with midazolam:</u> 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<sub>0-t</sub>), and area under the curve extrapolated to infinity (AUC<sub>0-inf</sub>). The C<sub>max</sub> 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<sub>0-24h</sub>) was 0.65, and the GMR for the trough concentration (C<sub>min</sub>) 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<sub>max</sub> was 0.87, for AUC<sub>0-24h</sub> 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<sub>max</sub>, AUC<sub>0-24h</sub>, 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<sub>0-24h</sub>), 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 <sup>(4)</sup> (Figure 2).





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<sup>(6)</sup> 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.<sup>(23,24,26)</sup> Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism.<sup>(8)</sup> 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.<sup>(9)</sup>

Preclinical *in vitro* data shows linezolid is active against MTB, including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1  $\mu$ g/mL.<sup>(38)</sup> 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.<sup>(36)</sup> (Table 3, below)

#### Table 3: Murine Lung CFU counts during Treatment with Linezolid

	Mean lung log <sub>10</sub> CFU count (± S.D.) at:									
Regimen	D0	Month 1	Month 2	Month 3						
Untreated	6.17 <u>+</u> 0.27	6.47 <u>+</u> 0.06								
2RHZ/4R H		3.47 <u>+</u> 0.37	1.59 <u>+</u> 0.25	0.50 <u>+</u> 0.51						
L		4.97 <u>+</u> 0.26								

Monotherapy versus Standard Therapy

In recent years linezolid has been used to treat patients with MDR<sup>(28)</sup> 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.<sup>(41)</sup> 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.<sup>(9, 27, 34)</sup> 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.<sup>(9)</sup> 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 sputumsmear 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).<sup>(9)</sup> 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.<sup>(3,9)</sup> The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label.<sup>(23,24,26)</sup> 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.
- 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  $\leq$ 600 mg daily vs. 60.75% (95%CI 42.69–78.81) for >600 mg daily (*P* = 0.05).<sup>(3)</sup>

In a trial reported by Lee et al in S Korea<sup>(9)</sup>, seven of 41 participants had myelosuppression, including anemia and neutropenia, <u>primarily within the first 5 months</u>, 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 ( $\geq$ 3 months) and in all patients reporting new visual symptoms, regardless of length of therapy.<sup>(26)</sup>

In Lee, NEJM, 2012<sup>(9)</sup>, 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<sup>(32)</sup>, 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<sup>(27)</sup>, 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<sup>(34)</sup>, 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 <sup>(5,36)</sup> 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<sup>(15)</sup> and in a subsequent study it was more active in the mouse model than HRZ.<sup>(16)</sup> 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.<sup>(37)</sup>

#### 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 rela	psing after treatment for:
Regimen	2 months	3 months
2RHZ/RH*		8/14 <b>(57%)</b>
BPa		3/14 <b>(21%)</b>
3BPaL **	6/15 <b>(40%)</b>	0/15# <del>†</del> <b>(0%)</b>
2BPaL/1BPa***		0/15# <del>†</del> <b>(0%)</b>
1BPaL/2BPa	9/15 <b>(60%)</b>	0/15# <del>†</del> <b>(0%)</b>

#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<sub>CFU(0-14)</sub>

Treatment Group	Ν	Daily Mean (SD) EBA <sub>CFU(0-14)</sub>
Pretomanid + pyrazinamide + moxifloxacin	13	0.23 (0.128)
Pretomanid + pyrazinamide	14	0.15 (0.040)
Pretomanid + bedaquiline	15ª	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)

Derived Using Bi-Linear Regression, Study NC-001

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<sub>(0-14)</sub>).

#### Table 6: NC-003 Efficacy Results: Daily BAlog<sub>CFU(0-14)</sub>

Arm	logCFU
BPaZC	.124
BPaZ	.180
BPaC	.086
BZC	.098
Z	.036
С	025
Rifafour <sup>®</sup>	.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

	BPaZ C	BPaZ	BPa C	BZC	Z	С	HRZ E	Total	
Ν	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  $\geq$ 500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of  $\geq$ 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  $\geq$ 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 failer through the 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. Fortynine 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.

<u>Safety of the B-Pa-L Regimen in the Nix-TB Study</u>: 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<sup>(28)</sup>. 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.<sup>(43)</sup> 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 (aged 18 and over in Russia and Belarus), 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	<ul> <li><u>Linezolid 1200 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
2	<ul> <li><u>Linezolid 1200 mg daily for 9 weeks followed by linezolid placebo for 17 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
3	<ul> <li><u>Linezolid 600 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
4	<ul> <li><u>Linezolid 600 mg daily for 9 weeks</u> followed by linezolid placebo for <u>17 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>

# 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. Retesting 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 18 years or older.

#### Disease Characteristics:

- 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
    - 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<sup>2</sup>
- 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.

#### Previous and Concomitant Therapy

- 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<sup>3</sup>;
  - f. Absolute neutrophil count (ANC) < 1500/ mm<sup>3</sup>;
  - 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
  - I. 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 noncompliance 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.

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

# 5.5 Participant Progress Definitions

\* 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 Deta	ails
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Treatment Group	Active and Placebo
<u>Linezolid 1200 mg</u> <u>daily for 26 weeks</u>	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> </ul>
<u>Linezolid 1200 mg</u> daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>
<u>Linezolid 600 mg</u> daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> </ul>
<u>Linezolid 600 mg</u> daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 600 mg tablets once daily for 17 weeks</li> </ul>

# 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 300 mg 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<sup>(5,6)</sup>. The complete formulations of linezolid are found in the Package Inserts<sup>(23,24,26)</sup>.

The IMP will be packaged as follows:

- Bedaquiline: Bottles containing:
  - 200 mg QD dose- 28 tablets- bedaquiline 100 mg
  - o 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:
  - o 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
  - o 300 mg Dose (for reductions): 1 row of 7 active 600 mg tablets for 7 days of dosing

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- 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 <u>4</u>).
- 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 <u>7</u>) 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 <u>5</u>). 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<sub>2</sub>, 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 <u>6</u>) 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<sub>T</sub>,  $C_{mean}$ , 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.

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).

 Table 10:
 Adverse Events Attribution/Causality Ratings

# 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  $\frac{2}{2}$  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 nonleading 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.

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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 timeperiods:

- 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 <u>will follow the same time lines for a SAE</u> (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<sup>(5,6)</sup> and Package Inserts.<sup>(23,24,25,26)</sup>

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  $\leq$  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.

# СРК

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-ofcare 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</p>
    - 480 msec < QT/QTc < 500 msec</p>
    - QT/QTc > 500 msec
  - o QTc changes from baseline will be classified into the following categories:
    - increase < 30 msec,</li>
    - 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 <u>3</u>), 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, AUCT, 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. <sup>(30)</sup>

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 described from Policy as 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

<u>Source:</u> 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 <sub>x</sub> = 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 <sup>3</sup>	750-999/mm <sup>3</sup>	500-749/mm <sup>3</sup>	<500/mm <sup>3</sup>		
Platelets	75,000- 99,999/mm <sup>3</sup>	50,000- 74,999/mm <sup>3</sup>	20,000- 49,999/mm <sup>3</sup>	<20,000/mm <sup>3</sup>		
WBCs	11,000-13,000/ mm <sup>3</sup>	13,000-15,000 /mm <sup>3</sup>	15,000- 30,000/mm <sup>3</sup>	>30,000 or <1,000 /mm <sup>3</sup>		
% 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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
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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; outpatienttreatm ent 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% FEV₁ of peak flow	requires treatment; normalizes with bronchodilator; FEV <sub>1</sub> 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV <sub>1</sub> 25% - 50% of peak flow; or retractions present	cyanosis: FEV <sub>1</sub> < 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

De	scrip			
Able to carry on normal activity and to work; no special care needed.	/			
	1			
I hable to work: able to live at home and care for most personal peeds: varving amount of assistance	(			
needed	I			
	I			
	[			
I Inable to care for self: requires equivalent of institutional or hospital care: disease may be progressing				
ranidly				
rapidiy.				

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109<sup>(22)</sup>.

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## 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		

Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version 28FEB2017 Protocol Name: ZeNix



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Patie	ent Initials			DRIE	Patient				KOPAII		JUK						
		Durin	ig Trea	tment	Scree	ening	We 4	ek	Week 8		Week 12	N	/eek 16	w	eek 20	Week 23	(
1.	Visit Circle One)	Post	Treatm	ent	12	Week		26 Weeks			52 Weeks				78 V	Veeks	
		Othe	r		E	nd of or I from	Early Trea	Witl atme	ndrawal nt		For n	Unscheduled new onset or worsening peripheral neuropathy O treatment extension (+ culture or interruptions)					R
2.	Date of Ass	essme	nt		D	D	I	M	М	N	1	Υ	Y		Υ	Y	
INTERFERENCE WITH WALKING OR SLEEPING																	
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Duri you	ng the last experience	14 da ed:	ys, hav	/e	5. "Pin	is and ne	edles	" in f	eet or legs	?							
					6. Nun	nbness (I	ack o	f fee	ling) in fee	t or	legs?						
																	_

# Appendix 6: Brief Peripheral Neuropathy Screening

19-Jan-17 version

		BRIE	F PERIPHER	al n	EUROF	PATH	/ SCR	EEN				
Patient Initials			Patient ID									
			PERCEPT			ATIO	N					1
<ul> <li>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.</li> <li>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".</li> <li>Repeat for the great toe on the other foot</li> <li><u>Vibration Perception Grade Scale:</u> 0 - Vibration felt for &gt;10 seconds (mild loss)</li> <li>2 - Vibration felt for 5 seconds or less (moderate loss)*</li> <li>3 - No feeling of vibration (severe loss)*</li> <li>9 - Unable to evaluate or did not assess*</li> </ul>												
0 0/10						Ria	ht			Le	ft	
7. Measured V	Ē											
			DEEP T	ENDO	N REFL	EXES						
<ul> <li>The exidegrees</li> <li>The tenfrom the</li> <li>Repeat</li> <li>Ankle m</li> <li>0 – Abs</li> <li>1 – Hyp</li> <li>2 – Nor</li> <li>3 – hyp</li> <li>4 – clor</li> <li>9 – una</li> </ul>	<ul> <li>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.</li> <li>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.</li> <li>Repeat for ankle on other leg         <ul> <li>Ankle reflex grade scale:</li> <li>0 – Absent</li> <li>1 – Hypoactive</li> <li>2 – Normal deep tendon reflexes</li> <li>3 – hyperactive deep tendon reflexes (e.g. with prominent spread of toes)</li> <li>4 – clonus</li> </ul> </li> </ul>								90 ay			
8 Measured an	ikle reflex ara	ade		-		Rig	ht			Le	eft	
	gru											
				сомм	ENTS							

Name of Completi	Perso ng For	n m							Name of C (if required)	liniciar	ו								
Signature Completi	e of Pe ng For	rson m								Signature of Clinician									
Date	D	D	М	М	М	Υ	Υ	Υ	Υ	Date	D	D	М	Μ	М	Υ	Υ	Υ	Υ

19-Jan-17 version

## 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  $[\square]$  one box for each symptom.

If you did not experience the symptom during the past 7 days, please tick (2) "None" for that symptom.

If you **did** experience the symptom **during the past 7 days**, please tick ( $\square$ ) whether the intensity of the symptom you experienced was "Mild", "Moderate" or "Severe".

o symptom	Rate your experience of each symptom over the past 7 days.								
Feeling feverish	□ None	□ Mild	Moderate	Severe					
eeling chills	□ None	Mild	Moderate	Severe					
Excessive sweating	□ None	D Mild	Moderate	Severe					
Shortness of breath	□ None	Mild	Moderate	Severe					
Chest pain	□ None	D Mild	Moderate	Severe					
Feeling unwell	□ None	D Mild	□ Moderate	Severe					
Firedness/weakness	□ None	□ Mild	Moderate	Severe					
Cough	□ None	D Mild	□ Moderate	Severe					
Coughing up mucus	□ None	D Mild	Moderate	Severe					
Coughing up blood	□ None	Mild	Moderate	Severe					

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;<sup>(31,39)</sup>; 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.
- 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 <u>2</u>). 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 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 Version/Date:	1.0 RUS/BEL 28 February, 2017
Country Amendment for the Russian Federation	1.0 / 15 November, 2017
Protocol Name:	ZeNix

#### SPONSOR PROTOCOL SIGNATURE PAGE

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

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

Protocol Version/Date: 1.0 RUS/BEL 28 February, 2017

Local Amendment for the Russian Federation: 1.0 / 15 November, 2017

Protocol Name: ZeNix

## SPONSOR

I agree to the terms of this trial protocol.



Signature of Senior Medical Officer

November 16, 2017 | 4:48 PM EST

Date

Dan Everitt

Printed Name

40 Wall Street, 24th Floor New York, NY 10005 Phone 646-616-8671 email: daniel.everitt@tballiance.org

#### LEAD INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

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

Protocol Version/Date: 1.0 RUS/BEL 28 February, 2017

Local Amendment for the Russian Federation: 1.0 / 15 November, 2017

Protocol Name: ZeNix

#### LEAD INVESTIGATOR

I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations.

DocuSigned by: Dr. Francesca (anradic Signer Name: Dr. Francesca Conradie Signing Reason: I approve this document Signing Time: 20 November 2017 | 09:48 EST 8F3C422D6DE04C72AD395BC608A22CC5

Signature

Dr. Francesca Conradie

Printed Name

November 20, 2017 | 9:48 AM EST

Date

Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version RUS/BEL V1.0 28FEB2017 Country Amendment for RUS v. 1.0/15NOV2017 Protocol Name: ZeNix

#### PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

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

Protocol Version/Date: 1.0 RUS/BEL 28 February, 2017

Local Amendment for the Russian Federation: 1.0 / 15 November, 2017

Protocol Name: ZeNix

#### PRINCIPAL INVESTIGATOR

I hereby confirm that I have read the above protocol and agree to conduct this clinical trial as outlined in the above protocol. I will provide copies of the protocol and access to all the information required to conduct the clinical trial according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature

Printed Name

Date

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#### Abbreviations and Definition of Terms

Lamivudine
ABaCavir
Adverse Drug Reactions
Adverse Event
Acquired Immune Deficiency Syndrome
Alkaline Phosphatase
ALanine aminoTransferase
Age Related Eve Disease Scale 2
Anti-Retroviral Therapy
ASpartate aminoTransferase
AminoTransferase
Area Under Curve over a dosing interval
Redaquiline
Body Mass Index
heats per minute
Brief Perinheral Neuropathy Scale
Clofazimine
Colony Forming Units
Creatine Kinase (MB isoenzyme)
plasma Concentration (maximum) (minimum)
Carbon diOvido
Creating December Lingso
Clinically Significant
Cutochromo D450 244
Division of Microbiology and Infection Disease
Division of which oblology and infection disease
Department of Health
Drug Induced Liver Injury
Data Safety Monitoring Committee
Drug Sensitivity Testing
Ethambutol
Early Bacteriocidal Activity
Ethics Committee
ElectroCardioGram
EFaVirenz
(electronic) Case Report Form
FluoroQuinolone
Emtricitabine
GastroIntestinal
Good Clinical Practice
Gamma-Glutamyl Transferase
Geometric Mean Ratio
Isoniazid
Human <i>Ether-à-go-go</i> Related Gene
Human Immunodeficiency Virus
Isoniazid, Rifampicin, Pyrazinamide, Ethambutol

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUATLD IWRS	International Union Against Tuberculosis and Lung Disease Interactive Web Randomization System
kg	kilogram
L	Linezolid
LLN	Lower Limit of Normal
LPV	LoPinaVir
Μ	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
NRII	(Triple) Nucleosidase Reverse Transcriptase Inhibitor
Pa	Pretomania
PD	PharmacoDynamic
PP	Per Protocol
PK	PharmacoKinetic
PR	PR interval
QD	Once Daily
R	Ritampicin
S	Streptomycin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan Strantomicial Series id Diferenciain Ethernhuitel
SIRE	Streptomycin Isoniazio Rifampicin Ethambutoi
50C	System Organ Class
	i ubel culosis serum Total Bil irubin
	Tenofovir
	Treatment Emergent Adverse Events
	Time above minimum inhibitory concentration
	three times a week
$(R\Delta) TTP$	(Bacteriocidal Activity) Time To Positivity
	Unper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
XDR-TB	eXtensively Drug Resistant Tuberculosis
. –	

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micrograms (per deciliter) pyraZinamide µg(/dl) Z

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## 1 Synopsis

## 1.1 Synopsis Summary

Name of	Global Alliance for TB Drug Development
Sponsor/Company	
Name of Finished	bedaquiline (B), pretomanid (Pa) and linezoild (L)
Products:	NO 007: A Dhase 2 partially blinded randomized trial appending the adjaty
Protocol Number/ Little:	NC-007: A Phase 3 partially-blinded, randomized that assessing the salety
	bedaguiline 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
	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 IB.
	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 intelerant/non responsive MDP nulmonany tuberculosis
	Participants male and female aged 18 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	The test product will be supplied as:
Mode of Administration:	bedaquiline 100 mg tablets
	pretomanid 200 mg tablets
	linezolid (scored) 600 mg tablets
	<ul> <li>placebo linezolid (scored) 600 mg tablets</li> </ul>
	Inezolid half tablet (pre-cut) 300 mg
	<ul> <li>placebo linezolid half tablet (pre-cut) 300 mg</li> </ul>
	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

Name of	Global Alliance for TB Drug Development
Sponsor/Company	
Name of Finished	bedaquiline (B), pretomanid (Pa) and linezolid (L)
Products:	
	<ul> <li>Treatment will be administered orally, once daily, with a full glass of water and a meal in the following dosing schemes (treatment arms):</li> <li><u>Participants will receive the following:</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks plus;</li> <li>Linezolid- participants will be randomly assigned to receive one of the</li> </ul>
	<ul> <li><u>Linezolid 1200 mg daily for 26 weeks</u></li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> </ul>
	<ul> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> </ul>
	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
	<ul> <li>Linezolid 600 mg daily for 26 weeks</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> </ul>
	<ul> <li><u>Linezolid 600 mg daily for 9 weeks</u></li> <li>Weeks 1-9 <ul> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> </ul> </li> </ul>
	<ul> <li>Weeks 10-26</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>
	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
	<ul> <li>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:</li> <li>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 300 mg QD to</li> </ul>

Nome of	Clobal Alliance for TD Drug Development
Name of	Global Alliance for TB Drug Development
Name of Einished	bodaquiling (B) protomanid (Ba) and linezolid (L)
Products:	bedaquinne (b), pretornanio (Fa) and intezono (c)
	<ul> <li>placebo) managed by the IWRS as per instructions in pharmacy manual and/or IWRS user manual.</li> <li>Temporary pause of linezolid due to a linezolid-specific toxicity should be considered and implemented per quidance in the monitoring and safety.</li> </ul>
	<ul> <li>Permanent discontinuation of linezolid.</li> </ul>
	drugs in the regimen (B-Pa), the full regimen may be halted for up to 35 consecutive days.
	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.
Primary Endpoint: Incidence of bacteriologic fatteratment.	ailure or relapse or clinical failure through follow up until 26 weeks after the end of
Abbreviated Definitions, full Bacteriologic failure	definitions will be described in the Statistical Analysis Plan (SAP): e: During the treatment period, failure to attain or maintain culture conversion to
<ul> <li>negative.</li> <li>Bacteriologic relaps status, with culture genetically identica</li> </ul>	se: During the follow-up period, failure to maintain culture conversion to negative conversion to positive status with a strain of <i>Mycobacterium tuberculosis</i> (MTB) I to the infecting strain at baseline.
<ul> <li>Clinical failure: A ch protocol specified to related death.</li> </ul>	nange from protocol-specified TB treatment to a new regimen before end of reatment due to treatment failure, retreatment for TB during follow up, or TB-
<ul> <li>Note:</li> <li>Culture conversion apart.</li> </ul>	requires at least 2 consecutive culture negative/positive samples at least 7 days
<ul> <li>Participants who an considered to be re Further details of definit</li> </ul>	e documented at a visit as unable to produce sputum and who are clinically sponding well to treatment will be considered to be culture negative at that visit. ions to be provided in the SAP.
Secondary Endpoints: Incidence of bacteri	ologic failure or relapse or clinical failure through follow up until 78 weeks after
<ul><li>the end of treatmen</li><li>Time to sputum cult</li><li>Proportion of particities</li></ul>	t. ture conversion to negative status through the treatment period. pants with sputum culture conversion to negative status at weeks 4, 6, 8, 12, 16
and end of treatme	nt.

• Change from baseline TB symptoms.

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

• 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<sub>trough</sub>, C<sub>max</sub>, AUC<sub>T</sub>, C<sub>mean</sub>, 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	Global Alliance for TB Drug Development									
Sponsor/Company										
Name of Finished	bedaquiline (B), pretomanid (Pa) and linezolid (L)									
Products:										
Statistical Methods:	a testi a ti a che a la colla con a differenti a consiste a constante a constante a constitue a di la che cons									
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 control the overall type I error secondary analysis populat	the dosing and duration of linezolid and effect on efficacy and safety and to or rate the following analysis strategy will be adopted for both the primary and ions:									
The primary comparison wil L1200 2 months and L600 2 weeks <b>will only be tested</b> is comparing the L1200 9 wee comparisons the lower bour	I be for the linezolid 1200mg taken for 26 weeks arm (L1200 6 months) with the 26 weeks <b>only being tested if</b> L1200 26 weeks is a success. Similarly, L600 9 <b>if</b> L600 26 weeks is a success. A Bonferroni adjustment will be made for ks and L600 26 weeks arms simultaneously, using p<0.025. For these and 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:

 $\sim$ 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).

Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version RUS/BEL V1.0 28FEB2017 Country Amendment for RUS v 1.0/15NOV2017 Protocol Name: ZeNix

# 1.2 Synopsis Flowchart

Period	Screening <sup>a</sup>		Treatment															to	ž	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 Visits every 3	VISITS EVERY 3 weeks if extended due IMP pause or culture (+) at week 16 <sup>b</sup>	End of OR Ear Withdrawal frc Treatment <sup>c</sup>	4 weeks	8 weeks	12 weeks	26 weeks	39 weeks	52 weeks	65 weeks	78 weeks
Visit Window <sup>q</sup>	N/A	+/- 3 days										-	+/- 5	days	;	-		⊦/- 7 days	Post last dose IMP +7 days		+/- 14 days						
Informed Consent	Х																										
Demography	Х																										
Med/Trtmnt/Smoking History	Х																										
Inclusion/Exclusion <sup>d</sup>	Х	Х																									
Randomization		Х																									
Karnofsky Assessment	Х																										
HIV Status <sup>e</sup>	Х																										
CD4 Count and Viral Load <sup>†</sup>	Х																		Х								
Chest X-Ray <sup>g</sup>	Х																		Х								
Urine Pregnancy Test <sup>h</sup>	Х	Х								Х				Х					Х								
TB Symptoms Profile	Х									Х				Х					Х				Х		Х		Х
Patient Reported Health Status	Х									Х				Х					Х				Х		Х		Х
Slit Lamp Exam <sup>1</sup>	Х																		X'			Х					
Ophthalmic Exam <sup>j</sup>	Х					Х				Х		Х		Х		Х		Х	Х	Х							
Vital Signs	Х	Х	Х	Х		Х		Х		Х		Х		Х		Х		Х	Х			Х	Х	Х	Х	Х	Х
Single 12-LeadECG <sup>k</sup>	Х	Х	Х			Х				Х				Х					Х								
Limited Physical Exam <sup>1</sup>			Х	Х		Х		Х		Х		Х		Х		Х		Х				Х	Х	Х	Х	Х	Х
Full Physical Exam	Х	Х																	Х								
Laboratory Safety Tests (includes Full Blood Count) <sup>m</sup>	х	х	Х	Х	Х	х		х		Х		Х		Х		Х	х	х	Х								
Full Blood Count							Х		Х		Х		Х		Х												
Con Meds	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Adverse Events	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Study Medication/Compliance <sup>n</sup>		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		$\square$						
PK Sampling <sup>o</sup>		Х		Х						Х		Х				Х			Xo								
Early Morning & Spot Sputum <sup>r</sup>	Х	Х	Х	Х	Х	Х		Х		Х	Х	Х		Х		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Peripheral Neuropathy	V		1	1	1	v	1	1	1	v		v	1	v	1	v	v	V	v			v	v		v		V
Assessment	X					X				X		X		X		X	Х	X	X	'		X	X		Х		X
Investigator Assessment <sup>p</sup>																							Х				Х
# 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 Éarly 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 HİV-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 < 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 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.
- I. **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, sérum 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
  - 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:

	Sample Tests									
Visit	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 - wk 4 if baseline negative or contaminated	٠	•		S		С	С	С		
All Visits Post Baseline	•	•		S						
Positive for MTB at/after EoT				S	S	С	С	С		

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*s*/

**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).

At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, need to confirm 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 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.<sup>(43)</sup> 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.<sup>(28)</sup> In another report from South Africa of 114 patients with XDR-TB, 22% completed treatment successfully.<sup>(21)</sup> 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.<sup>(17)</sup> Reports of the outcome of XDR-TB treatment from Peru (43 patients, 42% treatment success)<sup>(2)</sup> and Ukraine (114 patients, 22% treatment success)<sup>(11)</sup> 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%.<sup>(29)</sup> 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.<sup>(43)</sup> 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<sup>(9)</sup> 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).<sup>(1)</sup>

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 bedaguiline 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 bedaguiline with pretomanid and pyrazinamide over an 8 week period. One arm was to enroll 60 patients who were to be given this regimen with bedaguiline 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 bedaguiline 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, guantitative and gualitative 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.

#### Efficacy of bedaquiline 200 mg daily dose vs the marketed dosing scheme over 8 weeks

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.

#### Safety of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.

#### Pharmacokinetics of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.<sup>(14)</sup> 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<sub>max</sub>, 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 relapsefree 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<sup>™</sup>. 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 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. Drugdrug 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 multipledose efavirenz (EFV) resulted in approximately a 20% decrease in the AUC<sub>inf</sub> of bedaquiline with no alteration in the C<sub>max</sub>. 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.<sup>(5)</sup>

#### Safety of Bedaquiline

The Investigator's Brochure for bedaquiline provides detailed safety information.<sup>5</sup>

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.

Adverse Drug Reactions (ADRs) in the Controlled Studies (C208 Stage 1 and Stage 2)								
During the investigational Treatment Phase								
		Any BDQ	Any Placebo					
ADR (Grouped term), n (%)	Frequency	N=102	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 <sup>a</sup>	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)					

#### Table 1:ADRs C208 Stage 1 and Stage 2

<sup>a.</sup> 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.<sup>(7)</sup>

# 2.2.2 Pretomanid

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

# 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,  $\leq 0.015$  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. <sup>(6)</sup>

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), <sup>(33)</sup> 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.<sup>(12,13)</sup>

# 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.<sup>(18,19,20,36,40)</sup> 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.<sup>(6)</sup>

# 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  $\geq 100 \text{ mg/kg/day}$ , and early deaths occurred at doses  $\geq 500 \text{ mg/kg/day}$ . Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at  $\geq 450/300 \text{ mg/kg/day}$ . These effects were reversible when dosing stopped and were absent at  $\leq 30 \text{ mg/kg/day}$  in rats and  $\leq 150 \text{ mg/kg/day}$  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.

<u>Drug interaction with midazolam:</u> 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<sub>max</sub>), area under the curve to the last available time point (AUC<sub>0-t</sub>), and area under the curve extrapolated to infinity (AUC<sub>0-inf</sub>). The C<sub>max</sub> 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<sub>max</sub>) and half-life (t<sub>1/2</sub>) 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<sub>max</sub>) was 0.71, the GMR for the 24-hour area under the time-concentration curve (AUC0-24h) was 0.65, and the GMR for the trough concentration (Cmin) 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 PKevaluable participants, the GMR for C<sub>max</sub> was 0.87, for AUC<sub>0-24h</sub> was 0.83, and for C<sub>min</sub> 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 Cmax, AUC0-24h, and Cmin 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 (AUCo-

<sup>24h</sup>), and trough concentration (C<sub>min</sub>) 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 <sup>(4)</sup> (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<sup>(6)</sup> 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.<sup>(23,24,26)</sup> Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism.<sup>(8)</sup> 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.<sup>(9)</sup>

Preclinical *in vitro* data shows linezolid is active against MTB, including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1  $\mu$ g/mL.<sup>(38)</sup> 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.<sup>(36)</sup> (Table 3, below)

#### Table 3: Murine Lung CFU counts during Treatment with Linezolid

	Mean lung log <sub>10</sub> CFU count (± S.D.) at:										
Regimen	D0	Month 1	Month 2	Month 3							
Untreated	6.17 <u>+</u> 0.27	6.47 <u>+</u> 0.06									
2RHZ/4R H		3.47 <u>+</u> 0.37	1.59 <u>+</u> 0.25	0.50 <u>+</u> 0.51							
L		4.97 <u>+</u> 0.26									

|--|

In recent years linezolid has been used to treat patients with MDR<sup>(28)</sup> 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.<sup>(41)</sup> 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.<sup>(9, 27, 34)</sup> 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.<sup>(9)</sup> 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 sputumsmear 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).<sup>(9)</sup> 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.<sup>(3,9)</sup> The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label.<sup>(23,24,26)</sup> 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.
- 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  $\leq 600$  mg daily vs. 60.75% (95%CI 42.69–78.81) for >600 mg daily (P = 0.05). <sup>(3)</sup>

In a trial reported by Lee et al in S Korea<sup>(9)</sup>, seven of 41 participants had myelosuppression, including anemia and neutropenia, <u>primarily within the first 5 months</u>, 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 ( $\geq$ 3 months) and in all patients reporting new visual symptoms, regardless of length of therapy.<sup>(26)</sup>

In Lee, NEJM, 2012<sup>(9)</sup>, 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<sup>(32)</sup>, 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<sup>(27)</sup>, 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<sup>(34)</sup>, 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 <sup>(5,36)</sup> 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<sup>(15)</sup> and in a subsequent study it was more active in the mouse model than HRZ.<sup>(16)</sup> 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.<sup>(37)</sup>

#### Table 4:Murine Relapse Data

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

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

#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

IBPAL/2010 Initialis I month on the full regiment and a third month on only bra

 ${\sf B-bed a quiline, \ H-isoniazid, \ L-linezolid, \ Pa-pretomanid, \ R-rifampicin, \ Z-pyrazinamide}$ 

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 cardiovascularsafety 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<sub>CFU(0-14)</sub>

Treatment Group	Ν	Daily Mean (SD) EBA <sub>CFU(0-14)</sub>
Pretomanid + pyrazinamide + moxifloxacin	13	0.23 (0.128)
Pretomanid + pyrazinamide	14	0.15 (0.040)
Pretomanid + bedaquiline	15 <sup>a</sup>	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)

Derived Using Bi-Linear Regression, Study NC-001

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<sub>CFU</sub> and log<sub>TTP</sub> that was at least as good as the HRZE control. The daily log<sub>CFU</sub> results are presented in Table 6. Similar results were found when TTP was used to calculate the bactericidal activity over 14 days (BA<sub>(0-14)</sub>).

