CONFIDENTIAL

PROTOCOL

Protocol Title: A Phase 3 open-label trial assessing the safety and efficacy of bedaquiline plus pretomanid plus linezolid in Subjects with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB) or treatment intolerant / non-responsive multi-drug resistant tuberculosis (MDR-TB).

Protocol Number: Nix-TB-(B-L-Pa)

Working Protocol Version: 5.0 (FINAL)

Working Protocol Date: 16 FEB 2018

COMBINATION OF THE FOLLOWING APPROVED FINAL DOCUMENTS:
Protocol V1.0 dated 21 April 2014
Protocol V2.0 dated 18 March 2015 Protocol V3.0 dated 22 JAN 2016
Protocol V4.0 dated 24 April 2017

PROTOCOL SIGNATURE PAGE

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Protocol Number: Nix-TB (B-L-Pa)

Protocol Version: 5.0

Protocol Date: 16 FEB 2018

SPONSOR

I agree to the terms of this study protocol.

DocuSigned by:
Daniel Everitt
Signer Name: Dan Everitt
Signing Reason: I approve this document
Signing Time: 4/9/2018 7:40:34 PM EDT
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Daniel Everitt, MD

Signature of Senior Medical Officer
April 9, 2018 | 7:40 PM EDT

Printed Name

Date

CO-ORDINATING 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 principals of current Good Clinical Practice (cGCP) and local regulations.

DocuSigned by:
Francesca Conradie
Signer Name: Francesca Conradie
Signing Reason: I approve this document
Signing Time: 4/10/2018 4:07:57 AM EDT
8F3C422D6DE04C72AD395BC608A22CC5

Francesca Conradie, MD

Signature
April 10, 2018 | 4:08 AM EDT

Printed Name

Date

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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Protocol Number: Nix-TB (B-L-Pa)

Protocol Version: 5.0

Protocol Date: 16 FEB 2018

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

Development Phase	3
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AREDS2	Age Related Eye Disease Study 2
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration time curve
$AUC_{(0-24)}$	Area under the plasma concentration time curve from zero to end of dosing interval
$AUC_{(0-t)}$	Area under the PK plasma concentration time (t) curve from zero to the last quantifiable PK plasma concentration prior to the subsequent dose, using the linear trapezoidal rule
BA	Bactericidal Activity
B	Bedaquiline (formerly J, TMC-207)
BID	Twice daily dosing
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood urea nitrogen
C	Clofazimine
°C	Degrees Celsius
CFU	Colony Forming Units
CK	Creatine Phosphokinase
CK-MB	Creatine Phosphokinase of Muscle Brain
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration at the end of the dosing interval
CNS	Central Nervous System
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interactions
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic acid
DOTS	Directly Observed Treatment, Short Course
DS	Drug-Sensitive
DSMC	Data Safety Monitoring Committee
DST	Drug Sensitivity Testing
eCRF	Electronic Case Report Form
EBA	Early Bactericidal Activity
ECG	Electrocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
ERPF	Effective Renal Plasma Flow
FDA	United States Food and Drug Administration

FF	Filtration Fraction
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyltransferase
hERG	Human ether-à-go-go-related gene
HIV	Human Immunodeficiency Virus
hr	Hour
HRZE	isoniazid plus rifampicin plus pyrazinamide plus ethambutol
HRZM	Isoniazid plus rifampicin plus pyrazinamide plus moxifloxacin
IB	Investigator Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IUATLD	International Union Against Tuberculosis and Lung Disease
i.v., IV	Intravenous
Kg	Kilogram
LDH	Lactate Dehydrogenase
L	Linezolid
LFT	Liver Function Test
lKr	Delayed rectifier potassium current
LH	Luteinizing Hormone
LSLV	Last Subject Last Visit
m	Meters
M	Moxifloxacin
MAOI	Monoamine Oxidase Inhibitor
MBD	Minimum Bactericidal Dose
M2	Bedaquiline metabolite M2
MDR	Multi Drug-Resistant
MED	Minimum Effective Dose
mg	Milligrams
mg/dl	milligram per decilitre
MGIT	Mycobacterial Growth Indicator Tube
MIC	Minimum inhibitory concentration
ml	Millilitre
mmHg	Millimeter of mercury
M. tb.	*Mycobacterium tuberculosis*
ms	Millisecond
NIH	National Institute of Health
NLME	Non-linear Mixed Effect
NOAEL	No Observed Adverse Effect Level
Pa	Pretomanid (formerly PA-824)

PD	Pharmacodynamic
PE	Physical Examination
PK	Pharmacokinetic
PR	Electrocardiographic PR interval
q.d./QD	Once daily dosing
QRS	Electrocardiographic QRS interval
QT	Electrocardiographic QT interval
QTc	Corrected QT interval
QTcB	QT interval corrected by Bazett's method
QTcF	QT interval corrected by Fridericia's method
RR	Electrocardiographic RR interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sc	Subcutaneous
SIRE	Streptomycin, Isoniazid, Rifampicin and Ethambutol
SSCC	Serial Sputum Colony Counts
T	Time
$t_{½}$	Apparent terminal elimination phase half-life
TB	Tuberculosis
TEAEs	Treatment-Emergent Adverse Events
TIW	Three times a week
T_{max}	Time at which C_{max} is observed
TMIC	Time over Minimum Inhibitory Concentrations
TTP	Time to Sputum Culture Positivity
UA	Uric Acid
ULN	Upper Limit of Normal
µg/ml	microgram per millilitre
WBC	White Blood Cell
WHO	World Health Organization
XDR	Extensively drug-resistant
Z	Pyrazinamide

1. PROTOCOL SYNOPSIS

1.1. Synopsis

Name of Sponsor/Company:	Global Alliance for TB Drug Development
Name of Finished Products:	bedaquiline tablets; pretomanid tablets; linezolid tablets.
Protocol Title:	A Phase 3 open-label trial assessing the safety and efficacy of bedaquiline plus pretomanid plus linezolid in Subjects with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB) or treatment intolerant / non-responsive multi-drug resistant tuberculosis (MDR-TB)
Treatment Indication:	Pulmonary XDR-TB and treatment intolerant/non-responsive MDR-TB
Trial Objective:	To evaluate the efficacy, safety, tolerability and pharmacokinetics of bedaquiline plus pretomanid plus linezolid after 6 months of treatment (option for 9 months for subjects who remain culture positive or revert to being culture positive between month 4 and month 6 visits) in Subjects with either pulmonary XDR tuberculosis, treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).
Trial Design:	An open-label clinical trial. Treatment: • bedaquiline 400 mg once daily for 2 weeks then 200mg 3 times per week plus pretomanid 200mg once daily plus linezolid 1200mg once daily. All IMP to be given with a meal. Treatment Duration: • 6 months • If subjects are still culture positive at month 4, option to extend treatment to 9 months or withdraw. Follow-Up: • Subjects who complete treatment will return for follow-up visits 1, 2 and 3 months after end of treatment then every 3 months up to 24 months after end of treatment. • Subjects who withdraw after ≤14 days of IMP administration are to return for an Early Withdrawal visit only; • Subjects who withdraw after ≥15 days of IMP are to return for the Early Withdrawal, and for the 3, 6, and 24 month follow up visits after their last dose of IMP. Data Safety Monitoring Committee (DSMC) Reviews: Interim Safety/Efficacy data will be reviewed by DSMC as follows: • At least every 6 months after the first subject is enrolled; • Ad hoc meetings can be called by Sponsor/DSMC based on rates of SAEs or to review results of futility analysis or if safety concerns arise during the trial.
Patient Population:	A total of up to 200 male or female Subjects aged 14 and over with confirmed sputum culture-positive pulmonary XDR-TB or MDR-TB with a documented intolerability or nonresponse to treatment.

Name of Sponsor/Company:	Global Alliance for TB Drug Development
Name of Finished Products:	bedaquiline tablets; pretomanid tablets; linezolid tablets.
Test Product, Dose and Mode of Administration:	The Investigational Medicinal Product (IMP) will be supplied as: • Bedaquiline 100mg tablets • Pretomanid 200mg tablets • Scored Linezolid 600 mg tablets The assigned treatment regimen will be administered orally for 6 months (possibly 9 months) at the following doses and intervals: • Bedaquiline 400 mg once daily for 2 weeks then 200 mg 3 times per week; plus pretomanid 200mg once daily; plus linezolid 1200mg once daily. A reduction in the dose of linezolid (to either 600 mg qd or 300 mg qd) or temporary cessation of linezolid (due to a linezolid-specific toxicity), or of the full regimen per Investigator discretion will be allowed for suspected drug related toxicity. Re-introduction of the regimen could be considered post a cessation not greater than 35 consecutive days. If subjects have toxicity issues with linezolid prohibiting further treatment with that drug, they can remain on the bedaquiline and pretomanid study IMP if they received the initial total of 1200 mg daily dose of linezolid for at least the first 4 consecutive weeks of treatment and they are smear negative, or with trace/scanty results and judged to be clinically improving by the Investigator.

Criteria for Evaluation:

Primary Endpoint:
Incidence of bacteriologic failure or relapse or clinical failure through follow up until 6 months 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 culture conversion to negative.
- Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status in culture, with culture conversion to positive status with a Mycobacterium tuberculosis (*M.tb*.) strain that is genetically identical to the infecting strain at baseline.
- Clinical failure: A change from protocol-specified TB 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.
- Subjects 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.

Secondary Endpoints:

- Incidence of bacteriologic failure or relapse or clinical failure through follow up until 24 months after the end of treatment as a confirmatory analysis.
- Time to sputum culture conversion to negative status through the treatment period.
- Proportion of subjects with sputum culture conversion to negative status at 4, 6, 8, 12, 16 and 26 or 39 weeks.
- Linezolid dosing (actual) and efficacy will be explored.
- Change from baseline TB symptoms.
- Change from baseline in Patient Reported Health Status.
- Change from baseline weight.

Name of Sponsor/Company:	Global Alliance for TB Drug Development
Name of Finished Products:	bedaquiline tablets; pretomanid tablets; linezolid tablets.

Safety and Tolerability:

- All cause mortality.
- Incidence of Treatment Emergent Adverse Events (TEAEs) will be presented by severity (DMID Toxicity Grade), drug relatedness and seriousness, leading to early withdrawal and leading to death.
- Quantitative and qualitative clinical laboratory result measurements, including observed and change from baseline.
- Quantitative and qualitative measurement of ECG results, 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.
- These data will be presented as descriptive analyses, and no inferential tests will be carried out.

Pharmakokinetics (PK):

Pharmacokinetics will consist of two separate schedules:

- All Subjects- Pre-dose sampling at weeks 2, 8 and 16 to measure C_{trough} levels of bedaquiline, bedaquiline metabolite M2, linezolid and pretomanid.
- PK Sub-study Subjects- in addition to the C_{trough} samples, there will be intensive PK sampling at week 16 at pre-dose, 0.5, 1, 2, 4, 8 12, 12.5, 13, 14, 16, 20 and 24 hours after dosing in a sub-group of 20 evaluable Subjects across selected sites.

For the PK sub-study samples, the following PK parameters will be estimated from the individual (per Subject) PK plasma concentrations: Minimum observed PK plasma concentration (C_{min}), maximum observed PK plasma concentration(C_{max}), time to reach C_{max} obtained without interpolation (T_{max}), area under the PK plasma concentration time (t) curve from zero to the last quantifiable PK plasma concentration prior to the subsequent dose, using the linear trapezoidal rule ($AUC_{(0-t)}$), area under the PK plasma concentration time (t) curve from zero to 24 hours ($AUC_{(0-24)}$). Oral apparent clearance (CL/F) by non-compartment model. These will be derived for each analyte. In addition, for linezolid analyte BID dose, the AUC_{0-12}, C_{max}, C_{min}, CL/F and $t_{1/2}$ will be calculated based on dose interval 0-12 hrs.

Exploratory:

- Evaluate whether any of the secondary endpoints predicts relapse free cure.
- Subgroup analyses of the primary endpoint on the MITT analysis population will be considered
- Correlation of Time over mitochondrial protein synthesis inhibition (MPS50) with linezolid toxicity (The MPS50 will be an assumed value from the literature).

Mycobacteriology Characterization:

M.tb. isolates at baseline and initial relapse (first positive at end of treatment or during follow-up) will be processed at the central lab(s) for:

- MIC of bedaquiline, pretomanid and linezolid;
- Drug Susceptibility Testing in liquid culture for rifampicin, isoniazid, streptomycin, ethambutol, and second line TB drugs including fluoroquinolones and injectables;
- Extraction of bacterial (*M.tb*) DNA for molecular genotyping;

M.tb. isolates at baseline and initial relapse (first positive at end of treatment or during follow-up) or any positive at or after the week 16 visit will also be processed at the study lab (lab where study samples are initially sent from site for culture) for:

- Speciation of the infecting organism by molecular or antigen based test to confirm *M.tb*.

Name of Sponsor/Company:	Global Alliance for TB Drug Development
Name of Finished Products:	bedaquiline tablets; pretomanid tablets; linezolid tablets.

Statistical Methods:

The primary efficacy endpoint is treatment failure, defined as bacteriologic failure, or relapse, or clinical failure through follow-up until 6 months after the end of treatment. The probability of treatment failure through follow-up until 6 months after the end of treatment, as a function of time after assignment of study treatment, will be analyzed using Kaplan-Meier analysis. The binomial proportion for subjects with bacteriologic failure will be presented. No multiplicity adjustments for alpha will be done as this is an exploratory trial.

Futility Analysis:

Timing of initial interim analysis will be conducted when the first 15 participants reach 6 months after completion of IMP Further interim analyses will be specified in the statistical analysis plan (SAP).

Once all patients have been recruited or have completed the treatment period, no further futility analyses will be performed.

Trial Duration:

Estimated date of first Subject enrolled: Quarter 4 2014
Estimated date of last Subject enrolled: Quarter 3 2017
Estimated date of last Subject completed: Quarter 4 2020

Duration of Study:

~6 Years (An enrolment period of at least 42 months plus 9 days pre-treatment plus 6-9 month treatment period plus 24 months post treatment follow-up.

1.2. Trial Flow Chart

Period	Screening[a]	Treatment																			9 Month Treatment ONLY[p]			Early Withdrawal (Treatment)	Post Treatment Follow-up Period[b]									
Time of Visit	Up to 9 days prior to Treatment	Day 1[c]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16	Week 20	Week 26	Week 30	Week 34	Week 39		1 month	2 month	3 month	6 month	9 month	12 month	15 month	18 month	21 month	24 month
Visit Window[q]	N/A	+/- 3 days																	+/- 7 days					+/- 2 weeks									
Informed Consent	X																																
Demography	X																																
Medical/Treatment History	X																																
Inclusion/Exclusion	X	X																															
Karnofsky Assessment	X																																
HIV Status[d]	X																																
CD4 Count[e]	X																																
Chest X-Ray[f]	X																																
Serum or Urine Pregnancy Test[g]	X	X								X										X[h]			X[h]	X									
TB Symptoms Profile	X									X										X[h]			X[h]	X					X				X
Patient Reported Health Status	X									X										X[h]			X[h]	X					X				X
Slit Lamp Exam[i]	X																			X[h]			X[h]	X			X						
Ophthalmic Exam[j]	X					X				X				X				X	X	X	X	X	X	X			X	X		X				X
Vital Signs	X	X	X	X		X		X		X				X				X	X	X	X	X	X	X			X	X	X	X	X	X	X	X
Single 12-LeadECG	X	X	X			X				X								X		X[h]	X		X[h]	X									
Limited Physical Exam[k]			X	X		X		X		X				X				X	X		X	X					X	X	X	X	X	X	X
Full Physical Exam[k]	X	X																		X[h]			X[h]	X									
Laboratory Safety Tests[l]	X	X	X	X		X		X		X				X				X	X	X	X	X	X	X									
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication/Compliance[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
PK Sampling[n]				X						X								X															
Early Morning & Spot Sputum[o]	X	X	X	X		X		X		X				X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete/Full Blood Count					X		X		X		X	X	X		X	X	X																	
Peripheral Neuropathy	X					X				X				X				X	X	X	X	X	X	X			X	X		X				X

Note:

- Unscheduled visits should be planned to assess, confirm, and follow up on clinically relevant AEs or laboratory abnormalities.
- All assessments are to be performed pre-dosing unless otherwise specified.
- On days where the following assessments are done the order should be: ECG before vital signs, blood draws (for Safety or PK).

a. **Screening:** Screening assessments can occur on different days within nine days prior to treatment. If a subject fails screening, a full re-screen (all screening procedures must be repeated) may occur at a later date.

b. **Follow-up Visits for Early Withdrawal Subjects:** Once a Subject has been permanently withdrawn from the trial, they will be required to attend an Early Withdrawal visit. If they receive/take less than 15 doses, additional visits are not required. If they received 15 or more doses, Month 3, Month 6 (if not already performed) and Month 24 follow-up visits are required. The Month 6 follow-up will be a full study visit as outline in section 4.4.3.4. Month 6(if already performed) and Month 24 visit will collect any AEs (Adverse Events), Serious Adverse Event (SAE), Concontimant medication information, including verification of survival and patient reported TB outcome information only and may be telephonic, a home or a site visit.

c. **Day 1 (baseline):** All procedures are to be completed prior to dosing.

d. **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 trial start, it should not be repeated as long as documentation of testing method and negative results can be provided.

e. **CD4 count:** For all HIV-positive Subjects.

f. **Chest X-Ray:** Chest X-Ray at Screening or within 1 year prior to Screening. The Investigator is responsible for its review and analysis for subject inclusion.

g. **Serum or Urine Pregnancy:** Women of child-bearing potential only, whether they are sexually active or not.

h. **Final Treatment Visit:** Serum or Urine Pregnancy Test, TB Symptoms Profile, Full Physical Examination, 12-lead ECG, Patient Reported Health Status and Slit Lamp Examination are only performed at the subjects' applicable End of Treatment Visit dependent on their treatment duration (week 26, week 39 or when final IMP completed for scenarios where interruptions extend treatment, as applicable). If Week 26 is not the Final Treatment Visit, only a limited physical exam should be done.

i. **Slit-Lamp Exam:** Slit Lamp examination will be performed by an Ophthalmologist with AREDS2 training. See section 4.4.2.12 and 4.4.3 for details on what follow-up slit lamp exams are necessary for subjects who withdrawal early.

j. **Ophthalmic Exam:** to include Ophthalmologic Medical history at Screening; All exams to include Visual Acuity and Color 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. **Physical Exam: Full Physical Exams** to include gross neurological exam. All other PEs should be **limited** to weight and a pulmonary, cardiovascular and abdominal exam.

l. **Safety Laboratory Assessments** (refer to section 6.3 for details of laboratory safety assessments)

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

n. **PK Sampling:** Pharmacokinetics will consist of two separate schedules:
   1. **All Subjects** - Pre-dose C_{trough} sampling at weeks 2, 8 and 16, must be taken within 1 hour before the next scheduled dose.
   2. **PK Sub-study Subjects** - in addition to the C_{trough} samples, there will be intensive PK sampling at week 16 at pre-dose, 0.5, 1, 2, 4, 8 12, 12.5, 13, 14, 16, 20 and 24 hours after dosing in a sub-group of evaluable 20 Subjects across selected sites. To be collected at the specified time points within the allowed applicable window periods: Pre-dose: 0-5 minutes before dose; 0.5- 1 hours post-dose: +/- 5 minutes; 2-8 hours post dose: +/- 5 minutes; 12 hours post-dose: +/- 5 minutes and prior to next dose for BID treatment arm, 12.5 – 13 hours +/- 5 minutes and 14- 24 hours +/- 10 minutes and prior to next dose. All PK sub-study participants must have received IMP at stable doses for at least two weeks prior to the sub-study sampling. If participant is in the midst of an IMP interruption at week 16, the PK draw should be post-poned until the regimen is resumed for 2 weeks.

o. **Sputum Sampling:**
   1. Screening (Day -9 to -1): A single spot sputum will be collected at the research site under the coaching and observation of the trial staff. The following analysis will be performed on this sample:
      - Smear microscopy for acid-fast bacilli (AFB);
      - Culture for presence or absence of *M.tb.*;
      - Gene Xpert, Hain Assay MTBDRplus or an alternative molecular or antigen-based test to confirm M.tb;
   2. All visits from Day 1 (baseline) up to and including Month 24: Two sputum samples, one early morning brought from home or in the hospital if hospitalized, and one spot at the research site under the coaching and observation of the trial staff (or if hospitalized, in the morning at least 1 hour after the early morning sample) will be collected. If early morning is not available, site should make every attempt to collect two spot samples at least 1 hour apart on site. sputum samples obtained at Month 4, End of Treatment (Week 26/39) or end of follow-up Month 24 are contaminated, the Subject should return for an unscheduled visit(s) to give additional samples or to document the Subject is not able to produce sputum. The following analyses will be performed on sputum samples at the study lab (lab that receives samples directly from the site):
      - Culture for presence or absence of *M.tb.*;
      - Speciation (on baseline and first positive at end of treatment or during follow-up or any positive at or after the week 16 visit)
      - If MGIT is performed, TTP in liquid medium.

   If participant has received at least 4 consecutive weeks of linezolid at a total daily dose of 1200 mg, and Investigator would like to consider discontinuing linezolid dosing and continuing bedaquiline and pretomanid dosing:
      - A smear microscopy for acid fast bacilli (AFB) should be requested by the site and performed at the study lab.

   3. First culture positive sample at or following end of treatment: Two sputum samples, one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff (or if hospitalized, in the morning at least 1 hour after the ealry morning

sample) will be collected. If early morning is not available,site should make every attempt to collect two spot samples at least 1 hour apart on site.

- Culture for presence or absence of M.tb.;
- Extraction of bacterial (M.tb.) DNA for molecular genotyping
- Speciation (for initial relapse (first positive at end of treatment or during follow-up) or any positive at or after week 16))

Mycobacteriology Characterisation Tests, Performed on:

1. Day 1 (baseline) spot sputum samples (or Screening up to Week 4 if the baseline is contaminated or negative);
2. Confirmed Positive Cultures at or after end of treatment.