#### Table 6: NC-003 Efficacy Results: Daily BAlog<sub>CFU(0-14)</sub>

Arm	logCFU
BPaZC	.124
BPaZ	.180
BPaC	.086
BZC	.098
Z	.036
С	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

	BPaZ C	BPaZ	BPa C	BZC	Z	С	HRZ E	Total
Ν	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

	BPaZ C	BPaZ	BPa C	BZC	Z	С	HRZ E	Total
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  $\geq$ 500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of  $\geq$ 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  $\geq$ 60 ms reported for 4 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  $\geq$ 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-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 6 months after the end of treatment. Secondary Endpoints include: incidence of bacteriologic failure or relapse or clinical failure 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. Fortynine 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. <u>Safety of the B-Pa-L Regimen in the Nix-TB Study</u>: 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<sup>(28)</sup>. 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.<sup>(43)</sup> 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 bedaguiline 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 (aged 18 and over in Russia and Belarus), 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	<ul> <li><u>Linezolid 1200 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
2	<ul> <li><u>Linezolid 1200 mg daily for 9 weeks followed by linezolid placebo for</u> <u>17 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
3	<ul> <li>Linezolid 600 mg daily for 26 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
4	<ul> <li><u>Linezolid 600 mg daily for 9 weeks followed by linezolid placebo for</u> <u>17 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>

# Figure 4: Trial Schematic



Participants will be randomized to 1 of the 4 groups listed above.

N = 45 Participantsper group for a total of 180. 30 XDR-TB participantsper 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. Retesting 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. It is the intent of the protocol that the participants are hospitalized according to local practices and at the judgment of the treating physician.

#### 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 18 years or older.

#### Disease Characteristics:

- 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) <  $17 \text{ kg/m}^2$
- 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. <u>Participants with any of the following conditions where the use of linezolid is</u> <u>contraindicated:</u>
  - <u>A history of thyrotoxicosis</u>
  - <u>A history of uncontrolled arterial hypertension</u>
  - <u>A history of pheochromocytoma</u>
  - <u>A history of carcinoid syndrome</u>
  - A history of bipolar disorder
  - <u>A history of schizoaffective disorder</u>
- 12. 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.
- 13. 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.
- 14. Participants with lactose intolerance, lactase deficiency and/or glucose-galactose

malabsorption.

Previous and Concomitant Therapy

- 15. Concomitant use of Monoamine Oxidase Inhibitors (MAOIs) or prior use within 2 weeks of randomization.
- 16. 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.
- 17. 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).
- 18. Concomitant use of any drug known to induce myelosuppression.
- 19. 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.
- 20. <u>Concomitant use of adrenomimetics (including, but not limited to pseudoephedrine, phenylpropanolamine, epinephrine, norepinephrine, dobutamine), dopaminomimetics (e.g. dopamine).</u>
- 21. Concomitant use of 5-HT1 agonists (triptans), meperidine or buspirone.
- 22. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP.
- 23. 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.
- 24. 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.
- 25. 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**

26. 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<sup>3</sup>;
- f. Absolute neutrophil count (ANC) < 1500/ mm<sup>3</sup>;
- g. Aspartate aminotransferase (AST)
  - Grade 3 or greater ( $\geq$  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 ( $\geq$  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
- I. 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;
  - $\circ~$  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.

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 IMPParticipants who complete all follow visits			
Completed Treatment / Discontinued FU	Participants who complete the full course of IMP Participants who do not complete applicable follow-up visits, regardle 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 FUParticipants 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			

#### 5.5 Participant Progress Definitions

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 reviewBoard (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

<b>Treatment Group</b>	Active and Placebo
Linezolid 1200 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> </ul>
<u>Linezolid 1200 mg</u> <u>daily for 9 weeks</u>	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>
Linezolid 600 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> </ul>
Linezolid 600 mg daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>

## 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 300 mg 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<sup>(5,6)</sup>. The complete formulations of linezolid are found in the Package Inserts<sup>(23,24,26)</sup>.

The IMP will be packaged as follows:

- Bedaquiline: Bottles containing:
  - o 200 mg QD dose- 28 tablets- bedaquiline 100 mg
  - o 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:
  - o 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
  - o 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
  - o 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

# Bedaquiline and pretomanid treatment will not be blinded. Linezolid treatment dose and duration will be double-blinded.

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.

#### Individuals who will have access to the linezolid randomization scheme will be restricted to the IWRS vendor and IMP supply administrator and the unblinded statisticians providing safety and efficacy outputs for the DSMC. Individuals from pharmacovigilance and regulatory may be unblinded following controlled steps in order to fulfil any regulatory requirements regarding reporting of expedited reports. All other parties including the Sponsor, CRO, Vendors and site staff, will be blinded.

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 <u>4</u>).
- 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 <u>7</u>) 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 <u>5</u>). 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<sub>2</sub> 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):
  - o 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 <u>6</u>) 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<sub>T</sub>,  $C_{mean}$ , 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
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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 nonleading 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 timeperiods:

- 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 <u>will follow the same time lines for a SAE</u> (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<sup>(5,6)</sup> and Package Inserts.<sup>(23,24,25,26)</sup>

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  $\leq$  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-ofcare 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</li>
    - 450 msec < QT/QTc < 480 msec</p>
    - 480 msec < QT/QTc < 500 msec</p>
    - QT/QTc > 500 msec
  - o QTc changes from baseline will be classified into the following categories:
    - increase < 30 msec,</li>
    - 30 msec and < 60 msec, and
    - increase <u>></u> 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 <u>3</u>), 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, AUCT, 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 Pl/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 retum; 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. <sup>(30)</sup>

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 Policv 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.

## 16 References

- 1. "A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis". ClinicalTrials.gov, 25 January 2017. https://www.clinicaltrials.gov/ct2/show/NCT02333799
- Bonilla CA, Crossa A, Jave HO, Mitnick CD, Jamanca RB, Herrera C, Ascencios L, Mendoza A, Bayona J, Zignol M and Jaramillo E (2008). "Management of Extensively Drug-Resistant Tuberculosis in Peru: Cure Is Possible". <u>PLoS One</u> 3(8): e2957.
- 3. Cox H, Ford, N. "Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis" <u>INT J TUBERC LUNG DIS</u> 16(4):447–454, 2012.
- 4. Diacon AH, Dawson R, du Bois J, Narunsky K, Venter A, Donald PR, van Niekerk C, Erondu N, Ginsberg AM, Becker P and Spigelman MK (2012). "Phase II Dose-Ranging Trial of the Early Bactericidal Activity of PA-824". <u>Antimicrobial Agents and Chemotherapy</u>; 56(6): 3027-3031.
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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

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

**ABBREVIATIONS:** Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal	
R <sub>x</sub> = 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 <sup>3</sup>	750-999/mm <sup>3</sup>	500-749/mm <sup>3</sup>	<500/mm <sup>3</sup>		
Platelets	75,000- 99,999/mm <sup>3</sup>	50,000- 74,999/mm <sup>3</sup>	20,000- 49,999/mm <sup>3</sup>	<20,000/mm <sup>3</sup>		
WBCs	11,000-13,000/ mm <sup>3</sup>	13,000-15,000 /mm <sup>3</sup>	15,000- 30,000/mm <sup>3</sup>	>30,000 or <1,000 /mm <sup>3</sup>		
% 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> life threatening arrhythmia or tetany
<b>Hypercalcemia</b> (correctfor 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 <i>with</i> 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 <i>with</i> 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
<b>Hyperuricemia</b> (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
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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; outpatienttreatm ent 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 <sub>1</sub> of peak flow	requires treatment; normalizes with bronchodilator; FEV <sub>1</sub> 50% - 70% (of peak flow )	no normalization with bronchodilator;FEV <sub>1</sub> 25% - 50% of peak flow;or retractions present	cyanosis: FEV <sub>1</sub> < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy
GASTROINTESTINAL				
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	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 w eek	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 w eek	>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 sw allow ing	some limits on eating/drinking	eating/talking very limited; unable to sw allow solid foods	unable to drink fluids; requires IV fluids

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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 w eakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective w eakness 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 w rists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and low er extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

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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 sw elling – but not interfering with function	moderate pain with inflammation, erythema or joint sw elling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint sw elling –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 w ork	unable to care for self

# Appendix 3: Cardiovascular Safety

# Vital Signs

The following abnormalities will be defined for vital signs:

Abnormality Code		Vital S	igns 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

	Description	%
	Normal no complaints; no evidence of disease.	100
Able to carry on normal activity	Able to carry on normal activity; minor signs or	90
and to work; no special care	symptoms of disease.	90
needed.	Normal activity with effort; some signs or symptoms of	80
	disease.	00
	Cares for self; unable to carry on normal activity or to	70
Unable to work; able to live at	do active work.	10
home and care for most personal	Requires occasional assistance, but is able to care for	60
needs; varying amount of	most of his personal needs.	00
assistance needed.	Requires considerable assistance and frequent medical	50
	care.	50
	Disabled; requires special care and assistance.	40
I loople to care for self: requires	Severely disabled; hospital admission is indicated	30
equivalent of institutional or	although death not imminent.	50
bosnital care: disease may be	Very sick; hospital admission necessary; active	20
progressing rapidly	supportive treatment necessary.	20
progressing rapidly.	Moribund; fatal processes progressing rapidly.	10
	Dead	0

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

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109<sup>(22)</sup>.

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# 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	

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Patient Initials       Patient ID         During Treatment       Screening       Week       Week       Week       Yeek       Y					BRIE	F PER	IPHER	AL N	EU	ROPATH	YS	SCRE	ΞN					
During Treatment       Screening       Week       23         1.       Visit       Other       End of or Early Withdrawal from Treatment       Inscheduled       Inscheduled       To memore demon (- Londe or ellempton)       Inscheduled       Inscheduled       V       Y	Patie	ent Initials				Patient	ID											
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# Appendix 6: Brief Peripheral Neuropathy Screening

19-Jan-17 version

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19-Jan-17 version

Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version RUS/BEL V1.0 28FEB2017 Country Amendment for RUS v 1.0/15NOV2017 Protocol Name: ZeNix

# 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  $(\square)$  one box for each symptom.

If you did not experience the symptom during the past 7 days, please tick (2) "None" for that symptom.

If you **did** experience the symptom **during the past 7 days**, please tick ( $\square$ ) whether the intensity of the symptom you experienced was "Mild", "Moderate" or "Severe".

eeling feverish	□ None	D Mild	Moderate	Severe
eeling chills	□ None	Mild	Moderate	Severe
xcessive sweating	□ None	D Mild	□ Moderate	Severe
hortness of breath	□ None	☐ Mild	Moderate	Severe
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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;<sup>(31,39)</sup>; 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 hepatoœllular 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.
- 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 <u>2</u>). 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.



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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)
Protocol Amendment	
Version/Date:	V 2.0/13 June 2018, Incorporating Amendment 1
Protocol Name:	ZeNix

# PROTOCOL SIGNATURE PAGE

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

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

Protocol Date: V 2.0 13 JUNE 2018

Protocol Name: ZeNix

# SPONSOR

I agree to the terms of this trial protocol.

- DocuSigned by:

Signer Name: Dan Everitt Signing Reason: I approve this document Signing Time: 6/14/2018 9:00:18 PM EDT -32534894D9294A59B14B10FC37E90452

Signature of Senior Medical Officer

June	14,	2018	9:00	PM	EDT

Date

П

# LEAD INVESTIGATOR

Dan Everitt

Printed Name

40 Wall Street, 24th Floor New York, NY 10005 Phone 646-616-8671 email: daniel.everitt@tballiance.org

I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations.

Francesca Conradie

Signer Name: Francesca Conradie Signing Reason: I approve this document Signing Time: 6/20/2018 11:09:19 AM EDT —8F3C422D6DE04C72AD395BC608A22CC5

Signature

June 20, 2018 | 11:12 AM EDT

Date

D

Francesca Conradie

Printed Name

# PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

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

Protocol Date: V2.0 13 JUNE 2018 Protocol Name: ZeNix

I hereby confirm that I have read the above protocol and agree to conduct this clinical trial as outlined in the above protocol. I will provide copies of the protocol and access to all the information required to conduct the clinical trial according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature

Printed Name

Date

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# Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse drug reactions
AE	Adverseevent
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	Aminotransferase
AUC	Area under curve over a dosing interval
В	Bedaquiline
BMI	Body mass index
bpm	Beats per minute
BPNS	Briefperipheral neuropathy scale
С	Clofazimine
CFU	Colony forming units
CK(-MB)	Creatine kinase (-MB isoenzyme)
$C_{(max),}$	Plasma concentration (maximum), (minimum)
(min)	
CO <sub>2</sub>	Carbon dioxide
CPK	Creatinephosphokinase
CS	Clinically significant
$C_{trough}$	Plasma concentration trough
CYP3A4	Cytochrome P450 3A4
DMID	Division of microbiology and infection disease
DNA	Deoxyribonucleicacid
DOH	Department of health
DILI	Drug induced liver injury
DSMC	Data safety monitoring committee
	, ,

DST	Drug susceptibility testing
EBA	Early bactericidal activity
EC	Ethics committee
ECG	Electrocardiogram
	Etawrenz
	Electronic case report form
FQ	Fluoroquinoione
	Grams per liter
GI	Gastrointestinal
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GMR	Geometric mean ratio
Н	Isoniazid
hERG	Human ether-à-go-go related gene
HIV	Human immunodeficiency virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
	Informed consent form
	International Conterence on Harmonization
IRR	Institutional review board
	International Union Against Tuberculosis and Lung Disease
IXRS	Interactive Voice and Web Response System
ka	Kilogram
/Ľ	Liter
L	Linezolid
LLN	Lower Limit of Normal
LPV	Lopinavir
	Monagemine evideo e (Inhibiter)
MAD(I)	Minimum bactoricidal doso
MIC	Minimum inhibitory concentration
MTB	Mycobacteriumtuberculosis
MDR-TB	Multi drug resistant tuberculosis
MGIT	Mycobacterial growth inhibiting tube
mITT	Modified intent to treat
mL	Milliliter
ms	Millisecond
NCS	Not clinically significant
	New England Journal of Medicine
	Newrapine
NOAFI	No observed adverse effect level
NRTI	(Triple) nuleosidase reverse transcriptase inhibitor
Pa	Pretomanid
PD	Pharmacodynamic
PP	Perprotocol
PK	Pharmacokinetic
PR	PRinterval
QD	Oncedaily
R	Rifampicin
S	Streptomycin
SAE	Serious adverse event

SAP SIRE	Statistical analysis plan Streptomycin isoniazid rifampicin ethambutol 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

Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version V2.0 13 JUNE 2018 Protocol Name: ZeNix

# 1 Synopsis

# 1.1 Synopsis Summary

Name of	Global Alliancefor TB D	rug Development												
Name of Finished	bedaguiline (B) pretomanid (Pa) and linezolid (L)													
Products:	bedaquillie (b), pretorna													
Protocol Number/Title:	NC-007: A Phase 3 part	ially-blinded. randomized trial	assessing the safety											
	and efficacy of various d	oses and treatment durations	of linezolid plus											
	bedaquiline and pretoma	anid in participants with pulmo	nary infection of either											
	extensively drug-resista	nttuberculosis (XDR-TB), pre-2	XDR-TB or treatment											
	intolerant or non-response	sive multi-drug resistant tuber	culosis (MDR-TB)											
Treatment Indication:	Pulmonary XDR-TB, pre MDR-TB	-XDR-TB, and treatment intole	erantor non-responsive											
Trial Objective:	To evaluate the efficacy	, safety and tolerability of vario	us 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													
Trial Danimur	intolerant or non-responsive MDR-TB.													
Trial Design:	treatment groups Beda	quiling and pretomanid treats	nent will not be blinded											
	Linezolid treatment dose	and duration will be double-b	linded											
	Participants will have	a screening period of up t	o 14 days and will be											
	randomized to receive o	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 t	o make this decision. All decis	ions regarding treatment											
	Monitor before implement	ntation	y the sponsor metrical											
	Participants will be followed for 78 weeks after end of treatment.													
	Participants will be follow	wed for 78 weeks after end of	reatment.											
Patient Population:	Participants will be follow A total of up to 180 parti	wed for 78 weeks after end of f cipants, male and female, age	reatment. d 14 and over Sponsor											
Patient Population:	Participants will be follow A total of up to 180 parti may consider replacement detailed in the statistical	wed for 78 weeks after end of t cipants, male and female, age ent of late screen failure and u analysis plan) participants	reatment. d 14 and over Sponsor n-assessable (as											
Patient Population:	Participants will be follow A total of up to 180 parti may consider replacement detailed in the statistical The regimen will be sup	wed for 78 weeks after end of f cipants, male and female, age ent of late screen failure and un analysis plan) participants. plied as the following:	reatment. d 14 and over Sponsor n-assessable (as											
Patient Population: Test product, Dose and Mode of Administration:	Participants will be follow A total of up to 180 parti may consider replacement detailed in the statistical The regimen will be sup	wed for 78 weeks after end of f cipants, male and female, age ent of late screen failure and un analysis plan) participants. plied as the following:	reatment. d 14 and over Sponsor n-assessable (as											
Patient Population: Test product, Dose and Mode of Administration:	Participants will be follow A total of up to 180 parti may consider replacement detailed in the statistical The regimen will be sup	wed for 78 weeks after end of f cipants, male and female, age ent of late screen failure and un analysis plan) participants. plied as the following: Tablet Strength	reatment. d 14 and over Sponsor n-assessable (as <b>Abbreviation</b>											
Patient Population: Test product, Dose and Mode of Administration:	Participants will be follow A total of up to 180 parti may consider replacement detailed in the statistical The regimen will be sup <b>Product</b> Bedaquiline	wed for 78 weeks after end of 1 cipants, male and female, age ent of late screen failure and un analysis plan) participants. plied as the following: Tablet Strength 100 mg	reatment. d 14 and over Sponsor n-assessable (as Abbreviation (B)											
Patient Population: Test product, Dose and Mode of Administration:	Participants will be follow A total of up to 180 parti may consider replacemend detailed in the statistical The regimen will be sup <b>Product</b> Bedaquiline Pretomanid	wed for 78 weeks after end of f cipants, male and female, age ent of late screen failure and un analysis plan) participants. plied as the following: Tablet Strength 100 mg 200 mg	Abbreviation (Pa)											
Patient Population: Test product, Dose and Mode of Administration:	Participants will be follow A total of up to 180 parti may consider replacement detailed in the statistical The regimen will be sup <b>Product</b> Bedaquiline Pretomanid Linezolid (scored)	wed for 78 weeks after end of 1 cipants, male and female, age ent of late screen failure and un analysis plan) participants. plied as the following: <b>Tablet Strength</b> 100 mg 200 mg 600 mg	Abbreviation (B) (L)											
Patient Population: Test product, Dose and Mode of Administration:	Participants will be follow A total of up to 180 parti may consider replaceme detailed in the statistical The regimen will be sup <b>Product</b> Bedaquiline Pretomanid Linezolid (scored) Placebo Linezolid	wed for 78 weeks after end of f cipants, male and female, age ent of late screen failure and un analysis plan) participants. plied as the following: <b>Tablet Strength</b> 100 mg 200 mg 600 mg placebo	Abbreviation (B) (L) (L) (L)											
Patient Population: Test product, Dose and Mode of Administration:	Participants will be follow A total of up to 180 parti may consider replacement detailed in the statistical The regimen will be sup <b>Product</b> Bedaquiline Pretomanid Linezolid (scored) Placebo Linezolid (scored)	wed for 78 weeks after end of f cipants, male and female, age ent of late screen failure and un analysis plan) participants. plied as the following: Tablet Strength 100 mg 200 mg 600 mg placebo	Abbreviation (B) (L) (L)											
Patient Population: Test product, Dose and Mode of Administration:	Participants will be follow A total of up to 180 parti may consider replacement detailed in the statistical The regimen will be sup <b>Product</b> Bedaquiline Pretomanid Linezolid (scored) Placebo Linezolid (scored)	wed for 78 weeks after end of f cipants, male and female, age ent of late screen failure and un analysis plan) participants. plied as the following: Tablet Strength 100 mg 200 mg 600 mg placebo	Abbreviation (B) (L) (L)											

Placebolinezolid 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 admini a meal in the following do	istered orally, once daily, with a bosing schemes (treatment arm	a full glass of water and is):										
<ul> <li>Participants will receive t</li> <li>Bedaquiline 200 m 18 weeks plus;</li> <li>Pretomanid 200 m</li> <li>Linezolid- participa following four blind</li> </ul>	<u>he following:</u> ng once daily for 8 weeks then ng once daily for 26 weeks plus ants will be randomly assigned ed linezolid treatment doses a	100 mg once daily for s; to receive one of the and durations:										
Linezolid 1200 mg daily 2 linezolid 600 mg 1/2 (one half) place	for <u>26 weeks</u> active tablets once daily for 26 po linezolid tablet once daily fo	3 weeks r 26 weeks										
Linezolid 1200 mg daily Weeks 1-9 • 2 linezolid 600 mg • $\frac{1}{2}$ (one half) place Weeks 10-26 • 2 placebo linezolid • $\frac{1}{2}$ (one half) place	for 9 weeks active tablets once daily for 9 po linezolid tablet once daily fo tablets once daily for 17 week po linezolid tablet once daily fo	weeks r 9 weeks :s r 17 weeks										
Linezolid 600 mg daily fo 1 linezolid 600 mg 1 placebo linezolid 1/2 (one half) placebo	o <u>r 26 weeks</u> active tablet once daily for 26 I tablet once daily for 26 weeks too linezolid tablet once daily fo	weeks s r 26 weeks										
Linezolid 600 mg daily fo Weeks 1-9 1 linezolid 600 mg 1 placebo linezolid 1/2 (one half) placeb	o <u>r 9 weeks</u> active tablet once daily for 9 w I tablet for 9 weeks po linezolid tablet once daily fo	reeks r9weeks										
Weeks 10-26 • 2 placebo linezolid • ½ (one half) placeb	l tablets once daily for 17 week oo linezolid tablet once daily fo	s r 17 weeks										
Treatment Modification The above treatment sc noted below. All dose m Medical Monitor prior to required urgently for a sa within 24 hours of the ch	<b>1s:</b> hemes may require modificatio odifications should be discuss implementation, unless a paus afety concern; the Medical Mo hange if not discussed prior to	on due to toxicities as ed with the Sponsor se or dose reduction is nitor should be informed 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:
	• <b>Blinded</b> 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.
	<ul> <li>1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or</li> <li>600 mg QD to 300 mg QD, 300mg QD to placebo</li> <li>Temporary pause of linezolid.</li> </ul>
	Permanent discontinuation of line zolid
	<ul> <li>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.</li> </ul>
	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 fa	ilure 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<sub>trough</sub>, C<sub>max</sub>, AUC<sub>T</sub>, C<sub>mean</sub>, 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:

~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).

# 1.2 Synopsis Flowchart

Period	Screening <sup>a</sup>	Treatment										arly om	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	Visits every 3 weeks if treatment extended <sup>b</sup>	End of OR Ea Withdrawal fr Treatment <sup>c</sup>	4 weeks	8 weeks	12 weeks	26 weeks	39 weeks	52 weeks	65 weeks	78 weeks/EW°
Visit Window <sup>q</sup>	N/A		+/- 3 days				+/- 5 days							+/- 7 days	Post last dose IMP +/- 14 days +7 days												
Informed Consent	Х																										1
Demography	Х																										
Med/Trtmnt/Smoking History	Х																										ĺ
Inclusion/Exclusion <sup>d</sup>	Х	Х																									1
Randomization		Х																									1
KarnofskyAssessment	Х																										
HIV Status <sup>e</sup>	Х																										(
CD4 Count and Viral Load <sup>f</sup>	Х																		Х								
Chest X-Rav <sup>g</sup>	Х																		Х								
Urine Pregnancy Test <sup>h</sup>	X	Х								Х				Х					X								
TB Symptoms Profile	X		1							X				X	1				X				Х		Х		X
Patient Reported Health Status	X		1							X				X	1				X				X		X		X
Slit Lamp Exam <sup>i</sup>	X																		Vi			Х					Ê
Ophthalmic Exam <sup>j</sup>	X					х				х		х		Х		Х	х	X	X	х		X					
Vital Signs	X	Х	Х	Х		X		Х		X		X		X		X		X	X	~		X	Х	Х	Х	х	X
Single 12-LeadECG <sup>k</sup>	X	X	X			X				X				X					X			7.		~			Ê
Limited Physical Fxam <sup>1</sup>	χ	~	X	х		X		х		X		х		X		Х		Х	X			Х	Х	х	х	Х	X
Full Physical Exam <sup>1</sup>	X	х		, î		~		, î		~									X			~	~	~	~	~	Ê
Laboratory Safety Tests (includes Full Blood Count) <sup>m</sup>	x	X	х	х	х	х		х		х		х		х		х	х	Х	X								
Full Blood Count							Х		Х		Х		Х		Х												1
Con Meds	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Adverse Events	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Study Medication/Compliance <sup>n</sup>		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	Х								
PK Sampling <sup>o</sup>		X		X						X		X				X			Y0								
Farly Morning & Spot Sputum <sup>r</sup>	х	X	X	X	х	х		х		X	х	X	1	X	1	X	X	X	X	х	Х	Х	Х	х	х	х	X
Peripheral Neuropathy		Ê		Ê	Ê	$\hat{\ldots}$		Ê		$\hat{\Box}$			1								~				$\hat{\cdot}$		É.
Assessment	X					Х				Х		X		X		X	Х	X	Х			Х	Х		Х		X
Investigator Assessment <sup>p</sup>				I	l I		I	I				1				1							Х				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 <u>6.3</u>, 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 AFTÉR 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  $\leq$  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.
- **Ophthalmic Exam:** to include Ophthalmologic Medical history at Screening; All exams to j. 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.
- Single 12-Lead ECG: When possible, should be performed at approximately the same time k. 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.
- **Physical Exam:** Limited Physical exams should include weight and a gross neurological, 1 pulmonary, cardiovascular and abdominal exam. Height will only be collected as part of full exam at screening.
- Safety Laboratory Assessments/Urine Drug Screen: The Safety Laboratory sampling m 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.
  - amphetamines. Urine Screen: Cannabinoids, Drug cocaine, 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.
- Study Medication/Compliance: Study medication administration will be supervised per local n. site practice to assure compliance to regimen.
- PK Sampling: The dates and times of the two doses of IMP taken prior to all pre-dose PK Ο. 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 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:

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

**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.<sup>(43)</sup> 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, bedaguiline 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.<sup>(28)</sup> In another report from South Africa of 114 patients with XDR-TB, 22% completed treatment successfully.<sup>(21)</sup> 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.<sup>(42)</sup> A meta-analysis of 397 patients with XDR-TB from 31 centers, with HIV coinfection <10%, reported 32% treatment success.<sup>(17)</sup> Reports of the outcome of XDR-TB treatment from Peru (43 patients, 42% treatment success)<sup>(2)</sup> and Ukraine (114 patients, 22% treatment success)<sup>(11)</sup> 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%.<sup>(29)</sup> 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.<sup>(43)</sup> 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<sup>(9)</sup> 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).<sup>(1)</sup>

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 (200 mg) 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.

### Efficacy of bedaquiline 200 mg daily dose vs the marketed dosing scheme over 8 weeks

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.

### Safety of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.

### Pharmacokinetics of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.<sup>(14)</sup> 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<sub>max</sub>, 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 bedaguiline or pyrazinamide over 14 days in the early bacteriocidal activity (EBA) Study NC-001-(B-M-Pa-Z), in combination with either bedaguiline 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 relapsefree 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<sup>™</sup>. 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. Drugdrug 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/riton avir, 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 multipledose efavirenz (EFV) resulted in approximately a 20% decrease in the AUC<sub>inf</sub> of bedaquiline with no alteration in the C<sub>max</sub>. Modeling based on the data from this DDI study predicts average steadystate 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.<sup>5</sup>

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.

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)					
Cardiacdisorders								
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)					
He patobiliary disorders								
Transaminases increased <sup>a</sup> 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)					

## Table 1:ADRs C208 Stage 1 and Stage 2

<sup>a.</sup> 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.<sup>(7)</sup>

# 2.2.2 Pretomanid

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

# 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,  $\leq 0.015$  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.<sup>(6)</sup>

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), <sup>(33)</sup> 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.<sup>(12,13)</sup>

## 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.<sup>(18,19,20,36,40)</sup> 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.<sup>(6)</sup>

# 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  $\geq$ 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  $\geq 100 \text{ mg/kg/day}$ , and early deaths occurred at doses  $\geq 500 \text{ mg/kg/day}$ . Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at  $\geq 450/300 \text{ mg/kg/day}$ . These effects were reversible when dosing stopped and were absent at  $\leq 30 \text{ mg/kg/day}$  in rats and  $\leq 150 \text{ mg/kg/day}$  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  $\geq 150 \text{ mg/kg/day}$ .

## 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.

<u>Drug interaction with midazolam:</u> 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<sub>0-t</sub>), and area under the curve extrapolated to infinity (AUC<sub>0-inf</sub>). The C<sub>max</sub> 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<sub>max</sub>) was 0.71, the GMR for the 24-hour area under the time-concentration curve (AUC<sub>0-24h</sub>) was 0.65, and the GMR for the trough</sub>concentration (C<sub>min</sub>) 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<sub>max</sub> was 0.87, for AUC<sub>0-24h</sub> was 0.83, and for C<sub>min</sub> 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<sub>max</sub>, AUC<sub>0-24h</sub>, and C<sub>min</sub> 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<sub>0-</sub>

 $_{24h}$ ), and trough concentration (C<sub>min</sub>) 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 or al 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 <sup>(4)</sup> (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<sup>(6)</sup> 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 concem.

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.<sup>(23,24,26)</sup> Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism.<sup>(8)</sup> 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.<sup>(9)</sup>

Preclinical *in vitro* data shows linezolid is active against MTB, including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1  $\mu$ g/mL.<sup>(38)</sup> 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.<sup>(36)</sup> (Table 3, below)

Table 3:	Murine Lung CFU counts during Treatment with Linezolid
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	Mean lung log <sub>10</sub> CFU count (± S.D.) at:							
Regimen	D0	Month 1	Month 2	Month 3				
Untreated	6.17 <u>+</u> 0.27	6.47 <u>+</u> 0.06						
2RHZ/4R H		3.47 <u>+</u> 0.37	1.59 <u>+</u> 0.25	0.50 <u>+</u> 0.51				
L		4.97 <u>+</u> 0.26						

#### Monotherapy versus Standard Therapy

In recent years linezolid has been used to treat patients with MDR<sup>(28)</sup> 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.<sup>(41)</sup> 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.<sup>(9, 27, 34)</sup> 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.<sup>(9)</sup> 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 sputumsmear 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). <sup>(9)</sup> 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.<sup>(3,9)</sup> The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label.<sup>(23,24,26)</sup> 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.
- 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 hypoglycemic reactions when treated with linezolid, 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 Coxwhich noted the proportion of adverse events necessitating treatment discontinuation was significantly different by dose:

29.49% (95%Cl 3.24–55.74) for  $\leqslant$ 600 mg daily vs. 60.75% (95%Cl 42.69–78.81) for >600 mg daily (P = 0.05).  $^{(3)}$ 

In a trial reported by Lee et al in S Korea<sup>(9)</sup>, seven of 41 participants had myelosuppression, including anemia and neutropenia, <u>primarily within the first 5 months</u>, 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 ( $\geq$ 3 months) and in all patients reporting new visual symptoms, regardless of length of therapy.<sup>(26)</sup>

In Lee, NEJM, 2012<sup>(9)</sup>, 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<sup>(32)</sup>, 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<sup>(27)</sup>, 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<sup>(34)</sup>, 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 <sup>(5,36)</sup> 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<sup>(15)</sup> and in a subsequent study it was more active in the mouse model than HRZ.<sup>(16)</sup> 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.<sup>(37)</sup>

## 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					
2DU7/DU*		8/14					
		(57%)					
RDa		3/14					
DFa		(21%)					
3BDal **	6/15	0/15#†					
JDFaL	(40%)	(0%)					
280al /180a***		0/15#†					
		(0%)					
1BDal /2BDa	9/15	0/15#†					
	(60%)	(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<sub>CFU(0-14)</sub>

Treatment Group	N	Daily Mean (SD) EBA <sub>CFU(0-14)</sub>		
Pretomanid + pyrazinamide + moxifloxacin	13	0.23 (0.128)		
Pretomanid + pyrazinamide	14	0.15 (0.040)		
Pretomanid + bedaquiline	15ª	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)		

Derived Using Bi-Linear Regression, Study NC-001

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<sub>(0-14)</sub>).

### Table 6: NC-003 Efficacy Results: Daily BAlog<sub>CFU(0-14)</sub>

Arm	logCFU
BPaZC	.124
BPaZ	.180
BPaC	.086
BZC	.098
Z	.036
С	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

	BPaZ C	BPaZ	BPa C	BZC	Z	С	HRZ E	Total
Ν	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		1						1
of study drug		I						I
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  $\geq$ 500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of  $\geq$ 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

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visits of  $\geq$ 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 the 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. Fortynine 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.

<u>Safety of the B-Pa-L Regimen in the Nix-TB Study</u>: 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

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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<sup>(28)</sup>. 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.<sup>(43)</sup> 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 bedaguiline 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	<ul> <li><u>Linezolid 1200 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
2	<ul> <li>Linezolid 1200 mg daily for 9 weeks followed by linezolid placebo for 17 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
3	<ul> <li><u>Linezolid 600 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
4	<ul> <li>Linezolid 600 mg daily for 9 weeks followed by linezolid placebo for <u>17 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>

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. Retesting 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.

### Disease Characteristics:

- 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 <u>or</u> using effective methods of birth control, as defined below:

### Non-childbearing potential:

- a. Participant not heterosexually active or practices sexual abstinence; or
- 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) <  $17 \text{ kg/m}^2$
- 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 with in 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 (<u>Appendix 2</u>). Or, participants with a Grade 1 or 2 neuropathywhich 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<sup>3</sup> or < 100 x 10<sup>9</sup>/L;
  - f. Absolute neutrophil count (ANC) < 1500/ mm<sup>3</sup> or <  $1.5 \times 10^{9}/L$ ;
  - g. Aspartate aminotransferase (AST)
    - Grade 3 or greater ( $\geq$  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 ( $\geq$  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
  - I. 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, 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 followup visits as described in <u>Table 9</u>:

Treatment Duration at EW visit	Ophthalmology Examination at EW <sup>a</sup>	Ophthalmology Examination 12 week Post treatment follow- up visit <sup>a</sup>	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

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

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).
- <u>At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status,</u> 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 IMPParticipants 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 o 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 reviewBoard (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 <u>Table 9</u>. 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
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Treatment Group	Active and Placebo
Linezolid 1200 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>1/2 (one half) placebo linezolid tablet once daily for 26 weeks</li> </ul>
<u>Linezolid 1200 mg</u> <u>daily for 9 weeks</u>	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid tablets once daily for 17 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 17 weeks</li> </ul>
Linezolid 600 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid tablet once daily for 26 weeks</li> <li>1⁄2 (one half) placebo linezolid tablet once daily for 26 weeks</li> </ul>
Linezolid 600 mg daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9 <ul> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid tablet for 9 weeks</li> <li>1/2 (one half) placebo linezolid tablet once daily for 17 weeks</li> <li>2 placebo linezolidtablets once daily for 17 weeks</li> <li>1/2 (one half) placebo linezolid tablet once daily for 17 weeks</li> </ul> </li> </ul>

# 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;
  - o 600 mg QD to 300 mg QD, 300 mg 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<sup>(5,6)</sup>. The complete formulations of linezolid are found in the Package Inserts<sup>(23,24,26)</sup>.

The IMP will be packaged as follows:

- Bedaquiline: Bottles containing:
  - o 200 mg QD dose- 28 tablets- bedaquiline 100 mg
  - o 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:
  - o 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
  - o 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
  - o 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 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.

## 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-Chemiluminesœnœ).
  - 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 (<u>Appendix 4</u>).
- 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<sub>2</sub>, 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<sub>T</sub>,  $C_{mean}$ , 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).

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- 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.

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).

## Table 11: Adverse Events Attribution/Causality Ratings

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

See <u>Appendix 2</u> 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 nonleading 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.

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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 <u>will follow the same time lines for a SAE</u> (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<sup>(5,6)</sup> and Package Inserts.<sup>(23,24,25,26)</sup> Please reference section <u>6.3</u> 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 <u>Appendix 5</u> – 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  $\leq$  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<sup>9</sup>/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-ofcare 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 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 (L120026 weeks) with the L12009 weeks and L60026 weeks only being tested if L120026 weeks is a success. Similarly, L6009 weeks will only be tested if L60026 weeks is a success. A Bonferroni adjustment will be made for comparing the L12009 weeks and L60026 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;
  - o 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</li>
    - 450 msec < QT/QTc < 480 msec</p>

- 480 msec < QT/QTc < 500 msec</p>
- QT/QTc <u>></u>500 msec
- o QTc changes from baseline will be classified into the following categories:
  - increase < 30 msec,</li>
  - 30 msec and < 60 msec, and
  - increase <u>>60 msec.</u>
- 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 <u>Appendix 3</u>), 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, AUCT, 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, ICHGCP, 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 Pl/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 retum; 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 reviewsite 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. <sup>(30)</sup>

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 Access described Foundation's Open Policy as 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, eitherfor 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.

# 16 References

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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

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

**ABBREVIATIONS:** Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal	
$R_x$ = Therapy	Reg = 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 <sup>3</sup>	750-999/mm <sup>3</sup>	500-749/mm <sup>3</sup>	<500/mm <sup>3</sup>	
Platelets	75,000- 99,999/mm <sup>3</sup>	50,000- 74,999/mm <sup>3</sup>	20,000- 49,999/mm <sup>3</sup>	<20,000/mm <sup>3</sup>	
WBCs	11,000-13,000/ mm <sup>3</sup>	13,000-15,000 /mm <sup>3</sup>	15,000- 30,000/mm <sup>3</sup>	>30,000 or <1,000 /mm <sup>3</sup>	
% 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 w ith gross bleeding or w ith 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 Throm boplastin (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 <i>with</i> 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 <i>with</i> 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 <i>with</i> ketoacidosis or seizures	

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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 <i>with</i> life threatening arrhythmia or tetany
<b>Hypercalcemia</b> (correctfor 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 (w hen 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

Hematuriamicroscopic only <10 rbc/hpf	gross, w ith or w ithout clots, OR red blood cell casts	obstructive or required transfusion
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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; outpatienttreatm ent 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 w ith 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 <sub>1</sub> of peak flow	requires treatment; normalizes with bronchodilator; FEV <sub>1</sub> 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV <sub>1</sub> 25% - 50% of peak flow; or retractions present	cyanosis: FEV <sub>1</sub> < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea w ith normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy
GASTROINTESTINAL				
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	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 w eek	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 w eek	<ul> <li>7 loose stools/day         <ul> <li>or bloody diarrhea;</li> <li>or orthostatic</li> <li>hypotension or</li> <li>electrolyte</li> <li>imbalance or &gt;2L</li> <li>N fluids required</li> </ul> </li> </ul>	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty sw allow ing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

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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 w eakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective w eakness 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 w rists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and low er 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 w ith activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint sw elling – but not interfering with function	moderate pain with inflammation, erythema or joint sw elling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint sw elling –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 w ork	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 v	alues			
"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	%
	Normal no complaints; no evidence of disease.	100
Able to carry on normal activity	Able to carry on normal activity; minor signs or	90
and to work; no special care	symptoms of disease.	
needed.	Normal activity with effort; some signs or symptoms of disease.	80
l babla ta warke abla ta liva at	Cares for self; unable to carry on normal activity or to	70
home and care for most personal needs; varying amount of	do active work.	
	most of his personal needs.	60
assistance needed.	Requires considerable assistance and frequent medical	50
	care.	
	Disabled; requires special care and assistance.	40
I lnable to care for self: requires	Severely disabled; hospital admission is indicated	30
equivalent of institutional or hospital care; disease may be progressing rapidly.	although death not imminent.	00
	Very sick; hospital admission necessary; active	20
	supportive treatment necessary.	20
	Moribund; fatal processes progressing rapidly.	10
	Dead	0

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109<sup>(22)</sup>.

# 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;<sup>(31,39)</sup>; 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.
- 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 bilirub in 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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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:

To contact us by email send messages to: christi.baine@tballiance.org

# 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. In addition, you must notify DocuSign, Inc to arrange for your new email address to be reflected in your DocuSign account by following the process for changing e-mail in DocuSign.

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Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS): Internet Explorer 6.0?, Mozilla FireFox	
	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

#### Required hardware and software

\*\* 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

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#### 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:**

<ul> <li>Synopsis Summary, 1.2 Synopsis Flowchart and</li> <li>Removed limitation of 60 non-XDR participants/rewho are either XDR, pre-XDR or MDR intolerant of Trial Design)</li> </ul>	4.2 Treatment Plan: Schedule of Assessments, 5. Trial Population.) equirement for 120 XDR participants. Enrollment to include 180 participants or non-responsive. (In section 1.1 Synopsis summary and 4.1 Summary of
2 <b>Removed</b> limitation of 60 non-XDR participants/re who are either XDR, pre-XDR or MDR intolerant of Trial Design)	equirement for 120 XDR participants. Enrollment to include 180 participants or non-responsive. (In section 1.1 Synopsis summary and 4.1 Summary of
who are either XDR, pre-XDR or MDR intolerant of	or non-responsive. (In section 1.1 Synopsis summary and 4.1 Summary of
Trial Design)	
Thai Design)	
3 Updated randomization details, specifically abbre	viation of phone/web system utilized (changed IWRS to IXRS) and
"minimization" to "stratification". (In section 1.1 S	nopsis Summary, 4.1 Summary of Trial Design, and 6.5 Method of
Treatment Assignment)	
4 <b>Clarified</b> 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 S	ynopsis Summary, 1.2 of Synopsis Flowchart, and 4.1 Summary of Trial
Design)	
5 <b>Clarified</b> language throughout the protocol to spe	cify when Sponsor Medical Monitor's approval vs. notification required (In
section 1.1 Synopsis, 4.1 Summary of Trial Desig	n, 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 f	or Specific Toxicities)
6 <b>Clarified</b> descriptions of regimen and dosing inst	ructions to note linezolid 600 mg full or half tablets and placebo full or half
tablets vs. 300 mg half tablet or linezolid 300 or 6	00 mg placebo. (In section 1.1 Synopsis Summary, 6.1 IMP Administration,
and 6.4 IMP Packaging and Labelling)	
7 <b>Clarified</b> 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 dosi	ng required (when missed more than 7 days) and deleted (when repetitive)
or moved wording. (In section 1.1 Synopsis Sum	mary and 6.3 Treatment Modification[s])

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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	<b>Updated</b> 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)

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	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)
	<b>Clarified</b> use of pre-screening, adding scenario to support testing for inclusion into the trial. (In section 1.2 Synopsis
	Flowchart)
	<b>Removed</b> details on handling of pre-screening samples. (In section 1.2 Synopsis Flowchart and 7.5 Mycobacteriology
	Characterization and Variable and Procedures)
	<b>Moved</b> 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)
	<b>Clarified</b> 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	<b>Removal</b> 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
	temale 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 normone 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 <b>removal</b> 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)

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	<b>Removed</b> 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) <b>Changed</b> 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	<b>Updated</b> Discontinuation from Treatment/Trial section: <b>Clarified</b> when participant "must" be withdrawn ys "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 visite/assessments are done post early withdrawal (In section 5.4.3 Unscheduled Visite)
	<b>Removed</b> 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)

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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 fort 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

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		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 re an ongoing TB infection current treatment to 39 16 and week 26 are con- isolated positive withour results should be used treatment extension sl Sponsor Medical Moni- Participants will be foll	eceive 26 weeks of treation, Investigator may con 9 weeks. If the culture rontaminated, missing or ut clinical significance, a d to make this decision. hould be discussed with itor before implementation owed for 78 weeks after	ment they may have sider extending esults between week considered an vailable culture All decisions regarding and approved by the on. 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 par Sponsor may consider assessable (as detaile	ticipants male and fema r replacement of late scr ed in the statistical analy	ale, aged 14 and over. een failure and un- sis plan) participants.	2
3	Summary	<ul> <li>bedaquiline 100 mg tablets</li> <li>pretomanid 200 mg tablets</li> <li>linezolid (scored) 600 mg tablets</li> <li>placebo linezolid (scored) 600 mg tablets</li> <li>linezolid half tablet (pre-cut) 300 mg</li> <li>placebo linezolid half tablet (pre-cut) 300 mg</li> <li>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.</li> <li>Treatment will be administered orally, once daily, with a full glass of water and a meal in the following dosing schemes (treatment arms):</li> </ul>	Product Bedaquiline Pretomanid Linezolid (scored) Placebo Linezolid (scored) Linezolid 600 mg half tablet (pre- cut) Placebo linezolid 600 mg half tablet (pre-cut)	Tablet Strength 100 mg 200 mg 600 mg placebo 300 mg placebo	Abbreviation (B) (Pa) (L) (L) (L) (L)	Ū
		<ul> <li>Participants will receive the following:</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks plus;</li> <li>Linezolid- participants will be randomly assigned to receive one of the following four linezolid treatment doses and durations:</li> </ul>	Linezolid treatment v or placebo) and one for all possible dosin Instructions for Dosing	will be supplied as 2 row row of half-tablets (activ ig options while maintair <u>1:</u>	s of full tablets (active æ or placebo) to allow ning the blind.	

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<ul> <li>Linezolid 1200 mg daily for 26 weeks</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> </ul>	Treatment will be administered orally, once daily, with a full glass of water and a meal in the following dosing schemes (treatment arms):
<ul> <li>Linezolid 1200 mg daily for 9 weeks</li> <li>Weeks 1-9 <ul> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> </ul> </li> <li>Weeks 10-26 <ul> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> </ul> </li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>	<ul> <li>Participants will receive the following:</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks plus;</li> <li>Linezolid- participants will be randomly assigned to receive one of the following four blinded linezolid treatment doses and durations:</li> <li>Linezolid 1200 mg daily for 26 weeks</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 26 weeks</li> </ul>
<ul> <li>Linezolid 600 mg daily for 26 weeks</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> <li>Linezolid 600 mg daily for 9 weeks</li> <li>Weeks 1-9 <ul> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 9 weeks</li> <li>2 placebo linezolid 600 mg tablet once daily for 9 weeks</li> </ul> </li> <li>1 placebo linezolid 600 mg tablet once daily for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 9 weeks</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>	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 ½ (one half) placebo linezolid tablet once daily for 26 weeks ½ (one half) placebo linezolid tablet once daily for 26 weeks ½ (one half) placebo linezolid tablet once daily for 9 weeks ½ (one half) placebo linezolid tablet once daily for 9 weeks 2 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 2 linezolid 600 mg active tablet once daily for 9 weeks 2 linezolid 600 mg active tablet once daily for 9 weeks 2 linezolid 600 mg active tablet once daily for 9 weeks 2 linezolid 600 mg active tablet once daily for 9 weeks 2 linezolid 600 mg active tablet once daily for 9 weeks 2 linezolid 600 mg active tablet once daily for 9 weeks 2 linezolid 600 mg active tablet once daily for 9 weeks 2 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 3 linezolid 600 mg active tablet once daily for 9 weeks 4 linezolid 600 mg active tablet once daily for

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			• 1/2 (one half) placebo linezolid tablet once daily for 17 weeks	
			Linezolid 600 mg daily for 9 weeks	
			<ul> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> </ul>	
			<ul> <li>1 placebo linezolid tablet for 9 weeks</li> </ul>	
			• 1/2 (one half) placebo linezolid tablet once daily for 9 weeks	
			Weeks 10-26	
			<ul> <li>2 placebo linezolid tablets once dally for 17 weeks</li> <li>1/2 (one half) placebo linezolid tablet once daily for 17 weeks</li> </ul>	
	1.1 Synopsis	Treatment Modifications:	Treatment Modifications:	
	Summary	The above treatment schemes may require modification due to toxicities	The above treatment schemes may require modification due to	7
		as noted below. All dose modifications should be discussed with the	toxicities as noted below. All dose modifications should be	
		Sponsor Medical Monitor prior to implementation, unless a pause or	discussed with the Sponsor Medical Monitor prior to	
		Monitor should be informed within 24 hours of the change if not	urgently for a safety concern; the Medical Monitor should be	
		discussed prior to implementation	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	In the event of linezolid specific toxicities, the following should be	
		for specific toxicities section of protocol. Every effort should be made for	considered and implemented per guidance in the monitoring and	
4		required:	safety for specific toxicities section (8.3) of protocol:	
		Blinded one step reductions (maximum 3 steps) in the dose of	• Blinded one step reductions (maximum 2 steps) in the dose	
		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	of linezolid managed by the IXRS as per instructions in	
		in pharmacy manual and/or IWRS user manual.	$\circ$ 1200 mg QD to 600 mg QD, 600 mg QD to 300 mg	
		Temporary pause of linezolid due to a linezolid-specific toxicity	QD or	
		monitoring and safety for specific toxicities section of protocol.	<ul> <li>600 mg QD to 300 mg QD, 300mg QD to placebo</li> <li>Temporary pause of linezolid</li> </ul>	
		Permanent discontinuation of linezolid.	<ul> <li>Permanent discontinuation of linezolid.</li> </ul>	
		For participants experiencing suspected drug related toxicities due to	Participants who have a linezolid reduction can go back to a	
		other drugs in the regimen (B-Pa), the full regimen may be halted for up	nigner dose (1 step or 2 steps) post discussion with and approval by Sponsor Medical Monitor.	
		to 35 consecutive days.		

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5	1.1 Synopsis Summary 1.1 Synopsis Summary	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.         Primary Endpoint: Incidence of bacteriologic failure or relapse or clinical failure through follow up until 26 weeks after the end of treatment.         • 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,	<ul> <li>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.</li> <li>Interruptions/pauses of all Investigational Medicinal Product (IMP) must not exceed 8 weeks (56 days) cumulatively.</li> <li>When treatment is extended to 39 weeks, interruptions/pauses of all IMP must not exceed 13 weeks (91 days) cumulatively.</li> <li>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.</li> <li>At no time should the participant be treated with a single agent.</li> <li>Every effort should be made for participants to receive a total of 9 weeks of linezolid, even if pauses are required</li> <li>Primary Endpoint:</li> <li>Incidence of bacteriologic failure or relapse, or clinical failure at 26 weeks after the end of treatment.</li> <li>Descriptive statistics of ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2]) lens opacity will be summarized in a frequency table for the right or data for lens</li> </ul>	8 9
		respectively, including change from baseline.	and left eye, respectively, including observed and change from baseline	
7	1.1 Synopsis Summary	<b>Trial Duration:</b> ~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).	<b>Trial Duration:</b> ~3.5 Years (An enrolment period of at least 18 months plus 14 days pre-treatment plus 6 month <u>s</u> 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

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9	1.2 Synopsis Flowchart	<i>Captured in synopsis flowchart/</i> table (after week 23 treatment): Visits every 3 weeks if extended due to IMP pause or culture (+) at week 16	<i>Captured in synopsis flowchart/table (after week 23 treatment):</i> 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. <b>Screening:</b> 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	<ul> <li>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.</li> <li>1. If participant completes treatment at week 26, end of treatment visit should be done within 7 days after last dose of week 26.</li> <li>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.</li> <li>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)</li> </ul>	<ul> <li>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).</li> <li>1. End of treatment visit (final treatment visit) should be done within 7 days AFTER the last dose of IMP.</li> <li>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.</li> <li>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).</li> <li>4. Follow-up visits should be scheduled based on timing of end of last dose of IMP.</li> </ul>	12

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		<ul> <li>weeks plus 7-day window), visit at week 39 would be the end of treatment visit.</li> <li>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).</li> </ul>	follow-up to be scheduled 4 weeks after last dose of IMP).	
14	1.2 Synopsis Flowchart	<ul> <li>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:</li> <li>1. Received/took ≤ 14 doses, no additional follow-up visits are required.</li> <li>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 survival as per section "r".</li> </ul>	<ul> <li>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:</li> <li>1. Received/took ≤ 14 doses, no additional follow-up visits are required.</li> <li>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.</li> <li>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.</li> </ul>	11
15	1.2 Synopsis Flowchart	e. <b>HIV testing:</b> 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. <b>HIV testing:</b> 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

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		HIV testing, during the Screening period is permitted for indeterminate HIV results.	during the Screening period is permitted for indeterminate HN results.	
16	1.2 Synopsis Flowchart	f. <b>CD4 count and viral load:</b> For all HIV-positive participants, viral load and CD4 at screening, CD4 only tested at end of treatment or early withdrawal.	f. <b>CD4 count and viral load:</b> 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. <b>Chest X-Ray:</b> 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. <b>Chest X-Ray:</b> 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	<ol> <li>Physical Exam: Limited Physical exams should include weight and a gross neurological, pulmonary, cardiovascular and abdominal exam.</li> </ol>	I. <b>Physical Exam:</b> 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	<ul> <li>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: <ol> <li>Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count).</li> <li>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).</li> </ol> </li> <li>Urinalysis (pH, specific gravity, protein, glucose, microalbumin, ketones, bilirubin, creatinine, nitrite, sodium,</li> </ul>	<ul> <li>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:</li> <li>Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count).</li> <li>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,</li> </ul>	18

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		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.	<ul> <li>bicarbonate/CO2, creatine phosphokinase (CPK). GGT will be done at screening.</li> <li>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 cellinjury, hepatobiliary disease, hepatic viral infection).</li> <li>Urinalysis (pH, specific gravity, protein, glucose, microalbumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis.</li> <li>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.</li> </ul>	
21	1.2 Synopsis Flowchart	<ul> <li>o. PK Sampling: Specific PK blood draws as follows: <ol> <li>Day 1; pre-dose (within 2 hours prior to dosing)</li> <li>Week 2: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose</li> <li>Week 8: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose</li> <li>Week 12: pre-dose (within 2 hours prior to dosing)</li> <li>Week 12: pre-dose (within 2 hours prior to dosing)</li> <li>Week 12: pre-dose (within 2 hours prior to dosing)</li> <li>Week 12: pre-dose (within 2 hours prior to dosing)</li> <li>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.</li> </ol> </li> <li>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.</li> <li>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</li> </ul>	<ul> <li>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.</li> <li>Specific PK blood draws will be obtained as follows (pre-dose to be done after ECGs): <ol> <li>Day 1; pre-dose (within 2 hours prior to dosing)</li> <li>Week 2: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose</li> <li>Week 8: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose</li> <li>Week 12: pre-dose (within 2 hours prior to dosing)</li> <li>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</li> </ol> </li> <li>When participant is discharged and seen as an outpatient, site should make every effort to collect 6-8</li> </ul>	19

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#### Protocol Amendment Template

		cor line bec	mponents are ac ezolid due to tox daquiline and pre	dminis icity, etoma	stered samp anid a	d. If the bling sh are dos	site ha	as perr	nanen on a d	tly disc ay whe	ontinue In the	3	• • •	nour s ogist Hosp collect f the shoul resur PK s oartic Linez Sites unscl collect admin	san ica ital cteo full d b nec olic ma olic ma ct P nist	nple lly fe izat d in reg e de l. oline st ha ay b ule c Ks ere	at v easi ion i the ime elay g sh line s be ring d vis to el d.	weel ble. nforn eCR n or ed u ould een p part it (c nsur	a a transformation material from transformation bern icip an co e di	wher ion ( zolic full r com bse h nane bant b bccu raw i	d is d is egin plet has l ently back r ou s dc	erati disc paus nen ced e beer disc cat a tside one v	charg sed, l or lin low contin sch e of vi when	ly and ge date) wil PK samplir lezolid are f the ered or nued. eduled or isit window IMP is	ll be ng vs) to								
	1.0.0	r.	Sputum Sampling:									'	Sputum Sam	oling:												5 and 20							
	1.2 Synopsis Flowchart			Sa	mple			T	ests		_					Sam	ple		a) <sup>2</sup>		1	Tests	1	- 0									
											Visit	EMS*	Spot	AFB Smear microscopy	AGIT culture speciation	Molecular testing	MIC: B, Pa, L	Liquid DST	Genotyping		Visit		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 -9 to -1)		••	s	s	s					Screening (Day -14 to -1			•		S	S	s		
			Baseline (Day 1) or screen - wk4 if baseline negative or contaminated	•	•		s		с	с	С		Baseline (Day or 1st positive between scree and wk4 if Day negative or	1) ning 1			•				С	с	с	L (when applicable, with isolate below)									
22			All Visits Post Baseline	•	•		S						contaminated All Visits Post		-	-			6														
22			Positive for MTB at/after EoT		•		s	s	С	с	с		Screening 1st positive for at/after week	MTB 6 for	•	•			3														
		SP eve BA	C - Central laborator S - Study Laboratory	y (special y (facility t ES GE bllect lable,	lized faci that recei ENER two s site	AL: If E pot sar will rec	EMS is mples a	not ava at least	ailable t 30 mi reening inclus	, site sh nutes a g culture	nould ma apart. e that v	ke as	participant not responding to therapy and/o positive during follow-up for potential new infection C – Central S – Study N L – Lab (as "Preferably f contaminate	1st Mycobacte applicabl om EMS I, or the te	eriolo riology e per ( Samp est nee	gy Lab / Labor Country le wher eds to b	oratory atory (fa ) that po available repea	(special acility th erforms ble. Altr ated.	ized fa at rece extend ernate	s cility) eives spu ded DST isolate c	C utum sa beyond an be r	C Imples d d panel a equester	C lirectly fro at Centra d if initial	L om site) ti lab one is									

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#### **Protocol Amendment Template**

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	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 proceeded and explanated in the lab manual	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-screeping culture/isolate/DNA	
	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.	<ul> <li>from current TB diagnosis/disease course to be sub-cultured and shipped and/or tested:</li> <li>at the study lab if/when those samples could support inclusion in trial.</li> <li>at the study/central lab for relevant participants with no</li> </ul>	
	<ul> <li>MOLECULAR TESTING:</li> <li>At Screening: GeneXpert, Hain MTBDR<i>plus</i> or equivalent to determine MTB complex and R resistance.</li> <li>Positive MTB at/after end of treatment: Hain MTBDR<i>plus</i> and HainMTBR<i>sl</i></li> <li>LIQUID DST: for SIRE, Z and second line anti-TB drugs, including but not limited to FQ and injectables.</li> </ul>	<ul> <li>baseline (no positive cultures from screening through week 4).</li> <li>MOLECULAR TESTING: <ul> <li>At Screening: GeneXpert, Hain MTBDRplus or equivalent to determine MTB complex and Rifampicin resistance.</li> <li>Positive MTB at/after week 16: Hain MTBDRplus and HainMTBRs/</li> </ul> </li> </ul>	
	<ul> <li>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.</li> <li>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.</li> </ul>	<b>LIQUID DST</b> : for SIRE, Z and second line anti-TB drugs, including but not limited to fluoroquinolones and injectables. <b>STORAGE: MTB</b> 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.	
	<b>UNSCHEDULED VISITS</b> : If cultures of both spot sputum samples are contaminated <i>at the following visits</i> , 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:	<b>CENTRAL LAB</b> : 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).	