The *M.tb.* isolates will be processed at 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 such as fluoroquinolones, and injectables;
- Extraction of bacterial (*M.tb.*) DNA for molecular genotyping;
- Speciation of the infecting organism by molecular/antigen tests

All Day 1 (baseline) *M.tb.* isolates and isolates from positive cultures to be stored at the study microbiology laboratory (or until requested to transfer to the central lab(s) for testing), until trial closure for the applicable study tests. The extracted *M.tb.* DNA and isolates will be stored for potential further work to validate new assay tools for a maximum of 5 years after trial closure.

p. **Visit Schedule:** Subjects who are culture positive or revert to being culture positive between month 4 and month 6 visits, will be withdrawn, or will receive a total of 9 months of treatment. *(Week 30, 34 and 39 visits should not be done for Subjects who complete study treatment in 6 months).* If the duration of treatment is extended due to dose interruptions (e.g., takes participant 8 months to complete 6 months of therapy), Unscheduled visits should be added every 4 weeks through last dose of IMP, then post final treatment visit, follow-up visits should be scheduled. Unscheduled Visits to include: Ophthalmology Examination, Vital Signs, Limited Physical Exam, Laboratory Safety Tests, Con Meds, Adverse Events, Study Medication/Compliance, Early Morning and Spot Sputum and the Peripheral Neuropathy Exam.

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. Sites should make every effort to ensure all other procedures should be done on the same day when possible.

2. INTRODUCTION

2.1. Background

Although some progress has been made in recent years in controlling TB globally, TB has remained a persistent problem in many countries. TB is currently one of the top three fatal infectious diseases, 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. The current first-line anti-tuberculosis agents have been in use for over 20 years and although the current regimens and drugs have been very successful in controlled clinical trials resulting in the permanent cure of more than 95% of trial Subjects, treatment takes 6 months to complete. This, plus side effects, result in poor compliance which is particularly likely to occur after the second month of treatment. As a result of poor treatment compliance, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB – extensively drug resistant TB (XDR-TB) - are growing. Novel drugs for tuberculosis are needed for the growing numbers of patients with untreatable strains.

WHO is tracking the increase of drug resistant strains. They estimate that there are about 650,000 MDR-TB cases in the world at any one time. On average, an estimated 9.6% of MDR-TB cases have XDR-TB, defined as resistance to at least isoniazid and rifampicin, as well as to any fluoroquinolone, and to any of the three second-line injectables (amikacin, capreomycin, and kanamycin)[20]. XDR-TB has been reported by 92 countries. Among a subset of 795 XDR-TB patients in 26 countries, treatment success was 20% overall and 44% of patients died; South Africa reports the most XDR-TB cases[22]. In 2006 a report from rural South Africa noted that 52 patients died of 53 patients identified with XDR-TB and HIV co-infection; the mean survival was 16 days from the time of diagnosis[21]. A recent report from South Africa documented the very grave long term prognosis of patients with XDR-TB[23]. Between 2008 and 2012 107 patients with XDR-TB from 3 provinces in South Africa were followed for long term outcomes. At 60 months of follow up 12 patients (11%) had a favourable outcome, 78 (73%) had died, four (4%) had defaulted, and 11 (10%) had failed treatment. With such dire outcomes for patients with XDR-TB, novel drug combinations are needed to improve treatment outcomes. Recently, linezolid was identified as a potentially efficacious drug to use with patients with XDR-TB when added to a failing regimen[24].

Following the declaration of TB as a global emergency by the World Health Organization (WHO) in 1993, there has been a resurgence of efforts to develop improved TB therapies and several promising new agents are presently in or approaching clinical evaluation. On December 28, 2012 the U.S. Food and Drug Administration approved bedaquiline (Sirturo™) as part of combination therapy to treat adults with multi drug-resistant pulmonary tuberculosis (MDR-TB) when other alternatives are not available. On December 20, 2013 the CHMP recommended approval of bedaquiline by the EMA as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) when other treatments are not available. In November of 2013, the CHMP recommended that delamanid be approved by the EMA for treatment of pulmonary MDR-TB in combination with the WHO optimized background regimen. Although both of these regulatory actions are positive steps, more work needs to be done to develop new regimens for both drug-sensitive (DS-TB) and drug resistant TB (MDR-TB/XDR-TB). New combination regimens are desperately needed for two reasons; to shorten treatment to a duration more easily manageable by patients and public health services for DS-TB and to provide more efficacious, safer, better tolerated and affordable treatment for the growing number of patients suffering from MDR-TB and XDR-TB.

The Nix-TB study offers a new opportunity to treat patients with XDR-TB with three drugs for which there is no expected pre-existing resistance. Bedaquiline, pretomanid and linezolid are active against many drug resistant strains of *M.tb.* and substantial preclinical and clinical data are available to demonstrate their potential for individual and combined microbicidal and sterilizing activity in TB disease. To further development of novel

regimens, TB Alliance is currently conducting a series of Phase 2 studies to evaluate building blocks of this regimen. A recently completed 14 day Early Bactericidal Activity (EBA) study in South Africa (Study NC-003) demonstrated bactericidal activity of the bedaquiline-pretomanid-pyrazinamide regimen. This regimen is now being taken into an "SSCC" 8 week trial designed to investigate the combination of bedaquiline, pretomanid and pyrazinamide (B-Pa-Z) in DS-TB and bedaquiline, moxifloxacin, pretomanid and pyrazinamide in MDR-TB.

The current study (Nix-TB) is an open label trial designed to investigate the combination of bedaquiline, linezolid, and pretomanid in XDR-TB. Since patients with XDR-TB are failing nearly all drugs, there is no useful standard of care (SOC) to use for comparison. Because the long term outcome of patients in South Africa treated with available SOC is up to 75% mortality[23], this open label study offers the opportunity to identify a substantially better outcome without the need for a comparison group. This study will provide patients with an oral regimen that contains three novel drugs with the potential for a shorter treatment, better outcomes and with fewer side effects than the drugs currently being used.

The information presented below first details the key preclinical information and human efficacy and safety information for each of the drugs in the regimen and then present preclinical and clinical data to support the combination of these drugs in a regimen to treat patients with XDR-TB.

2.2. Agents to be Studied

2.2.1. Bedaquiline

Bedaquiline (formerly known as TMC-207; Sirturo™ package insert[3]) is a new agent being developed for TB treatment. As detailed in the Investigator's Brochure[4,5] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate (ATP) synthase[6]. *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. Tb* isolates[7,8], and is also bactericidal against non-replicating *M. tb.*[9] In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampicin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. tb.*[1, 2]. There appears to be a synergistic interaction with pyrazinamide: 100% of mice were culture negative after 8 weeks of treatment with bedaquiline and pyrazinamide compared to 0% of mice treated with the standard regimen of rifampicin, isoniazid and pyrazinamide[10]. Collectively, these findings in the mouse model have led to the suggestion that regimens containing bedaquiline and pyrazinamide could be effective in the treatment of both drug sensitive and drug resistant TB and shorten treatment duration in patients. While the combination of bedaquiline and pretomanid in the murine model of TB appeared somewhat antagonistic relative to bedaquiline alone, it was as active as the triple combination of HRZ[10] and in a subsequent study it was more active in the mouse model than HRZ[11]. Thus a novel regimen with a bedaquiline plus pretomanid core could be effective in the treatment of MDR-TB/XDR-TB by providing two novel drugs for which there is no known pre-existing resistance.

To date, bedaquiline has been studied as monotherapy in two dose-ranging EBA trials (C202 and TMC207-CL001)[12,13], in two combination EBA trials (NC-001[14] and NC-003) and in 2 Phase 2b studies (C208 and C209). In the monotherapy studies, bedaquiline was dosed over a range of 100-400 mg/day. Subjects with TB had approximately a 1 log decrease in logCFU over 14 days at all doses studied. The first 14 day EBA combination study (NC-001) demonstrated that bedaquiline in combination with pyrazinamide (B-Z) and bedaquiline in combination with pretomanid (B-Pa) had positive EBA activity. The second 14 day EBA combination study (NC-003), currently undergoing analysis, included a number of bedaquiline-containing arms: bedaquiline, pyrazinamide and clofazimine (B-Z-C), bedaquiline, pretomanid and clofazimine (B-Pa-C); bedaquiline, pretomanid and pyrazinamide (B-Pa-Z) and bedaquiline, pretomanid, pyrazinamide and clofazimine (B-Pa-Z-C). Among these, B-Pa-Z had the best activity which was at least as good as the HRZE control.

The 2 completed Phase 2b studies form the pivotal studies reviewed by the FDA for accelerated approval of bedaquiline (Sirturo ™). Together, these clinical studies provide justification for proceeding to the current study and are described briefly below and in greater detail in the IB.

2.2.1.1. Bedaquiline Preclinical Studies

Full details of the preclinical studies are provided in the current bedaquiline Investigator's Brochure[4, 5] and Sirturo ™ label[3]. *In vitro* studies have demonstrated that the range of minimum inhibitory concentrations (MICs) for *M. tb.* H37Rv, the international reference strain, and 6 fully drug-susceptible clinical isolates, was 0.030 to 0.120 µg/ml. The activity of bedaquiline appears to be specific for mycobacteria, as the MICs for non-mycobacteria were at least 500-fold higher. The activity of the main metabolite of bedaquiline, M2, was determined against *M. tb.* H37Rv in both solid and liquid media and its MIC was found to be 0.1 µg/ml. This MIC shows that M2 is active against *M. tb.* but 3-6 times less active than the parent compound bedaquiline. Bedaquiline demonstrated similar *in vitro* efficacy against *M. tb.* clinical isolates resistant to the known anti-TB drugs (isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol, or fluoroquinolones). As expected, from the lack of cross-resistance with currently used anti-tuberculosis agents, bedaquiline retained activity against MDR-TB isolates.

The non-clinical safety evaluation of bedaquiline includes pharmacology, pharmacokinetics, toxicology and metabolism studies that were conducted in accordance with current ICH guidelines. Repeated dose toxicity studies were performed with dosing durations up to 3 months in mice and up to 6 months in rats and in dogs. Recovery was studied in rats and dogs. In repeated dose toxicity studies up to 3 months in mice, up to 6 months in the rat and up to 9 months in dogs, bedaquiline was associated with target organ changes in the mononuclear phagocytic system (indicative of phospholipidosis), stomach, liver, pancreas, and muscle. Toxicity was often associated with an increased presence of neutrophils in some tissues such as the female genital tract and this was preceded by a peripheral neutrophilia. For more detailed information please refer to the bedaquiline IB[4,5].

Respiratory parameters in rats were unaffected by treatment. There were no effects suggestive of neurological impairment or delayed neurotoxicity in rats. In single dose toxicity studies there were no mortalities following oral doses of up to 200 mg/kg in mice and rats. No mutagenicity or clastogenic effects were seen in a series of *in vitro* and *in vivo* genotoxicity tests. Bedaquiline was evaluated for possible developmental toxicity effects in the rat and the rabbit. No teratogenic effects were found. *In vitro*, bedaquiline slightly to moderately inhibited the delayed rectifier potassium current (IKr) in the human ether-à-go-go-related gene (hERG) model. Bedaquiline and M2 had no notable effects on IKr at 0.01 µM (0.006 and 0.005 µg/mL, respectively). However, at higher concentrations (0.03 to 3 µM), both compounds had a slight to strong concentration-dependent effect with a 50% inhibitory concentration (IC_{50}) of 0.37 µM (0.2 µg/mL) for bedaquiline and up to 0.45 µM (0.24 µg/mL) for M2. However, this effect did not manifest as a prolongation of repolarization in subsequent *in vivo* studies. There were no relevant effects on the isolated right atrium of guinea pigs *in vitro*, or in the isolated Langendorff-perfused rabbit heart. *In vivo*, positive chronotropic effects were seen in the anesthetized guinea pig after IV administration, but not in the conscious dog. In conscious, telemetered dogs, oral bedaquiline had no relevant effects on cardio-hemodynamic andelectrocardiogram (ECG) parameters.

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 [15].The effect of pretomanid dosing alone on QT interval appeared to be due to discomfort related to the SC route of administration and not related to the plasma exposure (please see the pretomanid (formerly PA-824) Investigators Brochure for more detail).

2.2.1.2. Bedaquiline Clinical Studies

In the clinical studies conducted to date, a total of approximately 645 Subjects (including 265 healthy volunteers) have been exposed to bedaquiline in the Phase 1 and 2 clinical trials conducted as a part of the development program for the treatment of MDR-TB. An additional 45 Subjects received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in study NC-001, and 45 more in study NC-003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). Four short-term Phase 2a trials enrolled treatment-naïve Subjects (C202, TMC207-CL001, NC-001 and NC-003). One long-term, open-label, Phase 2 trial, in MDR-TB Subjects (bedaquiline-TiDP13-C209) and one long-term, Phase 2b trial, consisting of 2 different stages in Subjects infected with newly diagnosed sputum smear-positive pulmonary MDR-TB (bedaquiline-TiDP13-C208), have been completed. The principal findings of these trials are summarized below. Full details of the completed clinical studies are provided in the current bedaquiline IB [4,5] and Sirturo ™ label[3].

The Phase 1 trials have provided a basic understanding of bedaquiline's pharmacokinetic characteristics, drug-drug interaction potential, and short-term safety/tolerability profile in healthy Subjects. Bedaquiline was well absorbed with time to reach the maximum plasma concentration at approximately 5 hours post-dose. The maximum plasma concentration and AUC increased proportionally up to the highest doses studied (up to 700 mg in a single dose-ranging study, 800 mg single dose in study bedaquiline-TBC1003 and 400 mg q.d. multiple doses). Accumulation from Days 1 to 14 was approximately 2-fold expressed as increase in AUC, while trough concentrations increased up to 3.5-fold. The pharmacokinetics of bedaquiline were comparable between healthy Subjects and Subjects with pulmonary TB. The apparently close to steady-state concentrations in plasma after 14 days of daily treatment is ascribed to the important amount of the drug that is eliminated from the circulation during the ά and β phases of the plasma concentration-time curve. The average terminal elimination half-life of bedaquiline and metabolite M2 noted on extended follow-up after repeat dosing of Subjects with TB infection is about 5.5 months.

Administration of bedaquiline as the tablet formulation with food, increased the relative bioavailability (by 95%) compared to administration without food, and drug-drug interaction trials confirmed the role of cytochrome P450 3A4 (CYP3A4) in the metabolism of bedaquiline to M2. A recently completed study (DMID 10-0043) demonstrated that when given in combination, rifampicin, and to a lesser degree rifabutin, decreased exposure to bedaquiline presumptively due to induction of P450 enzymes. The clinical significance of these findings is unknown, however the current study (NC-005) will not permit the concomitant use of bedaquiline with any rifamycin.

The efficacy of bedaquiline was initially demonstrated in two monotherapy EBA studies C202 and TMC207-CL001. Study C202 was a 7 day study of three daily doses of bedaquiline (25, 100 and 400mg) in treatment-naïve Subjects with MDR-TB. In this study, the 400mg dose group demonstrated positive EBA and was numerically superior to the 25 and 100mg doses. In study TMC207-CL001, doses of 100, 200, 300 and 400mg daily (following a 2-day loading dose) were studied in Subjects with newly-diagnosed pulmonary TB for 14 days. There were no statistically significant differences between the treatment groups, although there was a numerical trend suggesting a positive dose-response relationship. Taken together, these studies establish that bedaquiline monotherapy has EBA in Subjects with TB and that higher doses appear to have greater efficacy.

A 14 day EBA regimen study (TB Alliance Study NC-001-(B-M-Pa-Z)) evaluated bedaquiline administered as monotherapy at 400 mg/d or in combination at that dose with either pretomanid administered at 200 mg/d or weight-adjusted pyrazinamide, to Subjects with pulmonary TB at 2 clinical sites in South Africa. The results indicate that over 14 days, the mean logCFU decreased by 1.3 from baseline in the 15 Subjects given bedaquiline 400 mg/d after a 2 day loading dose. In the cohort of 15 Subjects given bedaquiline 400 mg/d after a loading dose plus weight-adjusted daily doses of pyrazinamide (Z), the mean logCFU decreased by 2.0 logs from

baseline, indicating that Z potentiates the early bactericidal effect of bedaquiline. In the cohort with 15 Subjects given bedaquiline 400 mg/d after a loading dose plus 200 mg/d pretomanid, the mean logCFU decreased by 1.9. While it appeared that the addition of pretomanid potentiated the anti-tuberculosis activity of bedaquiline, the mean logCFU decrease of the combination was similar to that of two previous EBA studies using pretomanid monotherapy at 200 mg/day.

The second 14 day EBA combination study (NC-003) included a number of bedaquiline-containing arms: bedaquiline, pyrazinamide and clofazimine (B-Z-C), bedaquiline, pretomanid and clofazimine (B-Pa-C), bedaquiline, pretomanid, and pyrazinamide (B-Pa-Z) and bedaquiline, pretomanid, pyrazinamide and clofazimine (B-Pa-Z-C). Among these, B-Pa-Z had the best activity which was at least as good as the HRZE control (Daily Log CFU – 0.167 vs 0.151, respectively).

The long-term efficacy of bedaquiline in Subjects with MDR-TB has been studied in a placebo-controlled, randomized Phase 2b trial (C208) and an open-label, uncontrolled, Phase 2b trial (C209). In the Phase 2b placebo-controlled trial, C208, the addition of bedaquiline to a 5-drug MDR-TB regimen resulted in significantly faster time to culture conversion compared to placebo. During the 8-week treatment in Stage 1, 47.6% of Subjects in the bedaquiline group became MGIT culture negative compared to 8.7% of Subjects in the placebo group. At Week 24 in Stage 1, after 8 weeks of investigational treatment and 24 weeks of background treatment, 81.0% of Subjects in the bedaquiline group and 65.2% of Subjects in the placebo group showed treatment success, (i.e., completed week 24 and were liquid culture negative at this time point).

For C208 Stage 2, in the interim analysis as well as in the primary efficacy analysis, a statistically significant difference in time to culture conversion between the treatment groups ($p < 0.0001$) in favour of bedaquiline was shown. In both analyses, an identical number of Subjects with culture conversion at week 24 (i.e., 24-week responders [missing = failure]) was observed: 78.8% in the bedaquiline group and 57.6% in the placebo group, which was statistically significantly different ($p = 0.008$) based on a logistic regression model with only treatment as covariate. Microbiological response at Week 24 was durable in C208 Stage 2: the percentage of responders (missing = failure) at week 72 was 71.2% in the bedaquiline group and 56.1% in the placebo group.

In the Phase 2b uncontrolled trial, C209, treatment with bedaquiline in combination with an individualized MDR-TB treatment regimen was effective against pulmonary MDR-TB both in newly diagnosed and in non-newly diagnosed Subjects. Culture conversion rates after 24 weeks of treatment with bedaquiline as part of an individualized anti-tuberculosis regimen were higher in Subjects with lower extent of resistance of the *M. Tb* strain and in Subjects with no lung cavitation compared to Subjects with cavitations (in one or both lungs).

2.2.1.3. Bedaquiline Clinical Safety

In the clinical studies conducted to date, a total of approximately 645 Subjects (including 265 healthy volunteers) have been exposed to bedaquiline in the Phase 1 and 2 clinical trials conducted as a part of the development program for the treatment of MDR-TB. An additional 60 Subjects received bedaquiline in a monotherapy EBA study of 14 days (study TMC207-CL001) 45 Subjects received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in study NC-001 and 45 more in study NC-003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). In these studies, bedaquiline has been shown to be an effective treatment for Subjects with both DS and MDR-TB. Specifically, the regimen B-Pa-Z was demonstrated to have efficacy at least as good as the HRZE control in study NC-003. Furthermore, bedaquiline is a novel agent with no pre-existing resistance and, based on mouse model data, may result in shortened treatment durations when included in novel regimens to treat both DS- and MDR-TB. Based on the combined experience in these clinical studies, the following known and potential risks have been identified.

Adverse Drug Reactions for bedaquiline

During the Investigational Treatment phase in the controlled trials, the most frequently reported Adverse Drug Reactions in the any bedaquiline group (> 10.0% of Subjects) were nausea, arthralgia, headache, vomiting, and dizziness. Details of Adverse Events, none of which were Serious, that were considered Adverse Drug Reactions are in the table below:

Table 1: Bedaquiline Adverse Drug Reactions

	Investigational Treatment Phase			
	Controlled Trials			
	TMC207		Placebo	
SOC ADR (Grouped term), n (%)	24 Weeks N = 79	Any N = 102	24 Weeks N = 81	Any N = 105
At least grade 3 ADR	*5 (6.3)*	*5 (4.9)*	*0*	*0*
Nervous system disorders Headache	**1 (1.3)** 1 (1.3)	**1 (1.0)** 1 (1.0)	**0** 0	**0** 0
Cardiac disorders ECG QT Prolonged	**0** 0	**0** 0	**0** 0	**0** 0
Gastrointestinal disorders Diarrhea Vomiting	**0** 0 0	**0** 0 0	**0** 0 0	**0** 0 0
Hepatobiliary disorders Transaminases increased[a]	**2 (2.5)** 2 (2.5)	**2 (2.0)** 2 (2.0)	**0** 0	**0** 0
Musculoskeletal and connective tissue disorders Arthralgia	**2 (2.5)** 2 (2.5)	**2 (2.0)** 2 (2.0)	**0** 0	**0** 0

Mortality

Overall, there was an imbalance in the number of deaths in the pooled Stage 1 and Stage 2 C208 trial. In the pooled analysis (Stage 1 and Stage 2), 12 Subjects in the Any bedaquiline group and 5 Subjects in the Any Placebo group experienced a SAE leading to death; causes of death were varied with only death due to TB reported more than once, and none of these Subjects had a treatment-emergent QTcF ≥ 500 ms. The imbalance in deaths is primarily driven by the C208 Stage 2 results in which the imbalance was 10 bedaquiline Subjects (12.7%) compared to 3 placebo Subjects (3.7%). Based on the pooled results (Stage 1 and 2) while being followed in the placebo-controlled trial, 7 Subjects in the Any bedaquiline group and 1 Subject in the Any Placebo group died. Of these deaths, 1 occurred during the Investigational Treatment phase with bedaquiline/placebo, the remaining deaths occurred afterwards. In the Any bedaquiline group, causes of death were myocardial infarction, TB (2 cases), alcohol poisoning, hepatitis and hepatic cirrhosis (1 case), septic shock and peritonitis (1 case), and cerebrovascular accident. In the Any Placebo group, cause of death was hemoptysis. The Investigator considered the SAEs leading to death not related to bedaquiline intake in the Any bedaquiline group and doubtfully related to investigational medication in the Any Placebo group. The analysis of long-term follow-up for survival outcomes in Subjects who prematurely discontinued in trial C208 (Stage 1 and 2), based on data collection every 24 weeks (6 months) after withdrawal (up to LSLV in the rollover arm [16 Oct 2012] in Stage 2), included 9 deaths. One Subject in the bedaquiline group (pulmonary TB) and 2 Subjects in the Placebo group (TB-related illness and pulmonary TB) in Stage 1 died, and 4 Subjects in the bedaquiline group (3 Subjects with TB-related illness, 1 Subject motor vehicle accident) and 2 Subjects in the Placebo group (both TB-related illness) died after they discontinued Stage 2 of the trial. None of these Subjects had a treatment-emergent QTcF ≥ 500 ms. 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, human immunodeficiency virus (HIV) status, or severity of disease was observed.