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		<ul> <li>End of treatment visit;</li> <li>Week 26 post treatment follow-up visit;</li> <li>Post treatment follow-up visits from week 8 through week 65 (in addition to week 26 follow-up);</li> <li>End of Follow-up Period (week 78 post treatment completion visit);</li> <li>Early Withdrawal (if applicable).</li> </ul> At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, need to confirm whether the participant has: <ul> <li>At least two sequential negative sputum culture results; or</li> <li>At least two sequential positive sputum culture results; or</li> <li>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</li></ul>	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.	
		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.		
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

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		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	<ol> <li>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</li> </ol>	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	<ul> <li>5. Participants with one of the following pulmonary TB conditions: <ul> <li>a. XDR-TB with</li> <li>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:</li> <li>ii. historical documented resistance to isoniazid, rifamycins, a fluoroquinolone AND an injectable during the current TB diagnosis/disease course;</li> <li>b. Pre-XDR-TB with</li> <li>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 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;</li> <li>ii. historical-documented resistance to isoniazid, rifamycins, and to a fluoroquinolone OR an injectable during the current TB diagnosis/disease course.</li> <li>c. MDR-TB with <ul> <li>i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected within 3 months prior to or at screening and;</li> </ul> </li> </ul></li></ul>	<ul> <li>5. Participants with one of the following pulmonary TB conditions: <ul> <li>a. XDR-TB with</li> <li>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:</li> <li>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);</li> <li>b. Pre-XDR-TB with</li> <li>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;</li> <li>ii. 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;</li> <li>ii. documented resistance to rifamycins, and to a fluoroquinolone <b>OR</b> an injectable during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid);</li> </ul> </li> </ul>	21

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	5.1 Inclusion	<ul> <li>3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and;</li> <li>ii. historical—documented resistance to isoniazid and rifamycins during the current TB diagnosis/disease course;</li> <li>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.</li> <li>d. MDR-TB with <ul> <li>d. MDR-TB with</li> <li>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:</li> <li>ii. historical documented resistance to isoniazid and rifamycins during the current TB diagnosis/disease course and;</li> <li>iii. who are unable to continue second line drug regimen due to a documented intolerance to:</li> <li>a. PAS, ethionamide, aminoglycosides or fluoroquinolones or;</li> <li>b. Current treatment not listed above that renders participant eligible for the study in the Investigator's opinion.</li> </ul> </li> </ul>	<ul> <li>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;</li> <li>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;</li> <li>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.</li> <li>d. MDR-TB with <ul> <li>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 during screening period (may be sensitive or resistant to isoniazid) and;</li> <li>iii. 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:</li> <li>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;</li> <li>iii. who are unable to continue second line drug regimen due to a documented intolerance to:</li> <li>a. PAS, ethionamide, aminoglycosides or fluoroquinolones or ;</li> <li>b. Current treatment not listed above that renders participant eligible for the study in the Investigator's opinion.</li> </ul> </li> </ul>	15
27	Criteria	by investigator or designee with results consistent with pulmonary TB in the opinion of the Investigator.	read locally by investigator or designee with results consistent with pulmonary TB in the opinion of the Investigator.	15
28	5.1 Inclusion Criteria	<ul> <li><u>Contraception:</u></li> <li>7. Be of non-childbearing potential or using effective methods of birth control, as defined below:</li> </ul>	<ul> <li><u>Contraception:</u></li> <li>7. Be of non-childbearing potential <u>or</u> using effective methods of birth control, as defined below:</li> </ul>	22

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#### **Protocol Amendment Template**



		<ul> <li><u>Non-childbearing potential:</u> <ul> <li>Participant - not heterosexually active or practices sexual abstinence; or</li> <li>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</li> <li>Male participant/sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to Screening.</li> </ul> </li> </ul>	<ul> <li><u>Non-childbearing potential:</u> <ul> <li>Participant - not heterosexually active or practices sexual abstinence; or</li> <li>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</li> <li>Male participant or female participant's male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to</li> </ul> </li> </ul>	
		<ul> <li>Effective birth control methods:</li> <li>A double contraceptive method should be used as follows:</li> <li>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</li> <li>b. Barrier method (one of the above) combined with hormone-based contraceptives or an intra-uterine device for the female participant/partner;</li> <li>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.</li> </ul>	<ul> <li><b>Effective birth control methods:</b></li> <li>a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or</li> <li>b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female participant;</li> <li>c. Male participant's female sexual partner: Double barrier method or hormone based contraceptives or an intra-uterine device for the female participant.</li> </ul>	
		<b>Note:</b> 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.	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. <b>Note:</b> 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.	<ol> <li>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.</li> </ol>	5 and 23

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30	5.2 Exclusion Criteria		<ol> <li>Participants with any of the following at Screening:</li> <li>QTcF interval on ECG &gt;500 msec. Participants with QTcF &gt; 450 must be discussed with the Sponsor Medical Monitor before enrolment.</li> <li>Heart failure</li> <li>A personal or family history of congenital QT prolongation</li> <li>A history of or known, untreated, ongoing hypothyroidism</li> <li>A history of or ongoing bradyarrhythmia</li> <li>A history of Torsade de Pointe</li> </ol>		<ul> <li>10. Participants with any of the following at Screening:</li> <li>QTcF interval on ECG &gt;500 msec. Participants with QTcF &gt; 450 must be discussed with and approved by the Sponsor Medical Monitor before enrolment. (Per measurements and reading done from screening central ECG.)</li> <li>Heart failure</li> <li>A personal or family history of congenital QT prolongation</li> <li>A history of or known, untreated, ongoing hypothyroidism</li> <li>A history of or ongoing bradyarrhythmia</li> <li>A history of Torsade de Pointe</li> </ul>	5 and 16
31	5.2 Exclusion Criteria	Prev 13. 14. 15. 16. 17. 18. 19.	<ul> <li><u>ious and Concomitant Therapy</u></li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs) or prior use within 2 weeks of randomization.</li> <li>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.</li> <li>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).</li> <li>Concomitant use of any drug s 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).</li> <li>Exceptions may include use of lopinavir/ritonavir regimen as noted in section 5.3.3.</li> <li>Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP.</li> <li>Participants with an existing TB diagnosis (a diagnosis made &gt; 4 weeks prior to screening) and HIV co-infection, must have been on an ART for at least 4 weeks prior to screening.</li> </ul>	Previ 13. 14. 15. 16. 17. 18.	ous and Concomitant Therapy Known (during screening) requirement for future Concomitant (during treatment) use of any prohibited and/or avoided medications noted in section 5.3. Prior use of Monoamine Oxidase Inhibitors (MAOIs) within 2 weeks of randomization. Prior use of serotonergic antidepressants within 3 days of randomization if Investigator foresees potential risks for serotonin syndrome when combined with linezolid. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP. 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. 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

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			r	
		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 quidance on ART treatment during the treatment period		
	5.2 Exclusion	Diagnostic and Laboratory Abnormalities	Diagnostic and Laboratory Abnormalities	25
	Critorio	Diagnostic and Eaboratory Abnormanites	Diagnostic and Laboratory Abrionnanties	25
	Cillena	22 Derticipants with any of the following toxisition at Corponing (John	10 Derticipants with any of the following toxisition at Corponing	
		22. Participants with any of the following toxicities at Screening (labs	19. Participants with any of the following toxicities at Screening	
		may be repeated during screening period) as defined by the	(labs may be repeated during screening period) as defined by	
		enhanced_Division of Microbiology and Infectious Disease (DMID)	the enhanced Division of Microbiology and Infectious Disease	
		adult toxicity table (November 2007):	(DMID) adult toxicity table (November 2007):	
		a Viral load > 1000 II I/ml (I Inless newly diagnosed HIV and not yet	a Viral load >1000 copies/mL (Lipless newly diagnosed HIV	
		on ART who otherwise qualify for participation).	and not vet on ART who otherwise qualify for participation).	
		b $CD4 + count < 100 colls/ul (HIV positive participants):$	CD4 + count < 100 colle/ul (HIV) positive participante);	
		b. CD4+ count < 100 cens/µL (110 positive participants),	b. $CD4+ COULL < 100 CENS/\mu (This positive participants),$	
		a. Hemoglobin $< 9.0 \text{ g/dL};$	d. Hemoglobin < 9.0 g/dL or < 90 g/L;	
		e. Platelets <100,000/mm3;	e. Platelets < $100,000/mm3$ or < $100 \times 10'9/L$ ;	
32		f. Absolute neutrophil count (ANC) < 1500/ mm3;	f. Absolute neutrophil count (ANC) < 1500/ mm3 or < 1.5 x	
52		g. Aspartate aminotransferase (AST)	10^9/L;	
		<ul> <li>Grade 3 or greater (&gt; 3.0 x ULN) to be excluded;</li> </ul>	g. Aspartate aminotransferase (AST)	
		• Results between 1.5 x ULN and 3 x ULN must be discussed with	<ul> <li>Grade 3 or greater (&gt; 3.0 x ULN) to be excluded;</li> </ul>	
		and approved by the Sponsor Medical Monitor	Results between 1.5 x ULN and 3 x ULN must be discussed	
		h. Alanine aminotransferase	with and approved by the Sponsor Medical Monitor	
		• Grade 3 or greater (> 3.0 x ULN) to be excluded:	h. Alanine aminotransferase	
		Results between 1.5 x ULN and 3 x ULN must be discussed with	<ul> <li>Grade 3 or greater (&gt; 3.0 x ULN) to be excluded:</li> </ul>	
		and approved by the Sponsor medical monitor.	Results between 1.5 x LII N and 3 x LII N must be discussed	
		i Total hilinihin	with and approved by the Sponsor medical monitor.	
		• areater than 1.5 x LII N to be excluded:	i Total hilinihin	
		1 1 5 x LIL N must be discussed with and approved by the	• areater than 1.5 x LILN to be excluded:	
		Sponsor Modical Monitor	y greater find 1.5 X OLIN to be excluded,	
		j Sponsor Nieurari Nioriitor	Sponsor Modical Manifor	
		J. Direct bill blits have all shell		
		Greater than ULN to be excluded	J. Direct bilirubin	
			Greater than ULN to be excluded	

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k.         Serum creatinine level greater than 1.5 times upper limit of normal         K.         Serum creatinine level greater than 1.5 times upper limit of normal         K.         Serum creatinine level greater than 1.5 times upper limit of normal           33         5.2 Exclusion Criteria         Albumin <3.0 g/dl         2           34         5.3.1 Prior and Concomitant Medicians and Other Treatments         The following concomitant medications are prohibited during the treatment medications and Other         The following concomitant medications are prohibited during the treatment completion:         5 an           •         Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, tincluding but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, copreomycin, quinolones, thioamides, and metroindiazole.         Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, clinctuding but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, clinctuding but not limited to amiodarone, bepridil, chloroquin, chlorpromazine, cisapride, cyclobenzaprine, clinithromycin, adisopyramide dofetilide, domperidone, droperidol, levythromycin, halofantrine, haloperidol, libutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalo, sparthoxacin, thoirdazine, elonomatine treatine treatment completion treat intercurrent non-TB infections and if the benefit of treatment outweighs the risk of prolonged QTc.	r				
normal 33         normal Criteria         normal 1.         Albumin <3.0 g/dl         normal 2           33         5.2 Exclusion Criteria         The following concomitant medications are prohibited during the treatment Concomitant Medications and Other Treatments         The following concomitant medications are prohibited during the treatment completion:         The following concomitant medications are prohibited during the treatment completion:         5 an           0 ther Treatments         Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, capreomycin, quinolones, thioamides, and metronidazole.         Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, mikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)         Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, divide, expendence, capreomycin, quinolones, thioamides, and metronidazole.         Medicinal products used Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)         Medicinal products used Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)         Medicinal products used Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)         Medicinal products used Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)         Medicinal products used Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)         Medicinal products used Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)			k. Serum creatinine level greater than 1.5 times upper limit of	k. Serum creatinine level greater than 1.5 times upper limit of	
33       1.       Albumin < 3.0 g/dl			normal	normal	
33         5.2 Exclusion Criteria         2           33         5.2 Exclusion Criteria         The following concomitant medications are prohibited during the treatment Concomitant Medications and Other Treatments         The following concomitant medications are prohibited during the period to axoid possible drug interactions with the IMP:         Image: Concomitant medications are prohibited during the period to axoid possible drug interactions with the IMP:         Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, knamycin, para-aminosalicylic acid, rifapentine, capreomycin, quinolones, thioamides, and metronidazole.         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.         Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, chlorpormazine, cisapride, cyclobenzaprine, clarithromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotatol, spafloxacin, thioridazine).         The following concomitant medications should be avoided during the treat intercurrent non-TB infections and if the benefit of treatment outweighs the risk of prolonged QTC.         Concomitant use of any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloropuine, chlorpomizen, cisapride, cyclobenzaprine, carithromycin, disopyramide dofetilide, domperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, worethadive, ex othibretha othibathon the the tolarditione, chlorpomi			I. Albumin <3.0 mg/dl	1. Albumin <3.0 g/dl or < 30 g/L	
33         Criteria         No protocol waivers will be granted by the TB Alliance.         5 ar           5.3.1 Prior and Concomitant Medications and Other Treatments         The following concomitant medications are prohibited during the treatment completion:         The following concomitant medications are prohibited during the period to avoid possible drug interactions with the IMP:         The following concomitant medications are prohibited during the Concomitant Medications and Other         The following concomitant medications are prohibited during the period to avoid possible drug interactions with the IMP:         The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:         5 ar           4         Medicinal products used to treat pulmonary TB: including but not limited to gatifoxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.         The following concomitant medications should be avoided during the reatment period and during the 14 days after treatment completion during that nue for any drug known to prolong QTc interations, halofantrine, haloperiod, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).         The following concomitant medications should be avoided during the reatment period and during the 14 days after treatment completion to avoid possible drug interactions with the IMP. Use of any drug known to 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 prolong QTc.         Concormitant use of any drug known to	~~	5.2 Exclusion			26
<ul> <li>5.3.1 Prior and Concomitant Medications and Other</li> <li>The following concomitant medications are prohibited during the treatment Medications and Other</li> <li>Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, frabutin, kanamycin, para-aminosalicylic acid, frapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of any drug known to prolong QTC interval (including but not limited to amiodarone, bepridil, chlorpromazine, cisapride, cyclobenzaprine, clainthromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamiline, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).</li> <li>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.</li> <li>Concomitant use of any drug known to induce myelosuppression.</li> <li>The systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, furconazole, furconazole, furconazole, ketotike outweigh the risk of prolonged QTC.</li> <li>Concomitant use of any drug known to induce myelosuppression.</li> <li>The systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, furconazole, furconazole, furconazole, furconazole, furconazole, keto the outweighs the risk of and wing the trie there were there there there are a merosalidine, and parefloxe, enthady, mesoridazine, clainthromycin, disopyramide dofetilide, domperidone, epentamidine, prozeida, procainamide, quinidine, chlorpromazine, cisapride, cyclobenzaprine, clainthromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, procainamide, quinidine, sotalol, sparfloxacin,</li> </ul>	33	Criteria		No protocol waivers will be granted by the TB Alliance.	
<ul> <li>The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone.</li> <li>The systemic dexamethasone.</li> <li>The systemic dexamethasone.</li> </ul>	34	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>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).</li> <li>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.</li> <li>Concomitant 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;</li> <li>The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone.</li> </ul>	<ul> <li>No protocol waivers will be granted by the TB Alliance.</li> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:         <ul> <li>Medicinal products used to treat pulmonary TB: includingbut not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> </ul> </li> <li>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:         <ul> <li>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).</li> <li>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.</li> </ul></li></ul>	5 and 27

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concommant use or serotonergic antidepressants should be avoid possible as participants on these agents and linezolid are at ris serotonin syndrome. Caution should be used in treating diabetic patients receiving insu oral hypoglycemic agents as cases have been reported of hypogly reactions when patients on these agents have been treated with line Any drug known to be hepatotoxic should be avoided as much as possible during screening and throughout the treatment period (incli- but not limited to acetaminophen/paracetamol, acetazolamide, allopurinol, amiodarone, amitriptyline, amoxicilin, amprenavir, atorvastatin, augmentin/co-amoxiclav, azathioprine, baclofen, bumetanide, captopril, carbamazepine, celecoxib, chlorpromazine, chlorpromazine, clindamycin, clopidogrel, contraceptive pill, co- trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapi fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril loperamide, losartan, methotrexate, metolazone, mitrazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drn paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sufasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphy tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).	<ul> <li>Concomitant use or any drug known to induce significant myelosuppression</li> <li>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;</li> <li>The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone.</li> <li>Concomitant use of serotonergic antidepressants should be avoided if possible as participants on these agents and linezolid are at risk for serotonin syndrome.</li> <li>Caution should be used in treating diabetic patients receiving insulin or oral hypoglycemic reactions when patients on these agents have been treated with linezolid.</li> <li>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, cotrimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mitrazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuwastatin,</li> </ul>


			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	<ul> <li>5.4 Discontinuation from Treatment/Trial The following may result in the discontinuation of trial treatment;</li> <li>Pregnancy;</li> <li>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: <ul> <li>Adverse event(s);</li> <li>Myco testing results from baseline (Screening through Week 4) indicate sensitivity to isoniazid and/or rifamycins;</li> <li>Myco testing results from baseline (Screening through Week 4) indicate resistance to bedaquiline, pretomanid or linezolid;</li> <li>In the opinion of the investigator, fails to comply with the protocol, including non-compliance to IMP.</li> </ul> </li> <li>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).</li> <li>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:</li> <li>Withdrawal of informed consent;</li> <li>Lost to follow-up;</li> </ul>	<ul> <li>5.4 Trial Discontinuation and Visits</li> <li>5.4.1 Treatment Discontinuation and Early Withdrawal</li> <li>A participant must be withdrawn from the trial due to the following; <ul> <li>Pregnancy; (unless female post visit for end of treatment/early withdrawal from treatment);</li> <li>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.</li> <li>At the specific request of the sponsor or termination of the trial by Sponsor;</li> <li>Lost to follow-up</li> <li>In the opinion of the investigator, fails to comply with the protocol, including non-compliance to IMP.</li> </ul> </li> <li>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.</li> <li>Myco testing results from baseline (Screening through Week 4) with MICs that indicate likely resistance to bedaquiline, pretomanid or linezolid;</li> </ul>	21 and 28

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		A participant may discontinue from the trial at any time at his/her request (withdrawal of consent)-	All partic withdraw requeste Follow U A particip request ( the discr administ the trial,	cipants who dis n consent) and re d to return for an e p visits, as per flo pant may disconti withdrawal of con etion of the invest rative issues. Who no additional follo	continue trial eceived at leas early withdrawa w chart (Sectio nue from the tria sent) or may be igator for safety en a participant w-up visits will l	treatment (b t one dose o l visit and app n 1.2). al at any time withdrawn a behavioral o withdraws co pe performed	ut have not of IMP will be blicable safety at his/her t any time at compliance or onsent from	
	5.4.2 Early Withdrawal Follow-up		5.4.2 E In case of all efford assessm Once a p be reque	Early Withdrawal of early withdrawa s shall be main nents. participant has be sted to attend follow-up Visits Require	I <b>Follow-up</b> Il during the trea de to comple en withdrawn e ow-up visits as red for Early Withd	atment or follo te the Early arly from the described in T rawal Participar	ow-up period, / Withdrawal trial, they will Table 9:	10 and 28
36			▲     Treatment       Duration a     EW visit       ▲     ▲       ▲     ★       ▲     ↓       ▲     ↓       ★     ↓       ▲     ↓       ★     ↓       ↓     ↓       ↓     ↓       ▲     ↓       ↓     ↓	Ophthalmology Examination at EW <sup>a</sup> NA     NA     NA     Required     diditional visit is required     ology examination will be t date.     nd 78 week post 1 t SAE informatio	Ophthalmology Examination           12 week Post treatment follow- up visita           NA           Required           for an ophthalmology e performed at this visit           treatment follow n (including version)	26 Week Post Treatment Follow-up Visit NA Required, if not already performed examination after it, and it will occur -up visits will rification of	78 Week Post         Treatment         Follow-up         Visit         NA         Required         Required         EWD, only the         12 weeks after the         be performed         survival) and	
			participa	nt reported TB o ic, a home or a sit	te visit.	ation. This	visit may be	

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	5.4.3	5.4.3 Unscheduled Visits	28
	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:	
37		<ul> <li>End of treatment visit;</li> <li>Week 26 post treatment follow-up visit;</li> <li>Post treatment follow-up visits from week 8 through week 65 (in addition to week 26 follow-up);</li> <li>End of Follow-up Period (week 78 post treatment completion visit);</li> <li>Early Withdrawal (if applicable).</li> </ul>	
		<ul> <li>At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, and to determine whether the participant has: <ul> <li>At least two sequential negative sputum culture results; or</li> <li>At least two sequential positive sputum culture results; or</li> <li>Has been unable to produce sputum after documentation of at least two negative sputum cultures with no intervening positive and are clinically asymptomatic.</li> </ul> </li> </ul>	
		If they <b>do not</b> 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	

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			<ul> <li>minimum of 7 days or more apart until they fall into one of the above categories.</li> <li><b>5.4.4 Lost to Follow-up</b></li> <li>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</li> </ul>	
~~	5.4.4 Early	Discontinuation from treatment due to TB	5.4.5 Early Withdrawal due to TB	28
38	to TB			
	6.1 IMP	Table 9: Investigational Medicinal Product Details	Table <b>10</b> : Investigational Medicinal Product Details	
39	Administration	Table 3. Investigational Medicinal Floudel Details	Table 10. Investigational Medicinal Product Details	ю
	Auministration			

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Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version: Version 2.0, dated 13 June 2018 Protocol Name: ZeNix



## Protocol Amendment Template

	Treatment Group	Active and Placebo	Treatment Group	Active and Placebo
	Linezolid 1200 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> </ul>	Linezolid 1200 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 26 weeks</li> </ul>
	Linezolid 1200 mg daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>	Linezolid 1200 mg daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid tablets once daily for 17 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 17 weeks</li> </ul>
	Linezolid 600 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> </ul>	Linezolid 600 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid tablet once daily for 26 weeks</li> </ul>

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		<ul> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretormanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>1 linezolid 600 mg daily for 9 weeks</li> <li>1 placebo linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>	et once daily s once daily mg active ; once daily ce daily for 9 ks et once daily illy for 17 et once daily
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 in the treatment period.	ed for unused 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: Halt treatment modifications should be discussed with 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: Halt treatment modifications should be discussed with Medical Monitor prior to implementation, unless a preduction is required urgently for a safety concern; Honitor should be informed within 24 hours of the change if not discussed prior to implementation. Hatter 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: Honitor should be discussed prior to specific toxicities section of protocol: Honitor should be discussed prior to Honitor should be discussed pr	h the Sponsor nause or dose it, the Medical change if not4, 5, and 7 <i>v</i> ing should be nonitoring and ps) in the dose instructions in7

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<ul> <li>Blinded one step re linezolid (1200 mg 0 or 300mg QD to instructions in phan</li> <li>Temporary pause of should be conside monitoring and safe</li> <li>Permanent disconti</li> <li>Participants experiencing s drugs in the regimen (B-Pa consecutive days.</li> <li>Pauses of the full regime cumulatively.</li> <li>If participant's week 16 sam consider option to extend c with the Sponsor Medical I positive culture at week 16, weeks (91 days) cumulative When total of missed dosin additional make-up doses s At no time should the partic</li> </ul>	eductions (maximum 3 steps) in the dose of QD to 600 mg QD, 600 mg QD to 300 mg QD placebo) managed by the IWRS as per macy manual and/or IWRS user manual. of linezolid due to a linezolid-specific toxicity pred and implemented per guidance in the ety for specific toxicities section of protocol. nuation of linezolid. uspected drug related toxicities due to other ), the full regimen may be halted for up to 35 en must not exceed 8 weeks (56 days) nple remains culture positive, Investigator may urrent treatment to 39 weeks, in consultation Vonitor. When treatment extended due to a pauses of the full regimen must not exceed 13 ely. g days and/or pauses is greater than 7 days, hould be dispensed/treatment extended. ipant be treated with a single agent.	<ul> <li>1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or;</li> <li>600 mg QD to 300 mg QD, 300mg QD to placebo).</li> <li>Temporary pause of linezolid</li> <li>Permanent discontinuation of linezolid.</li> <li>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.</li> <li>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.</li> <li>Interruptions/pauses of the full regimen must not exceed 8 weeks (56 days) cumulatively.</li> <li>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.</li> <li>When treatment extended to 39 weeks, pauses of the full regimen must not exceed 13 weeks (91 days) cumulatively.</li> <li>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.</li> <li>At no time should the participant be treated with a single agent.</li> </ul>	

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			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. The complete formulations of linezolid are found in the Package Inserts	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.	6
		The IMP will be packaged as follows:	The IMP will be packaged as follows:	
42		<ul> <li>Bedaquiline: Bottles containing:         <ul> <li>200 mg QD dose- 28 tablets- bedaquiline 100 mg</li> <li>100mg QD dose- 14 tablets- bedaquiline 100 mg</li> </ul> </li> <li>Pretomanid: Blister card containing 14 tablets- pretomanid 200 mg</li> <li>Linezolid: Blister Card containing 7 days of dosing as follows:             <ul> <li>1200 mg QD Dose</li> <li>2 blister strips of 7 tablets each (14 tablets) containing active linezolid 600 mg</li> <li>1 blister strip of 7 half tablets containing placebo linezolid 300 mg</li> <li>600 mg QD Dose:</li></ul></li></ul>	<ul> <li>Bedaquiline: Bottles containing:         <ul> <li>200 mg QD dose- 28 tablets- bedaquiline 100 mg</li> <li>100mg QD dose- 14 tablets- bedaquiline 100 mg</li> </ul> </li> <li>Pretomanid: Blister card containing 14 tablets- pretomanid 200 mg</li> <li>Linezolid: Blister Card containing 7 days of dosing as follows:             <ul> <li>1200 mg QD Dose</li> <li>2 blister strips of 7 tablets each (14 tablets) containing active linezolid 600 mg</li> <li>1 blister strip of 7 half tablets containing placebo linezolid</li> <li>600 mg QD Dose:</li></ul></li></ul>	

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		<ul> <li>1 blister strip of 7 half tablets containing placebo linezolid 300 mg</li> </ul>	<ul> <li>1 blister strip of 7 half tablets containing placebo linezolid</li> </ul>	
43	6.4 IMP Packaging and Labelling	<ul> <li>The packaging of each bottle/blister card will be labelled with, at a minimum, the following information:</li> <li>Name, address and telephone number of Sponsor.</li> </ul>	<ul><li>The packaging of each bottle/blister card will be labelled with, at a minimum, the following information:</li><li>Name of Sponsor.</li></ul>	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	<ul> <li>Clinically significant medical and treatment history (including past and current TB diagnosis and smoking)</li> </ul>	<ul> <li>Clinically significant medical and treatment history (including past and current TB diagnosis, alcohol use and smoking)</li> </ul>	32
47	7.1 Demographic and Background Variables	Serology: HIV and CD4 count.	<ul> <li>Serology: HIV, CD4 count and viral load.</li> <li>If an HIV test was performed within 1 month prior to trial start, it should not be repeated as long as</li> </ul>	33

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		<ul> <li>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).</li> </ul>	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	<ul> <li>TB Symptoms Profile:</li> <li>The TB Symptoms Profile (Appendix 7) will record participants' ratings of the severity of common TB symptoms.</li> <li>Patient Reported Health Status Variables and Procedures:</li> <li>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.</li> </ul>	<ul> <li>TB Symptoms Profile:</li> <li>The TB Symptoms Profile (found in the Subject Questionnaires Guideline) will record participants' ratings of the severity of common TB symptoms.</li> <li>Patient Reported Health Status Variables and Procedures:</li> <li>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.</li> </ul>	35
50	7.3 Safety and Tolerability Assessments	Brief Peripheral Neuropathy Screen (Appendix 6) will record ratings.	<ul> <li>Brief peripheral neuropathy screen (found in the Subject Questionnaires Guideline) will record ratings.</li> </ul>	35
51	7.5 Mycobacteriology Characterization Variable and Procedures	<ul> <li>The following Mycobacterial Characterization variables will be collected:</li> <li>Positive Culture (for MTB) from: <ul> <li>Day 1 or if Day 1 is not available, first positive between screening through Week 4;</li> <li>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</li> </ul> </li> </ul>	<ul> <li>The following Mycobacterial Characterization variables will be collected:</li> <li>Positive Culture (for MTB) from: <ul> <li>Day 1 or if Day 1 is not available, first positive between Screening through Week 4;</li> <li>If consent granted, and when applicable, Pre-screening culture/isolate to be sub cultured and shipped and/or tested:</li> <li>At the study lab if/when samples could support inclusion in the trial</li> </ul> </li> </ul>	35

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		<ul> <li>When applicable, end of treatment or visits with positive cultures during post-treatment follow-up.</li> </ul>	<ul> <li>To the study/central lab for relevant participants/with no baseline (positive cultures from screening through Week 4)</li> <li>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.</li> </ul>	
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

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			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

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Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version: Version 2.0, dated 13 June 2018 Protocol Name: ZeNix

### Protocol Amendment Template

TB ALLIANCE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Sponsor

I agree to the terms of this protocol amendment

Signature of Senior Medical Officer

Printed name

Date

### **Principal Investigator**

I hereby confirm I have read the above Protocol Amendment and agree to conduct this clinical trial as outlined in the above Protocol Amendment. I will provide copies of the Protocol Amendment and access to all of the information required to conduct the clinical trial according to the above Protocol Amendment to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature of Principal Investigator

Printed name

Date

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### 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	<b>Removed</b> 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
L	
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	<b>Clarified</b> 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])
-	

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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)

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	<ul> <li>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)</li> <li>Clarified use of pre-screening, adding scenario to support testing for inclusion into the trial. (In section 1.2 Synopsis Flowchart)</li> <li>Removed details on handling of pre-screening samples. (In section 1.2 Synopsis Flowchart and 7.5 Mycobacteriology Characterization and Variable and Procedures)</li> <li>Moved wording on isolate testing (EMS preference and scenarios for requesting second isolate) to footnote under table (In section 1.2 Synopsis Flowchart)</li> <li>Clarified that cultures should be stored (In section 1.2 Synopsis Flowchart)</li> <li>Clarified testing done at Central lab to describe scenarios for paired genotyping to determine relapse/reinfection (In section</li> </ul>
	1.2 Synopsis Flowchart) <b>Moved</b> details on unscheduled visits to section 5.4.3
21	<b>Removal</b> of Isoniazid (INH) resistance as an inclusion criteria (In section 5.1 Inclusion Criteria, section 5.4 Discontinuation from Treatment/Trial) <b>Clarified</b> 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	<ul> <li>Updated Contraception inclusion criteria to align clarify differences between female participants and male participant's female partners (In section 5.1 Inclusion Criteria)</li> <li>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)</li> <li>Removed "female partners of male participants" in note about hormone based contraception as female partners not taking IMP (In section 5.1 Inclusion Criteria)</li> </ul>
23	<b>Clarified</b> 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	<b>Updated</b> Previous and Concomitant Therapy exclusion section to: Reference restriction section (and <b>removal</b> 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)



	<b>Removed</b> 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)
	<b>Changed</b> 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	<b>Updated</b> 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	<ul> <li>Updated Discontinuation from Treatment/Trial section:</li> <li>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)</li> <li>Clarified that withdrawal for pregnancy not relevant post treatment completion trial (In section 5.4.1 Treatment Discontinuation and Early Withdrawal)</li> <li>Clarified withdrawal for safety reasons to include concerns of symptomatic TB (failure/relapse) (In section 5.4.1 Treatment Discontinuation and Early Withdrawal)</li> <li>Clarified withdrawal for safety reasons to include concerns of symptomatic TB (failure/relapse) (In section 5.4.1 Treatment Discontinuation and Early Withdrawal)</li> <li>Clarified withdraw at anytime at discretion of Investigator for safety, administrative, or compliance reasons (In section 5.4.1 Treatment Discontinuation and Early Withdrawal)</li> <li>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)</li> <li>Added section to clarify what visits/assessments are done post early withdrawal (In section 5.4.2 Early Withdrawal Follow-up)</li> <li>Moved section on unscheduled visits/assessments are done post early withdrawal (In section 5.4.3 Unscheduled Visits)</li> <li>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)</li> </ul>
29	<b>Clarified</b> that cards and bottles will be checked for unused tablets at each treatment visit (In section 6.2 Participant Compliance)

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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 RUS Protocol Version 1.0, dated 15-Nov-17	Amended Text RUS Protocol 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

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		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 red an ongoing TB infection current treatment to 39 16 and week 26 are co isolated positive without results should be used treatment extension sh Sponsor Medical Monit Participants will be follo	ceive 26 weeks of treatment of Investigator may consist weeks. If the culture re- ntaminated, missing or of the clinical significance, and to make this decision. A ould be discussed with a or before implementation owed for 78 weeks after	nent they may have ider extending esults between week considered an vailable culture Il decisions regarding and approved by the n. 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 18 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 par Sponsor may consider assessable (as detailed	ticipants male and fema replacement of late scre d in the statistical analys	le, aged 18 and over. een failure and un- is plan) participants.	2
	1.1 Synopsis	The test product will be supplied as:	The regimen will be su	pplied as the following:		6
	Summary	pedaquiline 100 mg tablets     protemonid 200 mg tablets	Product	Tablet Strength	Abbroviation	
		• pretomania 200 mg tablets	Bedaguilino	100 mg		
		<ul> <li>Intezolia (scored) 600 mg tablets</li> <li>placebe linezolia (scored) 600 mg tablets</li> </ul>	Pretomanid	200 mg	(D) (Pa)	
		<ul> <li>placebo intezolid (scored) 600 mg tablets</li> <li>linezelid helf tablet (pro out) 200 mg</li> </ul>	Linezolid (scored)	600 mg		
		<ul> <li>Intezolid half tablet (pre-cut) 500 mg</li> <li>placebe linezolid half tablet (pre-cut) 200 mg</li> </ul>	Placebo Linezolid	nlacebo		
		• placebo intezoliu nali tablet (pre-cut) 500 mg	(scored)	pidoebo	(=)	
3		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.	Linezolid 600 mg half tablet (pre- cut)	300 mg	(L)	
		Treatment will be administered orally, once daily, with a full glass of water and a meal in the following dosing schemes (treatment arms):	600 mg half tablet (pre-cut)	ріасеро	(L)	
		<ul> <li>Participants will receive the following:</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks plus;</li> <li>Linezolid- participants will be randomly assigned to receive one of the following for the f</li></ul>	Linezolid treatment w or placebo) and one r for all possible dosing Instructions for Dosing:	ill be supplied as 2 rows ow of half-tablets (active poptions while maintain	of full tablets (active e or placebo) to allow ing the blind.	

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	<ul> <li>nezolid 1200 mg daily for 26 weeks</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> </ul>	Treatment will be administered orally, once daily, with a full glass of water and a meal in the following dosing schemes (treatment arms):
Lir W Lir	<ul> <li>nezolid 1200 mg daily for 9 weeks</li> <li>Yeeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>Yeeks 10-26</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> <li>1 placebo linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> </ul>	<ul> <li>Participants will receive the following:         <ul> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks plus;</li> <li>Linezolid- participants will be randomly assigned to receive one of the following four blinded linezolid treatment doses and durations:</li> </ul> </li> <li>Linezolid 1200 mg daily for 26 weeks         <ul> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 26 weeks</li> </ul> </li> <li>Linezolid 1200 mg daily for 9 weeks</li> </ul>
<u>Lir</u> Wi	<ul> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> <li>nezolid 600 mg daily for 9 weeks</li> <li>/eeks 1-9</li> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>	<ul> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid tablets once daily for 17 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 17 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 26 weeks</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid tablet once daily for 26 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 26 weeks</li> </ul>
		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

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			• $\frac{1}{2}$ (one half) placebo linezolid tablet once daily for 17 weeks	
			Linezolid 600 mg daily for 9 weeks	
			Weeks 1-9	
			<ul> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> </ul>	
			<ul> <li>1 placebo linezolid tablet for 9 weeks</li> </ul>	
			<ul> <li><sup>1</sup>/<sub>2</sub> (one half) placebo linezolid tablet once daily for 9 weeks</li> </ul>	
			Weeks 10-26	
			<ul> <li>2 placebo linezolid tablets once daily for 17 weeks</li> </ul>	
			• $\frac{1}{2}$ (one half) placebo linezolid tablet once daily for 17 weeks	
	1.1 Synopsis	Treatment Modifications:	Treatment Modifications:	
	Summary			7
		The above treatment schemes may require modification due to toxicities	The above treatment schemes may require modification due to	
		as noted below. All dose modifications should be discussed with the	toxicities as noted below. All dose modifications should be	
		Sponsor Medical Monitor prior to implementation, unless a pause or	discussed with the Sponsor Medical Monitor prior to	
		Monitor should be informed within 24 hours of the change if not	urgently for a safety concern: the Medical Monitor should be	
		discussed prior to implementation	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	In the event of linezolid specific toxicities, the following should be	
		for specific toxicities section of protocol. Every effort should be made for	considered and implemented per guidance in the monitoring and	
4		participants to receive a total of 9 weeks of linezolid, even if pauses are required:	safety for specific toxicities section $(8.3)$ of protocol:	
		<ul> <li>Blinded one step reductions (maximum 3 steps) in the dose of</li> </ul>	• Blinded one step reductions (maximum 2 steps) in the dose	
		linezolid (1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or	of linezolid managed by the IXRS as per instructions in	
		300mg QD to placebo) managed by the IWRS as per instructions	pharmacy manual and/or IXRS user manual.	
		In pharmacy manual and/or IVVKS user manual.	<ul> <li>1200 mg QD to 600 mg QD, 600 mg QD to 300 mg</li> </ul>	
		<ul> <li>Temporary pause of imezonic due to a imezonic specific toxicity should be considered and implemented per guidance in the</li> </ul>	QD or	
		monitoring and safety for specific toxicities section of protocol	<ul> <li>out mg QU to suu mg QU, suumg QD to placebo</li> <li>Temperary pause of linestelid</li> </ul>	
		Permanent discontinuation of linezolid.	Permanent discontinuation of linezolid	
			<ul> <li>Perticipants who have a linezolid reduction can go back to a</li> </ul>	
		For participants experiencing suspected drug related toxicities due to	higher dose (1 step or 2 steps) post discussion with and	
		other drugs in the regimen (B-Pa), the full regimen may be halted for up	approval by Sponsor Medical Monitor.	
		to 35 consecutive days.		

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	1		1	
		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.	<ul> <li>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.</li> <li>Interruptions/pauses of all Investigational Medicinal Product (IMP) must not exceed 8 weeks (56 days) cumulatively.</li> <li>When treatment is extended to 39 weeks, interruptions/pauses of all IMP must not exceed 13 weeks (91 days) cumulatively.</li> <li>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.</li> <li>At no time should the participant be treated with a single agent.</li> <li>Every effort should be made for participants to receive a total of 9</li> </ul>	
			weeks of linezolid, even if pauses are required	
5	1.1 Synopsis Summary	Primary Endpoint: Incidence of bacteriologic failure or relapse or clinical failure through follow up until 26 weeks after the end of treatment.	Primary Endpoint: 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.	<ul> <li>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</li> </ul>	9
7	1.1 Synopsis Summary	<b>Trial Duration:</b> ~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).	<b>Trial Duration:</b> ~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

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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	<i>Captured in flowchart/table:</i> 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.	<i>Captured in flowchart/table</i> : 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. <b>Screening:</b> 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. <b>Screening:</b> 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	<ul> <li>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.</li> <li>1. If participant completes treatment at week 26, end of treatment visit should be done within 7 days after last dose of week 26.</li> <li>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.</li> <li>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)</li> </ul>	<ul> <li>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).</li> <li>1. End of treatment visit (final treatment visit) should be done within 7 days AFTER the last dose of IMP.</li> <li>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.</li> <li>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).</li> <li>4. Follow-up visits should be scheduled based on timing of end of last dose of IMP (e.g., 4-week</li> </ul>	12

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			<ul> <li>weeks plus 7-day window), visit at week 39 would be the end of treatment visit.</li> <li>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).</li> </ul>		follow-up to be scheduled 4 weeks after last dose of IMP).	
	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:	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:	11
14			<ol> <li>Received/took ≤ 14 doses, no additional follow-up visits are required.</li> <li>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".</li> </ol>		<ol> <li>Received/took ≤ 14 doses, no additional follow-up visits are required.</li> <li>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 <i>withdrawn from the trial due to meeting the treatment failure endpoint</i>. Participant may need to return for visits to collect sputum samples to determine outcome status.</li> <li>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.</li> </ol>	
15	1.2 Synopsis Flowchart	e.	<b>HIV testing:</b> 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.	<b>HIV testing:</b> 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

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		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. <b>CD4 count and viral load:</b> For all HIV-positive participants, viral load and CD4 at screening, CD4 only tested at end of treatment or early withdrawal.	f. <b>CD4 count and viral load:</b> 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. <b>Chest X-Ray:</b> 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. <b>Chest X-Ray:</b> 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	<ol> <li>Physical Exam: Limited Physical exams should include weight and a gross neurological, pulmonary, cardiovascular and abdominal exam.</li> </ol>	I. <b>Physical Exam:</b> 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	<ul> <li>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: <ol> <li>Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count).</li> <li>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).</li> </ol> </li> </ul>	<ul> <li>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:</li> <li>Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count).</li> <li>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,</li> </ul>	18

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	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.	<ul> <li>bicarbonate/CO2, creatine phosphokinase (CPK). GGT will be done at screening.</li> <li>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).</li> <li>Urinalysis (pH, specific gravity, protein, glucose, microalbumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis.</li> <li>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.</li> </ul>	
1.2 Synopsis Flowchart 21	<ul> <li>o. PK Sampling: Specific PK blood draws as follows: <ol> <li>Day 1; pre-dose (within 2 hours prior to dosing)</li> <li>Week 2: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose</li> <li>Week 8: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose</li> <li>Week 12: pre-dose (within 2 hours prior to dosing)</li> <li>Week 12: pre-dose (within 2 hours prior to dosing)</li> <li>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.</li> </ol> </li> <li>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.</li> <li>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</li> </ul>	<ul> <li>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.</li> <li>Specific PK blood draws will be obtained as follows (pre-dose to be done after ECGs): <ol> <li>Day 1; pre-dose (within 2 hours prior to dosing)</li> <li>Week 2: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose</li> <li>Week 8: pre-dose (within 2 hours prior to dosing), 2–3 hours post-dose and 6–8 hours post-dose</li> <li>Week 12: pre-dose (within 2 hours prior to dosing)</li> <li>Week 12: pre-dose (within 2 hours prior to dosing)</li> <li>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</li> </ol> </li> <li>When participant is discharged and seen as an outpatient, site should make every effort to collect 6-8</li> </ul>	19

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## **Protocol Amendment Template**

		-				16.0																			
		con  line  bed	nponents are ad zolid due to toxid laquiline and pre	minis city, s ₂toma	tered ampl nid a	. If the ing sha re dos	site ha ould be ed.	s perm	nanenti	y disco ay whe	n the		hour logist Hosp collee If the shou resur PK s partic Linez Sites unsc collee admi	san itcal itali itali ctec full d b mec amp cipa colic ma hed ct P nist	nple lly fe izati l in reç e de l. olinç l ha nt's l ha ulec Ks erec	e at easion the gime elay line s be ring d vis to e d.	wee ible. infor eCF en of ved u noulc ezoli een par sit (c nsu	r mati RF. r line until d be d do pern ticipa can c re dr	wher on ( zolic full r se h nane ant b occur aw is	i ope e.g. I is p egim plete as b ntly pack · out s do	eratio disch pause nen c ed ev een disce at a side ne w	narge ed, P or line ven if lowe ontin sche of vis hen l	/ and e date) will I K sampling ezolid are the red or ued. duled or sit windows MP is	be ) ) to	
		r.	Sputum Sampling:									r.	Sputum Sampling:												5 and 20
	1.2 Synopsis Flowchart	2		Sar	nple			Te	ests	Ť					Sar	nple			IS.	1	Tests				
			Visit	EMS*	Spot	AFB Smear microscopy	MGIT culture, speciation	Molecular testing	MIC: B, Pa, L	Liquid DST	Genotyping		Visit	EMS	SPOT	ISOLATE*	AFB Smear microscopy	MGIT culture, speciation	Molecular testing	MIC: B, Pa, L	MGIT DST	Genotyping	Extended DST (paired with baseline isolate)		
		3	Screening (Day -9 to -1)		••	s	s	s					Screening (Day -14 to -1)	-	:		S	s	S	¥6					
		8	Baseline (Day 1) or screen - wk4 if baseline negative or contaminated	•	•		s		с	с	с		Baseline (Day 1) or 1 <sup>st</sup> positive between screening and wk4 if Day 1 negative or			•				с	С	С	L (when applicable, with isolate below)		
22		2	All Visits Post Baseline	•	•		S				· · ·		contaminated All Visits Post	-	-			6	10		i - 1				
22		8	Positive for MTB at/after EoT		•		s	s	С	с	С		Screening 1 <sup>st</sup> positive for MTB at/after week 16 for				<u>,</u>	3	8						
		ž	C – Central laboratory S – Study Laboratory	y (special (facility tl	ized facili nat receiv	ty) es samples	s directly fro	m site)					participant not responding to therapy and/or 1 <sup>st</sup> positive during follow-up for potential new infection			•			s	С	С	С	L		
		SP	UTUM SAMPLE	S GE	NER	AL: If E	MS is	not ava	ailable,	site sho	ould mak	e	C – Central Mycoba S – Study Mycobact	cteriolo eriolog	ogy Lat y Labo	porator	y (speci (facility	that rec	acility) eives spi	utum sa	mples di	rectly from	m site)		
		eve	ry attempt to col	llect t	wo sp	ot san	nples a	t least	30 min	utes ap	oart.		L – Lab (as applicat *Preferably from EMS contaminated, or the	le per Samp test ne	Countr le whe eds to	y) that in avai be rep	perform lable. A eated.	ns exten liternate	ded DST isolate o	beyond an be r	d panel a equested	t Central i if initial	lab one is		
		BA use	SELINE: If avail d for the tests th	lable, nat qu	site alifie	will rea d the p	quest p articipa	ore-screant for	eening inclusio	culture on into	e that wa the trial t	s o													

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## **Protocol Amendment Template**

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.	<ul> <li>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.</li> <li>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</li> </ul>	
<b>POSITIVE MTB AT/AFTER END OF TREATMENT</b> : Only one isolate (preferably from EMS) should be shipped. Second isolate may be requested if first is contaminated.	<ul> <li>shipped and/or tested:</li> <li>at the study lab if/when those samples could support inclusion in trial.</li> </ul>	
<ul> <li>MOLECULAR TESTING:</li> <li>At Screening: GeneXpert, Hain MTBDR<i>plus</i> or equivalent to determine MTB complex and R resistance.</li> <li>Positive MTB at/after end of treatment: Hain MTBDR<i>plus</i> and HainMTBR<i>sl</i></li> <li>LIQUID DST: for SIRE, Z and second line anti-TB drugs, including but not limited to FQ and injectables.</li> </ul>	<ul> <li>at the study/central lab for relevant participants with no baseline (no positive cultures from screening through week 4).</li> <li>OLECULAR TESTING:</li> <li>At Screening: GeneXpert, Hain MTBDR<i>plus</i> or equivalent to determine MTB complex and Rifampicin resistance.</li> <li>Positive MTB at/after week 16: Hain MTBDR<i>plus</i> and HainMTBRs/</li> </ul>	
<ul> <li>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.</li> <li>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.</li> </ul>	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.	
<b>UNSCHEDULED VISITS</b> : If cultures of both spot sputum samples are contaminated <i>at the following visits</i> , 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:	<b>CENTRAL LAB</b> : 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).	

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		<ul> <li>End of treatment visit;</li> <li>Week 26 post treatment follow-up visit;</li> <li>Post treatment follow-up visits from week 8 through week 65 (in addition to week 26 follow-up);</li> <li>End of Follow-up Period (week 78 post treatment completion visit);</li> <li>Early Withdrawal (if applicable).</li> </ul> At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, need to confirm whether the participant has:	<b>EXTENDED DST TESTING:</b> 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.	
		<ul> <li>At least two sequential negative sputum culture results; or</li> <li>At least two sequential positive sputum culture results; or</li> <li>Has been unable to produce sputum after documentation of at least two negative sputum cultures with no intervening positive and are clinically asymptomatic.</li> </ul>		
		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.		
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

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		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	<ul> <li>5. Participants with one of the following pulmonary TB conditions: <ul> <li>a. XDR-TB with</li> <li>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:</li> <li>ii. historical documented resistance to isoniazid, rifamycins, a fluoroquinolone <b>AND</b> an injectable during the current TB diagnosis/disease course;</li> <li>b. Pre-XDR-TB with</li> <li>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 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;</li> <li>ii. historical-documented resistance to isoniazid, rifamycins, and to a fluoroquinolone <b>OR</b> an injectable during the current TB diagnosis/disease course.</li> <li>c. MDR-TB with <ul> <li>i. documented by culture positive or a molecular test positive (for MTB) from a sputum specimen collected results within</li> </ul> </li> </ul></li></ul>	<ul> <li>5. Participants with one of the following pulmonary TB conditions: <ul> <li>a. XDR-TB with</li> <li>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:</li> <li>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);</li> <li>b. Pre-XDR-TB with</li> <li>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;</li> <li>ii. 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;</li> <li>ii. documented resistance to rifamycins, and to a fluoroquinolone <b>OR</b> an injectable during the current TB diagnosis/disease course any time prior to or during screening period (may be sensitive or resistant to isoniazid);</li> </ul> </li> </ul>	21

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		-	-	
		<ul> <li>3 months prior to screening or MTB confirmed in sputum based on molecular test within 3 months prior to or at screening and;</li> <li>ii. historical—documented resistance to isoniazid and rifamycins during the current TB diagnosis/disease course;</li> <li>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.</li> <li>d. MDR-TB with <ul> <li>d. 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:</li> <li>ii. historical documented resistance to isoniazid and rifamycins during the current TB diagnosis/disease course and;</li> <li>iii. who are unable to continue second line drug regimen due to a documented intolerance to:</li> <li>a. PAS, ethionamide, aminoglycosides or fluoroquinolones or;</li> <li>b. Current treatment not listed above that renders participant eligible for the study in the Investigator's opinion.</li> </ul> </li> </ul>	<ul> <li>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;</li> <li>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;</li> <li>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.</li> <li>d. MDR-TB with <ul> <li>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:</li> <li>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;</li> <li>iii. who are unable to continue second line drug regimen due to a documented intolerance to:</li> <li>a. PAS, ethionamide, aminoglycosides or fluoroquinolones or ;</li> <li>b. Current treatment not listed above that renders participant eligible for the study in the Investigator's opinion.</li> </ul> </li> </ul>	
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	<ul> <li><u>Contraception:</u></li> <li>7. Be of non-childbearing potential or using effective methods of birth control, as defined below:</li> </ul>	<ul> <li><u>Contraception:</u></li> <li>7. Be of non-childbearing potential <u>or</u> using effective methods of birth control, as defined below:</li> </ul>	22

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Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version: V2.0 RUS, dated 13 June 2018 Protocol Name: ZeNix

## **Protocol Amendment Template**



		<ul> <li>Non-childbearing potential:</li> <li>a. Participant - not heterosexually active or practices sexual abstinence; or</li> <li>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</li> <li>c. Male participant/sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to Screening.</li> </ul>	<ul> <li>Non-childbearing potential:</li> <li>a. Participant - not heterosexually active or practices sexual abstinence; or</li> <li>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</li> <li>c. Male participant or female participant's male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to</li> </ul>	
		<ul> <li>Effective birth control methods: <ul> <li>A double contraceptive method should be used as follows:</li> <li>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</li> <li>b. Barrier method (one of the above) combined with hormone-based contraceptives or an intra-uterine device for the female participant/partner;</li> </ul> </li> <li>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</li> </ul>	<ul> <li>screening.</li> <li><u>Effective birth control methods:</u> <ul> <li>a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or</li> <li>b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female participant;</li> <li>c. Male participant's female sexual partner: Double barrier method or hormone based contraceptives or an intra-uterine device for the female participant.</li> </ul></li></ul>	
		<b>Note:</b> 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.	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	<ol> <li>TB infection with known resistance to pretomanid, delamanid, linezolid or bedaquiline.</li> </ol>	<ol> <li>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.</li> </ol>	5 and 23

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30	5.2 Exclusion Criteria	<ul> <li>10. Participants with any of the following at Screening:</li> <li>QTcF interval on ECG &gt;500 msec. Participants with QTcF &gt; 450 must be discussed with the Sponsor Medical Monitor before enrolment.</li> <li>Heart failure</li> <li>A personal or family history of congenital QT prolongation</li> <li>A history of or known, untreated, ongoing hypothyroidism</li> <li>A history of or ongoing bradyarrhythmia</li> <li>A history of Torsade de Pointe</li> </ul>	<ul> <li>10. Participants with any of the following at Screening:</li> <li>QTcF interval on ECG &gt;500 msec. Participants with QTcF &gt; 450 must be discussed with and approved by the Sponsor Medical Monitor before enrolment. (Per measurements and reading done from screening central ECG.)</li> <li>Heart failure</li> <li>A personal or family history of congenital QT prolongation</li> <li>A history of or known, untreated, ongoing hypothyroidism</li> <li>A history of or ongoing bradyarrhythmia</li> <li>A history of Torsade de Pointe</li> </ul>	5 and 16
31	5.2 Exclusion Criteria	<ul> <li>Previous and Concomitant Therapy</li> <li>15. Concomitant use of Monoamine Oxidase Inhibitors (MAOIs) or prior use within 2 weeks of randomization.</li> <li>16. 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.</li> <li>17. Concomitant use of any drug known to prolong QTc interval (including, but not limited to, amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, fluoroquinolones, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).</li> <li>18. Concomitant use of any drug known to induce myelosuppression.</li> <li>19. Concomitant use of any drug sor substances known to be strong inhibitors or inducers of cytochrome P450 enzymes (including but not limited to efavirenz, quinidine, tyramine, ketoconazole, fluconazole, testosterone, quinne, 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.</li> </ul>	<ul> <li>Previous and Concomitant Therapy</li> <li>15. Known (during screening) requirement for future Concomitant (during treatment) use of any prohibited and/or avoided medications noted in section 5.3.</li> <li>16. Prior use of Monoamine Oxidase Inhibitors (MAOIs) within 2 weeks of randomization.</li> <li>17. Prior use of serotonergic antidepressants within 3 days of randomization if Investigator foresees potential risks for serotonin syndrome when combined with linezolid.</li> <li>18. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP.</li> <li>19. 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.</li> <li>20. 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.</li> </ul>	24

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		<ol> <li>20. Concomitant use of adrenomimetics (including, but not limited to pseudoephedrine, phenylpropanolamine, epinephrine, norepinephrine, dobutamine), dopaminomimetics (e.g. dopamine).</li> <li>21. Concomitant use of 5-HT1 agonists (triptans), meperidine or buspirone.</li> <li>22. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP.</li> <li>23. Participants with an existing TB diagnosis (a diagnosis made &gt; 4 weeks prior to screening) and HIV co-infection, must have been on an ART for at least 4 weeks prior to screening.</li> <li>24. 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.</li> <li>25. 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.</li> </ol>		
32	5.2 Exclusion Criteria	<ul> <li>Diagnostic and Laboratory Abnormalities</li> <li>26. 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):</li> <li>a. Viral load &gt;1000 IU/ml (Unless newly diagnosed HIV and not yet on ART who otherwise qualify for participation);</li> <li>b. CD4+ count &lt; 100 cells/µL (HIV positive participants);</li> <li>c. Serum potassium less than the lower limit of normal for the laboratory;</li> <li>d. Hemoglobin &lt; 9.0 g/dL;</li> <li>e. Platelets &lt;100,000/mm3;</li> <li>f. Absolute neutrophil count (ANC) &lt; 1500/ mm3;</li> <li>g. Aspartate aminotransferase (AST)</li> </ul>	<ul> <li>Diagnostic and Laboratory Abnormalities</li> <li>21. 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):</li> <li>a. Viral load &gt;1000 copies/mL (Unless newly diagnosed HIV and not yet on ART who otherwise qualify for participation);</li> <li>b. CD4+ count &lt; 100 cells/µL (HIV positive participants);</li> <li>c. Serum potassium less than the lower limit of normal for the laboratory;</li> <li>d. Hemoglobin &lt; 9.0 g/dL or &lt; 90 g/L;</li> <li>e. Platelets &lt;100,000/mm3 or &lt; 100 x 10^9/L;</li> <li>f. Absolute neutrophil count (ANC) &lt; 1500/ mm3 or &lt; 1.5 x 10^9/L;</li> </ul>	25

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		• Grade 3 or greater (> 3.0 x ULN) to be excluded;	g. Aspartate aminotransferase (AST)	
		Results between 1.5 x ULN and 3 x ULN must be discussed with	• Grade 3 or greater (> 3.0 x ULN) to be excluded;	
		and approved by the Sponsor Medical Monitor	Results between 1.5 x ULN and 3 x ULN must be discussed	
		h. Alanine aminotransferase	with and approved by the Sponsor Medical Monitor	
		<ul> <li>Grade 3 or greater (&gt; 3.0 x ULN) to be excluded;</li> </ul>	h. Alanine aminotransferase	
		<ul> <li>Results between 1.5 x ULN and 3 x ULN must be discussed with</li> </ul>	<ul> <li>Grade 3 or greater (&gt; 3.0 x ULN) to be excluded;</li> </ul>	
		and approved by the Sponsor medical monitor;	<ul> <li>Results between 1.5 x ULN and 3 x ULN must be discussed</li> </ul>	
		i. Total bilirubin	with and approved by the Sponsor medical monitor;	
		<ul> <li>greater than 1.5 x ULN to be excluded;</li> </ul>	i. Total bilirubin	
		<ul> <li>1-1.5 x ULN must be discussed with and approved by the</li> </ul>	<ul> <li>greater than 1.5 x ULN to be excluded;</li> </ul>	
		Sponsor Medical Monitor	<ul> <li>1-1.5 x ULN must be discussed with and approved by the</li> </ul>	
		j. Direct bilirubin	Sponsor Medical Monitor	
		Greater than ULN to be excluded	j. Direct bilirubin	
		k. Serum creatinine level greater than 1.5 times upper limit of	Greater than ULN to be excluded	
		normal	k. Serum creatinine level greater than 1.5 times upper limit of	
		I. Albumin <3.0 mg/dl	normal	
		Ğ	I. Albumin <3.0 g/dl or < 30 g/L	
	5.2 Exclusion		5 0	26
33	Criteria		No protocol univers will be granted by the TB Alliance	_0
			No protocol waivers will be granted by the 16 Amance.	
	5.3.1 Prior and	The following concomitant medications are prohibited during the treatment	The following concomitant medications are prohibited during the	5 and 27
	5.3.1 Prior and Concomitant	The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:	The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:	5 and 27
	5.3.1 Prior and Concomitant Medications and	The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:	The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:	5 and 27
	5.3.1 Prior and Concomitant Medications and Other	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>Medicinal products used to treat pulmonary TB: including but not</li> </ul>	The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion: <ul> <li>Medicinal products used to treat pulmonary TB: including but</li> </ul>	5 and 27
	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin,</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin,</li> </ul>	5 and 27
	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone,</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine,</li> </ul>	5 and 27
	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, guinolones, thioamides, and metronidazole.</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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</li> </ul>	5 and 27
	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs), (e.g., and the concomitant use of Monoamine Oxidase Inhibitors (MAOIs).</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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.</li> </ul>	5 and 27
34	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine_isocarboxazid)</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs).</li> </ul>	5 and 27
34	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> </ul>	5 and 27
34	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of any drug known to prolong QTc interval (including hubble).</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of adrenomimetics (including, but not</li> </ul>	5 and 27
34	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine,</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of adrenomimetics (including, but not limited to pseudoephedrine, phenylpropanolamine,</li> </ul>	5 and 27
34	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin,</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of adrenomimetics (including, but not limited to pseudoephedrine, phenylpropanolamine, epinephrine, norepinephrine, dobutamine),</li> </ul>	5 and 27
34	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>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,</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of adrenomimetics (including, but not limited to pseudoephedrine, phenylpropanolamine, epinephrine, norepinephrine, dobutamine), dopaminomimetics (e.g. dopamine).</li> </ul>	5 and 27
34	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>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,</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of adrenomimetics (including, but not limited to pseudoephedrine, phenylpropanolamine, epinephrine, norepinephrine, dobutamine), dopaminomimetics (e.g. dopamine).</li> <li>Concomitant use of 5-HT1 agonists (triptans), meperidine or</li> </ul>	5 and 27
34	5.3.1 Prior and Concomitant Medications and Other Treatments	<ul> <li>The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the IMP:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>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,</li> </ul>	<ul> <li>The following concomitant medications are prohibited during the treatment period and during the 14 days after treatment completion:</li> <li>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.</li> <li>Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid)</li> <li>Concomitant use of adrenomimetics (including, but not limited to pseudoephedrine, phenylpropanolamine, epinephrine, norepinephrine, dobutamine), dopaminomimetics (e.g. dopamine).</li> <li>Concomitant use of 5-HT1 agonists (triptans), meperidine or buspirone.</li> </ul>	5 and 27

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<ul> <li>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.</li> <li>Concomitant use of any drug known to induce myelosuppression.</li> <li>The systemic use of CYP3A4 inhibitors (e.g., azole antifungals:</li> </ul>	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:
<ul> <li>ketoconazole, voriconazole, itraconazole, fluconazole; ketolids such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 3 consecutive days;</li> <li>The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone.</li> </ul>	<ul> <li>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,</li> </ul>
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,	<ul> <li>thioridazine).</li> <li>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.</li> <li>Concomitant use of any drug known to induce significant myelosuppression</li> <li>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;</li> <li>The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone.</li> <li>Concomitant use of serotonergic antidepressants should be avoided if possible as participants on these agents and linezolid are at risk for serotonin syndrome.</li> <li>Caution should be used in treating diabetic patients receiving insulin or oral hypoglycemic agents as cases have been</li> </ul>

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		tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).	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).	
	5.4 Trial Discontinuation and Visits	<ul> <li>5.4 Discontinuation from Treatment/Trial</li> <li>The following may result in the discontinuation of trial treatment;</li> <li>Pregnancy;</li> <li>Investigator considers it for safety reasons in the best interest of</li> </ul>	<ul><li>5.4 Trial Discontinuation and Visits</li><li>5.4.1 Treatment Discontinuation and Early Withdrawal</li></ul>	21 and 28
35		<ul> <li>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:         <ul> <li>Adverse event(s);</li> <li>Myco testing results from baseline (Screening through Week 4) indicate sensitivity to isoniazid and/or rifamycins;</li> </ul> </li> </ul>	<ul> <li>A participant must be withdrawn from the trial due to the following;</li> <li>Pregnancy;(unless female post visit for end of treatment/early withdrawal from treatment);</li> </ul>	

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		<ul> <li>Myco testing results from baseline (Screening through Week 4) indicate resistance to bedaquiline, pretomanid or linezolid;</li> <li>In the opinion of the investigator, fails to comply with the protocol, including non-compliance to IMP.</li> </ul> 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: <ul> <li>Withdrawal of informed consent;</li> <li>Lost to follow-up;</li> <li>Termination of the trial by the sponsor.</li> </ul>	<ul> <li>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.</li> <li>At the specific request of the sponsor or termination of the trial by Sponsor;</li> <li>Lost to follow-up</li> <li>In the opinion of the investigator, fails to comply with the protocol, including non-compliance to IMP.</li> <li>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.</li> <li>Myco testing results from baseline (Screening through Week 4) indicate sensitivity to rifamycins;</li> <li>Myco testing results from baseline (Screening through Week 4) with MICs that indicate likely resistance to bedaquiline, pretomanid or linezolid;</li> </ul>	
			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	10 and 28

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	1	1					1
		In case of e	arly withdrawal	during the trea	tment or follo	ow-up period,	
		all efforts	shall be mad	le to complet	e the Early	Withdrawal	
		assessment	S.		-		
		Once a part	icipant has bee	n withdrawn ea	arly from the	trial. they will	
		be requeste	d to attend follo	w-un visits as c	, lescribed in 1	Table 9	
		Table X: Follow	w-up Visits Require	ed for Early Withd	awal Participan	its	
		Treatment	Ophthalmology	Ophthalmology	26 Week	78 Week Post	
		Duration at	Examination at	Examination	Post	Treatment	
		EW VISIT	EVV	12 week Post	Follow-up	Visit	
				treatment follow-	Visit		
		≤ 14 davs	NA	NA	NA	NA	
		15 days to	NA	Required	Required	Required	
		> 12 weeks	Required	Required	Required, if not	Required	
					already performed		
		a. If an additi	onal visit is required f	or an ophthalmology	examination after l	EWD, only the	
		EWD visit da	y examination will be te.	performed at this visi	t, and it will occur	12 weeks after the	
		The 26 and	78 week post tr	eatment follow-	un visits will	he performed	
		to collect S	AF information	including ve	rification of	survival) and	
		narticinant	reported TB or	Itcome informa	ation This	visit may be	
			a home or a site	vieit		visit may be	
				, visit.			
	5.4.3	5.4.3 Unsch	neduled Visits				28
	Unscheduled						
	Visits	Any visit wh	ich is conducte	d in addition to	those require	d by the	
		Synopsis Flo	ow Chart and P	rocedures, sho	uld be consid	lered	
		unschedule	d regardless of	the reason for t	he visit. The	assessments	
37		which are ur	ndertaken as pa	art of an Unsche	eduled visit sl	hould be as	
51		clinically ind	icated.				
		The followin	g situation/s red	quire an unsche	duled visit/s:		
		<ul> <li>If cultures</li> </ul>	of both spot sr	utum samples	are contamin	ated at the	
		following	isits or if nece	ssarv in order to	help define	a	
		narticinan	t's outcome sta	tue/acces cult	ire status du	ring follows	
			rticipant chould	roturn for on u		visit(s) to divo	
		l up, ine pa	nicipant snould	return for an u	ischeduied v	isit(s) to give	

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			additional samples or to document the participant is not able to	
			produce sputum:	
			<ul> <li>End of treatment visit;</li> <li>Week 26 post treatment follow-up visit;</li> <li>Post treatment follow-up visits from week 8 through week 65 (in addition to week 26 follow-up);</li> <li>End of Follow-up Period (week 78 post treatment completion visit);</li> <li>Early Withdrawal (if applicable).</li> </ul>	
			<ul> <li>At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status, and to determine whether the participant has: <ul> <li>At least two sequential negative sputum culture results; or</li> <li>At least two sequential positive sputum culture results; or</li> <li>Has been unable to produce sputum after documentation of at least two negative sputum cultures with no intervening positive and are clinically asymptomatic.</li> </ul> </li> </ul>	
			If they <b>do not</b> 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.	
			<b>5.4.4 Lost to Follow-up</b> 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

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Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version: V2.0 RUS, dated 13 June 2018 Protocol Name: ZeNix



### **Protocol Amendment Template**

30	6.1 IMP	Table 9: Investigational Medicinal Product Details	Table <b>10</b> :	Investigational Medicinal Product Details	6
39	Administration				_

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Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version: V2.0 RUS, dated 13 June 2018 Protocol Name: ZeNix



# Protocol Amendment Template

Tr	reatment Group	Active and Placebo	Treatment Group	Active and Placebo
Line 120 dail wee	nezolid 200 mg aily for 26 eeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> </ul>	Linezolid 1200 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 26 weeks</li> </ul>
Line 120 dail wee	nezolid 200 mg aily for 9 eeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid 600 mg tablets once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>	Linezolid 1200 mg daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid tablets once daily for 17 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 17 weeks</li> </ul>
Line mg 26 v	nezolid 600 g daily for 3 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid 600 mg tablet once daily for 26 weeks</li> </ul>	<u>Linezolid</u> <u>600 mg</u> daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid tablet once daily for 26 weeks</li> </ul>

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		<ul> <li>1 placebo linezolid 300 mg half tablet once daily for 26 weeks</li> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 9 weeks</li> <li>2 placebo linezolid 600 mg tablet for 9 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> <li>1 placebo linezolid 300 mg half tablet once daily for 17 weeks</li> </ul>		• ½ (one half) placebo linezolid tablet once 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 8 weeks plus;         • 1 pretomanid 200 mg active tablet once daily for 26 weeks.         Weeks 1-9         • 1 linezolid 600 mg daily for 9 weeks         • 1 placebo linezolid tablet for 9 weeks         • 1 placebo linezolid tablet for 9 weeks         • 2 placebo linezolid tablets once daily for 17 weeks         • 2 placebo linezolid tablets once daily for 17 weeks
40	6.2 Participant Compliance	Additionally, participant cards will be checked for unused tablets in the blisters.	e	Additionally, participant cards/bottles will be checked for unused 29 tablets at each visit during the treatment period.
41	6.3 Treatment Modification(s)	All dose modifications should be discussed with the Sponsor Medic Monitor prior to implementation, unless a pause or dose reduction required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior implementation. All dose modifications should be discussed with the Sponsor Medic Monitor prior to implementation, unless a pause or dose reduction required urgently for a safety concern; the Medical Monitor should be informed within 24 hours of the change if not discussed prior implementation. In the event of linezolid specific toxicities, the following should be considered and implemented per guidance in the monitoring and safety f specific toxicities section of protocol:	al is e o al is e o r	<ul> <li>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.</li> <li>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):</li> <li>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</li> </ul>

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<ul> <li>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.</li> <li>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.</li> <li>Permanent discontinuation of linezolid.</li> <li>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.</li> <li>Pauses of the full regimen must not exceed 8 weeks (56 days) cumulatively.</li> <li>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.</li> <li>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.</li> </ul>	<ul> <li>1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or;</li> <li>600 mg QD to 300 mg QD, 300mg QD to placebo).</li> <li>Temporary pause of linezolid</li> <li>Permanent discontinuation of linezolid.</li> <li>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.</li> <li>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.</li> <li>Interruptions/pauses of the full regimen must not exceed 8 weeks (56 days) cumulatively.</li> <li>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.</li> </ul>	
	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.	