In the uncontrolled Phase 2b trial, C209, the most frequently reported AEs during the investigational phase were hyperuricemia, arthralgia, nausea, vomiting, headache, diarrhea, blood uric acid increased, hypokalemia, pruritus, injection site pain, insomnia, and tinnitus. From start of the trial up to the final analysis, 12 Subjects died during the C209 trial due to SAEs that included TB (5 cases), congestive cardiac failure, renal impairment, lung infection, cardiac arrest (underlying cause pneumonia), hemoptysis, hypertension, and pyopneumothorax/respiratory failure. All of these SAEs leading to death were considered not related to bedaquiline by the Investigator, except for renal impairment that was judged doubtfully related to bedaquiline.

The analysis of long-term follow-up for survival outcomes for Subjects who prematurely discontinued in trial C209, based on data collection every 24 weeks (6 months) after withdrawal, included 4 deaths (all described as TB-related). In total, since the start of the C209 trial, 16 Subjects (6.9%) have died (12 Subjects during the trial and 4 Subjects during the survival follow-up phase after premature discontinuation). None of the fatal SAEs were considered related to bedaquiline by the Investigator and none of these Subjects has a treatment-emergent adverse event.

Cardiovascular safety

During clinical trials with bedaquiline a prolongation of QTc interval was observed. The US Product Label for bedaquiline[3] notes that treatment initiation is not recommended in patients with:

- Heart failure;
- QTcF interval > 450 ms (confirmed by repeat electrocardiogram);
- A personal or family history of congenital QT prolongation;
- Concomitant administration of fluoroquinolone antibiotics that have a greater potential for significant QT prolongation (i.e., gatifloxacin, moxifloxacin and sparfloxacin).
- Hypokalemia

The US Product Label recommends that bedaquiline treatment must be discontinued if the patient develops clinically significant ventricular arrhythmia. An additive or synergistic effect on QT prolongation of bedaquiline when co-administered with other medicinal products that prolong the QT interval cannot be excluded. Caution is recommended when using bedaquiline concomitantly with medicinal products with a known risk of QT prolongation. In the event that co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

Hepatic safety

The US product label notes increases in transaminases were seen in clinical trials during administration of bedaquiline with the background regimen. Subjects should be monitored during treatment. Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in those Subjects with diminished hepatic reserve[3].

Additional safety information from a recently completed trial

In a recently completed phase I study not yet included in the bedaquiline Investigators Brochure that evaluated drug-drug interactions between bedaquiline and either rifampin or rifabutin, 7 Subjects experienced SAEs. Of those Subjects, 5 experienced SAEs of lymphocytopenia (all received rifabutin), which did not appear to be related to the AUC or C_{max} of TMC207 or rifabutin. One subject experienced an SAE of elevated Creatine Kinase (rifampicin arm) and one experienced a grade 4 Total Bilirubin SAE (rifampicin arm). Lymphopenia was previously noted to be an infrequent toxicity associated with rifabutin, but not previously seen with bedaquiline. The

bedaquiline/rifabutin regimen demonstrated significant reversible lymphopenia, which did not appear to be related to the AUC or C_{max} of TMC-207 or rifabutin.

2.2.2. Pretomanid

As detailed in the Investigator's Brochure[15], pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazo-oxazines, which possess significant anti-tuberculosis activity and a unique mechanism of action[16]. Pretomanid demonstrated *in vitro* activity against both DS- and MDR-TB[17], and *in vivo* activity in a mouse model of tuberculosis[16,17].

Pretomanid has been studied in four 14-day EBA trials to date, including two monotherapy dose-ranging studies and two combination EBA studies. Pretomanid monotherapy has demonstrated substantial mycobactericidal activity. The efficacy data from study PA-824-CL-007 indicated that all doses of pretomanid (200, 600, 1000 and 1200 mg) produced an equivalent decrease in sputum CFU counts over the 14-day treatment period. In study PA-824-CL-010, an EBA study with a similar design to study PA-824-CL-007 except for the use of lower doses of pretomanid (50, 100, 150 and 200 mg/day), results indicated that pretomanid treatment resulted in a measurable dose-dependent mycobactericidal activity over the dose range studied, and supported a clinical dose of 200mg per day. In study NC-001-(B-M-Pa-Z) an EBA study with multiple treatment combinations, the three drug combination of pretomanid (200 mg per day), moxifloxacin and pyrazinamide (Pa-M-Z) demonstrated potential as a treatment shortening regimen and was progressed into an 8 week "SSCC" study (NC-002) in which the combination was shown to be statistically better that the HRZE control on some measures of activity. In the second 14-day combination EBA study (NC-003), the bedaquiline, pretomanid and pyrazinamide (B-Pa-Z) regimen showed promising activity and has been selected to move forward in development and is the focus of an 8-week study in patients with DS and MDR-TB (NC-005) that will be initiated in 2014.

2.2.2.1. Pretomanid Preclinical Studies

Microbiology

In vitro studies have demonstrated that the minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive *M. tb.* isolates is similar to the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of *M. tb.,* with MIC values ranging from 0.03 to 0.53 µg/mL. The minimum effective dose (MED) of pretomanid was 12.5 mg/kg/day in a mouse model of TB. The MED is defined as the lowest dose able to prevent the development of macroscopic lung lesions and splenomegaly. The minimum bactericidal dose (MBD) was 100 mg/kg/day in the same mouse model. The MBD is defined as the lowest dose able to reduce the lung TB colony forming unit (CFU) counts by 99%. The magnitude of CFU reduction by pretomanid at this dose is similar to that seen with the highest dose of isoniazid tested in the same study (25 mg/kg/day).

Nonclinical Safety Studies

The non-clinical safety evaluation of pretomanid includes pharmacology, pharmacokinetics, toxicology and metabolism studies that were conducted in accordance with current ICH guidelines.

Pretomanid was negative in all genotoxicology studies performed. One of its metabolites (M50) that is found in rat, monkey, and human plasma was positive in a screening Ames assay. M50 is not a major metabolite in humans and the exposure relative to parent drug is higher in the rat (24%) and monkey (18%) than in humans (6%).

Pretomanid-induced effects in respiratory, CNS, and cardiovascular safety pharmacology studies were generally mild and reversible; effects were most prominent at 450 mg/kg/day. Pretomanid is a weak inhibitor (IC_{50}=20µM) of the hERG channel. In a telemetry monkey study, in the dose range 50-450 mg/kg, there was no or minor

prolongation of the QT interval, depending on the method of correction. The weight of evidence suggests that there should be no effect on QT in the dose range being explored in the clinical studies.

Repeat-dose toxicology studies with pretomanid have been conducted in male and female rats (14 days to 6 months), and in male and female monkeys (7 days to 3 months). In all studies, dose-dependent reduced food consumption and reduced weight gain or weight loss were noted. In addition, testicular atrophy was observed in rats while cataracts were observed by indirect ophthalmoscopy in both rats and monkeys. In general, toxicity in both rat and monkey was significantly greater when exposures exceeded approximately 300 µg•hr/mL in the 14-day studies and approximately 200 µg•hr/mL in the 3-month studies.

Reproductive toxicology studies show that pretomanid is not teratogenic in rats or rabbits. In the rat fertility study, dose-dependent reduced fertility rates, due to decreased sperm numbers and decreased motility, were observed at doses of 30 mg/kg and greater. This effect was partially reversible. As in the 3-month rat toxicology study, irreversible testicular lesions were not observed at 30 mg/kg, only at 100 and 300 mg/kg.

To more fully characterize the cataract and male reproductive system findings, a 3-month monkey study in sexually mature males (0, 50, 150, 300 mg/kg/day), and a 6-month rat study (0, 30, 100, 300 mg/kg) in males and females were conducted. Ocular assessments were conducted in a much more careful and systematic manner than in the initial 3-month toxicology studies described above. In each of the later studies, all ophthalmologic examinations were conducted by a single ophthalmologist, using both indirect ophthalmoscopy and slit-lamp biomicroscopy. Animals were screened before dosing to ensure no animal had cataracts at baseline, and then monthly during dosing and recovery. In this monkey study, although similar drug exposures were attained as in the original 3 month monkey study, no cataracts or testes effects (semenology, organ weights, histopathology, or hormones [testosterone, follicle-stimulating hormone, Inhibin B]) were observed at any point during dosing or during a 20-week recovery period. Pretomanid does not appear to cause cataracts or testicular toxicity in monkeys. In the 6-month rat study, pretomanid caused irreversible cataracts at 100 mg/kg from Day 118 of the study in males and females. In contrast to the original 3-month rat report, rats in this more carefully conducted study developed cataracts while on drug but not during recovery. The NOAEL was 30 mg/kg for cataracts and 10 mg/kg for testicular toxicity. Rats that developed cataract and testicular toxicity also experienced marked decreases in body weight gain and food consumption. The AUC safety multiples (relative to the exposures obtained at the anticipated clinical dose of 200 mg/day) for cataract are ~1.5x in the rat; in the monkey at the highest dose tolerated, where there were no cataracts in the second well conducted study, the multiple is at least 3.7x.

To summarize, cataracts have been detected in multiple animals from two similar rat studies at mid-to-high doses. In contrast, the finding of cataracts in one monkey study could not be confirmed in a follow-up study. Thus, both cataracts and the testicular effects appear to be species-limited.

An overall summary of the findings from animal safety and toxicology studies is contained in Table 2.

Table 2: Pretomanid Key Animal Safety and Toxicology Findings

• Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behavior at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
• Testicular toxicity Testicular degeneration/atrophy, occurred in rats with repeated doses of pretomanid at ≥30 mg/kg/day but did not occur in monkeys at any dose level. Testicular effects showed evidence of being partially reversible, albeit very slowly, in rats dosed for 7 days, but not in rats dosed for 14 days. As would be expected, there was a dose-related decrease in fertility in male rats at ≥30 mg/kg/day that was associated with decreased sperm numbers and motility. This effect on fertility in male rats was partially reversible.
• Cataracts Cataracts developed with prolonged daily dosing in rats at pretomanid 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 Pretomanid inhibited hERG current with IC_{50} 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.

2.2.2.2. Pretomanid Clinical Studies

Phase 1

The safety, tolerability and pharmacokinetics of pretomanid have been studied in 10 Phase 1 studies, which are summarized in Table 3. In these trials, pretomanid has been administered in doses ranging from 50 to 1500 mg, as 50 or 200 mg tablets or as an oral suspension. PK parameters have largely been consistent in each study and can be summarized as follows:

- Pretomanid is moderately rapidly absorbed, with median T_{max} values across Subjects and dose levels ranging from 4 to 7 hours.
- The mean half-life for elimination ($t_{½}$) across Subjects and dose levels was approximately 16 - 25 hours.
- Exposure increased approximately linearly but less than dose-proportionally, with increasing doses up to approximately 600 – 1000 mg, while higher doses achieved minimal additional increases in either C_{max} or AUC.

Two studies using radiolabeled pretomanid in an oral-suspension formulation have been conducted to investigate the metabolism and excretion patterns of pretomanid in humans: Study PA-824-CL-004, which used [benzyl-^{14}C] pretomanid and Study PA-824-CL-008, which used [imidazooxazine-^{14}C] pretomanid. The mass balance results from the two studies were very similar. In each study, the majority (53-65%) of radioactivity was excreted in the urine; an additional 26-38% was collected in the feces such that approximately 91% of the administered dose was ultimately recovered in the excreta.

Radioprofiling and metabolite identification work have been completed on samples from the two human studies as well as from analogous work in rat and monkey using both radiolabeled pretomanid preparations. The metabolism of pretomanid proceeds via a combination of reductive metabolism (~20 – 25% of the dose) and oxidative metabolism (remainder of the characterized metabolites). The metabolic profile of pretomanid *in vivo* was qualitatively similar in the three species, with quantitative differences being minor. No human unique metabolites were detected and there is no one single metabolic path that can be considered major. Furthermore, there are no major metabolites in human plasma.

Study PA-824-CL-006, a drug-drug interaction study with midazolam to assess the extent of CYP3A inhibition by pretomanid, results indicate that dosing of pretomanid 400 mg once daily for 14 days did not have a major effect on the exposure of midazolam or its major metabolite 1-hydroxy midazolam. For midazolam, the geometric mean ratio of Day 17 (midazolam+pretomanid) vs. Day 1 (midazolam alone) for C_{max} was 0.84 and AUC was 0.85. For the 1-hydroxy midazolam metabolite, the corresponding geometric mean ratio for Cmax was 1.05 and AUC was 1.11. The data suggests that pretomanid does not cause clinically significant drugs interactions with drugs metabolized by CYP3A.

Two additional studies have recently been completed and are currently undergoing analysis: Study DMID 10-0058 (a Thorough QT study comparing pretomanid and pretomanid plus moxifloxacin to moxifloxacin alone) and Study ACTG 5603 (a drug-drug interaction study evaluating the effects of concomitantly administered Efavirenz, Ritonavir-Boosted Lopinavir or rifampicin on the PK parameters of pretomanid). The first study found that single doses of pretomanid of 400mg and 1000mg did not have a clinically significant effect on the QTc interval, and when pretomanid at 400mg is co-administered with moxifloxacin (400mg) it did not increase the QTc prolongation substantially over what is seen with moxifloxacin alone. The second study found that when administered with Efavirenz, Ritonavir-Boosted Lopinavir, or Rifampicin, pretomanid (200mg) median pretomanid concentrations ($AUC_{0\text{-}24h}$) were reduced 35% by EFV, 17% by LPV/r, and 66% by rifampin. The clinical significance of these findings requires further investigation.

Study PA-824-CL-009, a food effects study pretomanid (200 mg and 50 mg); results indicate that the food effect observed is dependent on the pretomanid dose administered. When a single dose of pretomanid was administered with a high fat, high calorie meal, C_{max} and AUC of the 50 mg dose increased 1.40-fold and 1.45-fold respectively, whereas for the 200 mg dose, C_{max} increased 1.76-fold and AUC increased 1.88-fold.

Table 3: Pretomanid Phase 1 Clinical Studies

Study	Design	Pretomanid Dose	Enrolled	Key Findings
CL-001	Double-blind, placebo-controlled, single-dose, dose-escalating, PK and safety study	0, 50, 250, 500, 750, 1000, 1250, 1500	53	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE.
CL-002	Double-blind, placebo-controlled 7-day multidose, escalating, PK and safety study	0, 200, 600, 1000	24	• Well tolerated; no effects on ECG, vital signs, or PE. • After 5 days' dosing at 1000 mg/d, progressive moderate creatinine elevation: reversed during 7-day washout period. • No consistent effect on BUN. • A planned 1400-mg cohort not enrolled.
CL-003	Open-label, single-dose, food effects	1000	16	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • Treatment-emergent AEs affecting more than one Subject occurred more frequently after dosing in the fed condition than the fasted condition, and more frequently among women than men. • Bioavailability is 3.5-to-4.5-fold higher when pretomanid is administered within 30 minutes of a high-fat, high-calorie meal than when it is administered after an overnight fast.
CL-004	Open-label, single-dose, ADME	~860, oral suspension [benzyl-^{14}C]pretomanid	6	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • No significant radioactivity captured as [benzyl-^{14}C]CO_2. • ~91% of dose recovered (~65% in urine; ~26% in feces) • Plasma: parent drug and one major metabolite. • Urine: little or no parent drug; multiple major metabolites. • Feces: minimal unchanged parent drug; numerous low-abundance metabolites.

Study	Design	Pretomanid Dose	Enrolled	Key Findings
CL-005	Double-blind, 8-day multidose, renal effects	0, 800, 1000	47	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • As anticipated, serum/plasma creatinine levels increased significantly (up to ~ 40%) during treatment; reversed during 7-day washout period. • No effect during treatment on GFR, ERPF, FF, BUN or UA.
CL-006	Open-label, multidose, DDI	400	14	• Well tolerated; no dose-limiting AEs. • For midazolam, the geometric mean ratio of Day 17 (midazolam+Pa-824) vs. Day 1 (midazolam alone) for C_{max} was 0.84 and $AUC_{(0\text{-infinity})}$ was 0.85. • For the 1-hydroxy midazolam metabolite, the corresponding geometric mean ratio for Cmax was 1.05 and $AUC_{(0\text{-infinity})}$ was 1.11.
CL-008	Open-label, single-dose, ADME	~1100, oral suspension [imidazooxazine-^{14}C] pretomanid	6	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • No significant radioactivity captured as [imidazooxazine-^{14}C] CO_2. • ~91% of dose recovered (~53% in urine; ~38% in feces) Plasma: parent drug. Urine: little or no parent drug; multiple major metabolites. • Feces: unchanged parent drug and numerous low-abundance metabolites.
CL-009	Open-label, single-dose, food effects	50 and 200	32	• Well tolerated; no dose-limiting AEs. • In the presence of high fat, high calorie diet, C_{max} and AUC of the 50-mg dose increased 1.40-fold and 1.45-fold respectively, whereas for the 200-mg dose, C_{max} increased 1.76-fold and AUC increased 1.88-fold.
A5306	Antiretroviral DDI	200	48	• Based on preliminary data – the study is currently undergoing analysis. • Co-administration with Efavirenz resulted in a 35% reduction in pretomanid AUC. • Co-administration with Ritonavir-Boosted Lopinavir resulted in a 17% reduction in pretomanid AUC. • Co-administration with rifampicin resulted in a 66% reduction in pretomanid AUC.

Study	Design	Pretomanid Dose	Enrolled	Key Findings
10-0058	Thorough QT Study	400 and 1000	75	• Pretomanid, alone and in combination with moxifloxacin, was well tolerated. • Pretomanid doses of 400 mg and 1000 mg did not cause QT interval prolongation to a level of clinical concern as the upper limit of the 90% CI associated with any LS mean ΔΔQTcI value did not exceed 4.4 ms for the 400-mg dose or 6.1 ms for the 1000-mg dose, and both were well below 10 ms. • The effect of pretomanid 400 mg plus moxifloxacin 400 mg on QTcI was similar to the effect of moxifloxacin administered alone. • No Subject receiving pretomanid or moxifloxacin alone had an observed QTcI value that exceeded 450 ms or experienced a change-from-baseline in QTcI that exceeded 30 ms. • The PK of pretomanid was not affected by the co-administration of moxifloxacin.

- **Phase 2**

Study PA-824-CL-007, a 14 day monotherapy EBA study, indicated that all doses of pretomanid (200, 600, 1000 and 1200mg a day) produced a measurable and equivalent decrease in sputum CFU counts over the 14-day treatment period. Study PA-824-CL-010 was an EBA study with a similar design to study PA-824-CL-007 except for the use of lower doses of pretomanid (50, 100, 150 or 200 mg/day). Results indicate that pretomanid treatment resulted in a measurable dose-dependent mycobactericidal activity, with the 50 mg dose demonstrating less activity than the 100, 150 and 200 mg doses, which were all equivalent.

Study NC-001-(B-M-Pa-Z) was a 14 day EBA study that assessed the two-week EBA of the following drug combinations: pretomanid plus pyrazinamide, pretomanid plus pyrazinamide plus moxifloxacin, along with two other non-pretomanid containing combinations. Results indicate that the three drug combination of pretomanid (200 mg per day), moxifloxacin and pyrazinamide has potential as a treatment shortening regimen. In the study this three drug combination has an EBA 0-14, which is believed indicative of sterilizing activity, numerically better than the current 4-drug intensive phase treatment of HRZE.

The recently completed Phase 2b study, NC-002, was a multi-center open-label partially randomized clinical trial with four treatment groups. Subjects with drug-sensitive TB were randomized to receive moxifloxacin 400 mg plus PA-824 100 mg plus pyrazinamide 1500 mg (M-PA100-Z) or moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg (M-PA200-Z) or standard HRZE therapy. HRZE was included as a control arm for the drug-sensitive treatments and for the laboratory methodology. Subjects with MDR-TB received moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg (M-PA200-Z MDR). The study population included a total of up to 230 male and female newly diagnosed Subjects with drug-sensitive or multi drug-resistant, smear positive pulmonary tuberculosis aged 18 to 65 years (inclusive). The primary efficacy endpoint was the rate of change in the logarithm of colony forming unit (CFU) (or log[CFU]) count) over 8 weeks of treatment analysed by a Joint Bayesian Non-linear Mixed Effect (NLME) regression.
Preliminary analyses of NC-002 indicate that a total of 207 Subjects were enrolled, with 60 randomized to M-PA100-Z, 62 randomized to M-PA200-Z, and 59 to HRZE. An additional 26 Subjects were treated in the M PA200-Z MDR-TB arm. Of note, more Subjects in the MDR-TB arm did not complete the full 8 weeks of treatment, primarily because many were withdrawn as late-exclusions (*M. Tb* resistant to pyrazinamide determined in culture after enrollment in the study). Twenty-one MDR-TB Subjects were in the study with active treatment through day

14 and 10 were in the study through the full 8 weeks of treatment (9 with evaluable results for the primary microbiological endpoint). In contrast, the following number of Subjects in the study with active treatment through 8 weeks in the 3 randomized arms with evaluable results for the primary microbiological endpoint: 55 in the M-PA100-Z arm, 54 in the M-PA200-Z arm and 54 in the HRZE arm. For the primary endpoint, Subjects in the M-PA200-Z arm had a statistically significantly greater decline in the log CFU count over the 8 weeks, than the Subjects in the HRZE arm. Finally, pretomanid has recently been studied in combination with bedaquiline and other agents in a 2 week EBA study (NC-003).