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			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	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:	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:	6
42		<ul> <li>Bedaquiline: Bottles containing:         <ul> <li>200 mg QD dose- 28 tablets- bedaquiline 100 mg</li> <li>100mg QD dose- 14 tablets- bedaquiline 100 mg</li> </ul> </li> <li>Pretomanid: Blister card containing 14 tablets- pretomanid 200 mg</li> <li>Linezolid: Blister Card containing 7 days of dosing as follows:             <ul> <li>1200 mg QD Dose</li> <li>2 blister strips of 7 tablets each (14 tablets) containing active linezolid 600 mg</li> <li>1 blister strip of 7 half tablets containing placebo linezolid 300 mg</li> <li>600 mg QD Dose:</li></ul></li></ul>	<ul> <li>Bedaquiline: Bottles containing:         <ul> <li>200 mg QD dose- 28 tablets- bedaquiline 100 mg</li> <li>100mg QD dose- 14 tablets- bedaquiline 100 mg</li> </ul> </li> <li>Pretomanid: Blister card containing 14 tablets- pretomanid 200 mg</li> <li>Linezolid: Blister Card containing 7 days of dosing as follows:             <ul> <li>1200 mg QD Dose</li> <li>2 blister strips of 7 tablets each (14 tablets) containing active linezolid 600 mg</li> <li>1 blister strip of 7 half tablets containing placebo linezolid</li> <li>600 mg QD Dose:</li></ul></li></ul>	

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		<ul> <li>1 blister strip of 7 half tablets containing placebo linezolid 300 mg</li> </ul>	<ul> <li>1 blister strip of 7 half tablets containing placebo linezolid</li> </ul>	
43	6.4 IMP Packaging and Labelling	<ul> <li>The packaging of each bottle/blister card will be labelled with, at a minimum, the following information:</li> <li>Name, address and telephone number of Sponsor.</li> </ul>	<ul><li>The packaging of each bottle/blister card will be labelled with, at a minimum, the following information:</li><li>Name of Sponsor.</li></ul>	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	<ul> <li>Clinically significant medical and treatment history (including past and current TB diagnosis and smoking)</li> </ul>	<ul> <li>Clinically significant medical and treatment history (including past and current TB diagnosis, alcohol use and smoking)</li> </ul>	32
47	7.1 Demographic and Background Variables	Serology: HIV and CD4 count.	<ul> <li>Serology: HIV, CD4 count and viral load.</li> <li>If an HIV test was performed within 1 month prior to trial start, it should not be repeated as long as</li> </ul>	33

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		<ul> <li>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).</li> </ul>	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	<ul> <li>TB Symptoms Profile:</li> <li>The TB Symptoms Profile (Appendix 7) will record participants' ratings of the severity of common TB symptoms.</li> <li>Patient Reported Health Status Variables and Procedures:</li> <li>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.</li> </ul>	<ul> <li>TB Symptoms Profile:</li> <li>The TB Symptoms Profile (found in the Subject Questionnaires Guideline) will record participants' ratings of the severity of common TB symptoms.</li> <li>Patient Reported Health Status Variables and Procedures:</li> <li>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.</li> </ul>	35
50	7.3 Safety and Tolerability Assessments	• Brief Peripheral Neuropathy Screen (Appendix 6) will record ratings.	<ul> <li>Brief peripheral neuropathy screen (found in the Subject Questionnaires Guideline) will record ratings.</li> </ul>	35
51	7.5 Mycobacteriology Characterization Variable and Procedures	<ul> <li>The following Mycobacterial Characterization variables will be collected:</li> <li>Positive Culture (for MTB) from: <ul> <li>Day 1 or if Day 1 is not available, first positive between screening through Week 4;</li> <li>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</li> </ul> </li> </ul>	<ul> <li>The following Mycobacterial Characterization variables will be collected:</li> <li>Positive Culture (for MTB) from: <ul> <li>Day 1 or if Day 1 is not available, first positive between Screening through Week 4;</li> <li>If consent granted, and when applicable, Pre-screening culture/isolate to be sub cultured and shipped and/or tested:</li> <li>At the study lab if/when samples could support inclusion in the trial</li> </ul> </li> </ul>	35

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		-	-	
		<ul> <li>When applicable, end of treatment or visits with positive cultures during post-treatment follow-up.</li> </ul>	<ul> <li>To the study/central lab for relevant participants/with no baseline (positive cultures from screening through Week 4)</li> <li>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.</li> </ul>	
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
	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.	5
53			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.	
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

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			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

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Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version: V2.0 RUS, dated 13 June 2018 Protocol Name: ZeNix



### Sponsor

I agree to the terms of this protocol amendment

DocuSigned by: Daniel Event

Signer Name: Dan Everitt
 Signing Reason: I approve this document
 Signing Time: 6/27/2018 7:50:39 AM EDT

Signature of Senior Medical Officer

Dan Everitt

Printed name

June 27, 2018 | 7:50 AM EDT

Date

### **Principal Investigator**

I hereby confirm I have read the above Protocol Amendment and agree to conduct this clinical trial as outlined in the above Protocol Amendment. I will provide copies of the Protocol Amendment and access to all of the information required to conduct the clinical trial according to the above Protocol Amendment to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

**Protocol Amendment Template** 

Signature of Principal Investigator

Printed name

Date

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#### **Certificate Of Completion**

Envelope Id: 26F4BA008E4D4A4DAEF105C1028E3501 Subject: Please DocuSign: NC-007 RUS\_Prot\_Amend v 1 13JUN2018.pdf Source Envelope: Document Pages: 37 Signatures: 1 Certificate Pages: 1 Initials: 0 AutoNav: Enabled EnvelopeId Stamping: Disabled Time Zone: (UTC-05:00) Eastern Time (US & Canada)

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#### Signer Events

Dan Everitt dan.everitt@tballiance.org VP & Senior Medical Officer Global Alliance for TB Drug Development (Part 11 Compliant) Security Level: Email, Account Authentication (Required)

April Everitt

Holder: Erica Egizi

Signature

Signature ID: 32534894-D929-4A59-B14B-10FC37E90452 Using IP Address: 38.105.215.226

erica.egizi@tballiance.org

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Envelope Summary Events	Status	Timestamps
Envelope Sent Certified Delivered Signing Complete Completed	Hashed/Encrypted Security Checked Security Checked Security Checked	6/26/2018 5:33:24 PM 6/27/2018 7:50:22 AM 6/27/2018 7:50:50 AM 6/27/2018 7:50:50 AM
Payment Events	Status	Timestamps



#### 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:**

**Updated** patient population from 14 and over to 18 and over as Moldova will not enroll patients under 18 (In section 1.1 Synopsis Summary, 4.1 Summary of Trial Design, and 5.1 Inclusion Criteria)

#	Section	Previous Text Version 1.0, dated 23-Feb-17	Amended Text MDA Protocol Version 1.0, dated 13-Jun-18 (incorporating Country Specific Amendment 1.0) Additional text - bold font. Deleted text - strike-through.	Reason for Change Insert reason # from table above
1	1.1 Synopsis Summary	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.	A total of up to 180 participants, male and female, aged 18 and over Sponsor may consider replacement of late screen failure and un- assessable (as detailed in the statistical analysis plan) participants.	1
2	4.1 Summary of Trial Design	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.	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 18 and over, will be randomized to receive one of the 4 active treatment arms.	1
3	5.1 Inclusion Criteria	4. Male or female, aged 14 years or older.	4. Male or female, aged 18 years or older.	1

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Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version: MDA Protocol Version 1.0, dated 13 June 2018 (incorporating Country Specific Amendment 1.0) Protocol Name: ZeNix

Protocol Amendment Template



#### Sponsor

I agree to the terms of this protocol amendment

DocuSigned by:

Daniel Everitt

Signer Name: Dan Everitt
 Signing Reason: I approve this document
 Signing Time: 6/27/2018 7:49:29 AM EDT
 32534894D9294A59B14B10FC37E90452

Signature of Senior Medical Officer

Dan Everitt

Printed name

June 27, 2018 | 7:49 AM EDT

Date

## **Principal Investigator**

I hereby confirm I have read the above Protocol Amendment and agree to conduct this clinical trial as outlined in the above Protocol Amendment. I will provide copies of the Protocol Amendment and access to all of the information required to conduct the clinical trial according to the above Protocol Amendment to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature of Principal Investigator

Printed name

Date

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#### Signer Events

Dan Everitt dan.everitt@tballiance.org VP & Senior Medical Officer Global Alliance for TB Drug Development (Part 11 Compliant) Security Level: Email, Account Authentication (Required)

erica.egizi@tballiance.org

Signature

Anil Everitt

Holder: Erica Egizi

Signature ID: 32534894-D929-4A59-B14B-10FC37E90452 Using IP Address: 38.105.215.226

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Notary Events	Signature	Timestamp
Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	6/26/20185:38:15 PM
Certified Delivered	Security Checked	6/27/20187:49:18 AM
SigningComplete	Security Checked	6/27/20187:49:31 AM
Completed	Security Checked	6/27/20187:49:31 AM
Payment Events	Status	Timestamps



### 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 \_\_/\_\_/\_\_\_

Sum	Summary - Protocol section changed		
		YES	NO
А	Purpose of trial		Х
В	Design of trial		Х
С	Informed consent		Х
D	Recruitment procedure		Х
E	Measures of efficacy		Х
F	Schedule of samples		Х
G	Addition or deletion of tests or measures		Х
Η	Number of participants		Х
_	Age range of participants		Х
J	Inclusion criteria		Х
K	Exclusion criteria		Х
L	Safety monitoring		Х
М	Duration of exposure to the investigational medicinal product(s)		Х
Ν	Change of posology of the investigational medicinal product(s)		Х
0	Change of comparator		Х
Ρ	Statistical analysis	Х	

TMP-C-SOP01-CV1.030-Nov-2018



### 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	GLOBAL ALLIANCE	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

TMP-C-SOP01-CV1.030-Nov-2018



### Protocol Amendment or Administrative Change

	6.6	The blind must not be broken except in the case of a medical emergency, where treatment of the	The blind for a participant must not be broken by the site or sponsor except in the case of a	1
		participant is influenced by the knowledge of	medical emergency, where treatment of the a	
		what dose and duration of linezolid the	participant is influenced by the knowledge of	
		participant is receiving. The investigator should	what dose and duration of linezolid the	
		discuss breaking the blind with the Sponsor	participant is receiving. The investigator should	
		the blind unless knowledge of treatment arm is	Medical Monitor (or designee) prior to breaking	
		required urgently for a safety concern. The	the blind unless knowledge of treatment arm is	
		Sponsor Medical Monitor should be informed of	required urgently for a safety concern. The	
		the blind break within 24 hours if not discussed	Sponsor Medical Monitor should be informed of	
		prior. IXRS will be programmed with blind-	the blind break within 24 hours if not discussed	
		breaking instructions, described in the user	prior. IARS will be programmed with birnd- breaking instructions described in the user	
•		the blind to fulfil any regulatory requirements	manual. The Sponsor reserves the right to break	
3		regarding reporting of SAEs. If a participant is	the blind to fulfil any regulatory requirements	
		unblinded, they are not required to be withdrawn	regarding reporting of SAEs. If a participant is	
		from the study.	unblinded, they are not required to be withdrawn	
		In the absence of any medical emergencies	nom the study.	
		requiring a blind break. the blind for all	In the absence of any medical emergencies	
		participants will be broken once all clinical data	requiring a blind break, the blind for all	
		and outcome parameters have been captured,	participants will be broken once all clinical data	
		no more data queries are pending and the	and outcome parameters have been captured,	
		statistical analysis plan has been infalized.	no more data queries are pending and the statistical analysis plan has been finalized.	
			otatiotical analysis plan nas seen intaized.	
			There will be three unblinded analyses which	
			will contain results by linezolid treatment	
			group in aggregate (see section 9.3). The first	

TMP-C-SOP01-CV1.030-Nov-2018



## 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.	

TMP-C-SOP01-C V1.0 30-Nov-2018



## 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	1
			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 and of	
			treatment).	

TMP-C-SOP01-CV1.030-Nov-2018



## 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
			<ul> <li>There will be two three database locks for the three planned unblinded data analyses and trial reports generated for this trial:</li> <li>1. When all participants have completed 26 weeks of treatment</li> <li>4. 2. When all participants have completed 26 weeks of follow-up after end of treatment.</li> <li>2. 3. When all participants have completed 78 weeks of follow-up from after end of treatment.</li> </ul>	

TMP-C-SOP01-CV1.030-Nov-2018



## Protocol Amendment or Administrative Change

#### Sponsor

I agree to the terms of this Protocol Amendment or Administrative Change.



Signature of Senior Medical Officer

Dan Everitt

Printed name

March 11, 2020 | 3:24 PM EDT

Date

### **Principal Investigator**

I hereby confirm I have read the above Protocol Amendment or Protocol Administrative Change and agree to conduct this clinical trial as outlined in the above. I will provide copies of the Protocol Amendment or Protocol Administrative Change and access to all of the information required to conduct the clinical trial according to the above Protocol Amendment or Protocol Administrative Change to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature of Principal Investigator

Printed name

Date

TMP-C-SOP01-C V1.0 30-Nov-2018



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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)
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

# PROTOCOL SIGNATURE PAGE

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

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

Protocol 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

# SPONSOR

I agree to the terms of this trial protocol.

Signature of Senior Medical Officer

Printed Name

40 Wall Street, 24th Floor New York, NY 10005

email: daniel.everitt@tballiance.org

Phone 646-616-8671

Date

# LEAD INVESTIGATOR

I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations.

Signature

Printed Name

Date

Protocol Number: NC-007-(B-Pa-L) Protocol Version V3.0 10 MARCH 2020 Protocol Name: ZeNix

# PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

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

Protocol 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

I hereby confirm that I have read the above protocol and agree to conduct this clinical trial as outlined in the above protocol. I will provide copies of the protocol and access to all the information required to conduct the clinical trial according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature

Printed Name

Date

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# 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
AUCτ	Area under curve over a dosing interval
В	Bedaguiline
BMI	Body mass index
bpm	Beats per minute
BPNS	Brief peripheral neuropathy scale
С	Clofazimine
CFU	Colony forming units
CK(-MB)	Creatine kinase (-MB isoenzyme)
C <sub>(max)</sub> ,	Plasma concentration (maximum), (minimum)
(min)	
CO <sub>2</sub>	Carbon dioxide
CPK	Creatine phosphokinase
CS	Clinically significant
Ctrough	Plasma concentration trough
CYP3A4	Cytochrome P450 3A4
DMID	Division of microbiology and infection disease
DNA	Deoxyribonucleic acid
DOH	Department of health
וווס	Drug induced liver injury
DSMC	Data safety monitoring committee
DST	Drug susceptibility testing
F	Ethambutol
FRA	Early bactericidal activity
EC.	Ethics committee
ECG	Electrocardiogram
FEV	Efavirenz
(e)CRF	Electronic case report form
FQ	Fluoroquinolone
FTC	Emtricitabine
a/l	Grams per liter
GI	Gastrointestinal
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMR	Geometric mean ratio
H	Isoniazid
hERG	Human ether-à-ao-ao related gene
HIV	Human immunodeficiency virus
HRZE	Isoniazid, Rifampicin, Pvrazinamide. Ethambutol
ICF	Informed consent form
ICH	International Conference on Harmonization
IMP	Investigational medicinal product

IRB IUATLD IXRS	Institutional review board International Union Against Tuberculosis and Lung Disease Interactive Voice and Web Response System
kg	Kilogram
/L	Liter
	Linezolia Lower Limit of Normal
M	Moxifloxacin
	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	Newrapine
	Nitric oxide
	(Triple) pulsosidose reverse transprintese inhibitor
	(Thple) huleosidase reverse transcriptase minibitor
	Pharmacodynamic
	Per protocol Bharmaackingtig
	PR interval
	Once daily
R	Rifampicin
S	Streptomycin
SAE	Serious adverse event
SAP	Statistical analysis plan
SIRE	Streptomycin isoniazid rifampicin ethambutol
SOC	System organ class
ТВ	Tuberculosis
TBL	Serum total bilirubin
TDF	Tenofovir
TEAE	Treatment emergent adverse events
I>MIC	Time above minimum inhibitory concentration
t.i.w.	Inree times a week
(BA) I IP	(Bacteriocidal activity) time to positivity
	White blood cell
WHO	World Health Organization
	Extensively drug resistant tuberculosis
	Microgram
۳A	morogram

Z Pyrazinamide

Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version V3.0 10 March 2020 Protocol Name: ZeNix

# 1 Synopsis

# 1.1 Synopsis Summary

Name of Sponsor/Company	Global Alliance for TB D	rug Development					
Name of Finished	bedaquiline (B), pretoma	anid (Pa) and linezolid (L)					
Products:							
Protocol Number/Title:	NC-007: A Phase 3 part	ially-blinded, randomized tria	l assessing the safety				
	and efficacy of various d	loses and treatment durations	s of linezolid plus				
	bedaquiline and pretoma	and in participants with pulme	onary infection of either				
	extensively drug-resista	nt tuberculosis (XDR-IB), pre	-XDR-IB or treatment				
Treatment Indication:	Dulmonany YDP TB pro	Sive multi-drug resistant tube	Iculosis (IVIDR-IB)				
	MDR-TB		relation non-responsive				
Trial Objective:	To evaluate the efficacy	, safety and tolerability of vario	ous doses and durations				
	of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in						
	intolerant or non-responsive MDR-TB.						
Trial Design:	A phase 3, multi-center,	partially-blinded, randomized	clinical trial in four parallel				
	treatment groups. Beda	quiline and pretomanid treat	ment will not be blinded.				
	Linezolid treatment dos	e and duration will be double-	blinded.				
	Participants will have	a screening period of up t	o 14 days and will be				
	randomized to receive o	one of the 4 active treatment	arms. Participants will be				
	randomized to one of th	e four regimens in a 1:1:1:1	ratio, using an interactive				
	voice and web response	se system (IXRS) which will	l utilize a randomization				
	system using stratification with a random element to allocate participants evenly						
	Each participant will receive 26 weeks of treatment. If participant's sputum						
	sample is culture positiv	ve between the week 16 and	week 26 treatment visits				
	and their clinical condition suggests they may have an ongoing IB 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 t	to make this decision. All deci	sions regarding treatment				
	extension should be discussed with and approved by the Sponsor Medical						
	Monitor before implementation.						
	Participants will be followed for 78 weeks after and of treatment						
Patient Population:	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.						
Test product, Dose and	st product, Dose and The regimen will be supplied as the following:						
Mode of Administration:							
	Product	Tablet Strength	Abbreviation				
	Bedaquiline	100 mg	(B)				
		7/11/1000	10				
		200 mg	(Pa)				
	Linezolid (scored)	600 mg	(Pa) (L)				
	Linezolid (scored) Placebo Linezolid (scored)	600 mg placebo	(Pa) (L) (L)				
	Linezolid (scored) Placebo Linezolid (scored) Linezolid 600 mg half	200 mg 600 mg placebo 300 mg	(Pa) (L) (L) (L)				
Placebo linezolid half tablet (pre-cut)	placebo	(L)					
---	--	---	--	--	--	--	--
Linezolid treatment wi placebo) and one row possible dosing optior	Il be supplied as 2 rows of full of half-tablets (active or place as while maintaining the blind.	tablets (active or bo) to allow for all					
Instructions for Dosing: Treatment will be administered orally, once daily, with a full glass of wate a meal in the following dosing schemes (treatment arms):							
<ul> <li>Participants will receive</li> <li>Bedaquiline 200 n 18 weeks plus;</li> <li>Pretomanid 200 m</li> <li>Linezolid- particip following four blind</li> </ul>	<u>the following:</u> ng once daily for 8 weeks ther ng once daily for 26 weeks plu ants will be randomly assigne ded linezolid treatment doses	n 100 mg once daily for Is; d to receive one of the and durations:					
Linezolid 1200 mg daily 2 linezolid 600 mg 1/2 (one half) place	<u>for 26 weeks</u> active tablets once daily for 2 bo linezolid tablet once daily f	26 weeks for 26 weeks					
Linezolid 1200 mg daily Weeks 1-9 • 2 linezolid 600 mg • ½ (one half) place Weeks 10-26 • 2 placebo linezolid • ½ (one half) place	for 9 weeks active tablets once daily for 9 bo linezolid tablet once daily f d tablets once daily for 17 wee bo linezolid tablet once daily f	) weeks for 9 weeks eks for 17 weeks					
Linezolid 600 mg daily f 1 linezolid 600 mg 1 placebo linezolid 1⁄2 (one half) place	or <u>26 weeks</u> active tablet once daily for 26 d tablet once daily for 26 week bo linezolid tablet once daily f	6 weeks s for 26 weeks					
Linezolid 600 mg daily fr Weeks 1-9 1 linezolid 600 mg 1 placebo linezolic 1/2 (one half) placebo	or 9 weeks active tablet once daily for 9 v I tablet for 9 weeks bo linezolid tablet once daily fo	weeks or 9 weeks					
Weeks 10-26 • 2 placebo linezolic • ½ (one half) place	l tablets once daily for 17 wee bo linezolid tablet once daily fo	ks or 17 weeks					
Treatment Modification The above treatment so noted below. All dose m Medical Monitor prior to required urgently for a s within 24 hours of the cl	ons: chemes may require modificat nodifications should be discus implementation, unless a pau afety concern; the Medical Me hange if not discussed prior to	ion due to toxicities as sed with the Sponsor use or dose reduction is onitor should be informed o implementation					

Protocol Marrie: Zeinix								
	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:							
	<ul> <li>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.         <ul> <li>1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or</li> <li>600 mg QD to 300 mg QD, 300mg QD to placebo</li> </ul> </li> <li>Temporary pause of linezolid.</li> <li>Permanent discontinuation of linezolid.</li> <li>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.</li> </ul>							
	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:								
Incidence of bacteriologic fa	ilure or relapse, or clinical failure at 26 weeks after the end of treatment.							
Abbreviated Definitions, full Bacteriologic failure negative.	definitions will be described in the Statistical Analysis Plan (SAP): be: During the treatment period, failure to attain or maintain culture conversion to							
<ul> <li>Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negatistatus, with culture conversion to positive status with a strain of <i>Mycobacterium tuberculosis</i> (MTI genetically identical to the infecting strain at baseline.</li> </ul>								
<ul> <li>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.</li> </ul>								
Culture conversion i	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<sub>T</sub>,  $C_{mean}$ , 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 <sup>a</sup>								Tre	eatm	ent								ب ق	Ро	st T	rea	itm e	ənt F	Follc	)w-	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	Visits every 3 weeks if treatment extended <sup>b</sup>	End of OR Ear Withdrawal fro Treatment <sup>c</sup>	4 weeks	8 weeks	12 weeks	26 weeks	39 weeks	52 weeks	65 weeks	78 weeks/EW⁰
Visit Window <sup>q</sup>	N/A		+/- 3 days			+/- 5 days			+/- 7 days	Post last dose IMP +7 days			+/-	- 14	l day	ys											
Informed Consent	Х																										
Demography	Х																										
Med/Trtmnt/Smoking History	Х																										
Inclusion/Exclusion <sup>a</sup>	Х	Х																						$\Box$			
Randomization		Х																					$\square$	$\square$			1
Karnofsky Assessment	Х																							$\Box$			
HIV Status <sup>e</sup>	Х																							$\square$			i
CD4 Count and Viral Load <sup>f</sup>	Х																		Х					$\square$			
ChestX-Ray <sup>g</sup>	Х																		Х				$\square$	$\square$	$\square$		
Urine Pregnancy Test <sup>h</sup>	Х	Х								Х				Х					Х					$\square$			
TB Symptoms Profile	Х									Х				Х					Х				Х	$\square$	Х		Х
Patient Reported Health Status	Х									Х				Х					Х				Х	$\square$	Х		Х
Slit Lamp Exam <sup>1</sup>	Х																		X'			Х		$\Box$	$\square$		
Ophthalmic Exam <sup>j</sup>	Х					Х				Х		Х		Х		Х	Х	Х	Х	Х		Х		$\square$			i
Vital Signs	Х	Х	Х	Х		Х		Х		Х		Х		Х		Х		Х	Х			Х	Х	Х	Х	Х	Х
Single 12-LeadECG <sup>k</sup>	Х	Х	Х			Х				Х				Х					Х					$\square$			
Limited Physical Exam <sup>1</sup>			Х	Х		Х		Х		Х		Х		Х		Х		Х				Х	Х	Х	Х	Х	Х
Full Physical Exam <sup>1</sup>	Х	Х																	Х				$\square$	$\square$	$\square$		1
Laboratory Safety Tests (includes Full Blood Count) <sup>m</sup>	х	х	х	х	х	х		х		х		х		Х		Х	Х	х	х								
Full Blood Count							Х		Х		Х		Х		Х												
Con Meds	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Adverse Events	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Study Medication/Compliance <sup>n</sup>		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х								
PK Sampling <sup>o</sup>		Х		Х						Х		Х				Х			Xo				$\square$	$\square$	$\square$		
Early Morning & Spot Sputum <sup>r</sup>	Х	Х	Х	Х	Х	Х		Х		Х	Х	Х		Х		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Peripheral Neuropathy	v		I	I		v	I			v	1	v		v		V	v	v	v					$\square$			v
Assessment	^					^		1	1	^	1	^	1	^		^	^	^	^		1	$^{\circ}$	$^{\sim}$		^		^
Investigator Assessment <sup>p</sup>																							Х	$\square$	$\square$		Х

# 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 <u>6.3</u>, 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 AFTÉR 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  $\leq$  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  $\leq$  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.
- I. **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:

		San	nple	Tests							
Visit	SMB	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 1 <sup>st</sup> positive between screening and wk4 if Day 1 negative or contaminated			٠				С	С	С	L (when applicable, with isolate below)	
All Visits Post Screening	•	•			S						
1 <sup>st</sup> positive for MTB at/after week 16 for participant not responding to therapy and/or 1 <sup>st</sup> positive during follow-up for potential new infection			•			S	С	С	С	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 SAM PLES:** 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 MTBDRplus and HainMTBRs/

**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.<sup>(43)</sup> 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, bedaguiline 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.<sup>(28)</sup> In another report from South Africa of 114 patients with XDR-TB, 22% completed treatment successfully.<sup>(21)</sup> 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.<sup>(17)</sup> Reports of the outcome of XDR-TB treatment from Peru (43 patients, 42% treatment success)<sup>(2)</sup> and Ukraine (114 patients, 22% treatment success)<sup>(11)</sup> 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%.<sup>(29)</sup> 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.<sup>(43)</sup> 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<sup>(9)</sup> 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).<sup>(1)</sup>

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 bedaguiline 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 bedaguiline 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 bedaguiline 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 bedaguiline 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.

#### Efficacy of bedaquiline 200 mg daily dose vs the marketed dosing scheme over 8 weeks

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.