Table 4: Pretomanid Phase 2 Studies

Study	Design	Pretomanid Doses	Enrolled	Key Findings
CL-007	Partially double-blinded (blinded as to pretomanid dose), 14-day multidose, extended early bactericidal activity.	200, 600, 1000, 1200	69	• Overall well tolerated with relatively few AEs and no dose-limiting AEs or laboratory findings. No clinically significant effects on ECG, vitals, or PE noted. • Two SAEs occurred during study, both were considered possibly related to TB disease (hemoptysis). • Pretomanid treatment produced a measurable decrease in log CFU, with the magnitude of effect equivalent for all doses.
CL-010	Partially double-blinded (blinded as to pretomanid dose), 14-day multidose, extended early bactericidal activity.	50, 100, 150, 200	69	• Well tolerated. • Pretomanid treatment produced a measurable decrease in log CFU with some evidence of dose dependence.
NC-001	Partially double-blinded (blinded as to combination within Pa or B containing arms), 14-day multidose, extended early bactericidal activity.	200	85	• Well tolerated. • Pretomanid plus moxifloxacin plus pyrazinamide combination treatment produced a decrease in log CFU at least comparable to that of the Rifafour e-275® control group.
NC-002	Multi-center open-label partially randomized clinical trial in four treatment groups. Subjects with drug-sensitive TB randomized to receive moxifloxacin 400 mg plus pretomanid 100 mg plus pyrazinamide 1500 mg or moxifloxacin 400 mg plus pretomanid 200 mg plus pyrazinamide 1500 mg or Rifafour e-275®.	100, 200	207	Based on preliminary results: • For the primary endpoint Subjects in the M-PA200-Z arm had a statistically significantly greater decline in the log CFU count over the 8 weeks than the Subjects in the HRZE arm. • Well tolerated overall. • Eleven serious adverse events (SAEs) were reported in 9 Subjects, with one Subject in each of the M-PA100-Z and the Rifafour® groups, and 7 Subjects in the M-PA200-Z group.

Study	Design	Pretomanid Doses	Enrolled	Key Findings
NC-003	Multi-center, open-label, randomized clinical trial with seven parallel treatment arms. Fifteen Subjects were enrolled in each of the following treatment arms: TMC207 plus pretomanid plus pyrazinamide plus clofazimine, TMC207 plus pretomanid plus pyrazinamide, TMC207 plus pretomanid plus clofazimine, TMC207 plus pyrazinamide plus clofazimine, pyrazinamide alone, clofazimine alone, and Rifafour e-275®.	200	105	• Among the regimens studied, the combination B-PA-Z demonstrated the highest EBA, with results at least comparable to the HRZE control. • The treatments administered in this trial were well tolerated by the trial population. • No deaths were reported in this trial. Serious AEs were reported for 1 Subject (1.0%) in the clofazimine alone arm: gastroenteritis, anemia, and deep vein thrombosis (none of which were considered to be related to the treatment).

2.2.2.3. Pretomanid Clinical Safety

Across the 15 clinical studies with pretomanid completed to date, a total of 649 Subjects have been exposed to pretomanid, including 289 healthy Subjects across the 10 Phase 1 studies and 360 Subjects 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 Subjects 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 and/or clofazimine) at a dose of 100 mg or 200 mg for up to 56 days. The overall safety profile determined from the clinical studies completed to date indicates pretomanid is well tolerated in healthy adults and in TB Subjects when administered alone and in combination with moxifloxacin, pyrazinamide, bedaquiline and clofazimine.

In the Phase 1 studies in healthy volunteers the most common side effects or AEs associated with pretomanid exposure include:

- Headache;
- Benign, isolated and reversible elevations of serum creatinine;
- Stomach discomfort (nausea, vomiting, flatulence, and/or diarrhea);
- Skin and subcutaneous tissue disorders.

Key safety considerations of special concern, based on preclinical or clinical findings in the program to date, are noted below and will be under close scrutiny in future trials:

Cataracts

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 Nix-TB. These examinations are to follow up on the finding of cataracts in rats exposed to pretomanid in preclinical studies.

Testicular Toxicity

Clinical evaluations of potential testicular toxicity in NC-002 failed to demonstrate any effect, based on evaluations of testosterone, LH and FSH values at baseline and after 2 months of daily dosing of the M-Pa-Z regimen. However to follow up on findings in the male rat of testicular toxicity, all male subjects in the upcoming Phase 3 trial of the M-Pa-Z regimen will have evaluations of male hormones, and a substudy will evaluate changes in semen and sperm parameters in a subset of patients receiving the regimen over 6 months.

Central Nervous System

The pretomanid pre-clinical program identified potential CNS-related toxicities and one Subject treated with pretomanid in clinical study NC-002 experienced a seizure while on treatment. Close surveillance will be in place to identify any seizures or significant central nervous system (CNS) signs or symptoms during the Nix-TB study.

Hepatic Safety

Hepatic enzyme increases have been seen in Subjects treated with pretomanid in combinations with various other medications during the clinical development program. It is difficult to assign specific causality to any one drug within a regimen; nonetheless, the Nix-TB will include specific monitoring of hepatic enzymes.

Detailed Safety Findings in Pretomanid Clinical Development

In Phase 1 trials at the clinical dose of 200mg or lower, the incidence of headache was approximately 20-30% and similar to placebo. At doses of 800mg and higher, usually in trials without a placebo or comparator arm, the incidence of headache reached 80%. Headache occurrence was typically higher in studies with longer confinement periods. Throughout the development program, other common TEAEs include elevated serum creatinine, stomach discomfort (including nausea and other gastrointestinal symptoms such as flatulence and/or diarrhea), and skin and subcutaneous tissue disorders (including erythema, pruritus and rash). Skin and subcutaneous tissue disorders, followed by stomach discomfort were the most commonly reported TEAEs in the Phase 2 monotherapy studies (PA-824-CL-007 and PA-824-CL-010). Within Study PA-824-CL-007, a higher incidence of pretomanid TEAEs were observed in the higher pretomanid dose groups (pretomanid 200 mg: 7%; pretomanid 600 mg: 13%; pretomanid 1000 mg: 31%; and pretomanid 1200 mg: 33%). The incidence of the TEAEs in the Rifafour® treated group was 25%. Study PA-824-CL-010, among the four pretomanid treatment groups (50 mg, 100 mg, 150 mg, and 200 mg) and the Rifafour® treatment group, a higher incidence of TEAEs was observed in the 50mg pretomanid group (66.7%) when compared with Rifafour® (50.0%) and the other pretomanid treatment groups. For the multidose, placebo-controlled Studies PA-824-CL-002 and PA-824-CL-005, overall AE frequency tended to be greater among pretomanid Subjects than among placebo Subjects, and tended to be higher in higher pretomanid dose groups.

Study PA-824-CL-005 was undertaken to determine the mechanism responsible for the elevation in serum creatinine seen with pretomanid dosing in studies PA-824-CL-001 and PA-824-CL-002. This study explored the effects of pretomanid on kidney function by measuring glomerular filtration rate (GFR), effective renal plasma flow (ERPF), filtration fraction (FF, calculated as GFR/ERPF), and creatinine clearance. Subjects were dosed in blinded fashion with placebo, 800 mg pretomanid, or 1000 mg pretomanid for 8 days. Serum creatinine levels rose in both the 800- and 1000-mg/day pretomanid groups, by an average of 0.18 mg/dL (19%) and 0.25 mg/dL (27%) in the two groups respectively by Day 8; the largest individual increase was approximately 40% over baseline. In this study, although serum creatinine levels rose, no meaningful effects were noted during the dosing period on GFR, ERPF, BUN, uric acid or FF. As expected, creatinine clearance was reduced concomitantly with maximally elevated serum creatinine levels relative to baseline. Taken together, these results indicate that pretomanid does not negatively affect renal function. Instead, the drug can be assumed to cause its effects on serum creatinine by inhibiting tubular creatinine secretion; such an effect has been reported with other approved drugs (e.g. cimetidine) and is not considered clinically significant.

Across all studies, the great majority (>~95%) of AEs resolved without sequelae. In Study PA-824-CL-005, one Subject treated with 800 mg pretomanid was discharged with three ongoing AEs (proteinuria [nephrotic range during the study, but non-nephrotic range in follow-up], hypoalbuminemia, and iron deficiency). The proteinuria and hypoalbuminemia were moderate in severity and the iron deficiency was mild. This Subject substantially improved, and the Subject is seen periodically by a nephrologist. A renal biopsy performed 20

months post-study revealed focal segmental glomerulosclerosis likely secondary type, although the Subject remains fundamentally healthy with normal renal function indices and no signs of peripheral edema or hypertension. A complete review of her screening and check-in laboratory values suggests, in the opinion of the Sponsor, that she might have had a pre-existing undiagnosed clinical condition including atypical lipid profile, BUN below the lower limit of the normal range, and ALT and AST above the upper limit of normal range. Furthermore, her eosinophil count was above-normal at Screening at 6.7% and progressively rose during the study to 8.9% by Day 15 and she reported a personal and family history of allergies and rhinorrea. The Investigator considered this individual normal and meeting the protocol entry criteria, and enrolled this Subject.

In most of the completed Phase 2 studies, no Subjects discontinued from the study as a result of AEs. In Study PA-824-CL-002, dosing for all Subjects in the 1000 mg dose group was discontinued on Day 5 in response to rising serum creatinine levels. In Study PA-824-CL-005, one Subject was discontinued for safety reasons in relation to a severe rash that developed approximately 32 hours after the 8th and last dose of pretomanid (1000 mg). The rash symptoms were treated with diphenhydramine, prednisone, and hydroxyzine at various points during the ensuing approximately 9 days until the symptoms completely resolved. In Study PA-824-CL-007, two Subjects (one in the 200 mg/day pretomanid group and one in the control arm) were discontinued as a result of disease-related hemoptysis. Each of these events was classified as an SAE, both resolved with treatment in hospital and neither was considered possibly related to the study drugs. In Study PA-824-CL-010, one Subject was withdrawn due to the SAE of pneumothorax after 4 days' dosing, which resulted in hospitalization and later resolved. The SAE was deemed related to the Subject's concurrent tuberculosis and unrelated to pretomanid.

Post-study follow-up ophthalmic examinations were performed on Subjects and Subjects enrolled in two studies (PA-824-CL-005 [n=30] and PA-824-CL-007 [n=46]) where Subjects received the highest doses of pretomanid for the longest duration among the clinical studies conducted to date. Male and female healthy volunteers were treated at doses up to 1000 mg/day for 8 days in study PA-824-CL-005, and male and female TB Subjects were treated at doses up to 1200 mg/day for 14 days in study PA-824-CL-007. Two ocular events were reported, one cataract was among the 12 Subjects from the 1200 mg pretomanid group in study PA-824-CL-007 and the other cataract was from among the 5 Subjects within the HRZE group.

In NC-001-(B-M-Pa-Z), five Subjects were discontinued prior to completion of their treatment with a pretomanid containing arm. One Subject receiving pretomanid (200mg), moxifloxacin (400 mg), and pyrazinamide (dosed by weight) experienced an SAE considered by the Investigator unrelated to the drug combination. The SAE consisted of convulsion as well as aggressive and violent behaviours. After a CT scan, the Subject was diagnosed with neurocysticercosis. A second Subject receiving pretomanid (200mg), moxifloxacin (400 mg), and pyrazinamide (dosed by weight) was withdrawn on Treatment Day 5 based on a protocol specified criterion of an increase from baseline in QTcF and QTcB greater than 60 msec on repeated ECGs and accompanied by clinically relevant T-wave morphology changes. On Day 5, the Subject had prolonged QTc values (>60 msec) on the pre-dose ECG; however, on repeat ECGs, the QTc values stabilized satisfactorily. Five hours post-dose on Day 5, ECG QTc values were again increased (>60 msec) from baseline and repeat ECGs also revealed T-wave changes. The Subject was, therefore, withdrawn from the study as specified in the protocol. In addition, two Subjects receiving pretomanid (200mg), and pyrazinamide (dosed by weight) were withdrawn due to Grade 3 ALT levels, although the elevation in ALT in one of these Subjects occurred prior to the first dose of study medication. One Subject receiving pretomanid (200 mg) and bedaquiline (400 mg) was withdrawn due to a Grade 3 ALT elevation. Overall in the trial, 53% of the 15 Subjects in the pretomanid + pyrazinamide treatment arm experienced treatment-emergent adverse events, as compared with 53% of the 15 Subjects in the pretomanid + pyrazinamide + moxifloxacin arm and 25% of the 8 Subjects in the HRZE (control) arm. All of these adverse events were rated by the Investigator as mild or moderate. 7% of Subjects in the pretomanid + pyrazinamide treatment arm experienced liver enzyme elevations, as compared with 20% of Subjects in the

pretomanid + pyrazinamide + moxifloxacin arm and 0% in the Rifafour® arm, accounting for most of the imbalance between groups. All liver enzyme elevations were < 3x ULN except for two cases.

Also in NC-001-(B-M-Pa-Z), changes in QT interval were assessed pre-dose and at 2hrs and 5 hrs post-dose on each day of the study for the pretomanid + pyrazinamide and pretomanid + pyrazinamide + moxifloxacin treatment arms. On Day 14, the last dosing day, no Subject in either treatment group had a corrected QT interval (QTcF) > 450 msec. One Subject in the pretomanid + pyrazinamide arm had a QTcF increase of between 30 and 60 msec; no Subject had a QTcF increase > 60 msec. No Subjects in the pretomanid + pyrazinamide + moxifloxacin had a QTcF increase > 30 msec.

Safety Findings in 8-Week Study NC-002

Preliminary data analyses of the study NC-002 indicate that a total of 207 Subjects were enrolled, with 60 randomized to M-PA100-Z, 62 randomized to M-PA200-Z, and 59 to HRZE. An additional 26 Subjects were treated in the M-PA200-Z MDR-TB arm. In this study 88% of all Subjects had a treatment emergent adverse event (TEAE), including 87% in the M-PA100-Z group, 92% in the M-PA-Z group, 85% in the HRZE group and 89% in the M-PA-Z MDR-TB group. Adverse events were graded according to the NIH Division of Microbiology and Infectious Diseases Adult Toxicity Table.

Eleven serious adverse events (SAEs) were reported in 9 Subjects, with one Subject in each of the M-PA100-Z and the HRZE groups, and 7 Subjects in the M-PA200-Z group. The Subject in the M-PA100-Z group died of an unknown cause 39 days after a single dose of study drug regimen and the death was not considered related to study drug by the Investigator or the Sponsor. Four other SAEs were considered not related to study drug, including a pneumothorax, a bone fracture, dyspnea requiring hospitalization, and second degree heart block considered on evaluation to be existing prior to entry in to the trial. SAEs considered possibly related or related to the study drug regimen included hyperuricemia likely secondary from pyrazinamide, drug-induced hepatitis and elevated liver enzymes. One Subject had an episode of agranulocytosis that resolved after the study drug regimen was stopped and one Subject had a seizure witnessed by the family and was discontinued from the study.

The protocol required that Subjects with hepatic enzyme ALT or AST elevations greater than 3X the Upper limit of Normal (ULN) must have study drug discontinued. Consequently, 25 Subjects were withdrawn from the study across the study arms for elevations in hepatic enzymes. The distribution of elevations in ALT across the study arms is presented in Table 5. While more Subjects in the M-PA200-Z group had elevations in ALT >3 – 5X ULN, those with elevations >5X ULN or >8X ULN were fairly evenly distributed across the groups of Subjects with drug-sensitive *M. tb*.

Table 5: NC-002 Elevations in Alanine Aminotransferase

ALT	Statistic	M-PA100-Z (N=60)	M-PA200-Z (N=62)	HRZE Control (N=59)	M-PA200-Z MDR (N=26)
> 3X ULN	N (%)	7	10	5	3
> 5X ULN	N (%)	4	5	4	2
> 8X ULN	N (%)	2	4	3	1

Note: Groups are not mutually exclusive: >3X includes >5X and >8X; >5X includes >8X

Ophthalmologic Evaluations

All Subjects received ophthalmologic evaluations using the AREDS2 grading system across a range of 0-4 including visual acuity testing and slit lamp examinations at baseline and 3 months after completion of study drug dosing. All Subjects enrolled with the required zero score grade for all regions of the lens except for 1 Subject who was blind in one eye. Among all Subjects in the trial, 4 Subjects had lens evaluations with a grade of greater than zero. One Subject in the M-PA100-Z group and 3 Subjects in the M-PA200-Z group had grades of 0.5 or 1.0 in a single eye in one of the 3 zones of the lens. It is unlikely these findings represent a drug-induced lens opacity given the low incidence, the unilateral nature of all findings and the differing zone locations of the findings. It is common in persons with no clinical abnormalities to have grades of 0.5 – 1.0+ in the AREDS2 rating on a slit lamp evaluation.

Reproductive Hormone Evaluations

In study NC-002 men were evaluated with plasma samples for the reproductive hormones LH, FSH and Testosterone at baseline and at the end of the dosing period. If the study drug regimen caused testicular toxicity, the most sensitive measure from these hormones would be an increase in levels of FSH. Among Subjects in the M-PA100-Z group the mean baseline FSH was 9.027 U/L which decreased to 8.338 U/L at the end of therapy. Among Subjects in the M-PA200-Z group the mean baseline FSH was 6.531 U/L at baseline and this decreased to a mean of 6.061 at the end of therapy. Men in the Rifafour® group had a mean baseline of 7.394 U/L which decreased to 6.714 at the end of therapy. This gives relative reassurance that the M-Pa-Z regimen is not likely to cause testicular toxicity in men.

Electrocardiographic Conduction Interval Changes

Subjects in NC-002 had supine resting ECGs taken at baseline, Day 4 and weekly through the 8 week dosing period and 2 weeks after the end of dosing. All ECGs were read by a central cardiology service. No Subjects had a corrected QT interval (QTcF) greater than 500 msec during the study. A small number of Subjects had asymptomatic increases in QTcF from baseline over 60 msec: Two in the M-PA100-Z group, 4 in the M-PA200-Z group, none in the Rifafour® group and 2 in the M-PA200-Z MDR group. An evaluation of the mean change from baseline across all post-baseline ECGs notes increases of 11.1 msec in the Rifafour® group, 11.1 in the M-PA100-Z group, 17.8 msec in the M-PA200-Z group and 6.7 in the M-PA200-Z MDR-TB group. Of note, many Subjects were tachycardic at baseline with their active pulmonary *M. tb.* and had heart rates decrease over the first week of therapy. This fact complicates interpretation of the data based on the QT correction factors that are imperfect when correcting for heart rates that change over time.

2.2.3. Linezolid

Linezolid is a synthetic antibacterial agent of the oxazolidanone class approved in many countries around the world (including South Africa), 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[18, 31, 34]. Antimicrobial effects likely come from inhibition of protein synthesis in the ribosomes of the infecting organism[25]. Resistance of *M.tb*. 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[24].

Preclinical *in vitro* data shows linezolid is active against *Mycobacterium tuberculosis* (*M.tb.*), including MDR strains with minimum inhibitory concentrations (MICs) that range from 0.125-1 μg/mL[26]. Recent studies of the bactericidal and sterilizing activity of linezolid in a mouse model of *M.tb.* infection have demonstrated linezolid alone causes marked reductions in lung colony forming units (CFUs) from mice following 1-3 months of therapy[5]. (Table 6, below)

Table 6: Murine Lung CFU counts during Treatment with Linezolid monotherapy versus Standard Therapy

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

In recent years linezolid has been used to treat patients with MDR 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.[27] 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[28, 29, 30] . 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[24]. Forty-one patients who had sputum culture–positive XDR-TB and who had not had a response to any available chemotherapeutic option during the previous 6 months were randomized to start linezolid at 600 mg daily or to delay therapy with linezolid at 600 mg daily for 2 months without changing their failing background regimen. After confirmed sputum-smear conversion, or at 4 months, patients underwent a second randomization to continued linezolid therapy at a dose of 600 mg per day or 300 mg per day for at least an additional 18 months. Thirty four of 39 (87%) of the patients had a negative sputum culture within 6 months after linezolid had been added to their drug regimen. As of the cutoff date prior to publication, of the 38 patients who received linezolid, 17 were still receiving the treatment per protocol, and 13 had completed treatment, including 6 with no relapse during the treatment period, 4 with no relapse at the 6-month follow-up, and 3 with no relapse at the 12-month follow-up (end of study).

While the standard dose of linezolid for short term use for severe bacterial infections is 600 mg bid, some clinicians and clinical trials using linezolid as Group 5 therapy to treat TB use only 300 mg or 600 mg daily due to concerns about toxicity developing when used over a period of months[24] (see below for a review of linezolid toxicity). However, there are no data to indicate what dose of linezolid is required or optimal to effectively treat TB infection. Consequently the 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. 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.

Linezolid Clinical Safety

Linezolid is currently marketed globally, including South Africa, for a variety of acute infectious diseases and has been studied for the treatment of XDR-TB in several recent trials, including in South Africa[24,33]. The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label[18,31, 34]. 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. Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.
- 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 (≥ 3 months) 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.

Longer term use of linezolid in patients with TB has been limited by the high cost of the drug and concerns about the toxicities of myelosuppression, peripheral neuropathy and optic neuropathy. Published reports of observational trials and case series note use of linezolid at doses ranging from 300 mg daily to 1200 mg daily over many months. The most complete review is a meta-analysis by Cox which noted the proportion of adverse events necessitating treatment discontinuation was significantly different by dose: 29.49% (95%CI 3.24–55.74) for ⩽600 mg daily vs. 60.75% (95%CI 42.69–78.81) for >600 mg daily (P = 0.05) [33].