#### Safety of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.

#### Pharmacokinetics of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.<sup>(14)</sup> 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<sub>max</sub>, 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 bedaguiline 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 bedaguiline 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 relapsefree 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<sup>™</sup>. 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. Drugdrug 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 multipledose efavirenz (EFV) resulted in approximately a 20% decrease in the AUC<sub>inf</sub> of bedaquiline with no alteration in the C<sub>max</sub>. Modeling based on the data from this DDI study predicts average steadystate concentrations of bedaquiline and M2 to be reduced by 52% with chronic co-administration of bedaquiline and EFV.<sup>(5)</sup>

#### Safety of Bedaquiline

The Investigator's Brochure for bedaquiline provides detailed safety information.<sup>5</sup>

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.

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	Hepatobiliary disorders								
Transaminases increased <sup>a</sup> Common 7 (6.9) 1 (1.0)									
Musculoskeletal and connective tissue disorders									
ArthralgiaVery Common30 (29.4)21									
Myalgia	Common	6 (5.9)	7 (6.7)						

#### Table 1:ADRs C208 Stage 1 and Stage 2

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.<sup>(7)</sup>

# 2.2.2 Pretomanid

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

# 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,  $\leq 0.015$  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. <sup>(6)</sup>

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), <sup>(33)</sup> 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.<sup>(12,13)</sup>

# 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.<sup>(18,19,20,36,40)</sup> 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 .<sup>(6)</sup>

# 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  $\geq 100 \text{ mg/kg/day}$ , and early deaths occurred at doses  $\geq 500 \text{ mg/kg/day}$ . Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at  $\geq 450/300 \text{ mg/kg/day}$ . These effects were reversible when dosing stopped and were absent at  $\leq 30 \text{ mg/kg/day}$  in rats and  $\leq 150 \text{ mg/kg/day}$  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.

<u>Drug interaction with midazolam</u>: 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<sub>0-t</sub>), and area under the curve extrapolated to infinity (AUC<sub>0-inf</sub>). The C<sub>max</sub> 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 (Cmax) was 0.71, the GMR for the 24-hour area under the time-concentration curve (AUC<sub>0-24h</sub>) was 0.65, and the GMR for the trough concentration (Cmin) 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 Cmax was 0.87, for AUC0-24h was 0.83, and for C<sub>min</sub> 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 Cmax, AUC 0-24h, and Cmin 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<sub>max</sub>), area under the concentration-time curve (AUC<sub>0</sub>-

 $_{24h}$ ), and trough concentration (Cmin) 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 <sup>(4)</sup> (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<sup>(6)</sup> 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.<sup>(23,24,26)</sup> Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism.<sup>(8)</sup> 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.<sup>(9)</sup>

Preclinical *in vitro* data shows linezolid is active against MTB, including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1  $\mu$ g/mL.<sup>(38)</sup> 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.<sup>(36)</sup> (Table 3, below)

### Table 3: Murine Lung CFU counts during Treatment with Linezolid

	Mean lung log₁₀ CFU count (± S.D.) at:										
Regimen	D0	Month 1	Month 2	Month 3							
Untreated	6.17 <u>+</u> 0.27	6.47 <u>+</u> 0.06									
2RHZ/4R H		3.47 <u>+</u> 0.37	1.59 <u>+</u> 0.25	0.50 <u>+</u> 0.51							
L		4.97 <u>+</u> 0.26									

#### Monotherapy versus Standard Therapy

In recent years linezolid has been used to treat patients with MDR<sup>(28)</sup> 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.<sup>(41)</sup> 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.<sup>(9, 27, 34)</sup> 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.<sup>(9)</sup> 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 sputumsmear 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).<sup>(9)</sup> 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.<sup>(3,9)</sup> The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label.<sup>(23,24,26)</sup> 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.
- 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  $\leq$ 600 mg daily vs. 60.75% (95%CI 42.69–78.81) for >600 mg daily (*P* = 0.05). <sup>(3)</sup>

In a trial reported by Lee et al in S Korea<sup>(9)</sup>, seven of 41 participants had myelosuppression, including anemia and neutropenia, <u>primarily within the first 5 months</u>, 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 ( $\geq$ 3 months) and in all patients reporting new visual symptoms, regardless of length of therapy.<sup>(26)</sup>

In Lee, NEJM, 2012<sup>(9)</sup>, 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<sup>(32)</sup>, 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<sup>(27)</sup>, 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<sup>(34)</sup>, 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 <sup>(5,36)</sup> 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<sup>(15)</sup> and in a subsequent study it was more active in the mouse model than HRZ.<sup>(16)</sup> 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.<sup>(37)</sup>

#### 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 <b>(57%)</b>						
BPa		3/14 <b>(21%)</b>						
3BPaL **	6/15 <b>(40%)</b>	0/15# <del>†</del> <b>(0%)</b>						
2BPaL/1BPa***		0/15#† <b>(0%)</b>						
1BPaL/2BPa	9/15 <b>(60%)</b>	0/15# <del>†</del> <b>(0%)</b>						

#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 cardiovascularsafety 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<sub>CFU(0-14)</sub>

Treatment Group	Ν	Daily Mean (SD) EBA <sub>CFU(0-14)</sub>
Pretomanid + pyrazinamide + moxifloxacin	13	0.23 (0.128)
Pretomanid + pyrazinamide	14	0.15 (0.040)
Pretomanid + bedaquiline	15 <sup>a</sup>	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)

Derived Using Bi-Linear Regression, Study NC-001

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<sub>CFU</sub> and log<sub>TTP</sub> that was at least as good as the HRZE control. The daily log<sub>CFU</sub> results are presented in Table 6. Similar results were found when TTP was used to calculate the bactericidal activity over 14 days (BA<sub>(0-14)</sub>).

#### Table 6: NC-003 Efficacy Results: Daily BAlog CFU(0-14)

Arm	logCFU
BPaZC	.124
BPaZ	.180
BPaC	.086
BZC	.098
Z	.036
С	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

	BPaZ C	BPaZ	BPa C	BZC	Z	С	HRZ E	Total
Ν	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		1						1
of study drug		•						I
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  $\geq$ 500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of  $\geq$ 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  $\geq$ 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 the 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. Fortynine 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.

<u>Safety of the B-Pa-L Regimen in the Nix-TB Study</u>: 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

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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<sup>(28)</sup>. 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.<sup>(43)</sup> 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	<ul> <li>Linezolid 1200 mg daily for 26 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
2	<ul> <li>Linezolid 1200 mg daily for 9 weeks followed by linezolid placebo for <u>17 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
3	<ul> <li>Linezolid 600 mg daily for 26 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
4	<ul> <li>Linezolid 600 mg daily for 9 weeks followed by linezolid placebo for 17 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>

Figure 4: Trial Schematic



Participants will be randomized to 1 of the 4 groups listed above.

N = 45 Participantsper group for a total of 180. 30 XDR-TB participantsper 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. Retesting 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.

#### Disease Characteristics:

- 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
    - 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 <u>or</u> using effective methods of birth control, as defined below:

#### Non-childbearing potential:

- a. Participant not heterosexually active or practices sexual abstinence; or
- 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<sup>2</sup>
- 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 (<u>Appendix 2</u>). 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<sup>3</sup> or < 100 x 10<sup>9</sup>/L;
  - f. Absolute neutrophil count (ANC) < 1500/ mm<sup>3</sup> or <  $1.5 \times 10^{4}$ /L;
  - g. Aspartate aminotransferase (AST)
    - Grade 3 or greater ( $\geq$  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 ( $\geq$  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
  - I. 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, 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 followup visits as described in <u>Table 9</u>:

Treatment Duration at EW visit	Ophthalmology Examination at EW <sup>a</sup>	Ophthalmology Examination 12 week Post treatment follow- up visit <sup>a</sup>	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

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

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).
- <u>At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status,</u> 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 treatment visit and it cannot be completed	b be contacted on or before their final e confirmed whether treatment was

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

# 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;
  - o 600 mg QD to 300 mg QD, 300 mg 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<sup>(5,6)</sup>. The complete formulations of linezolid are found in the Package Inserts<sup>(23,24,26)</sup>.

The IMP will be packaged as follows:

- Bedaquiline: Bottles containing:
  - o 200 mg QD dose- 28 tablets- bedaquiline 100 mg
  - o 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:
  - o 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
  - $\circ~$  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.

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## 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 (<u>Appendix 4</u>).
- 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<sub>2</sub> 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<sub>T</sub>,  $C_{mean}$ , 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.

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).

#### Table 11: Adverse Events Attribution/Causality Ratings

#### 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 <u>Appendix 2</u> 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 nonleading 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.

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# 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<sup>(5,6)</sup> and Package Inserts.<sup>(23,24,25,26)</sup> Please reference section <u>6.3</u> 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 <u>Appendix 5</u> – 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  $\leq$  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<sup>9</sup>/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<sup>9</sup>/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-ofcare 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 < QT/QTc < 480 msec</p>
    - 480 msec < QT/QTc < 500 msec</p>
    - QT/QTc > 500 msec
  - o QTc changes from baseline will be classified into the following categories:
    - increase < 30 msec,</li>
    - 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 <u>Appendix 3</u>), 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, AUCT, 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 Pl/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. <sup>(30)</sup>

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

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

**ABBREVIATIONS:** Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R <sub>x</sub> = 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 <sup>3</sup>	750-999/mm <sup>3</sup>	500-749/mm <sup>3</sup>	<500/mm <sup>3</sup>		
Platelets	75,000- 99,999/mm <sup>3</sup>	50,000- 74,999/mm <sup>3</sup>	20,000- 49,999/mm <sup>3</sup>	<20,000/mm <sup>3</sup>		
WBCs	11,000-13,000/ mm <sup>3</sup>	13,000-15,000 /mm <sup>3</sup>	15,000- 30,000/mm <sup>3</sup>	>30,000 or <1,000 /mm <sup>3</sup>		
% 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		
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 <i>with</i> 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 <i>with</i> 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 <i>with</i> ketoacidosis or seizures		

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Hypocalcemia				< 6.1 mg/dL or abnormal
(corrected for	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	calcium with life threatening
Hypercalcemia		11.6 - 12.5		> 13.5 mg/dL or abnormal
(correct for albumin)	10.6 - 11.5 mg/dL	mg/dL	12.6 - 13.5 mg/dL	calcium <i>with</i> 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 <i>with</i> 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 <i>with</i> 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
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CARDIOVASCULAR	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; outpatienttreatm ent 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 <sub>1</sub> of peak flow	requires treatment; normalizes with bronchodilator; FEV <sub>1</sub> 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV 1 25% - 50% of peak flow; or retractions present	cyanosis: FEV <sub>1</sub> < 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 w eek	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 w eek	<ul> <li>&gt;7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or &gt;2L N fluids required</li> </ul>	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty sw allow ing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

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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 w eakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective w eakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non- narcotic analgesia required	severe discomfort; or narcotic analgesia required w ith 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 w rists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and low er 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 sw elling – but not interfering with function	moderate pain with inflammation, erythema or joint sw elling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint sw elling –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 w ork	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				
	Normal no complaints; no evidence of disease.	100		
Able to carry on normal activity	Able to carry on normal activity; minor signs or	90		
and to work; no special care	symptoms of disease.	30		
needed.	Normal activity with effort; some signs or symptoms of	80		
	disease.	00		
	Cares for self; unable to carry on normal activity or to	70		
Unable to work; able to live at	do active work.	70		
home and care for most personal	Requires occasional assistance, but is able to care for	60		
needs; varying amount of	most of his personal needs.	00		
assistance needed.	Requires considerable assistance and frequent medical	50		
	care.			
	Disabled; requires special care and assistance.	40		
I lnable to care for self: requires	Severely disabled; hospital admission is indicated	30		
equivalent of institutional or	although death not imminent.	50		
hospital care: disease may be	Very sick; hospital admission necessary; active	20		
nrogressing ranidly	supportive treatment necessary.	20		
	Moribund; fatal processes progressing rapidly.	10		
	Dead	0		

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109<sup>(22)</sup>.

# 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;<sup>(31,39)</sup>; 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 hepatoœllular 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.
- 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.





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:	Version 2.0 MDA dated 10 March 2020 (incorporating Protocol V2.0 dated 13 Jun 2018, Country Specific Protocol Amendment for Moldova V1.0 dated 13 Jun 2018 and Protocol Amendment 2.0 dated 10 March 2020).
Protocol Name:	ZeNix

## PROTOCOL SIGNATURE PAGE

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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Protocol Name: ZeNix

## SPONSOR

I agree to the terms of this trial protocol.

Signature of Senior Medical Officer

**Printed Name** 

40 Wall Street, 24th Floor New York, NY 10005

email: daniel.everitt@tballiance.org

Phone 646-616-8671

Date

## LEAD INVESTIGATOR

I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations.

Signature

Printed Name

Date

# PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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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Protocol Name: ZeNix

I hereby confirm that I have read the above protocol and agree to conduct this clinical trial as outlined in the above protocol. I will provide copies of the protocol and access to all the information required to conduct the clinical trial according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature

Printed Name

Date

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Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version V2.0 MDA / 10 Mar 2020 Protocol Name: ZeNix

## Abbreviations and Definition of Terms

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
Μ	Moxifloxacin
MAO(I)	Monoamine oxidase (Inhibitor)
MBD	Minimum bactericidal dose
MIC	Minimum Inhibitory concentration
MIB	Mycobacterium tuberculosis
MDR-1B	Muschasterial growth inhibiting tube
MGII	Mycobacterial growth inhibiting tube
ml	Millilitor
me	Millisocond
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
IB	
IBL	Serum total bilirubin
	Treatment amorgant advarga aventa
	Time above minimum inhibitory concentration
tiw	Three times a week
$(B\Delta) TTP$	(Bacteriocidal activity) time to positivity
	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

	Global Alliance for TB Drug Development												
Name of Finished	bedaguiline (B), pretomanid (Pa) and linezolid (L)												
Products:	bedaquime (b), pretomania (r a) and mezona (c)												
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 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.												
	and their clinical condition suggests they may have an ongoing TB infection,												
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Patient Population: Test product, Dose and Mode of Administration:	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.A total of up to 180 participants, male and female, aged 18 and over Sponsor may consider replacement of late screen failure and un-assessable (as detailed in the statistical analysis plan) participants.The regimen will be supplied as the following: <b>ProductProductTablet StrengthAbbre viation</b> (B) Pretomanid200 mg(Pa) Linezolid (scored)600 mg(L)												
Patient Population: Test product, Dose and Mode of Administration:	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.A total of up to 180 participants, male and female, aged 18 and over Sponsor may consider replacement of late screen failure and un-assessable (as detailed in the statistical analysis plan) participants.The regimen will be supplied as the following:ProductTablet StrengthAbbreviation Bedaquiline100 mg(B) PretomanidPretomanid200 mgQuo mg(L) Placebo LinezolidPlacebo Linezolidplacebo(L)												
Patient Population: Test product, Dose and Mode of Administration:	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.A total of up to 180 participants, male and female, aged 18 and over Sponsor may consider replacement of late screen failure and un-assessable (as detailed in the statistical analysis plan) participants.The regimen will be supplied as the following:ProductTablet StrengthAbbreviation Bedaquiline100 mg(B) PretomanidPretomanid200 mg(Pa) Linezolid (scored)600 mg(L) Placebo Linezolid (scored)												
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Placebo linezolid half	placebo	(L)
tablet (pre-cut)		
Linezolid treatment wi placebo) and one row possible dosing optior	Il be supplied as 2 rows of full of half-tablets (active or place ns while maintaining the blind.	tablets (active or bo) to allow for all
Instructions for Dosing Treatment will be admin a meal in the following d	<b>g:</b> istered orally, once daily, with osing schemes (treatment an	a full glass of water and ns):
<ul> <li>Participants will receive</li> <li>Bedaquiline 200 m 18 weeks plus;</li> <li>Pretomanid 200 m</li> <li>Linezolid- particip following four blind</li> </ul>	<u>the following:</u> ng once daily for 8 weeks ther ng once daily for 26 weeks plu ants will be randomly assigne ded linezolid treatment doses	ו 100 mg once daily for וs; d to receive one of the and durations:
Linezolid 1200 mg daily 2 linezolid 600 mg 1/2 (one half) place	<u>for 26 weeks</u> active tablets once daily for 2 bo linezolid tablet once daily f	26 weeks for 26 weeks
Linezolid 1200 mg daily	for 9 weeks	
<ul> <li>2 linezolid 600 mg</li> <li>½ (one half) place</li> <li>Weeks 10-26</li> </ul>	active tablets once daily for 9 bo linezolid tablet once daily f	) weeks or 9 weeks
<ul> <li>2 placebo linezolio</li> <li>1/2 (one half) place</li> </ul>	b tablets once daily for 17 wee bo linezolid tablet once daily f	ks for 17 weeks
Linezolid 600 mg daily fr 1 linezolid 600 mg 1 placebo linezolid 1/2 (one half) place	<u>or 26 weeks</u> active tablet once daily for 26 d tablet once daily for 26 week bo linezolid tablet once daily f	) weeks s for 26 weeks
Linezolid 600 mg daily fe	or 9 weeks	
<ul> <li>1 linezolid 600 mg</li> <li>1 placebo linezolic</li> <li>½ (one half) placebo</li> </ul>	active tablet once daily for 9 v I tablet for 9 weeks bo linezolid tablet once daily f	weeks or 9 weeks
Weeks 10-26 • 2 placebo linezolic • ½ (one half) placel	I tablets once daily for 17 wee bo linezolid tablet once daily f	ks or 17 weeks
Treatment Modificatio The above treatment so noted below. All dose m Medical Monitor prior to required urgently for a s within 24 hours of the ch	ns: chemes may require modificat nodifications should be discus implementation, unless a pau afety concern; the Medical M nange if not discussed prior to	ion due to toxicities as sed with the Sponsor use or dose reduction is onitor should be informed o implementation

Hotocor Name. Zenix											
	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:										
	<ul> <li>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.         <ul> <li>1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or</li> <li>600 mg QD to 300 mg QD, 300mg QD to placebo</li> </ul> </li> <li>Temporary pause of linezolid.</li> <li>Permanent discontinuation of linezolid.</li> <li>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.</li> </ul>										
	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 fa	ailure or relapse, or clinical failure at 26 weeks after the end of treatment.										
<ul> <li><u>Abbreviated Definitions, full</u></li> <li>Bacteriologic failure negative.</li> <li>Bacteriologic relaps status, with culture genetically identica</li> <li>Clinical failure: A ch protocol specified tr related death.</li> </ul>	definitions will be described in the Statistical Analysis Plan (SAP): During the treatment period, failure to attain or maintain culture conversion to se: During the follow-up period, failure to maintain culture conversion to negative conversion to positive status with a strain of <i>Mycobacterium tuberculosis</i> (MTB) I to the infecting strain at baseline. hange from protocol-specified TB treatment to a new regimen before end of reatment due to treatment failure, retreatment for TB during follow up, or TB-										
Note:     Culture conversion apart.	requires at least 2 consecutive culture negative/positive samples at least 7 days										

• 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<sub>T</sub>,  $C_{mean}$ , 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									Tre	atm	ent								Ро	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	Visits every 3 weeks if treatment extended <sup>b</sup>	End of OR Ear Withdrawal frc Treatment <sup>c</sup>	4 weeks	8 weeks	12 weeks	26 weeks	39 weeks	52 weeks	65 weeks	78 weeks/EW⁰
Visit Window <sup>q</sup>	N/A		+/- 3 days					+/- 5 days							+/- 7 days Post last dose IMP +7 days			+/- 14 days									
Informed Consent	Х																										
Demography	Х																										
Med/Trtmnt/Smoking History	Х																										
Inclusion/Exclusion <sup>a</sup>	Х	Х																									
Randomization		Х																									
KarnofskyAssessment	Х																										
HIV Status <sup>e</sup>	Х																										
CD4 Count and Viral Load <sup>f</sup>	Х																		Х				$\square$				
ChestX-Ray <sup>g</sup>	Х																		Х								
Urine Pregnancy Test <sup>h</sup>	Х	Х								Х				Х					Х								
TB Symptoms Profile	Х									Х				Х					Х				Х		Х		Х
Patient Reported Health Status	Х									Х				Х					Х				Х		Х		Х
Slit Lamp Exam <sup>1</sup>	Х																		X			Х					
Ophthalmic Exam <sup>j</sup>	Х					Х				Х		Х		Х		Х	Х	Х	Х	Х		Х					
Vital Signs	Х	Х	Х	Х		Х		Х		Х		Х		Х		Х		Х	Х			Х	Х	Х	Х	Х	Х
Single 12-LeadECG <sup>k</sup>	Х	Х	Х			Х				Х				Х					Х								
Limited Physical Exam <sup>1</sup>			Х	Х		Х		Х		Х		Х		Х		Х		Х				Х	Х	Х	Х	Х	Х
Full Physical Exam	Х	Х																	Х				$\square$				
Laboratory Safety Tests (includes Full Blood Count) <sup>m</sup>	х	х	х	х	х	х		х		х		Х		х		х	Х	Х	х								
Full Blood Count							Х		Х		Х		Х		Х												
Con Meds	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Adverse Events	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Study Medication/Compliance <sup>n</sup>		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х								
PK Sampling <sup>o</sup>		Х		Х						Х		Х				Х			Xo								
Early Morning & Spot Sputum <sup>r</sup>	Х	Х	Х	Х	Х	Х		Х		Х	Х	Х		Х		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Peripheral Neuropathy	v		1	1		v		Ī		v	1	v	1	v	1	v	V	v	v			$\mathbf{v}$					V
Assessment	^					^				^		^		^		^	^	^	^		<sup> </sup>	^	^	,	^		^
Investigator Assessment <sup>p</sup>			I	I						I			I			1	I						Х				Х

# 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 <u>6.3</u>, 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  $\leq$  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  $\leq$  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.
- I. **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:

		San	nple	Tests												
Visit	SMB	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 1 <sup>st</sup> positive between screening and wk4 if Day 1 negative or contaminated			٠				С	С	С	L (when applicable, with isolate below)						
All Visits Post Screening	•	•			S											
1 <sup>st</sup> positive for MTB at/after week 16 for participant not responding to therapy and/or 1 <sup>st</sup> positive during follow-up for potential new infection			•			S	С	С	С	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 MTBDRplus and HainMTBRs/

**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.<sup>(43)</sup> 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, bedaguiline 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.<sup>(28)</sup> In another report from South Africa of 114 patients with XDR-TB, 22% completed treatment successfully.<sup>(21)</sup> 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.<sup>(42)</sup> A meta-analysis of 397 patients with XDR-TB from 31 centers, with HIV coinfection <10%, reported 32% treatment success.<sup>(17)</sup> Reports of the outcome of XDR-TB treatment from Peru (43 patients, 42% treatment success)<sup>(2)</sup> and Ukraine (114 patients, 22% treatment success)<sup>(11)</sup> 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%.<sup>(29)</sup> 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.<sup>(43)</sup> 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<sup>(9)</sup> 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).<sup>(1)</sup>

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 bedaguiline 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 bedaguiline 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 bedaguiline 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 bedaguiline 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.

## Efficacy of bedaquiline 200 mg daily dose vs the marketed dosing scheme over 8 weeks

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.

## Safety of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.

## Pharmacokinetics of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.<sup>(14)</sup> 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<sub>max</sub>, 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 bedaguiline 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 bedaguiline 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 relapsefree 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<sup>™</sup>. 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. Drugdrug 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 multipledose efavirenz (EFV) resulted in approximately a 20% decrease in the AUC<sub>inf</sub> of bedaquiline with no alteration in the C<sub>max</sub>. Modeling based on the data from this DDI study predicts average steadystate concentrations of bedaquiline and M2 to be reduced by 52% with chronic co-administration of bedaquiline and EFV.<sup>(5)</sup>

#### Safety of Bedaquiline

The Investigator's Brochure for bedaquiline provides detailed safety information.<sup>5</sup>

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.

Adverse Drug Reactions (ADRs) in the Controlled Studies (C208 Stage 1 and Stage 2) During the Investigational Treatment Phase							
ADR (Grouped term), n (%)	Any BDQ Frequency N=102		Any Placebo N=105				
Nervous system disorders	Nervous system disorders						
Headache	Very Common	24 (23.5)	12 (11.4)				
Dizziness	Very Common	13 (12.7)	12 (11.4)				
Cardiac disorders	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 <sup>a</sup>	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)				

### Table 1:ADRs C208 Stage 1 and Stage 2

<sup>a.</sup> 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.<sup>(7)</sup>

# 2.2.2 Pretomanid

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

# 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,  $\leq 0.015$  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. <sup>(6)</sup>

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), <sup>(33)</sup> 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.<sup>(12,13)</sup>

## 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.<sup>(18,19,20,36,40)</sup> 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 .<sup>(6)</sup>

# 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  $\geq$ 100 mg/kg/day, and early deaths occurred at doses  $\geq$ 500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at  $\geq$ 450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at  $\leq$ 30 mg/kg/day in rats and  $\leq$ 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.

<u>Drug interaction with midazolam</u>: 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<sub>0-t</sub>), and area under the curve extrapolated to infinity (AUC<sub>0-inf</sub>). The C<sub>max</sub> 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<sub>1/2</sub>) 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 (Cmax) was 0.71, the GMR for the 24-hour area under the time-concentration curve (AUC<sub>0-24h</sub>) was 0.65, and the GMR for the trough concentration (Cmin) 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 Cmax was 0.87, for AUC0-24h was 0.83, and for C<sub>min</sub> 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 Cmax, AUC 0-24h, and Cmin 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<sub>max</sub>), area under the concentration-time curve (AUC<sub>0</sub>-

 $_{24h}$ ), and trough concentration (Cmin) 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 <sup>(4)</sup> (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<sup>(6)</sup> 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.<sup>(23,24,26)</sup> Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism.<sup>(8)</sup> 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.<sup>(9)</sup>

Preclinical *in vitro* data shows linezolid is active against MTB, including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1  $\mu$ g/mL.<sup>(38)</sup> 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.<sup>(36)</sup> (Table 3, below)

## Table 3: Murine Lung CFU counts during Treatment with Linezolid

	Me	Mean lung log <sub>10</sub> CFU count (± S.D.) at:			
Regimen	D0	Month 1	Month 2	Month 3	
Untreated	6.17 <u>+</u> 0.27	6.47 <u>+</u> 0.06			
2RHZ/4R H		3.47 <u>+</u> 0.37	1.59 <u>+</u> 0.25	0.50 <u>+</u> 0.51	
L		4.97 <u>+</u> 0.26			

#### Monotherapy versus Standard Therapy

In recent years linezolid has been used to treat patients with MDR<sup>(28)</sup> 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.<sup>(41)</sup> 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.<sup>(9, 27, 34)</sup> 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.<sup>(9)</sup> 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 sputumsmear 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).<sup>(9)</sup> 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.<sup>(3,9)</sup> The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label.<sup>(23,24,26)</sup> 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.
- 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  $\leq$ 600 mg daily vs. 60.75% (95%CI 42.69–78.81) for >600 mg daily (*P* = 0.05). <sup>(3)</sup>

In a trial reported by Lee et al in S Korea<sup>(9)</sup>, seven of 41 participants had myelosuppression, including anemia and neutropenia, <u>primarily within the first 5 months</u>, 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 ( $\geq$ 3 months) and in all patients reporting new visual symptoms, regardless of length of therapy.<sup>(26)</sup>

In Lee, NEJM, 2012<sup>(9)</sup>, 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<sup>(32)</sup>, 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<sup>(27)</sup>, 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<sup>(34)</sup>, 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 <sup>(5,36)</sup> 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<sup>(15)</sup> and in a subsequent study it was more active in the mouse model than HRZ.<sup>(16)</sup> 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.<sup>(37)</sup>

### 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 <b>(57%)</b>		
BPa		3/14 <b>(21%)</b>		
3BPaL **	6/15 <b>(40%)</b>	0/15# <del>†</del> <b>(0%)</b>		
2BPaL/1BPa***		0/15# <del>†</del> <b>(0%)</b>		
1BPaL/2BPa	9/15 <b>(60%)</b>	0/15# <del>†</del> <b>(0%)</b>		

#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 cardiovascularsafety 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<sub>CFU(0-14)</sub>

Treatment Group	Ν	Daily Mean (SD) EBA <sub>CFU(0-14)</sub>
Pretomanid + pyrazinamide + moxifloxacin	13	0.23 (0.128)
Pretomanid + pyrazinamide	14	0.15 (0.040)
Pretomanid + bedaquiline	15 <sup>a</sup>	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)

Derived Using Bi-Linear Regression, Study NC-001

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<sub>CFU</sub> and log<sub>TTP</sub> that was at least as good as the HRZE control. The daily log<sub>CFU</sub> results are presented in Table 6. Similar results were found when TTP was used to calculate the bactericidal activity over 14 days (BA<sub>(0-14)</sub>).

#### Table 6: NC-003 Efficacy Results: Daily BAlog CFU(0-14)

Arm	logCFU
BPaZC	.124
BPaZ	.180
BPaC	.086
BZC	.098
Z	.036
С	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

	BPaZ C	BPaZ	BPa C	BZC	Z	С	HRZ E	Total
Ν	15	15	15	15	15	15	15	105
Participants with:	•							
TEAEs	11	9	8	10	10	9	8	65
TEAEs leading to death:	TEAEs leading to death:							
Serious TEAEs						1		1
TEAES leading to early withdrawal		1						1
TEAEs leading to discontinuation		1						1
of study drug		•						I
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  $\geq$ 500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of  $\geq$ 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  $\geq$ 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 the 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. Fortynine 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.

<u>Safety of the B-Pa-L Regimen in the Nix-TB Study</u>: 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

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<sup>(28)</sup>. 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.<sup>(43)</sup> 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 18 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	<ul> <li><u>Linezolid 1200 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
2	<ul> <li>Linezolid 1200 mg daily for 9 weeks followed by linezolid placebo for 17 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
3	<ul> <li><u>Linezolid 600 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
4	<ul> <li>Linezolid 600 mg daily for 9 weeks followed by linezolid placebo for 17 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>

# 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. Retesting 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 18 years or older.

#### Disease Characteristics:

- 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
    - 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 <u>or</u> using effective methods of birth control, as defined below:

#### Non-childbearing potential:

- a. Participant not heterosexually active or practices sexual abstinence; or
- 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<sup>2</sup>
- 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 (<u>Appendix 2</u>). 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<sup>3</sup> or < 100 x 10<sup>9</sup>/L;
  - f. Absolute neutrophil count (ANC) < 1500/ mm<sup>3</sup> or <  $1.5 \times 10^{4}$ /L;
  - g. Aspartate aminotransferase (AST)
    - Grade 3 or greater ( $\geq$  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 ( $\geq$  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
  - I. 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, 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 followup visits as described in <u>Table 9</u>:

Treatment Duration at EW visit	Ophthalmology Examination at EW <sup>a</sup>	Ophthalmology Examination 12 week Post treatment follow- up visit <sup>a</sup>	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

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

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).
- <u>At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status,</u> 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 reviewBoard (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 <u>Table 9</u>. 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
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Treatment Group	Active and Placebo
Linezolid 1200 mg daily for 26 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>2 linezolid 600 mg active tablets once daily for 26 weeks</li> <li>1/2 (one half) placebo linezolid tablet once daily for 26 weeks</li> </ul>
<u>Linezolid 1200 mg</u> <u>daily for 9 weeks</u>	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>2 linezolid 600 mg active tablets once daily for 9 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 9 weeks</li> <li>Weeks 10-26</li> <li>2 placebo linezolid tablets once daily for 17 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 17 weeks</li> </ul>
<u>Linezolid 600 mg</u> <u>daily for 26 weeks</u>	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>1 linezolid 600 mg active tablet once daily for 26 weeks</li> <li>1 placebo linezolid tablet once daily for 26 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 26 weeks</li> </ul>
Linezolid 600 mg daily for 9 weeks	<ul> <li>2 bedaquiline 100 mg active tablets once daily for 8 weeks then 1 bedaquiline 100 mg active tablet once daily for 18 weeks plus;</li> <li>1 pretomanid 200 mg active tablet once daily for 26 weeks.</li> <li>Weeks 1-9</li> <li>1 linezolid 600 mg active tablet once daily for 9 weeks</li> <li>1 placebo linezolid tablet for 9 weeks</li> <li>½ (one half) placebo linezolid tablet once daily for 17 weeks</li> <li>2 placebo linezolidtablets once daily for 17 weeks</li> <li>16 (one half) placebo linezolid tablet once daily for 17 weeks</li> </ul>

# 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;
  - o 600 mg QD to 300 mg QD, 300 mg 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<sup>(5,6)</sup>. The complete formulations of linezolid are found in the Package Inserts<sup>(23,24,26)</sup>.