The linezolid product label[18, 31, 34] notes that "*In clinical trials 2.4 % of patients developed a platelet count less than 75% of the LLN/baseline. Thrombocytopenia appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment)." The label notes also, "In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pre-treatment levels."*

In the trial of Lee et al in S Korea[24], seven of 41 Subjects had myelosuppression, including anemia and neutropenia, primarily within the first 5 months, and only one Subject withdrew due to anemia. Six had clinically significant myelosuppression: 5 in 0-4 months and 1 in 4-8 months, with 0 in 8-12 months.

Peripheral and Optic Neuropathy:

The linezolid product label notes these adverse events have been " *…reported in patients, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual function should be monitored in all patients taking ZVYOX for extended periods (≥3 months) and in all patients reporting new visual symptoms, regardless of length of therapy*[32].

In Lee, NEJM, 2012[24], 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). Subjects 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 Subjects 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 Subjects 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 DOH review[29] 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[30], 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[30], 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-L-Pa) 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.

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 Subjects 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 *M.tb* [4,5] when compared to HRZ alone. While the combination of bedaquiline and pretomanid in the murine model of TB appeared somewhat antagonistic relative to bedaquiline alone, it was as active as the triple combination of HRZ[10] and in a subsequent study it was more active in the mouse model than HRZ[11]. 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 sterilizing activity of linezolid in an animal model where mice were given high dose aerosol *M.tb.* infection have demonstrated that L alone and in combination with bedaquiline and pretomanid causes marked reductions in lung colony forming units (CFUs) from mice following 1-3 months of therapy (Table 7, 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 *M.tb.* cultured from lungs when mice were sacrificed 3 months after the completion of therapy that lasted 3 months or more (Tables 7 and 8, below). That is in contrast to the 6 months required 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 done to determine whether shorter durations of an oxazolidinone such as Linezolid, with continuation of the other drugs, would result in relapse-free cure in the mouse (Table 8 below). Treatment with linezolid for the first 4- 8 weeks of a three month treatment also resulted in relapse-free cure when lungs from the mice were cultured 3 months after the completion of therapy.[5]

Table 7: Lung CFU counts assessed during Treatment and proportion of mice relapsing after treatment completion

	Mean (±SD) $\log_{10}$ CFU count at[a]:					Proportion (%) relapsing after treatment for:		
Drug Regimen	D-13	D0	M1	M2	M3	2 mos	3 mos	4 mos
Untreated	2.69±0.13	6.17±0.27	6.47±0.06					
2RIF+INH+PZA/ RIF+INH			3.47±0.37	1.59±0.25	0.50±0.51		13/15 (87)	1/20 (5)
BDQ			3.24±0.25					
PMD			4.57±0.22					
LZD			4.97±0.26					
SZD			3.85±0.37					
BDQ+PMD			4.21±0.40	1.62±0.19	0.52±0.36	15/15 (100)	10/15 (60)	2/20 (10)
BDQ+LZD			2.82±0.15	1.91±0.66				
BDQ+SZD			2.88±0.07	0.65±0.50				
PMD+LZD			3.23±0.41	1.48±0.12				
PMD+SZD			1.65±0.33	0.23±0.40				
BDQ+PMD+LZD			3.28±0.65	0.34±0.41	0.00±0.00	12/15 (80)	0/14 (0)	0/20 (0)
BDQ+PMD+SZD			0.94±0.14	0.00±0.00		14/20 (70)	1/14 (7)	

[a] Time points are shown in days (e.g., D-13, day-13; D0, day 0) or months (e.g., M1, 1 month) of treatment.

RIF=rifampicin, INH=isoniazid, PZA=pyrazinamide, BDQ=bedaquiline, PMD=pretomanid, LZD=linezolid, SZD=sutezolid (experimental oxazolidanone)

Table 8: Murine Relapse Data, Impact of L Treatment Duration Lung CFU counts assessed during treatment and proportion of mice relapsing after treatment completion

	Mean (±SD) log_{10} CFU count at[a]:				Proportion (%) relapsing after treatment for:	
Regimen	D-13	D0	M1	M2	2 mos	3 mos
Untreated	3.96±0.08	7.74±0.20				
2RIF+INH+PZA/ 1RIF+INH				1.94±0.27		8/14 (57)
BDQ+PMD			4.48±0.20	2.33±0.30		3/14 (21)
BDQ+PMD+TZD			4.20±0.13	1.67±0.41		
BDQ+PMD+AZD			4.07±0.36	1.43±0.36		
BDQ+PMD+RWJ			3.63±0.18	0.54±0.41		
BDQ+PMD+LZD_{50}			3.48±0.36	0.39±0.26		
1BDQ+PMD+LZD_{100}/ BDQ+PMD			2.69±0.37	0.93±0.49	9/15 (60)	0/15 (0)
2BDQ+PMD+LZD_{100}/ BDQ+PMD				0.66±0.39	6/15 (40)	0/15 (0)
2BDQ+PMD+LZD_{100}/ BDQ+PMD+LZD_{50}						0/12 (0)
BDQ+PMD+LZD_{100}						0/15 (0)
BDQ+PMD+SZD			1.88±0.22	0.00±0.00	1/14 (7)	0/14 (0)

[a] Time points are shown in days (e.g., D-13, day-13; D0, day 0) or months (e.g., M1, 1 month) of treatment.

* 2BDQ+PMD+LZD_{100}/BDQ+PMD means 2 months on the full regimen, and then just J and Pa for the 3rd month.
*1BDQ+PMD+LZD_{100}/2BDQ+PMD means 1 month on the full regimen, and then just J and Pa for the 2nd and 3rd months.
*LZD_{100} means a 100 mg/kg dose to the mice, which corresponds to the drug exposure attained by humans taking 600 mg twice daily.

In conclusion, linezolid increases the sterilizing activity of the bedaquiline-pretomanid combination; no *M.tb.* could be cultured from the lungs of mice 3 months after cessation of 3 months of treatment with the combination in contrast to *M.tb.* cultured from 13 of 15 mice treated with the standard 2RHZ/4RH regimen over 3 months. In addition, limiting the duration of L to the first month of treatment does not affect L's contribution to the sterilizing 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 Study NC-001

Study NC-001 was a partially double-blind, randomized, parallel group study in adult male and female subjects with newly diagnosed, uncomplicated, smear-positive, pulmonary TB. A total of 85 subjects met study eligibility criteria and were randomly assigned to one of the following six treatment groups: bedaquiline alone; bedaquiline + pyrazinamide; bedaquiline + pretomanid 200 mg; pretomanid 200 mg + pyrazinamide; pretomanid 200 mg + pyrazinamide, + moxifloxacin; or Rifafour e-275. All study treatments were given once daily for 14 days. Substantial EBA activity was demonstrated across subjects in all arms of the study and the daily reductions in cultured colony counts per mL of sputum are presented in Table 9 below.

Table 9: Summary Statistics for $EBACFU_{(0-14)}$ Derived Using Bi-Linear Regression, Study NC-001.

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

There were no Serious Adverse Events from the study among subjects treated with pretomanid and bedaquiline. Three Subjects in a bedaquiline-containing treatment arm were withdrawn: one subject on a bedaquiline only arm for a Grade 3 ALT and 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.

2.3.3. 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 subjects. Fifteen Subjects 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 logCFU and logTTP that was at least as good as the HRZE control. The daily logCFU results are presented in Table 10. Similar results were found when TTP was used to calculate the bactericidal activity over 14 days (BA(0-14)).

Table 10: NC-003 Efficacy Results: Daily $BAlogCFU_{(0-14)}$

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

Safety

Generally, the regimens in this study were well tolerated. Table 11 provides a list of the overall safety findings. The only SAE experienced in the study was in a Subject in the clofazimine monotherapy arm. Otherwise, the rates of treatment emergent AEs (TEAEs) were similar across the treatment arms. One Subject in the B-Pa-Z arm was withdrawn from the study due an adverse event of increased liver function tests (ALT, AST and GGT).

Table 11: NC-003 Safety Data

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

QT Prolongation

Because bedaquiline and clofazimine are both known to prolong the QT interval, intensive ECG monitoring was included in the study endpoints. The mean change from baseline in QTcB and QTcF tended to be larger at 5 hours than at 10 hours post-dose in the (B-Pa-Z-C) arm and in the (B-Pa-C) arm. No QTcB or QTcF ≥500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of ≥60 ms in QTcB was reported for 2 Subjects in the (B-Pa-C) arm and for 1 Subject in the clofazimine alone arm. An increase from baseline to Visit 5 and subsequent visits of ≥60 msec in QTcF was reported for 4 Subjects in the (B-Pa-C) arm and for 1 Subject 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 current Nix study.

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[23]. These patients have infection with *M.tb.* that is 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. This trial provides an opportunity to treat patients with XDR-TB with three active drugs, for which there is no or minimal pre-existing resistance, in a very closely controlled and monitored clinical trial setting. Subjects will be monitored closely and regular reviews of safety and efficacy will be made by the DSMC. While this is an untested combination regimen in patients with XDR-TB, 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 *M.tb.* 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 and thus their combined toxicity profile is not known. There is limited experience with both B and Pa to date and thus their safety profile is emerging. The greatest risks of key concern for subjects in this trial from linezolid are from the adverse events of

myelosuppression and peripheral and optic neuropathy. Subjects 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, or without linezolid if the subject received at least 4 weeks of the 1200 mg total daily dose, may be made cautiously. Subjects will be under close surveillance for hepatotoxicity, as that risk for pretomanid and bedaquiline is not yet well characterized. Other adverse events of special concern are seizures or other neurologic events. Seizures have been reported in patients taking linezolid, seizures have been noted in animal toxicology studies of pretomanid at higher doses, and one unexplained seizure was noted in a patient taking M-Pa-Z in Study NC-002.

Overall the benefit-risk balance justifies evaluating the B-L-Pa 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 RATIONALE AND OBJECTIVES

3.1. Trial Rationale

This trial will provide a regimen containing 3 drugs against which there is no expected *M.Tb.* 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 *M.tb*. Data from previous trials shows that the combination of B-Pa is well tolerated and has the potential to shorten treatment in Subjects who are susceptible to all drugs. The addition of linezolid will ensure each Subject receives at least 3 drugs active against their TB strain.

3.2. Dose Rationale

3.2.1. Bedaquiline

Bedaquiline will be administered as the dose regimen currently approved by the United States Food and Drug Administration for treatment of patients with MDR-TB: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment.

3.2.2. 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 EBA Study NC-001-(B-M-Pa-Z) and in combination with either bedaquiline and/or pyrazinamide and/or clofazimine over 14 days in the EBA Study NC-003-(B-C-Pa-Z). 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 Subjects 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 *M.tb.* 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. Consequently, in an upcoming Phase 3 trial for this regimen, the PaMZ regimen will be evaluated at both the doses of 100 mg/day and 200 mg/day. However because sterilizing relapse-free cure of TB in patients with XDR-TB may ultimately require a regimen with higher drug exposures, the 200mg dose has been chosen for this study.

3.2.3. Linezolid

The standard dose of linezolid for a multitude of indications is 400mg or 600 mg BID. Doses of linezolid used 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. This trial initially started all subjects on 600 mg bid of linezolid, the approved dose to treat bacterial infections for up to 28 days. Preliminary unpublished in-house top line results from a recently completed 2 week study sponsored by the TB Alliance have demonstrated that the Bactericidal effects of linezolid over 14 days are greatest at a total daily dose of 1200 mg and lowest at a 300 mg total daily dose (see Section 2.2.3 for more detail). This gives further rationale to begin treating all trial participants at the full daily dose of 1200 mg. Because toxicity is thought to be caused by mitochondrial toxicity and may be lessened by lowering the time the linezolid concentration is greater than the threshold for mitochondrial toxicity, the protocol has been amended to require all participants to begin treatment with linezolid at the 1200 mg qd single daily dose. If adverse events develop, the investigator will be able to interrupt dosing or to reduce the dose level to either 600 mg qd or 300 mg qd in an effort to allow this patient population with high mortality on standard care to continue to benefit from the study drug regimen. If subjects have toxicity issues with linezolid that would prohibit further treatment with that drug, they can remain on the bedaquiline and pretomanid study IMP if they received the initial 1200 mg total daily dose of linezolid for at least the first 4 consecutive weeks of treatment and they are smear negative or with trace/scanty results and judged to be clinically improving by the Investigator.

3.3. Trial Objectives

To evaluate the efficacy, safety, tolerability and pharmacokinetics of bedaquiline plus pretomanid plus linezolid after 6 months of treatment (with an option to treat for 9 months in Subjects who are culture positive or revert to being culture positive between month 4 and month 6 visits) in Subjects with either pulmonary XDR tuberculosis, treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).

4. TRIAL DESIGN

4.1. Summary

Up to 200 male and female Subjects aged 14 and over with confirmed sputum positive for *M.tb.* in culture pulmonary XDR-TB, or with pulmonary MDR-TB with a documented intolerability or non-response to the best treatment available for 6 months or more will be enrolled.

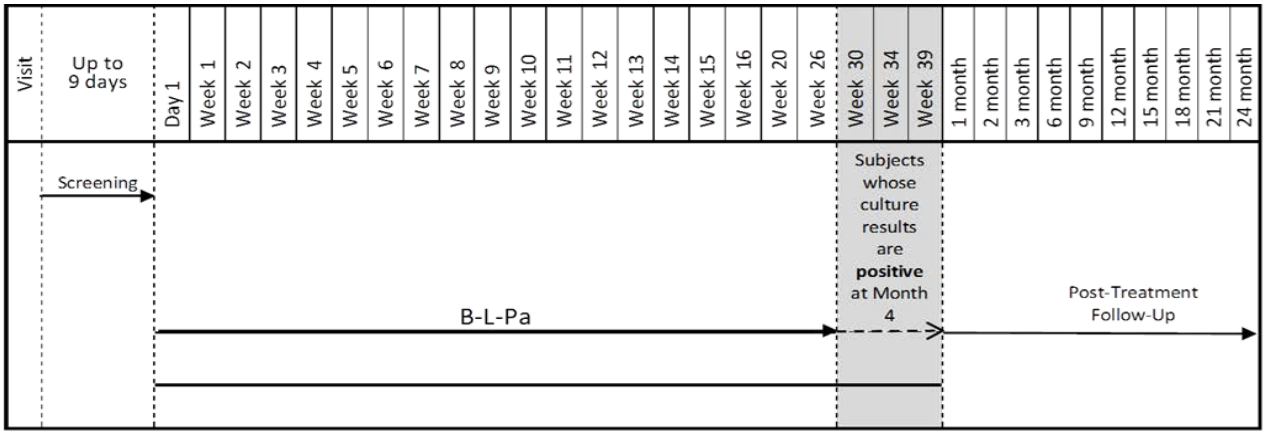
All Subjects will have up to a maximum of 9 days for screening, receive 6 months of treatment, and have follow-up visits performed 1 and 2 months after treatment completion and every 3 months after study treatment completion for 24 months. If a Subject is culture positive or revert to being culture positive between Month 4 and Month 6 visits and their clinical condition suggests they may have ongoing TB infection, they may have treatment extended to 9 months (with 24 months of Follow Up) or be withdrawn from the study. If culture results between month 4 and 6 are contaminated, missing or considered an isolated positive without clinical significance, please use available culture results to make this decision and consult with the TB Alliance Medical Monitor. All decisions regarding treatment extension should be discussed with the TB Alliance Medical Monitor before implementation.

Subjects who withdraw after $\leq$14 days of IMP should attend an Early Withdrawal visit. Subjects who withdraw after $\geq$15 days of IMP should return for an Early Withdrawal visit and follow-up visits at 3, 6 and 24 months after their last dose of IMP to check for survival, SAEs and resolution of TB symptoms.

Subjects will receive:

- B-L-Pa for the duration of treatment.

Figure 1: Trial Schematic



4.2. Trial Endpoints

4.2.1. Primary Endpoint

Incidence of bacteriologic failure or relapse or clinical failure through follow up until 6 months 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 culture conversion to negative.
- Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status in culture, with culture conversion to positive status with a *Mycobacterium tuberculosis* (*M.tb*.) strain that is genetically identical to the infecting strain at baseline.
- Clinical failure: A change from protocol-specified TB 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.
- Subjects 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.

4.2.2. Secondary Endpoints

4.2.2.1. Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure through follow up until 24 months after the end of treatment as a confirmatory analysis
- Time to sputum culture conversion to negative status through the treatment period.
- Proportion of subjects with sputum culture conversion to negative status at 4, 6, 8, 12, 16 and 26 or 39 weeks.
- Linezolid dosing (actual) and efficacy will be explored.
- Change from baseline TB symptoms.

- Change from baseline in Patient Reported Health Status.
- Change from baseline weight.

4.2.2.2. Safety and Tolerability:

- All cause mortality.
- Incidence of Treatment Emergent Adverse Events (TEAEs) will be presented by severity, (DMID Toxicity Grade), drug relatedness and seriousness, leading to early withdrawal and leading to death.
- Quantitative and qualitative clinical laboratory result measurements, including observed and change from baseline.
- Quantitative and qualitative measurement of ECG results, 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.
- These data will be presented as descriptive analyses, and no inferential tests will be carried out.

4.2.2.3. Pharmacokinetics:

Pharmacokinetics will consist of two separate schedules:

- All Subjects- Pre-dose sampling at weeks 2, 8 and 16 to measure C_{trough} levels of bedaquiline, bedaquiline metabolite M2, linezolid and pretomanid.
- PK Sub-study Subjects- in addition to the C_{trough} samples, there will be intensive PK sampling at Week 16 at pre-dose, 0.5, 1, 2, 4, 8 12, 12.5, 13, 14, 16, 20 and 24 hours after dosing in a sub-group of 20 evaluable Subjects across selected sites.

For the PK sub-study samples, the following PK parameters will be estimated from the individual (per Subject) PK plasma concentrations: Minimum observed PK plasma concentration (C_{min}), maximum observed PK plasma concentration(C_{max}), time to reach C_{max} obtained without interpolation (T_{max}), area under the PK plasma concentration time (t) curve from zero to the last quantifiable PK plasma concentration prior to the subsequent dose, using the linear trapezoidal rule ($AUC_{(0-t)}$), area under the PK plasma concentration time (t) curve from zero to 24 hours ($AUC_{(0-24)}$). Oral apparent clearance (CL/F) by non-compartment model. These will be derived for each analyte. In addition, for analyte linezolid at BID dose, the AUC_{0-12}, C_{max}, C_{min}, CL/F and $t_{1/2}$ will be calculated based on dose interval 0-12 hrs.

4.2.2.4. Exploratory

- Evaluate whether any of the secondary endpoints predicts relapse free cure.
- Subgroup analyses of the primary endpoint on the MITT analysis population will be considered
- Correlation of Time over mitochondrial protein synthesis inhibition (MPS50) with linezolid toxicity, (the MPS50 value will be an assumed value from literature).

4.2.2.5. General Mycobacteriology

Early Morning and Coached Spot Sputum Samples will be obtained at all scheduled visits, except the Screening Visit when only a Coached Spot Sputum Sample will be collected. Both (if feasible) sputum samples (Coached Spot and Early Morning; or two spot sputum if Early Morning is unavailable) collected will be used for identification for the presence or absence of *M.tb.* in culture and if liquid culture in the MGIT platform is used, for TTP in liquid medium.

The following mycobacteriology assays will be carried out according to procedures described in the Laboratory Manual:

Table 12: General Mycobacteriology

Sample	Type	Assessments
Screening	Coached Spot Sputum Sample	• Culture for presence or absence of M.tb.; • Smear microscopy for acid-fast bacilli (AFB); • Gene Xpert, Hain Assay MTBDRplus or an alternative molecular or antigen-based test to confirm *M.tb.*
Baseline **(Day 1)**	Early Morning and Coached Spot Sputum Samples	• Culture for presence or absence of *M.tb*.; • If liquid culture in the MGIT platform is used, TTP in liquid medium; • Speciation of the infecting organism by molecular / antigen test, to be done at study lab (lab where study samples are initially sent from site for culture). Only one sample should be used for testing at the Central Lab(s) for mycobacterium characterization tests outlined below. The early morning sputum is the most preferable, but if it is not available or the culture is contaminated, then the coached spot may be sent to the Central Lab(s). • MIC: bedaquiline, linezolid and pretomanid; • Drug susceptibility testing in liquid culture for rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide and second line TB drugs including fluoroquinolones and injectables; • Extraction of bacterial (*M.tb*.) DNA for molecular genotyping; •
All Visits Post Baseline	Early Morning and Coached Spot Sputum Samples	• Culture for presence or absence of *M.tb.;* • If liquid culture in the MGIT platform is used, TTP in liquid medium. • For any culture positive at or after month 4, Speciation of the infecting organism by molecular / antigen test to be done at study lab (lab where study samples are initially sent from site for culture). • If participant has received at least 4 consecutive weeks of linezolid at a total daily dose of 1200 mg, and Investigator would like to consider discontinuing linezolid dosing and continuing bedaquiline and pretomanid dosing: A smear microscopy for acid fast bacilli (AFB) should be requested by the site and performed at the study lab.

Sample	Type	Assessments
First culture positive sample at or following end of treatment. If the first positive turns out to be contaminated, then a subsequent positive, if available, should be sent for the characterization.	Early Morning or Coached Spot Sputum Sample	The following (Early Morning Sputum OR two Coached Spot Sputum sample) will be processed at the central lab(s): • MIC: bedaquiline, linezolid and pretomanid; • Drug susceptibility testing in liquid culture for rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide and second line TB drugs including fluoroquinolones and injectables; • Extraction of bacterial (*M.tb.)* DNA for molecular genotyping. • Speciation of the infecting organism by molecular / antigen test, to be done at study lab (lab where study samples are initially sent from site for culture) for initial relapse (first positive at end of treatment or during follow-up) or any positive at or after the week 16 visit.

- The extracted *M.tb.* DNA and isolates will be stored for potential further work to validate new assay tools for a maximum of 5 years after trial closure.
- Both the Early Morning and the Coached Spot sputum samples or two spot sputum if Early Morning is not available should be cultured for the culture/MGIT when feasible. If only one sample is cultured, the other should be kept as a back-up sample for use when the other sample is contaminated.
- Samples for mycocharacterization testing done at central myco lab(s) will be batched and sent for testing routinely. Only one sample should be sent for this testing, preferable the early morning.
- If a subject has a positive culture at or after end of treatment, only the first positive culture will be used for the mycocharacterization at the central myco lab(s). If the first positive culture is contaminated, a later positive culture, if available, may be used for characterization
- If the Subject was treated with study medication for less than 14 days, the mycobacteriology testing will be performed on the baseline sample isolate only.

4.3. Trial Population

4.3.1. Inclusion Criteria

1. Provide written, informed consent prior to all trial-related procedures (if under 18, include consent of legal guardian).
2. Body weight of ≥35 kg (in light clothing and no shoes).
3. Willingness and ability to attend scheduled follow-up visits and undergo study assessments
4. Provide consent to HIV testing (if an HIV test was performed within 1 month prior to trial start, 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.
5. Male or female, aged 14 years or above.
6. Subjects with one of the following pulmonary TB conditions:
    a. XDR-TB with
        i. documented culture positive (for *M.tb.*) results within 3 months prior to screening or *M.tb.* confirmed in sputum based on molecular test within 3 months prior to or at screening;
        ii. documented resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable historically at any time or at screening;
    b. MDR-TB documented by culture positive results (for *M.tb.*) within 3 months prior to or at screening 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;

c. MDR-TB documented by culture positive (for *M.tb.*) results within 3 months prior to or at screening who are unable to continue second line drug regimen due to a documented intolerance to:
   i. PAS, ethionamide, aminoglycosides or fluoroquinolones;
   ii. Current treatment not listed above that renders subject eligible for the study in the Investigator's opinion.

7. Chest X-Ray picture (taken within a year prior to screening) consistent with pulmonary TB in the opinion of the Investigator.
8. Be of non-childbearing potential or using effective methods of birth control, as defined below:

Non-childbearing potential:

a. Subject - not heterosexually active or practices sexual abstinence; or
b. Female Subject/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 Subject/sexual partner - vasectomised or has had a bilateral orchidectomy minimally 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 Subject/partner;
c. And are willing to continue practicing birth control methods throughout treatment and for 6 months (both male and female Subjects) after the last dose of study medication or discontinuation from study medication in case of premature discontinuation.

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

4.3.2. Exclusion Criteria

Medical History

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), where participation in the trial would compromise the well-being of Subject 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 Subjects' safety or ability to follow through with all protocol-specified visits and evaluations.
3. In the judgment of the Investigator, the patient is not expected to survive for more than 12 weeks.
4. Karnofsky score < 50 within 30 days prior to entry.
5. Body Mass index (BMI) < 17 kg/m²

6. History of allergy or known hypersensitivity to any of the trial Investigational Medicinal Products or related substances.
7. HIV infected Subjects having a CD4+ count ≤ 50 cells/µL;
   For HIV infected Subjects having a CD4+ count >50 cells/µL;
   a. Currently treated with or will need to initiate antiretroviral therapy (ART) which is not compatible with the allowed ARTs and is not considered an appropriate candidate for switching to a regimen of ARVs which is allowed. Examples of allowed treatment include but are not limited to the following. If there are any questions, discuss with the Sponsor Medical Monitor for confirmation of appropriate ARV regimen.
      i. Nevirapine based regimen consisting of nevirapine in combination with any NRTIs;
      ii. Lopinavir/ritonavir (Aluvia™) based regimen consisting of lopinavir/ritonavir (Aluvia™) in combination with any NRTIs;
      iii. The combination of tenofovir/lamivudine/abacavir should be considered in patients with normal renal function to address myelosuppression cross toxicity of zidovudine and linezolid;
      iv. An alternate regimen that may be considered if the above are not appropriate is a triple nucleosidase reverse transcriptase inhibitors (NRTI) based regimen consisting of zidovudine, lamivudine and abacavir may be used with caution. Regimens including zidovudine should be used with special caution as zivovudine and linezolid may both cause peripheral nerve toxicity;
      v. Raltegravir in combination with nucleoside reverse transcriptase inhibitors (NRTIs).
   b. Cannot ensure a 2 week interval between commencing IMP and the start of ART, if not already on ARTs.
8. Having participated in other clinical studies with dosing of investigational agents within 8 weeks prior to trial start or currently enrolled in an investigational study that includes treatment with medicinal agents. Subjects 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.
9. Significant cardiac arrhythmia requiring medication.
10. Subjects with the following at Screening:
    a. QTcF interval on ECG >500 msec. Subjects with QTcF > 450 must be discussed with the sponsor medical monitor before enrolment.
    b. History of additional risk factors for Torsade de Pointes, (e.g., heart failure, hypokalemia, family history of Long QT Syndrome);
    c. Clinically significant ventricular arrhythmias;
    d. Subjects with other cardiac abnormalities that may place them at risk of arrhythmias must be discussed with the sponsor medical monitor before enrolment. Such abnormalities include: Evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome); Electrocardiographic evidence of complete or clinically significant incomplete left bundle branch block or right bundle branch block; Evidence of second or third degree heart block; Intraventricular conduction delay with QRS duration more than 120 msec.
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, subjects 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.

Specific Treatments

13. Concomitant use of Monoamine Oxidase Inhibitors (MAOIs) or prior use within 2 weeks of treatment assignment.
14. Concomitant use of serotonergic antidepressants or prior use within 3 days of treatment assignment 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. Use of any drugs or substances within 30 days prior to dosing known to be strong inhibitors or inducers of cytochrome P450 enzymes(including but not limited to quinidine, tyramine, ketoconazole, fluconazole, testosterone, quinine, gestodene, metyrapone, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafylline, cimetidine, dextromethorphan). Exceptions may be made for subjects that have received 3 days or less of one of these drugs or substances, if there has been a wash-out period before administration of IMP equivalent to at least 5 half-lives of that drug or substance.
18. Subjects may have previously been treated for DS/MDR-TB (with specific excepetions for bedaquiline and/or linezolid as noted below) provided that treatment is/was discontinued at least 3 days prior to treatment assignment.
19. Subjects should not receive more than 2 weeks of bedaquiline or linezolid prior to enrolment/first dose of IMP.

Based on Laboratory Abnormalities

20. Subjects with the following toxicities at Screening (labs may be repeated) as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November 2007):
    a. serum potassium less than the lower limit of normal for the laboratory;
    b. Hemoglobin level grade 2 or greater (< 8.0 g/dL);
    c. Platelets grade 2 or greater(<75,000/mm^3);
    d. Absolute neutrophil count (ANC) < 1000/ mm^3;
    e. Aspartate aminotransferase (AST)
        - Grade 3 or greater ($\geq$ 3.0 x ULN) to be excluded;
        - Greater than ULN must be discussed with and approved by the sponsor Medical Monitor
    f. Alanine aminotransferase
        - Grade 3 or greater ($\geq$ 3.0 x ULN) to be excluded
        - greater than ULN must be discussed with and approved by the sponsor medical monitor ;
    g. Total bilirubin:
        - Grade 3 or greater (≥2.0 x ULN), or if ≥1.5 up to 2.0 x ULN when accompanied by an increase in other liver function test (ALT, AST, Alk Phos or GGT);
        - 1-1.5 x ULN must be discussed with and approved by the sponsor Medical Monitor
    h. Direct bilirubin:
        - Greater than ULN to be excluded
    i. Serum creatinine level greater than 2 times upper limit of normal

j. Albumin <32 g/L

4.4. Treatment Plan: Schedule of Assessments

The trial consists of three periods, as follows:

- Screening (Up to 9 days Prior to Treatment);
- Treatment Period (Day 1 to Week 26 OR Day 1 to Week 39);
- Follow-Up Period (1 month to 24 months post Treatment End).

Refer to:

- Study Flow Chart (Section 1.2) for the overview of the timing of all procedures and laboratory samples to be done at each visit.
- Trial Procedures (Section 6) for details regarding specific procedures or laboratory tests.

Visit Window:

- Week 1 through Week 16: ± 3 days
- Weeks 20 through End of Treatment (Week 26 or 39): ± 7 days
- Post-Treatment Follow-Up Visits (1-3 months): ± 2 weeks

Note: Subjects on 6 months of treatment should complete a full course of treatment (i.e. 26 weeks of prescribed doses) within 8 months of treatment assignment (a total halt of up to 60 days if on 6 months) while subjects on 9 months of treatment should complete a full course of treatment (i.e. 39 weeks of prescribed doses) within 12 months of treatment assignment (a total halt of 90 days if on 9 months of treatment).

4.4.1. Screening (Up to 9 Days Prior to Treatment)

4.4.1.1. Screening

The screening visit may occur over a number of days up to 9 days prior to treatment assignment, (i.e. all screening procedures do not have to be performed on the same day). If a subject fails screening, a full re-screen (all screening procedures must be repeated) may occur at a later date.

The following information will be collected and procedures performed:

- Written Informed Consent (Main study; HIV testing if applicable);
- Demographic Data;
- Medical and Treatment History;
- Eligibility Assessment;
- Karnofsky Score;
- HIV test and CD4 count:
    - If HIV status is a confirmed known positive, repeated 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 trial start, it should not be repeated as long as documentation of testing method and negative results can be provided.
    - Subjects may be on current antiretroviral therapy (ART) or commence ART once on the study provided there is at least a 2 week interval between commencing IMP and the start of ART;
- Chest X-Ray;

- Serum or Urine Pregnancy Test, (women of child bearing potential only, whether they are sexually active or not);
- TB Symptoms Profile;
- Patient Reported Health Status;
- Ophthalmology- Slit Lamp Examination;
- Ophthalmic Examination (Ophthalmologic Medical History, Visual Acuity, and Color Assessment);
- Single 12-lead ECG (the ECG should be done before vital signs and any lab assessments);
- Vital Signs, including weight (should be done prior to any lab assessments);
- Full Physical Examination including height;
- Laboratory Safety Assessments;
- Coached Spot Sputum Sample collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Peripheral Neuropathy Assessment

4.4.2. Treatment Period (Day 1 to Week 26 or Week 39)

4.4.2.1. Day 1

The following information will be collected and procedures performed pre-dosing:

- Eligibility Assessment;
- Serum or Urine Pregnancy Test, (women of child bearing potential only, whether they are sexually active or not);
- Vital Signs, including weight (should be done before any labs);
- Single 12-lead ECG (the ECG should be done before any vital signs and any labs);
- Full Physical Examination;
- Laboratory Safety Assessments;
- Treatment Assignment;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Investigational Medicinal Product (IMP) Administration.

4.4.2.2. Week 1

The following information will be collected and procedures performed pre-dosing:

- Vital Signs, including weight (should be done before any labs);
- Single 12-lead ECG (the ECG should be done before any vital signs and any labs);
- Limited Physical Examination;
- Laboratory Safety Assessments;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Investigational Medicinal Product (IMP) Administration.

4.4.2.3. Week 2

The following information will be collected and procedures performed pre-dosing:

- Vital Signs, including weight (should be done before any labs);
- Limited Physical Examination;
- Laboratory Safety Assessments;
- Pre-dose Pharmacokinetic Sampling (All Subjects);
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Investigational Medicinal Product (IMP) Administration.

4.4.2.4. Weeks 3, 5, 7, 9, 10, 11, 13, 14 and 15

- Complete Blood Count/Full Blood Count (performed pre-dosing);
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events.
- Study Medication/Compliance.

4.4.2.5. Week 4

The following information will be collected and procedures performed pre-dosing:

- Vital Signs, including weight (should be done before any labs);
- Single 12-lead ECG (the ECG should be done before any vital signs or labs);
- Limited Physical Examination;
- Laboratory Safety Assessments;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Ophthalmic Examination (Visual Acuity and Color Assessment);
- Adverse Events;
- Peripheral Neuropathy Assessment;
- Investigational Medicinal Product (IMP) Administration

4.4.2.6. Week 6

The following information will be collected and procedures performed pre-dosing:

- Vital Signs, including weight (should be done before any labs);
- Limited Physical Examination;
- Laboratory Safety Assessments;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Investigational Medicinal Product (IMP) Administration.

4.4.2.7. Week 8

The following information will be collected and procedures performed pre-dosing:

- Serum or Urine Pregnancy Test, (women of child bearing potential only, whether they are sexually active or not);

- TB Symptoms Profile/Patient Reported Health Status;
- Vital Signs, including weight (should be done before any labs);
- Single 12-lead ECG (the ECG should be done before any vital signs or labs);
- Limited Physical Examination;
- Laboratory Safety Assessments;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Peripheral Neuropathy Assessment.
- Ophthalmic Examination (Visual Acuity and Color Assessment);
- Pre-dose Pharmacokinetic Sampling (All Subjects);
- Investigational Medicinal Product (IMP) Administration.

4.4.2.8. Week 12

The following information will be collected and procedures performed pre-dosing:

- Vital Signs, including weight (should be done before any labs);
- Limited Physical Examination;
- Laboratory Safety Assessments
- Ophthalmic Examination (Visual Acuity and Color Assessment);
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Peripheral Neuropathy Assessment;
- Investigational Medicinal Product (IMP) Administration.

4.4.2.9 Week 16 (Week 30 when applicable)

The following information will be collected and procedures performed pre-dosing:

- Vital Signs, including weight (should be done before any labs);
- Single 12-lead ECG (the ECG should be done before any vital signs or labs);
- Limited Physical Examination;
- Laboratory Safety Assessments;
- Ophthalmic Examination (Visual Acuity and Color Assessment)
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Peripheral Neuropathy Assessment;
- Investigational Medicinal Product (IMP) Administration;
- Pre-Dose Pharmacokinetic Sampling (all subjects, this should be done prior to dosing with study medication)
- Intensive PK Sub-Study (20 evaluable across all participating sites) at pre-dose, 0.5, 1, 2, 4, 8, 12. 12.5, 13, 14, 16, 20 and 24 hours after dosing.

4.4.2.10 Week 20 (Week 34 when applicable)

The following information will be collected and procedures performed pre-dosing:

- Vital Signs, including weight (should be done before labs);
- Limited Physical Examination;
- Laboratory Safety Assessments;
- Ophthalmic Examination (Visual Acuity and Color Assessment);
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Peripheral Neuropathy Assessment;
- Investigational Medicinal Product (IMP) Administration.

4.4.2.11 Week 26 (Week 39 when applicable)

The following information will be collected and procedures performed when subject completes *end of treatment visit*:

- Serum or Urine Pregnancy Test, (women of child bearing potential only, whether they are sexually active or not);
- TB Symptoms Profile/Patient Reported Health Status;
- Vital Signs, including weight (should be done before any labs);
- Single 12-lead ECG (the ECG should be done before any vital signs or labs);
- Full Physical Examination;
- Laboratory Safety Assessments;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Ophthalmology Slit Lamp Examination;
- Ophthalmic Examination (Visual Acuity and Color Assessment);
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Peripheral Neuropathy Assessment;
- Investigational Medicinal Product (IMP) Administration.

When subject is scheduled to receive 9 months of treatment, the following assessments should be done at the week 26 visit:

- Vital Signs, including weight (should be done before any labs);
- Single 12-lead ECG (the ECG should be done before any vital signs or labs);
- Limited Physical Examination;
- Laboratory Safety Assessments;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Ophthalmic Examination (Visual Acuity and Color Assessment);
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Peripheral Neuropathy Assessment;
- Investigational Medicinal Product (IMP) Administration.

4.4.2.12 Early Withdrawal

In case of Early Withdrawal during the treatment period of the study (prior to completing 26 or 39 weeks of treatment as applicable), all efforts shall be made to complete the Early Withdrawal assessments. At the Early Withdrawal visit, the following information will be collected and procedures performed:

- Serum or Urine Pregnancy Test (for women of child bearing potential only, whether they are sexually active or not);
- TB Symptoms Profile/Patient Reported Health Status;
- Vital Signs, including weight (should be done before any labs);
- Single 12-lead ECG (the ECG should be done before any vital signs and labs);
- Full Physical Examination;
- Laboratory Safety Assessments;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Ophthalmology Slit Lamp Examination (if received ≥ 12 weeks of study treatment);
- Ophthalmic Examination (Visual Acuity and Color Assessment)
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Peripheral Neuropathy Assessment.

Follow-Up required for Early Withdrawals based on Treatment Duration

Treatment Duration at EWD visit	Ophthalmology Examination at EWD	Ophthalmology Examination Visit 3 months after EWD Visit	Month 6	Month 24
≤ 14 days	Not required	Not required	Not Required	Not Required
15 days to ≤ 12 weeks	Not required	Required	Required	Required
> 12 weeks	Required	Required	Required, if not already performed.	Required

Upon Early Withdrawal of IMP, All Subjects will be referred to a unit specializing in treatment of XDR-TB.

4.4.3 Follow-Up Period

4.4.3.1 1 Month Post-Treatment

- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events.

4.4.3.2 2 Months Post-Treatment

- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events.

4.4.3.3 3 Months Post-Treatment or Withdrawal

The following information will be collected and procedures performed:

- Vital Signs, including weight;
- Ophthalmology Slit Lamp Examination*;
- Ophthalmic Examination (Visual Acuity and Color Assessment);
- Limited Physical Examination;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Peripheral Neuropathy Assessment;
- Adverse Events.

* - Ophthalmology Slit Lamp Exam is required only for subjects who complete 15 days or more of treatment.

4.4.3.4 Months 6, and 24 Post-Treatment

The following information will be collected and procedures performed:

- TB Symptoms Profile/ Patient Reported Health Status (only at Months 6 and 24)
- Vital Signs, including weight;
- Ophthalmic Examination (Visual Acuity and Color Assessment)
- Limited Physical Examination;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Peripheral Neuropathy Assessment;
- Adverse Events.

For any Subjects who withdraw early (during the treatment period after more than 14 days treatment or follow-up), the Month 6 follow-up will be a full study visit if not already prerformed. If Month 6 is already performed, it will serve along with Month 24 visit to collect Adverse Event (AEs), Concomitant Medidcation and 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.

4.4.3.5 Months 9, 15, 18 and 21 Post-Treatment

- Vital Signs, including weight;
- Limited Physical Examination;
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events.

4.4.3.6 Unscheduled Visits

Any visit which is conducted in addition to those required by the Trial Flow Chart 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.

If the duration of treatment is extended due to dose interruptions (e.g., takes participant 8 months to complete 6 months of therapy or 12 months to complete 9 months of therapy), Unscheduled visits should be added every 4 weeks.

Visits to include:

- Vital Signs, including weight (should be done before labs);
- Limited Physical Examination;
- Laboratory Safety Assessments;
- Ophthalmology Examination (Visual Acuity and Color Assessment);
- Early Morning Sputum Collection;
- Coached Spot Sputum Sample Collection;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events;
- Peripheral Neuropathy Assessment;
- Investigational Medicinal Product (IMP) Administration.

If both spot sputum samples obtained between Month 4 and Month 6, at the End of Treatment (Week 26/39), End of follow-up Period or Early Withdrawal visits are contaminated, the subject should return for an unscheduled visit(s) to give additional samples or to document the Subject is not able to produce sputum.

In order to be able to define a Subject's primary outcome status it may be necessary in certain situations to contact a Subject and request they visit the site in order to collect additional Spot Sputum samples at Unscheduled Visits, as follows:

- To be assessed on sputum culture results from:
  - End of Treatment Period (Week 26/39);
  - End of Follow-up Period (Month 24);
  - Early Withdrawal (if applicable).

- Confirm whether the Subject has:
  - Two sequential negative sputum culture results; or
  - Two sequential positive sputum culture results; or
  - Has been unable to produce sputum after documentation of two negative sputum cultures with no intervening positive and are clinically asymptomatic.

- If they **do not** fall into one of these categories, keep collecting Spot Sputum samples x 2 (one Early Morning and one Spot at the research site under the coaching and observation of the trial staff OR two spot sputum at the research site if Early Morning is not available) 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.

4.5 Treatment Discontinuation and Subject Withdrawal

Any Subject for whom the Investigator decides to temporarily discontinue their IMP is to contact the Sponsor Medical Monitor and, if/when applicable, can be restarted on IMP as described in section 4.6

A Subject should immediately discontinue treatment and be prematurely withdrawn from the trial (withdrawal of informed consent or lost to follow-up) or treatment phase for the following reasons:

- Withdrawal of informed consent;
- Lost to Follow-Up;
- Investigator considers that for safety reasons (including specific toxicities as described in section 7.3), it is in the best interest of the Subject he/she be withdrawn;
- Pregnancy;

- Regimen halted > 35 days consecutively (providing subject is not smear negative or with trace/scanty results, judged to be clinically improving by the investigator) and did not receive at least 4 weeks of linezolid 1200 mg total daily dose since start of treatment;
- Regimen halted cumulatively greater than 60 days cumulatively for Subjects receiving 6 months of treatment and 90 days cumulatively for Subjects receiving 9 months of treatment;
- If subject did not receive at least 4 consecutive weeks of linezolid 1200 mg total daily dose at treatment start and Linezolid is:
    - **halted cumulatively greater than 60 days for Subjects receiving 6 months of treatment or**
    - **halted 90 days cumulatively for Subjects receiving 9 months of treatment or**
    - **interrupted for greater than 35 days consecutively.**
- At the specific request of the Sponsor or termination of the study by the Sponsor;
- Subject who, in the opinion of the Investigator or Sponsor, fails to comply with the Protocol, including non-compliance to IMP.

If at any time the investigator is unsure whether or not to withdraw the Subject, the Investigator is to contact the Sponsor Medical Monitor and discuss and agree on how the patient is to be handled. Subjects who withdraw from the trial after having received IMP will not be replaced.

Upon discontinuation of IMP, Subjects will be referred to a unit specializing in the treatment of XDR.

Subjects who withdraw early should have an early withdrawal visit and additional follow-up visits according to timing of withdrawal as outlined in section 4.4.3.4

Early Withdrawal due to TB

Ultimately it is the investigator's decision whether a Subject requires Early Withdrawal from the trial due to a concern that the Subject has symptomatic worsening TB and/or bacteriological failure/relapse.