The IMP will be packaged as follows:

- Bedaquiline: Bottles containing:
  - o 200 mg QD dose- 28 tablets- bedaquiline 100 mg
  - o 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:
  - o 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
  - $\circ~$  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 (<u>Appendix 4</u>).
- 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<sub>2</sub> 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<sub>T</sub>,  $C_{mean}$ , 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.

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).

#### Table 11: Adverse Events Attribution/Causality Ratings

#### 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
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy
GRADE 3	Severe	required. 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 <u>Appendix 2</u> 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 nonleading 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.

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## 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<sup>(5,6)</sup> and Package Inserts.<sup>(23,24,25,26)</sup> Please reference section <u>6.3</u> 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 <u>Appendix 5</u> – 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  $\leq$  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<sup>9</sup>/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-ofcare 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</li>
    - 450 msec < QT/QTc < 480 msec</p>
    - 480 msec < QT/QTc < 500 msec</p>
    - QT/QTc > 500 msec
  - o QTc changes from baseline will be classified into the following categories:
    - increase < 30 msec,</li>
    - 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 <u>Appendix 3</u>), 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, AUCT, 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 Pl/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. <sup>(30)</sup>

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

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

**ABBREVIATIONS:** Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R <sub>x</sub> = 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 <sup>3</sup>	750-999/mm <sup>3</sup>	500-749/mm <sup>3</sup>	<500/mm <sup>3</sup>
Platelets	75,000- 99,999/mm <sup>3</sup>	50,000- 74,999/mm <sup>3</sup>	20,000- 49,999/mm <sup>3</sup>	<20,000/mm <sup>3</sup>
WBCs	11,000-13,000/ mm <sup>3</sup>	13,000-15,000 /mm <sup>3</sup>	15,000- 30,000/mm <sup>3</sup>	>30,000 or <1,000 /mm <sup>3</sup>
% 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> ketoacidosis or seizures	

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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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> 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, w ith or w ithout clots, OR red blood cell casts	obstructive or required transfusion
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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; outpatienttreatm ent 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 <sub>1</sub> of peak flow	requires treatment; normalizes with bronchodilator; FEV <sub>1</sub> 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV 1 25% - 50% of peak flow; or retractions present	cyanosis: FEV <sub>1</sub> < 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 N 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 w eek	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 w eek	<ul> <li>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or &gt;2L N fluids required</li> </ul>	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty sw allow ing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

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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 w eakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective w eakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non- narcotic analgesia required	severe discomfort; or narcotic analgesia required w ith 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 w rists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and low er 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 sw elling – but not interfering with function	moderate pain with inflammation, erythema or joint sw elling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint sw elling –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 w ork	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			
	Normal no complaints; no evidence of disease.	100	
Able to carry on normal activity	Able to carry on normal activity; minor signs or	90	
and to work; no special care	symptoms of disease.	00	
needed.	Normal activity with effort; some signs or symptoms of	80	
	disease.	00	
	Cares for self; unable to carry on normal activity or to	70	
Unable to work; able to live at	do active work.	10	
home and care for most personal	Requires occasional assistance, but is able to care for	60	
needs; varying amount of	most of his personal needs.	00	
assistance needed.	Requires considerable assistance and frequent medica		
	care.		
	Disabled; requires special care and assistance.	40	
I lnable to care for self: requires	Severely disabled; hospital admission is indicated	30	
equivalent of institutional or	although death not imminent.	00	
hospital care; disease may be	Very sick; hospital admission necessary; active	20	
	supportive treatment necessary.	20	
progressing rapidly.	Moribund; fatal processes progressing rapidly.	10	
	Dead	0	

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109<sup>(22)</sup>.
## 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;<sup>(31,39)</sup>; 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 hepatoœllular 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.
- 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.





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 Version/Date:	V 3.0 RUS dated 18 March 2020 (incorporating: Protocol RUS/BEL V1.0 dated 23 Feb 2017 and Country specific Amendment for Russia V1.0 dated 15 Nov 2017 and Protocol Amendment 1 dated 13 June 2018 and Protocol Amendment 2 dated 10 Mar 2020

Protocol Name: ZeNix

## SPONSOR PROTOCOL SIGNATURE PAGE

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Country specific Amendment for Russia V1.0 dated15 Nov 2017
and Protocol Amendment 1 dated 13 June 2018 and Protocol
Amendment 2 dated 10 Mar 2020)
```

Protocol Name: ZeNix

## SPONSOR

I agree to the terms of this trial protocol.

Signature of Senior Medical Officer

Printed Name

Date

40 Wall Street, 24th Floor New York, NY 10005 Phone 646-616-8671 email: daniel.everitt@tballiance.org

## LEAD INVESTIGATOR PROTOCOL SIGNATURE PAGE

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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Protocol Name: ZeNix

## LEAD INVESTIGATOR

I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations.

Signature

Printed Name

Date

Global Alliance for TB Drug Development Protocol Number: NC-007-(B-Pa-L) Protocol Version V3.0 RUS / 18 MARCH 2020 Protocol Name: ZeNix

## PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

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

Protocol Version/Date: V3.0 RUS dated 18 March 2020, (incorporating Protocol RUS/BEL V1.0 dated 23 Feb 2017, Country specific Amendment for Russia V1.0 dated 15 Nov 2017 and Protocol Amendment 1 dated 13 June 2018 and Protocol Amendment 2 dated 10 Mar 2020)

Protocol Name: ZeNix

#### PRINCIPAL INVESTIGATOR

I hereby confirm that I have read the above protocol and agree to conduct this clinical trial as outlined in the above protocol. I will provide copies of the protocol and access to all the information required to conduct the clinical trial according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature

Printed Name

Date

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## Abbreviations and Definition of Terms

3TC	Lamiyudine
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 <sub>τ</sub>	Area under curve over a dosing interval
В	Bedaquiline
BMI	Body mass index
bpm	Beats per minute
BPNS	Brief peripheral neuropathy scale
С	Clofazimine
CFU	Colony forming units
CK(-MB)	Creatine kinase (-MB isoenzyme)
C <sub>(max),</sub>	Plasma concentration (maximum), (minimum)
(min)	
CO <sub>2</sub>	Carbon dioxide
CPK	Creatine phosphokinase
CS	
	Plasma concentration trough
	Cytochrome P450 3A4
	Division of microbiology and miection disease
	Department of health
DOH	
DILI	Drug induced liver injury
DSMC	Data safety monitoring committee
DST	Drug susceptibility testing
	Ethambutol
	Early Dactericidal activity
EC	Elastroardiagram
ECG	Electrocalulogram
	Electronic case report form
EO	Eluoroquinolone
FTC	Emtricitabine
a/l	Grams per liter
GI	Gastrointestinal
GCP	Good Clinical Practice
GGT	Gamma-qlutamyl transferase
GMR	Geometric mean ratio
Н	Isoniazid
hERG	Human <i>ether-à-go-go</i> 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
	Lower Limit of Normal
	LOPINAVI
	Monoamino ovidano (Inhihitor)
	Minimum bactorioidal doco
	Minimum inhibiton, 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	
	System organ class
	Tuberculosis Sorum total bilirubin
	Topofovir
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
ÙLŃ	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

Name of Finishedbedaquiline (B), pretomanid (Pa) and linezolid (L)Products:	
Products:	
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 eithe	r
extensively drug-resistant tuberculosis (XDR-IB), pre-XDR-IB or treatmen	
Intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB)	-
MDR-TB	ve
<b>Trial Objective:</b> To evaluate the efficacy, safety and tolerability of various doses and duration	ns
of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in	
intolerant or non-responsive MDR-TB.	
Trial Design: A phase 3, multi-center, partially-blinded, randomized clinical trial in four para	lle
treatment groups. Bedaquiline and pretomanid treatment will not be blind	ed.
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 interact	tive
voice and web response system (IXRS) which will utilize a randomiza	ion
system using stratification with a random element to allocate participants even	nıy
across the arms by HIV status and type of TB.	
Each participant will receive 26 weeks of treatment. If participant's spu	um
sample is culture positive between the week 16 and week 26 treatment vi	sits
and their clinical condition suggests they may have an ongoing TB infect	on,
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 cui results should be used to make this decision. All decisions regarding treats	ont
extension should be discussed with and approved by the Sponsor Med	cal
Monitor before implementation.	
Participants will be followed for 78 weeks after end of treatment.	<u></u>
may consider replacement of late screen failure and un-assessable (as	ונ
detailed in the statistical analysis plan) participants.	
<b>Test product, Dose and</b> The regimen will be supplied as the following:	
Mode of Administration:	
Product Tablet Strength Abbreviation	
Bedaquiline 100 mg (B)	
Pretomanid 200 mg (Pa)	
Linezolid (scored) 600 mg (L)	
Placebo Linezolid placebo (L)	
(SCOTED)	
tablet (pre-cut)	

Discense linematic half		(1.)
tablet (pre-cut)	ріасеро	(L)
Linezolid treatment wi placebo) and one row possible dosing optior	Il be supplied as 2 rows of full of half-tablets (active or place is while maintaining the blind.	tablets (active or bo) to allow for all
Instructions for Dosing Treatment will be admin a meal in the following d	<u>]:</u> istered orally, once daily, with osing schemes (treatment arr	a full glass of water and ns):
<ul> <li>Participants will receive</li> <li>Bedaquiline 200 m 18 weeks plus;</li> <li>Pretomanid 200 m</li> <li>Linezolid- particip following four bling</li> </ul>	the following: ng once daily for 8 weeks ther ng once daily for 26 weeks plu ants will be randomly assigned ded linezolid treatment doses	n 100 mg once daily for s; d to receive one of the and durations:
Linezolid 1200 mg daily 2 linezolid 600 mg 1/2 (one half) place	for 26 weeks active tablets once daily for 2 bo linezolid tablet once daily f	6 weeks or 26 weeks
Linezolid 1200 mg daily Weeks 1-9 • 2 linezolid 600 mg • ½ (one half) place Weeks 10-26 • 2 placebo linezolic • 1/ (one half) place	for 9 weeks active tablets once daily for 9 bo linezolid tablet once daily f d tablets once daily for 17 wee	weeks or 9 weeks ks
<ul> <li><u>Linezolid 600 mg daily fa</u></li> <li>1 linezolid 600 mg</li> <li>1 placebo linezolid</li> <li>½ (one half) place</li> </ul>	<u>or 26 weeks</u> active tablet once daily for 26 d tablet once daily for 26 week bo linezolid tablet once daily f	) weeks s for 26 weeks
Linezolid 600 mg daily fo Weeks 1-9 1 linezolid 600 mg 1 placebo linezolic 1/2 (one half) placel	<u>or 9 weeks</u> active tablet once daily for 9 v I tablet for 9 weeks bo linezolid tablet once daily fo	veeks or 9 weeks
Weeks 10-26 • 2 placebo linezolic • ½ (one half) placel	I tablets once daily for 17 weel bo linezolid tablet once daily fo	ks or 17 weeks
Treatment Modification The above treatment so noted below. All dose m Medical Monitor prior to required urgently for a s within 24 hours of the ch	ns: chemes may require modification odifications should be discuss implementation, unless a pau afety concern; the Medical Me nange if not discussed prior to	ion due to toxicities as sed with the Sponsor use or dose reduction is onitor should be informed 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:
	• <b>Blinded</b> 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.
	<ul> <li>1200 mg QD to 600 mg QD, 600 mg QD to 300 mg QD or</li> <li>600 mg QD to 300 mg QD, 300mg QD to placebo</li> <li>Temporary pause of linezolid</li> </ul>
	Permanent discontinuation of linezolid
	<ul> <li>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.</li> </ul>
	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:	
Incidence of bacteriologic f	ailure or relapse, or clinical failure at 26 weeks after the end of treatment.
Abbreviated Definitions, ful	definitions will be described in the Statistical Analysis Plan (SAP):
Bacteriologic failur	e: During the treatment period, failure to attain or maintain culture conversion to
negative. Bacteriologic relan	se: During the follow-up period, failure to maintain culture conversion to pegative
status, with culture	conversion to positive status with a strain of Mycobacterium tuberculosis (MTB)
genetically identica	al to the infecting strain at baseline.
<ul> <li>Clinical failure: A cliprotocol specified t protocol specified t</li> </ul>	reatment due to treatment failure, retreatment for TB during follow up, or TB-
Note:	
Culture conversion     apart.	requires at least 2 consecutive culture negative/positive samples at least 7 days
<ul> <li>Participants who an considered to be re</li> </ul>	re documented at a visit as unable to produce sputum and who are clinically esponding 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<sub>T</sub>,  $C_{mean}$ , 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 <sup>a</sup>		Treatment										ž	Ро	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	Visits every 3 weeks if treatment extended <sup>b</sup>	End of OR Ea Withdrawal fr Treatment <sup>c</sup>	4 weeks	8 weeks	12 weeks	26 weeks	39 weeks	52 weeks	65 weeks	78 weeks/EW⁰
Visit Window <sup>q</sup>	N/A		+/- 3 days				+/- 5 days							+/- 7 days	Post last dose IMP +7 days	+/- 14 days											
Informed Consent	Х																										
Demography	Х																										
Med/Trtmnt/Smoking History	Х																										
Inclusion/Exclusion <sup>a</sup>	Х	Х																									
Randomization		Х																									1
KarnofskyAssessment	Х																										
HIV Status <sup>e</sup>	Х																										
CD4 Count and Viral Load <sup>f</sup>	Х																		Х				$\square$				1
ChestX-Ray <sup>g</sup>	Х																		Х								
Urine Pregnancy Test <sup>h</sup>	Х	Х								Х				Х					Х								
TB Symptoms Profile	Х									Х				Х					Х				Х		Х		Х
Patient Reported Health Status	Х									Х				Х					Х				Х		Х		Х
Slit Lamp Exam <sup>1</sup>	Х																		X			Х					
Ophthalmic Exam <sup>j</sup>	Х					Х				Х		Х		Х		Х	Х	Х	Х	Х		Х					
Vital Signs	Х	Х	Х	Х		Х		Х		Х		Х		Х		Х		Х	Х			Х	Х	Х	Х	Х	Х
Single 12-LeadECG <sup>k</sup>	Х	Х	Х			Х				Х				Х					Х								
Limited Physical Exam <sup>1</sup>			Х	Х		Х		Х		Х		Х		Х		Х		Х				Х	Х	Х	Х	Х	Х
Full Physical Exam	Х	Х																	Х				$\square$				<u> </u>
Laboratory Safety Tests (includes Full Blood Count) <sup>m</sup>	х	х	х	х	х	х		х		х		Х		х		х	Х	Х	х								
Full Blood Count							Х		Х		Х		Х		Х												
Con Meds	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Adverse Events	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Study Medication/Compliance <sup>n</sup>		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х								
PK Sampling <sup>o</sup>		Х		Х						Х		Х				Х			Xo								
Early Morning & Spot Sputum <sup>r</sup>	Х	Х	Х	Х	Х	Х		Х		Х	Х	Х		Х		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Peripheral Neuropathy	v		1	1		v		Ī	Ī	v	1	v	1	v	1	v	V	v	v			v			$\mathbf{v}$		v
Assessment	^					^				^		^		^		^	^	^	^		<sup> </sup>	^	^		^		^
Investigator Assessment <sup>p</sup>			I	I						I			I			1	I						Х				Х

# 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 <u>6.3</u>, 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 AFTÉR 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  $\leq$  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  $\leq$  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.
- I. **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:

		San	nple	Tests										
Visit	SMB	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 1 <sup>st</sup> positive between screening and wk4 if Day 1 negative or contaminated			٠				С	С	С	L (when applicable, with isolate below)				
All Visits Post Screening	•	•			S									
1 <sup>st</sup> positive for MTB at/after week 16 for participant not responding to therapy and/or 1 <sup>st</sup> positive during follow-up for potential new infection			•			S	С	С	С	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 SAM PLES:** 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 MTBDRplus and HainMTBRs/

**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.<sup>(43)</sup> 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, bedaguiline 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.<sup>(28)</sup> In another report from South Africa of 114 patients with XDR-TB, 22% completed treatment successfully.<sup>(21)</sup> 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.<sup>(17)</sup> Reports of the outcome of XDR-TB treatment from Peru (43 patients, 42% treatment success)<sup>(2)</sup> and Ukraine (114 patients, 22% treatment success)<sup>(11)</sup> 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%.<sup>(29)</sup> 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.<sup>(43)</sup> 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<sup>(9)</sup> 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).<sup>(1)</sup>

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 bedaguiline 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 bedaguiline 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 bedaguiline 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 bedaguiline 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.

#### Efficacy of bedaquiline 200 mg daily dose vs the marketed dosing scheme over 8 weeks

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.

#### Safety of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.

#### Pharmacokinetics of bedaquiline 200 mg daily dose vs the marketed dosing scheme

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.<sup>(14)</sup> 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<sub>max</sub>, 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 bedaguiline 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 bedaguiline 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 relapsefree 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<sup>™</sup>. 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. Drugdrug 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 multipledose efavirenz (EFV) resulted in approximately a 20% decrease in the AUC<sub>inf</sub> of bedaquiline with no alteration in the C<sub>max</sub>. Modeling based on the data from this DDI study predicts average steadystate concentrations of bedaquiline and M2 to be reduced by 52% with chronic co-administration of bedaquiline and EFV.<sup>(5)</sup>

#### Safety of Bedaquiline

The Investigator's Brochure for bedaquiline provides detailed safety information.<sup>5</sup>

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.

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 <sup>a</sup>	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)									

## Table 1:ADRs C208 Stage 1 and Stage 2

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.<sup>(7)</sup>

## 2.2.2 Pretomanid

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

## 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,  $\leq 0.015$  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. <sup>(6)</sup>

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), <sup>(33)</sup> 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.<sup>(12,13)</sup>

## 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.<sup>(18,19,20,36,40)</sup> 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 .<sup>(6)</sup>

# 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  $\geq 100 \text{ mg/kg/day}$ , and early deaths occurred at doses  $\geq 500 \text{ mg/kg/day}$ . Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at  $\geq 450/300 \text{ mg/kg/day}$ . These effects were reversible when dosing stopped and were absent at  $\leq 30 \text{ mg/kg/day}$  in rats and  $\leq 150 \text{ mg/kg/day}$  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. Coadministration 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  $\geq 150$  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.

<u>Drug interaction with midazolam</u>: 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<sub>0-t</sub>), and area under the curve extrapolated to infinity (AUC<sub>0-inf</sub>). The C<sub>max</sub> 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<sub>1/2</sub>) 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 (Cmax) was 0.71, the GMR for the 24-hour area under the time-concentration curve (AUC<sub>0-24h</sub>) was 0.65, and the GMR for the trough concentration (Cmin) 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 Cmax was 0.87, for AUC0-24h was 0.83, and for C<sub>min</sub> 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 Cmax, AUC 0-24h, and Cmin 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<sub>max</sub>), area under the concentration-time curve (AUC<sub>0</sub>-

<sup>24h</sup>), and trough concentration (C<sub>min</sub>) 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 <sup>(4)</sup> (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<sup>(6)</sup> 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.<sup>(23,24,26)</sup> Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism.<sup>(8)</sup> 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.<sup>(9)</sup>

Preclinical *in vitro* data shows linezolid is active against MTB, including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1  $\mu$ g/mL.<sup>(38)</sup> 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.<sup>(36)</sup> (Table 3, below)
#### Table 3: Murine Lung CFU counts during Treatment with Linezolid

	Me	Mean lung log <sub>10</sub> CFU count (± S.D.) at:				
Regimen	D0	Month 1	Month 2	Month 3		
Untreated	6.17 <u>+</u> 0.27	6.47 <u>+</u> 0.06				
2RHZ/4R H		3.47 <u>+</u> 0.37	1.59 <u>+</u> 0.25	0.50 <u>+</u> 0.51		
L		4.97 <u>+</u> 0.26				

#### Monotherapy versus Standard Therapy

In recent years linezolid has been used to treat patients with MDR<sup>(28)</sup> 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.<sup>(41)</sup> 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.<sup>(9, 27, 34)</sup> 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.<sup>(9)</sup> 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 sputumsmear 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).<sup>(9)</sup> 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.<sup>(3,9)</sup> The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label.<sup>(23,24,26)</sup> 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.
- 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  $\leq$ 600 mg daily vs. 60.75% (95%CI 42.69–78.81) for >600 mg daily (*P* = 0.05). <sup>(3)</sup>

In a trial reported by Lee et al in S Korea<sup>(9)</sup>, seven of 41 participants had myelosuppression, including anemia and neutropenia, <u>primarily within the first 5 months</u>, 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 ( $\geq$ 3 months) and in all patients reporting new visual symptoms, regardless of length of therapy.<sup>(26)</sup>

In Lee, NEJM, 2012<sup>(9)</sup>, 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<sup>(32)</sup>, 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<sup>(27)</sup>, 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<sup>(34)</sup>, 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 <sup>(5,36)</sup> 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<sup>(15)</sup> and in a subsequent study it was more active in the mouse model than HRZ.<sup>(16)</sup> 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.<sup>(37)</sup>

#### 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 rela	psing after treatment for:
Regimen	2 months	3 months
2RHZ/RH*		8/14 <b>(57%)</b>
BPa		3/14 <b>(21%)</b>
3BPaL **	6/15 <b>(40%)</b>	0/15# <del>†</del> <b>(0%)</b>
2BPaL/1BPa***		0/15#† <b>(0%)</b>
1BPaL/2BPa	9/15 <b>(60%)</b>	0/15# <del>†</del> <b>(0%)</b>

#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 cardiovascularsafety 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<sub>CFU(0-14)</sub>

Treatment Group	Ν	Daily Mean (SD) EBA <sub>CFU(0-14)</sub>
Pretomanid + pyrazinamide + moxifloxacin	13	0.23 (0.128)
Pretomanid + pyrazinamide	14	0.15 (0.040)
Pretomanid + bedaquiline	15 <sup>a</sup>	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)

Derived Using Bi-Linear Regression, Study NC-001

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<sub>CFU</sub> and log<sub>TTP</sub> that was at least as good as the HRZE control. The daily log<sub>CFU</sub> results are presented in Table 6. Similar results were found when TTP was used to calculate the bactericidal activity over 14 days (BA<sub>(0-14)</sub>).

#### Table 6: NC-003 Efficacy Results: Daily BAlog CFU(0-14)

Arm	logCFU
BPaZC	.124
BPaZ	.180
BPaC	.086
BZC	.098
Z	.036
С	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

	BPaZ C	BPaZ	BPa C	BZC	Z	С	HRZ E	Total
Ν	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		1						1
of study drug		•						I
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  $\geq$ 500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of  $\geq$ 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  $\geq$ 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 the 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. Fortynine 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.

<u>Safety of the B-Pa-L Regimen in the Nix-TB Study</u>: 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<sup>(28)</sup>. 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.<sup>(43)</sup> 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 18 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	<ul> <li><u>Linezolid 1200 mg daily for 26 weeks</u></li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
2	<ul> <li>Linezolid 1200 mg daily for 9 weeks followed by linezolid placebo for 17 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
3	<ul> <li>Linezolid 600 mg daily for 26 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>
4	<ul> <li>Linezolid 600 mg daily for 9 weeks followed by linezolid placebo for 17 weeks</li> <li>bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks plus;</li> <li>pretomanid 200 mg once daily for 26 weeks.</li> </ul>	<ul> <li>30 XDR-TB</li> <li>Up to 15 Pre-XDR or MDR intolerant/non- responsive</li> </ul>

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. Retesting 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. It is the intent of the protocol that the participants are hospitalized according to local practices and at the judgment of the treating physician.

#### 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 18 years or older.

#### Disease Characteristics:

- 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
    - 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 <u>or</u> using effective methods of birth control, as defined below:

#### Non-childbearing potential:

- a. Participant not heterosexually active or practices sexual abstinence; or
- 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<sup>2</sup>
- 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. Participants with any of the following conditions where the use of linezolid is contraindicated:
  - A history of thyrotoxicosis
  - A history of uncontrolled arterial hypertension
  - A history of pheochromocytoma
  - A history of carcinoid syndrome
  - A history of bipolar disorder
  - A history of schizoaffective disorder
- 12. 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.

- 13. A peripheral neuropathy of Grade 3 or 4, according to DMID (<u>Appendix 2</u>). 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.
- 14. Participants with lactose intolerance, lactase deficiency and/or glucose-galactose malabsorption.

#### Previous and Concomitant Therapy

- 15. Known (during screening) requirement for future Concomitant (during treatment) use of any prohibited and/or avoided medications noted in section 5.3.
- 16. Prior use of Monoamine Oxidase Inhibitors (MAOIs) within 2 weeks of randomization.
- 17. Prior use of serotonergic antidepressants within 3 days of randomization if Investigator foresees potential risks for serotonin syndrome when combined with linezolid.
- 18. Participants who have received more than 2 weeks of bedaquiline, linezolid or delamanid prior to first dose of IMP.
- 19. 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.
- 20. 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

- 21. 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<sup>3</sup> or < 100 x 10<sup>4</sup>9/L;
  - f. Absolute neutrophil count (ANC) < 1500/ mm<sup>3</sup> or <  $1.5 \times 10^{9}/L$ ;
  - g. Aspartate aminotransferase (AST)
    - Grade 3 or greater ( $\geq$  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 ( $\geq$  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
- I. 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)
- Concomitant use of adrenomimetics (including, but not limited to pseudoephedrine, phenylpropanolamine, epinephrine, norepinephrine, dobutamine), dopaminomimetics (e.g. dopamine).
- Concomitant use of 5-HT1 agonists (triptans), meperidine or buspirone.

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 noncompliance 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 followup visits as described in <u>Table 9</u>:

Treatment Duration at EW visit	Ophthalmology Examination at EW <sup>a</sup>	Ophthalmology Examination 12 week Post treatment follow- up visit <sup>a</sup>	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

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

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).
- <u>At the end of 26 weeks and 78 weeks post treatment completion, to define outcome status,</u> 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.

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 treatment visit and it cannot be confirmed whether treatment visit completed			

# 5.5 Participant Progress Definitions

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

# 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;
  - o 600 mg QD to 300 mg QD, 300 mg 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<sup>(5,6)</sup>. The complete formulations of linezolid are found in the Package Inserts<sup>(23,24,26)</sup>.

The IMP will be packaged as follows:

- Bedaquiline: Bottles containing:
  - o 200 mg QD dose- 28 tablets- bedaquiline 100 mg
  - o 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:
  - o 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
  - o 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

Bedaquiline and pretomanid treatment will not be blinded. Linezolid treatment dose and duration will be double-blinded.

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.

Individuals who will have access to the linezolid randomization scheme will be restricted to the IWRS vendor and IMP supply administrator and the unblinded statisticians providing safety and efficacy outputs for the DSMC. Individuals from pharmacovigilance and regulatory may be unblinded following controlled steps in order to fulfil any regulatory requirements regarding reporting of expedited reports. All other parties including the Sponsor, CRO, Vendors and site staff, will be blinded.

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 (<u>Appendix 4</u>).
- 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<sub>2</sub> 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<sub>T</sub>,  $C_{mean}$ , 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.

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).

#### Table 11: Adverse Events Attribution/Causality Ratings

#### 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
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy
GRADE 3	Severe	required. 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 <u>Appendix 2</u> 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 nonleading 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.

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# 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<sup>(5,6)</sup> and Package Inserts.<sup>(23,24,25,26)</sup> Please reference section <u>6.3</u> 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 <u>Appendix 5</u> – 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  $\leq$  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<sup>9</sup>/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-ofcare 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 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.
- 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</p>
    - 480 msec < QT/QTc < 500 msec</p>
    - QT/QTc > 500 msec
  - o QTc changes from baseline will be classified into the following categories:
    - increase < 30 msec,</li>
    - 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 <u>Appendix 3</u>), 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, AUCT, 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 Pl/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. <sup>(30)</sup>

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

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

**ABBREVIATIONS:** Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R <sub>x</sub> = 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 <sup>3</sup>	750-999/mm <sup>3</sup>	500-749/mm <sup>3</sup>	<500/mm <sup>3</sup>
Platelets	75,000- 99,999/mm <sup>3</sup>	50,000- 74,999/mm <sup>3</sup>	20,000- 49,999/mm <sup>3</sup>	<20,000/mm <sup>3</sup>
WBCs	11,000-13,000/ mm <sup>3</sup>	13,000-15,000 /mm <sup>3</sup>	15,000- 30,000/mm <sup>3</sup>	>30,000 or <1,000 /mm <sup>3</sup>
% 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 <i>with</i> 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 <i>with</i> 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 <i>with</i> ketoacidosis or seizures		

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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 <i>with</i> life threatening arrhythmia or tetany
<b>Hypercalcemia</b> (correctfor 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 <i>with</i> 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 <i>with</i> 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
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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; outpatienttreatm ent 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 <sub>1</sub> of peak flow	requires treatment; normalizes with bronchodilator; FEV <sub>1</sub> 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV <sub>1</sub> 25% - 50% of peak flow; or retractions present	cyanosis: FEV <sub>1</sub> < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea w ith 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 N 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 w eek	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 w eek	<ul> <li>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or &gt;2L N fluids required</li> </ul>	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty sw allow ing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

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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 w eakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective w eakness 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 w rists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and low er 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 sw elling – but not interfering with function	moderate pain with inflammation, erythema or joint sw elling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint sw elling –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	Normal no complaints; no evidence of disease.			
	Able to carry on normal activity; minor signs or	90		
	symptoms of disease.	50		
needed.	Normal activity with effort; some signs or symptoms of	80		
	disease.			
	Cares for self; unable to carry on normal activity or to	70		
Unable to work; able to live at	do active work.	10		
home and care for most personal needs; varying amount of assistance needed.	Requires occasional assistance, but is able to care for	60		
	most of his personal needs.	00		
	Requires considerable assistance and frequent medical	50		
	care.	00		
	Disabled; requires special care and assistance.	40		
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	Severely disabled; hospital admission is indicated			
	although death not imminent.	50		
	Very sick; hospital admission necessary; active supportive treatment necessary.			
			Moribund; fatal processes progressing rapidly.	10
		Dead	0	

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109<sup>(22)</sup>.

# 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;<sup>(31,39)</sup>; 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 hepatoœllular 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.
- 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.