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

If the investigator decides to withdraw a Subject due to TB, additional sputum samples may need to be collected in order to ensure the Subject's outcome status may be determined (section 4.4.3.4).

All Early Withdrawal Subjects who are confirmed sputum positive (two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These Subjects will be referred to a unit that specializes in treatment of XDR-TB.

4.6 Temporary Dose Interruptions and Modifications

All dose interruption and modifications should be discussed with the Sponsor Medical Monitor prior to implementation.

For Subjects experiencing suspected drug related toxicities due to linezolid, the daily dose of linezolid may be reduced or may be temporarily halted for up to 35 consecutive days. Generally, if temporarily halted, it should be re-instituted at a lower dose. Generally a step down in dose could proceed from 1200 mg QD to 600 mg and then to 300 mg daily. Linezolid dose may be re-started at the same dose at Investigator discretion. If subjects have toxicity issues with linezolid that would prohibit further treatment with that drug, they can remain on the bedaquiline and pretomanid study IMP if they received the initial 1200 mg QD dose of linezolid for at least the

first 4 weeks of treatment and they are smear negative or with trace results and judged to be clinically improving by the Investigator.

For Subjects 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.

Subjects on 6 months of treatment should complete a full course of treatment (i.e. 26 weeks of prescribed doses) within 8 months of treatment assignment (a total halt of up to 60 days if on 6 months) while subjects on 9 months of treatment should complete a full course of (i.e. 39 weeks of prescribed doses) treatment within 12 months of treatment assignment (a total halt of 90 days if on 9 months of treatment). For Subjects who completed the first 4 consecutive weeks of treatment on the 1200 mg linezolid total dose and later in treatment only halted linezolid, treatment can be considered complete at 6 months, even if there were multiple interruptions and rechallenges of just linezolid while the participant remained on pretomanid and bedaquiline.

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

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

4.7 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. Subjects currently on treatment will receive an appropriate regimen and all Subjects will be referred to a unit specializing in the treatment of XDR-TB.

4.8 Subject Progress Definitions

All efforts should be made to contact subjects that do not attend scheduled trial visits. The investigator should attempt to follow up subjects that miss scheduled trial visits unless the subject has withdrawn consent.

If a subject fails to attend a scheduled trial visit, the site will attempt to contact the subject as soon as possible by phone (if applicable) and, if necessary, a home visit will be made, to encourage attendance at the earliest opportunity.

All Subjects will be categorized with two of the following definitions and this should be clearly documented on the eCRF.

4.8.1 Enrolment

Screening Failure

Subjects from whom informed consent is obtained and is documented in writing (that is, subject signs an informed consent form), but are not assigned treatment.

Enrolled

Subjects from whom informed consent is obtained and is documented in writing (that is, subject signs an informed consent form), and who are assigned treatment.

4.8.2 Completed Trial

Subjects who are assigned treatment and complete Treatment and Follow-Up.

4.8.3 Withdrawn

During Treatment- Subjects who are assigned treatment and withdraw/are withdrawn from the trial prior to completion of treatment visits.

During Follow-up- Subjects who are assigned and complete treatment, however withdraw/are withdrawn from the trial prior to completion of their follow-up visits.

4.9 Restrictions

4.9.1 Prior and Concomitant Medications and Other Treatments

Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are considered to be necessary for the Subject'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 subjects 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).

4.9.1.1 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.

4.9.1.2 Antiretroviral Therapy

Patients taking bedaquiline should avoid efavirenz due to drug-drug interactions with bedaquiline, and thus Examples of allowed treatment include but are not limited to the following. If there are any questions, discuss with the Sponsor Medical Monitor for confirmation of appropriate ARV regimen:

- Nevirapine based regimen consisting of nevirapine in combination with any NRTIs;
- Lopinavir/ritonavir (Aluvia™) based regimen consisting of lopinavir/ritonavir (Aluvia™) in combination with any NRTIs;
- The combination of tenofovir/lamivudine/abacavir should be considered in patients with normal renal function to address myelosuppression cross toxicity of zidovudine and linezolid;
- An alternate regimen that may be considered if the above are not appropriate is a triple nucleoside reverse transcriptase inhibitor (NRTI) based regimen consisting of zidovudine, lamivudine, and abacavir may be used with caution. Regimens including zidovudine and linezolid may both cause peripheral nerve toxicity;
- Raltegravir in combination with nucleoside reverse transcriptase inhibitors (NRTIs).

Subjects who are commencing ART may be entered onto the study provided there is at least a 2 week interval between commencing IMP and the start of ART.

4.9.1.3 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 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Trial Treatments

Subjects will receive oral dosing as described below.

Bedaquiline Days 1-14: 400mg once daily (4 x bedaquiline 100 mg tablets),

Bedaquiline Weeks 3-26/39*: 200mg three times per week (2 x bedaquiline 100 mg tablets); **plus**

Linezolid 1200mg once daily day 1 through week 26 or 39* (2 x scored linezolid 600 mg tablets); **plus**

Pretomanid 200mg once daily Day 1 through week 26 or 39* (1 x pretomanid 200 mg tablet)**.**

Subjects will receive a minimum of 6 months of treatment, (with 24 months of Follow Up). If a Subject is culture positive or revert to being culture positive between their Month 4 visits and their clinical condition suggests they may have ongoing TB infection, they may have treatment extended to 9 months (with 24 months of Follow Up), or be withdrawn from the study. If culture result between month 4 and 6 are contaminated, missing or considered an isolated positive without clinical significance, please use available culture results to make this decision and consult with the TB Alliance Medical Monitor. All decisions regarding treatment extension should be discussed with the TB Alliance Medical Monitor before implementation

5.2 Method of Assigning Subjects to Study Treatment

Eligible Subjects who have given written, informed consent will be enrolled onto the trial during Screening and will be identified by a study generated Subject identification code for anonymity (Subject number).

Once the screening results are available and subject is eligible to participate, the site will request their pharmacist/registered dispenser to assign an IMP treatment number to the Subject. The site pharmacist/registered dispenser will assign the next available applicable treatment number, in a sequential basis starting from the lowest unused treatment number.

The process of assigning a treatment number will be fully documented.

5.3 IMP Administration

The Subject should be instructed to:

- Take IMP orally once daily with food for 26 weeks, preferably at the same time every day, with a glass of water (approximately 240ml);
- Subjects should take IMP with a meal (generally allow the Subjects a window of 30 minutes before to 30 minutes after a meal);
- When Subjects are hospitalized or return for clinic visits, they will be dosed on site.

5.4 Subject Compliance

During site clinic visits or hospitalisation, the IMP will be administered by the Investigator/designated site personnel. During the study, sites will be responsible for ensuring Subjects are taking the IMP correctly and are fully trained on how IMP is to be taken. When possible, Subjects 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 mouth of the Subject will be checked to ensure that the Subject has swallowed the IMP).

5.5 Blinding and Procedures for Breaking the Blind

This is an open label study. There is no need for blinding or procedures to break the blind.

5.6 IMP Packaging and Labelling

The complete formulations of the bedaquiline and pretomanid are found in the applicable Investigator Brochures [4,5,15]. The complete formulations of linezolid are found in the applicable Package Inserts [18,31,34].

5.6.1 Packaging

IMP will be supplied as:

bedaquiline 100mg Tablets;
Scored linezolid 600mg Tablets;
pretomanid 200mg Tablets;

Subjects will receive oral dosing as described below.

Bedaquiline Days 1-14: 400mg once daily (4 x bedaquiline 100 mg tablets),

Bedaquiline Weeks 3-26/39*: 200mg three times per week (2 x bedaquiline 100 mg tablets); **plus**

Linezolid 1200mg once daily Day 1 through week 26 or 39* (2 x scored linezolid 600 mg tablets); **plus**

pretomanid 200mg once daily Day 1 through week 26 or 39* (1 x pretomanid 200 mg tablet)**.**

Subjects will receive a minimum of 6 months of treatment. If a Subject is culture positive or revert to being culture positive between Month 4 and Month 6 visits and their clinical condition suggests they may have ongoing TB infection, they may have treatment extended to 9 months or be withdrawn from the study.

Labelling

The test product will be packaged in blister cards with bulk card supplies available for the B-Pa weeks 1-2, B-Pa weeks 3-End of Treatment and Linezolid. The outer packaging of each bulk pack will be labelled with, at a minimum, the following information:

Name and address of the Sponsor
Telephone number of the investigational site
Name of medication, dosage, quantity and method of administration
Reference/Lot Number
Protocol number, visit numbers and space for completion of name of Investigator and site number
The statement “For Clinical Trial Use Only”
Storage conditions
Expiry date
The statement “Keep out of reach of children”

The inner packaging on each weekly treatment card will be labelled with, at a minimum, the following information:

Name and address of the Sponsor
Telephone number of the investigational site
Name of medication, dosage, quantity and method of administration
Reference/Lot Number
Protocol number and space for completion of name of Investigator, site and visit number
Directions for use
Subject Number and Initials
The statement “For Clinical Trial Use Only”
Storage conditions
Expiry date
The statement “Keep out of reach of children”

5.6.2 Storage

All study medication will be kept securely stored by the site pharmacist/registered dispenser in a secured area with limited access to designated site personnel only.

Test product containing treatment arms will be stored in the supplied containers (thereby protected from light and moisture), between 15 to 25 degrees Celsius.

5.7 Dispensing and Accountability

The site pharmacist/ delegated dispenser will be responsible for dispensing the IMP. Accurate accountability records will be kept by the site to assure that the IMP will not be dispensed to any person who is not a Subject under the terms and conditions set forth in this protocol (i.e. delivery to site, inventory at site, use by Subject, destruction, etc.) 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.

The Investigator undertakes to use the trial medication only as indicated in this protocol.

5.8 Returns and Destruction

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. If no supplies remain, this fact will be indicated in the drug accountability section of the final report.

6 TRIAL VARIABLES AND PROCEDURES

6.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected at the time points described in the trial flow chart:

- Visit Dates.
- Subject Disposition.
- Written Informed Consent (including HIV when applicable).
- Eligibility criteria.
- Demographic data: Date of birth, race and gender.
- Medical and treatment history.
- Screening Coached Spot Sputum Sample:
  - Smear microscopy for acid-fast bacilli.
  - Gene Xpert, Hain Assay MTBDRplus or an alternative molecular or antigen-based test to confirm *M.tb.*
- Serum or Urine pregnancy test: women of child-bearing potential only, whether they are sexually active or not.
- Serology: HIV and CD4 count.
  - Approval for this to be performed will be obtained from Subjects in the written informed consent process. If an HIV test was performed within 1 month prior to trial start, it should not be repeated as long as documentation can be provided (ELISA and/or Western Blot).
  - Prior to HIV testing and on receipt of the results, Subjects will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the Subject, HIV counselling provided to the Subject by the study site should be clearly documented in the Subject's medical records/source. Subjects have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the Subject's medical records/source.
- Karnofsky Score (Appendix 4).

- Chest X-Ray: A Chest X-Ray picture will be obtained from the clinic appointed radiology department or from the Subject if it has been taken within the previous 1 year. The Investigator is responsible for review and analysis for Subject inclusion.
- Method of Birth Control: Male and Female Subjects and their partners.
- IMP Details/Actual Dosing

6.2 Efficacy Variables and Procedures

Two sputum Samples are collected, (one Early Morning brought from home or done in the hospital ward and one spot at the research site under the coaching and observation of the trial staff OR two spot sputum at the research site if Early Morning is not available). 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:

- Culture result;
- If liquid culture in the MGIT platform is used, TTP in liquid medium.

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 subjects 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 (favourable) result. A subject who never achieves culture negative status due to inability to produce sputum, but has completed 6/24 months follow-up and is without clinical or biological evidence of relapse, will be considered to have a favorable outcome.

TB Symptoms Profile:

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

Patient Reported Health Status Variables and Procedures:

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

6.3 Safety and Tolerability Variables and Procedures

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:
    - Hematology/Complete Blood Count/Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count),

        - At Weeks 3, 5, 7, 9, 10, 11, 13, 14, 15, Complete Blood Count/Full Blood Count including red and white cell counts and indices and platelet count ***only*****;** no clinical chemistry or urinalysis at those visits.
    - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactic dehydrogenase (LDH), total amylase, lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, random/fasting glucose, bicarbonate/CO_2, creatine phosphokinase (CPK and CK-MB).
    - 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;
    - Methodology:
        - ECGs should be recorded prior to any lab draws and administration of IMP;
        - Subjects 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 ECG to be performed in single;
        - For each Subject, the ECGs should, to every extent possible, be collected at approximately the same time of the day and in the same fed/fast state (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 (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, which will be provided prior to the trial start. The following analyses will be performed: AREDS2 opacity typing and grading.
- Ophthalmic Examination. The ophthalmic examinations can 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 a separate Ophthalmic Examination Manual.
    - Ophthalmology History (Screening only);
    - Visual Acuity Test – Corrected. Near and Distance Vision;
    - Color Vision Assessment.
- Adverse Events.
- Brief Peripheral Neuropathy Screen (Appendix 6) will record ratings.

- Concomitant Medication/Other Treatments.

6.4 Pharmacokinetic Variables and Procedures

Pharmacokinetics will consist of two separate schedules:

- All Subjects- Pre-dose sampling at weeks 2, 8 and 16 to measure C_{trough} levels of B, B metabolite M2, linezolid and Pa.
- PK Sub-Study Subjects- in addition to the C_{trough} samples, there will be intensive PK sampling at week 16 at pre-dose, 0.5, 1, 2, 4, 8 12, 12.5, 13, 14, 16, 20 and 24 hours after dosing in a sub-group of 20 evaluable Subjects across selected sites.

Pharmacokinetic Analysis:
For the C_{trough} samples, only descriptive statistics will be prepared (average C_{trough}) derived for each analyte.

For the PK Sub-Study samples, the following PK parameters will be estimated from the individual (per Subject) PK plasma concentrations: minimum observed PK plasma concentration (C_{min}), maximum observed PK plasma concentration(C_{max}), time to reach C_{max} obtained without interpolation (T_{max}), area under the PK plasma concentration time (t) curve from zero to the last quantifiable PK plasma concentration prior to the subsequent dose, using the linear trapezoidal rule ($AUC_{(0-t)}$), area under the PK plasma concentration time (t) curve from zero to 24 hours ($AUC_{(0-24)}$). These will be derived for each analyte. In addition, for analyte linezolid at BID dose, the AUC_{0-12}, C_{max}, C_{min}, CL/F and $t_{1/2}$ will be calculated based on dose interval 0-12 hrs.

6.5 Mycobacteriology Characterization Variables and Procedures

The following Mycobacterial Characterization variables will be collected:

Samples from:

- Day 1 (baseline) Early Morning and coached spot sputum samples (or Screening to Week 4 if the baseline is contaminated or negative);
- Any culture positive sample at or following end of treatment.

The *M.tb.* 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 fluoroquinolones, and injectables;
- Extraction of bacterial DNA (*M.tb.*) for molecular genotyping;

The *M.tb.* isolates will be processed at study lab for:

- Speciation of the infecting organisms by molecular or antigen based test at baseline (Day 1 or screening to Week 4 if baseline is contaminated or negative) and initial relapse (first positive at end of treatment or during follow-up) or any positive at or after the week 16 visit

All Day 1 (baseline) *M.tb.* isolates and isolates from positive cultures to be stored at the study microbiology laboratory (or the central lab(s)) until trial closure for the applicable study tests. The extracted *M.tb.* DNA and isolates will be stored for potential further work to validate new assay tools for a maximum of 5 years after trial closure.

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.

7 ADVERSE EVENTS

The Investigators are responsible for eliciting adverse events by observing the Subject and recording adverse events observed by him/her or reported by the Subject during the trial.

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation Subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

7.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death;
- is life threatening (any event in which the Subject 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;
- results in persistent or significant disability/incapacity;
- 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 Subject 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”.

7.1.3 Unlisted (Unexpected) Adverse Event

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

7.1.4 Life Threatening

Any event in which the Subject 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.

7.1.5 Hopsitalization

Any adverse event leading to hospitalisation or prolongation of hospitalisation will be considered as serious, unless at least one of the following exceptions is met:

The admission results in a hospital stay of less than 12 hours;

or

The admission is pre-planned (i.e. elective or scheduled surgery arranged prior to the start of the study);

or

The admission is not associated with an adverse event (e.g. social hospitalisation for purposes of respite care);

or

Hospitalization is standard of care in the treatment of the subjects TB. However if the hospitalisation is prolonged due to the subjects TB symptoms worsening this will be considered serious.

However it should be noted that invasive treatment during any hospitalisation may fulfil the criteria of 'medically important', dependant on clinical judgement.

7.1.6 Associated with the Use of the Drug

An adverse event is considered associated with the use of the drug (Adverse Drug Reaction) if the attribution is possible, probable or very likely.

7.1.7 Attribution/Causality

The definitions for rating attribution/causality will be as described in Table 13.

Table 13: Adverse Events Attribution/Causality Ratings

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

7.1.8 Severity

Severity rating is to be made per the DMID Adult Toxicity Table (Appendix 2). For abnormalities **NOT found** elsewhere in the Toxicity Tables, the DMID scale described in Table 14 below is to be used to estimate grade of severity:

Table 14: Adverse Event Severity Ratings

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.

7.1.9 Other AE Definitions

The following definitions will be used for Adverse Event Reporting:

Action Taken with IMP

- IMP unchanged
- IMP interrupted
- IMP dose reduced
- IMP stopped
- Not applicable (Follow-up period)

Other Action Taken

- None
- Medication given
- Hospitalisation or prolongation of hospitalisation
- Therapeutic or diagnostic procedure

Outcome

- Resolved
- Improved
- Unchanged
- Worse
- Fatal
- Unknown

Occurrence

- Once
- Intermittent
- Continuous

7.2 Reporting

7.2.1 Adverse Event (AE)

Adverse events will be collected by the Investigator from the time a Subject signs the Informed Consent Form through to their Month 24 follow-up visit. The exception is early withdrawal Subjects who will only have SAEs collected from their time of early withdrawal to their Month 24 follow-up visit.

Any AE (serious or non-serious) observed by the Investigator or reported by the Subject will be recorded on the Adverse Event Case Report Form. The Investigator will review each AE and assess its relationship to drug treatment based on all available information at the time of the completion of the case report form. The following information will be recorded for each Adverse Event reported (definitions section 7.1):

- Diagnosis of the AE, if possible. In the case where an overall diagnosis cannot be made, each specific sign and/or symptom will be recorded as individual AEs;
- Date of onset;
- Stop Date (duration) if applicable;
- Severity;
- Action Taken with IMP;
- Other Action Taken;
- Outcome;
- Relationship to IMP;
- Occurrence;
- Seriousness.

7.2.2 Serious Adverse Event (SAE)

Any AE that occurs which is serious must be reported by the Investigator to the study monitor and copied to the Sponsor Medical Monitor within 24 hours of the site first being aware of the SAE, whether or not the serious event is deemed associated with the use of the drug.

In addition, the Investigator will provide a detailed, signed, written, and complete SAE report form that addresses the Investigator's estimates of the attribution/causality of the AE to the study drug and the seriousness of the AE in question to the study monitor and medical monitor within 24 hours of becoming aware of the SAE.

The study monitor will confirm receipt of the SAE Form with the Investigator and review the initial information on the SAE for diagnosis, consistency and completeness of data.

For submission of significant updated or additional information on a previously reported SAE, the Investigator will provide the study monitor and medical monitor with a newly completed Serious Adverse Event Form. This will be submitted to the study monitor and medical monitor within 24 hours of the Investigator receiving the information.

The study monitor will query for additional information from the Investigator, if necessary, to complete the profile of the SAE reported.

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

7.2.3 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.

7.2.4 Post-Trial Adverse Events

Any new SAEs reported by the Subject to the Investigator that occur after the last scheduled contact, and are determined by the Investigator to be possible, probable or certainly related to the use of the IMP, will be reported to the Sponsor, IEC/IRB and regulatory authorities on an expedited basis as required in accordance with local requirements and ICH guidelines for GCP.

7.2.5 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 Subject. 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 Subject, it is considered to be an adverse event.

7.2.6 Disease under Study

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

- worsened while the Subject is in the study; 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 Subject's TB; and
- not clinically significant;

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

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

7.2.7 Overdose

Overdose of IMP experienced by the Subject while on the study, 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 Subject's source documentation.

7.2.8 Drug Interaction

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

7.2.9 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 Subject 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 Subject withdrawn from the trial. Protocol-required procedures for trial discontinuation and follow-up will be performed unless contraindicated by the pregnancy. Should the female partner of a male Subject become pregnant during the study or in the 6 months after the completion of IMP and the Investigator becomes aware that this situation has occurred, consent will be requested from the female partner for collection of information on her pregnancy history and for information on the current pregnancy and birth.

Pregnancy reporting will **follow the same time lines and reporting structures as for a SAE** (see above). SAE reporting will also occur if the pregnancy outcome is a congenital anomaly. This will follow the reporting procedures described above for SAE reporting plus an additional clinical report compiled by the applicable company.

7.3 Monitoring and Safety for Specific Toxicities

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, Subjects should have a confirmatory measurement within 48 hours where possible. The recommendations for managing Subjects below assumes the laboratory abnormalities of concern have been confirmed.

Monitoring for specific toxicities is based upon target organs as defined in preclinical toxicity studies (Investigator's Brochures [4,5,15] and Package Inserts [3,18,31,34]).

7.3.1 ALT, AST and Alkaline Phosphatase elevations:

The Investigator should refer to Appendix 8 – Liver Toxicity Management to appropriately manage the Subject for clinically significant elevations of AST, ALT or Alkaline Phosphatase.

7.3.2 Amylase elevation

Grade 3 (> 2.0 to ≤ 5.0 x ULN):

Contact sponsor Medical Monitor to review. Further testing such as pancreatic amylase should be considered after consultation with the Sponsor Medical Monitor.

Grade 4 (> 5.1 x ULN):

Contact sponsor Medical monitor to review. Investigator should consider subjects with **confirmed Grade 4** elevations of total amylase for temporary or permanent discontinuation from the full regimen.

7.3.3 Lipase Elevation

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

Contact Sponsor medical Monitor to review. Investigator should consider subjects with **confirmed Grade 3 or 4** elevations of lipase for temporary or permanent discontinuation from the full regimen.

7.3.4 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):

Subjects with Grade 2 signs and symptoms should be followed closely. Subjects with Grade 3 or 4 signs and symptoms should be discussed with the Sponsor Medical Monitor and to consider withholding study medication.

Subjects having **Grade 3 (3.1 to 6 x ULN) or Grade 4 (> 6 x ULN) elevation in CK-MB subunit** (with a confirmatory measure 7 days after the initial lab), the Investigator should consider discontinuing the full regimen and discuss with the Sponsor Medical Monitor.

7.3.5 Cardiac Rhythm Disturbances

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

Subjects should be monitored closely. The Investigator should consider discontinuing the full regimen with the Sponsor Medical Monitor.

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 $\geq$ 500 msec, the full regimen should be withheld and the Sponsor Medical Monitor consulted.
- 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 withheld until the reading has been confirmed by the central cardiologist and the Subject is to be treated per the Investigator's clinical judgment. If it is confirmed by the central cardiologist, the Subject is to be withdrawn from the full regimen

7.3.6 Myelosuppression

Investigator should consider withholding linezolid for subjects with:

- Neutropenia with an absolute neutrophil count below 750 (confirmed by repeat);
- Thrombocytopenia below 50,000;
- A drop in haemoglobin to ≤ 6 g/dL;

- Per investigator discretion, a reduction in haemoglobin ≥ 25% of the Subject's baseline value.

For participants who completed the first 4 weeks on linezolid 1200 mg per day, linezolid can be re-started at a later date at Investigator's discretion. If participant did not complete first 4 consecutive weeks of linezolid at 1200 mg per day, a lapse in treatment of 35 consecutive days or more should result in withdrawal from the study.

7.3.7 Peripheral Neuropathy

Investigator should consider withholding linezolid or discontinuing the full regimen permanently for subjects who if in the investigators opinion there is a significant worsening in peripheral neuropathy.

For participants who completed the first 4 weeks on linezolid 1200 mg per day, linezolid may be re-started at a later date at investigator's discretion. If participant did not complete first 4 consecutive weeks of linezolid at 1200 mg per day, a lapse in treatment of 35 consecutive days or more should result in withdrawal from the study.

7.3.8 Optic Neuropathy

Investigator should consider withholding linezolid and obtain further consultation with the site ophthalmologist for subjects with:

- A drop in visual acuity of two or more lines on the Snellen charts.
- Detection of loss of color vision by Ishihara plates defined as > 4 errors on the 12 plate screening test.

For participants who completed the first 4 weeks on linezolid 1200 mg per day, linezolid may be re-started at a later date at investigator's discretion. If participant did not complete first 4 consecutive weeks of linezolid at 1200 mg per day, a lapse in treatment of 35 consecutive days or more should result in withdrawal from the study.

7.3.9. Lactic Acidosis

Investigator should consider withholding linezolid for subjects who experience unexplained lactic acidosis characterized with low bicarbonate levels, weakness and nausea, and subjects should receive immediate medical evaluation by the Investigator.

For participants who completed the first 4 weeks on linezolid 1200 mg per day, linezolid may be re-started at a later date at investigator's discretion. If participant did not complete first 4 weeks of linezolid at 1200 mg per day, a lapse in treatment of 35 consecutive days or more should result in withdrawal from the study.

7.3.10 Neurological

Subjects with co-administration of a serotonergic agent, including anti-depressants, should be monitored closely for signs of serotonin syndrome. The Investigator should determine whether permanent discontinuation of 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 withheld for subjects experiencing a seizure. The Sponsor Medical Monitor should be contacted to review details and discuss whether linezolid or full regimen should be resumed.

7.4 Safety Monitoring by the Data Safety Monitoring Committee

A DSMC will be appointed for the study. The primary responsibility of the DSMC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial Subjects by monitoring Subject safety, assess Subject 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. The DSMC may have an organisational 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 to occur every 6 months at a minimum. 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.

8 STATISTICAL ANALYSIS

The statistical analysis plan (SAP), which will contain details of the analyses described generally in this section, will be written and signed off prior to Clinical Database Lock.

8.1 Analysis Population

The intention-to-Treat (ITT) analysis population will comprise of all subjects who were assigned study treatment.

The Safety analysis population will contain all subjects included in the ITT analysis population and received at least one administration of study drug.

The analysis populations will be defined in the SAP.

8.2 Sample Size

The objective of this trial is to evaluate the efficacy, safety, tolerability and pharmacokinetics of combinations of bedaquiline, linezolid and pretomanid in Subjects with either pulmonary XDR-TB, treatment intolerant or non-responsive MDR-TB.

Formal sample size calculations have not been performed due to the exploratory nature of the trial (no formal statistical hypothesis is therefore to be tested).

No formal interim analyses will be done for this study.

8.3 Interim Analyses

Timing of initial interim analysis will be conducted when the first 15 participants reach 6 months after completion of IMP. Further interim analyses will be specified in the statistical analysis plan (SAP).

Once all patients have been recruited or have completed the treatment period, no further futility analyses will be performed.

8.4 Primary Endpoint Analysis

The primary efficacy endpoint is treatment failure, defined as bacteriologic failure or relapse or clinical failure through follow-up until 6 months after the end of treatment.

The probability of treatment failure through follow-up until 6 months after the end of treatment, as a function of time after assignment of treatment, will be analyzed using Kaplan-Meier analysis.

The binomial proportion for subjects with bacteriologic failure will be presented.

No multiplicity adjustments for alpha will be done as this is an exploratory trial.

8.5 Secondary Endpoint Analysis

8.5.1 Efficacy

The secondary efficacy endpoints and analyses are as follows are:

- Incidence of bacteriologic failure or relapse or clinical failure through follow-up until 24 months after the end of treatment as a confirmatory analysis.
- Time to sputum culture conversion to negative status through the treatment period.

The time to sputum culture conversion will be analyzed using Kaplan-Meier analysis.

- Proportion of Subjects with sputum culture conversion to negative status at 4, 6, 8, 12 and 16 weeks with no subsequent, confirmed, positive culture(s).

- Proportion of Subjects experiencing a change from baseline of TB symptoms.

The binomial proportion for subjects with sputum culture conversion at each timepoint and subjects experiencing a change from baseline of TB symptoms will be presented.

- Change from baseline in Patient Reported Health Status.
- Change from baseline weight.

The change from baseline in Patient Reported Health Status will be summarized using descriptive statistics by visit.

The effect of baseline covariates may be explored, including but not limited to the presence or absence of cavities on Chest X-Ray, the presence or absence of HIV infection and CD4 cell count.

8.6 Exploratory Endpoint Analysis

8.6.1 Efficacy

The exploratory efficacy endpoints and analyses are as follows:

- Evaluate whether any of the secondary endpoints predicts relapse free cure.
-
- Subgroup analyses of the primary endpoint on the MITT analysis population will be considered
- Correlation of Time over mitochondrial protein synthesis inhibition (MPS50) with linezolid toxicity, (The MPS50 value will be an assumed value from literature).

Details for the analysis of the aforementioned endpoint will be described in the SAP.

8.6.2 Safety and Tolerability Analysis

- The incidence of all cause mortality will be summarized.
- All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by Preferred Term within each MedDRA System Organ Class (SOC).
- Treatment-emergent adverse events (TEAEs) are defined as AEs which started at or after the first administration of IMP and includes those events started prior to the first administration of IMP but which worsened after the first intake. Adverse events starting after the last administration of IMP until the last scheduled visit/assessment/measurement will be regarded as treatment-emergent.

- The incidence of the following events will be summarized for further medical analysis:
    - Incidence of TEAEs;
    - Incidence of TEAEs by Severity;
    - Incidence of TEAEs by DMID toxicity grade;
    - Incidence of Drug-Related TEAEs;
    - Incidence of Serious TEAEs;
    - Incidence of TEAEs Leading to Early Withdrawal;
    - Incidence of TEAEs leading to Death.

- Cardiovascular Safety: QT intervals will be adjusted using Fridericia's correction and Bazett's correction. QT/QTc values and changes from pre-dose (average of Screening and Day 1 values) at each time point will be summarized using descriptive statistics by group and time of collection. These will be presented as descriptive analyses, and no inferential tests will be carried out.
    - Post-baseline QT/QTc intervals will be classified into the following categories:
        - QT/QTc < 450 msec
        - 450 msec $\leq$ QT/QTc < 480 msec
        - 480 msec $\leq$ QT/QTc < 500 msec
        - QT/QTc $\geq$ 500 msec
    - QTc changes from baseline will be classified into the following categories:
        - increase < 30 msec,
        - $\geq$ 30 msec and < 60 msec, and
        - increase $\geq$ 60 msec.
    - Frequency counts will be used to summarize the number of Subjects 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 Subject 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 Subject for both Visual Acuity and Color Assessments. Categorical data for changes in visual acuity and color vision from baseline will be summarized in a frequency table for the right and left eye, respectively.

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

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

8.7 Pharmacokinetics:

For each analyte (per visit), the PK plasma concentrations 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 median concentration-versus-time graphs will be provided (with error bars as appropriate).

For the PK sub-study samples, the following PK parameters will be estimated per analyte from the individual (per Subject) PK plasma concentrations: Minimum observed PK plasma concentration (C_{min}), maximum observed PK plasma concentration(C_{max}), time to reach C_{max} obtained without interpolation (T_{max}), area under the PK plasma concentration time (t) curve from zero to the last quantifiable PK plasma concentration prior to the subsequent dose, using the linear trapezoidal rule ($AUC_{(0-t)}$), area under the PK plasma concentration time (t) curve from zero to 24 hours ($AUC_{(0-24)}$).

8.8 Pharmacokinetics-Pharmacodynamics (PK-PD):

Further detail on correlations between plasma drug concentrations and efficacy and safety findings will be outlined in the SAP.

8.9 General Mycobacteriology

Descriptive summary statistics of the mycobacterial characteristics will be presented.

9 RECORDS MANAGEMENT

9.1 Data Collection

All CRF/eCRF pages will be completed for each Subject who receives any amount of IMP. For Screening Failure Subjects a Screening failure CRF/eCRF will be completed. For Subjects who are prematurely withdrawn, the visits up to withdrawal plus the withdrawal and applicable follow-up visits need to be completed.

9.2 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, 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 persons direct access to source documents.

9.3 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.

9.4 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 5 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 5 years have elapsed since the formal discontinuation of clinical development of the IMP.

The Sponsor will make financial provisions for the Investigator to deposit the documents at an external site for safekeeping for as long as required by regulations and the Sponsor.

10 QUALITY CONTROL AND ASSURANCE

10.1 Site Procedures

The Investigator undertakes to perform the clinical trial in accordance with this protocol, International GCP, and the ethical principles that have their origin in the Declaration of Helsinki, and applicable regulatory requirements.

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 study. Subject compliance will be monitored throughout the study.

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 study. However the Investigator maintains responsibility for the study and will supervise the Sub-Investigators. Written IEC/IRB approval will be obtained prior to involvement in the study.

The Investigator will ensure that all site personnel are adequately trained in GCP, the protocol, IB and all study procedures and requirements.

10.2 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 Subjects 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 for the purpose of monitoring various aspects of the study. Visits will take place usually within a predetermined interval, but this may vary during the course of the study. The Investigator and site staff will allow the study 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), Subject records and laboratory raw data, 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.

10.3 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 study. The audit will involve the review of all study-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all study-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.

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.

11 ETHICS AND REGULATORY

11.1 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.

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

The protocol and required study related documents will be reviewed by the sites respective IEC/IRB. The study will not start until the IEC/IRB has approved the protocol, written informed consent, any written information to be provided to the Subject or any modification thereof, plus any other study 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 the IRB/IEC. The records should be filed in the Investigator's Study File, and copies will be sent to the Sponsor. The Investigator may delegate IRB/IEC communication responsibilities to another party/vendor (e.g. CRO). This delegation should be clearly documented in writing and filed with the study documents at the site.

11.3 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.

11.4 Informed Consent

Written informed consent will be obtained from all Subjects (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 Subject 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 Subject being considered for inclusion in this trial is given a full explanation of the protocol. 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.

Once the appropriate essential information has been provided to the Subject and fully explained by the Investigators (or qualified designees) and it is felt that the Subject understands the implications of participating, the IEC/IRB approved written informed consent form will be signed and dated by both the Subject and the person obtaining consent (Investigators or designees), and by any other parties required by the IEC/IRB.

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 Subject. 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 Subject's medical record.

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

11.5 Confidentiality

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

12 PUBLICATION POLICY

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

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 study in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory Investigators, as appropriate.

13 PROTOCOL AMENDMENT POLICY

Any change to the protocol will be effected by means of a protocol amendment. Any changes which affect Subject 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 Subject'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.

14 FINANCIAL ASPECTS, INSURANCE AND INDEMNITY

The study Sponsor and funder 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 Subjects 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 Subjects will not receive any incentives for their involvement in the study. The Sponsor has made provision to reimburse the Subjects for out-of-pocket expenses such as travelling to and from the study site and other miscellaneous costs as a result of their study 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 DISEASES (DMID) ADULT TOXICITY TABLE

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

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

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

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

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

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

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

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
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 VITAL SIGNS

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[19]

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

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

APPENDIX 5 EQ-5D-5L QUESTIONNAIRE

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

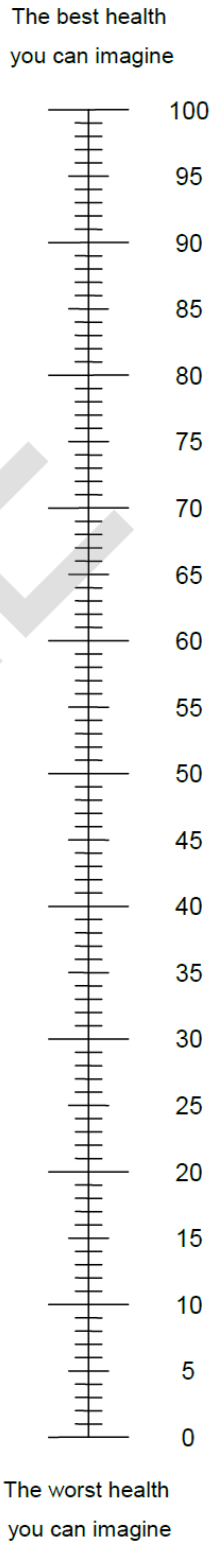
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 6 Brief Peripheral Neuropathy Screening

BRIEF PERIPHERAL NEUROPATHY SCREEN

Patient Initials				Patient ID										
1. Visit (Circle One)	All Subjects	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 26						
		3 Month	6 Month	12 Month	24 Month									
	9 Month Treatment **ONLY**	Week 30	Week 34	Week 39										
	Other	Early Withdrawal	Unscheduled For new onset or worsening peripheral neuropathy during treatment											
2. Date of Assessment		D	D	M	M	M	Y	Y	Y	Y				

INTERFERENCE WITH WALKING OR SLEEPING

3. In the last two weeks, have pain, aching or burning in your feet interfered with your walking or sleeping? (Check one)	Y	N

*If **YES**, ask the patient to rate the level of interference (1 to 10) to his walking or sleeping caused by this pain, ache or burning (circle one).*

3a.	Minimal			Modest				Severe		
	01	02	03	04	05	06	07	08	09	10

SUBJECT ELICITED SYMPTOMS

- *Using the faces below, ask the patient to rate the severity of the symptoms for the questions 4, 5, 6 on a scale of 1 (mild) to 10 (severe) for both feet. If the severity is different between the left and right foot, record the severity of the most affected foot.*
- *Enter a score for each symptom.*
- *If a symptom has been present in the past, but not since the last visit, enter '00 – Currently Absent'*
- *If a symptom has never been present, enter '11 – Always Been Normal'*

00	02	04	06	08	10
Very Happy, No Symptoms	Just a little bit	A little more	Even more	A whole lot	Worst

During the last 14 days, have you experienced:		Severity	
	4. Pain, aching or burning in feet or legs?		
	5. "Pins and needles" in feet or legs?		
	6. Numbness (lack of feeling) in feet or legs?		

BRIEF PERIPHERAL NEUROPATHY SCREEN

Patient Initials				Patient ID										

PERCEPTION OF VIBRATION

- *Press the ends of a 128 Hz tuning fork together so the sides touch and let go. Place the vibrating tuning fork on the bony prominence on the patient's wrist to be sure that they can recognize the vibration or "buzzing" quality of the tuning fork.*
- *Again, press the ends of the tuning fork hard enough so that the sides touch and let go. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of the great toe and begin counting the seconds. Instruct the Subject to tell you when they stop feeling the vibration or "buzzing".*
- *Repeat for the great toe on the other foot*

Vibration Perception Grade Scale:
0 – Vibration felt for >10 seconds (normal)
1 – Vibration felt for 6-10 seconds (mild loss)
*2 – Vibration felt for 5 seconds or less (moderate loss)**
*3 – No feeling of vibration (severe loss)**
*9 – Unable to evaluate or did not assess**

	Right	Left
7. Measured vibration grade of great toe DIP joint		

DEEP TENDON REFLEXES

- *The examiner uses one hand to press upward on the ball of the foot, dorsiflexing the Subject's ankle to 90 degrees. Using the reflex hammer (preferably long handled), the examiner strikes the Achilles tendon.*
- *The tendon reflex is felt by the examiner's hand as plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck.*
- *Repeat for ankle on other leg*

Ankle reflex grade scale:
0 – Absent
1 – Hypoactive
2 – Normal deep tendon reflexes
3 – hyperactive deep tendon reflexes ***(e.g. with prominent spread of toes)***
4 – clonus
9 – unable to evaluate or did not assess

	Right	Left
8. Measured ankle reflex grade		

COMMENTS

Name of Person Completing Form										Name of Clinician (if required)									
Signature of Person Completing Form										Signature of Clinician (if required)									
Date	D	D	M	M	M	Y	Y	Y	Y	Date	D	D	M	M	M	Y	Y	Y	Y

APPENDIX 7 TUBERCULOSIS SYMPTOM PROFILE (V3)

TUBERCULOSIS SYMPTOM PROFILE (V3)

This questionnaire asks about symptoms that patients with tuberculosis may or may not experience.

Please read each symptom carefully and think about your experience **during the past 7 days** when you make your response. Then tick (☑) one box for each symptom.

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

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

TB Symptom	**Rate your experience of each symptom over the past 7 days.**			
Feeling feverish	☐ None	☐ Mild	☐ Moderate	☐ Severe
Feeling chills	☐ None	☐ Mild	☐ Moderate	☐ Severe
Excessive sweating	☐ None	☐ Mild	☐ Moderate	☐ Severe
Shortness of breath	☐ None	☐ Mild	☐ Moderate	☐ Severe
Chest pain	☐ None	☐ Mild	☐ Moderate	☐ Severe
Feeling unwell	☐ None	☐ Mild	☐ Moderate	☐ Severe
Tiredness/weakness	☐ None	☐ Mild	☐ Moderate	☐ Severe
Cough	☐ None	☐ Mild	☐ Moderate	☐ Severe
Coughing up mucus	☐ None	☐ Mild	☐ Moderate	☐ Severe
Coughing up blood	☐ None	☐ Mild	☐ Moderate	☐ Severe
During the past 7 days, how would you rate your appetite? ☐ Good ☐ Fair ☐ Poor				

Approved, Issued Date 09-Apr-2012

APPENDIX 8 LIVER TOXICITY MANAGEMENT GUIDELINES

Standard anti-TB chemotherapy is known to cause derangement of liver function tests in a substantial number of patients. In many cases, these 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 subjects who are at risk of progressing to serious liver injury. The observation of altered liver function to a degree with a high risk of progressing further to liver failure has been referred to informally as *Hy's Law* (Temple 2001; Reuben 2004); this reflects pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo;
2. Among trial subjects 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 ALP) ;
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

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

Procedure

Blood tests for liver function will be taken routinely at Screening (Days -9 to -1), at the specific visits designated in the protocol and at Early Withdrawal. If at any other visit, the Investigator suspects derangement of liver function (e.g. the Subject describes nausea and vomiting, right upper abdominal pain or is jaundiced), blood should be taken for liver function tests and the Subject comprehensively assessed for evidence of hepatitis, hepatic impairment and any potentially contributing cause(s).

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 abnormal results that are clinically significant must be recorded as Adverse Events in the eCRF and graded clinically per the DMID Adult Toxicity Table (Appendix 2).

Assessments and decision making for elevations in aminotransferase values or bilirubin of various levels of concern are detailed below:

Decision to Consider Stopping Drug Regimen Administration

Consideration of stopping drug administration, at least temporarily, to subjects with liver function abnormalities or signs and symptoms of hepatitis should be discussed with the Sponsor Medical Monitor in the following situations:

- ALT or AST >8x ULN;
- ALT or AST >5x ULN for more than 2 weeks;

- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

*If a subject has ALT or AST ≥3x ULN **and** Total Bilirubin >2x ULN, the IMP should be interrupted and the Subject's clinical course discussed with the Sponsor Medical Monitor.*

More detailed assessments and decision making for various levels of elevations in aminotransferase values, alkaline phosphatase or bilirubin are detailed below:

Grade 3 per DMID, ALT, AST, AP ≥ 3x ULN to 8x ULN or if a substantial increase from baseline (such as > 2-fold increase):

- Contact the Subject and recall them as soon as possible. Assess the Subject for other signs and symptoms of more specific hepatic events including hepatic impairment and/or hepatitis. If you are concerned, you should consider arranging for the subject to present to a medical facility (e.g. emergency department) immediately for assessment.
- Assess the clinical significance - if the Subject has jaundice, a coagulation disorder or signs of hepatic encephalopathy, all study medication should be withheld pending assessment/improvement.
- Assess possible contributing factors – This should include (but is not limited to), alcohol, intra-venous and other drug use, travel, unwell contacts, any medications with known hepatotoxic potential, herbal products and dietary supplements, previous or known hepatitis infection and exposure to environmental chemical agents. Although anti-TB chemotherapy is known to cause liver function test derangement, the Subject should always be assessed for other possible cause(s) or contributing factor(s).
- The Subject should also be advised to stop taking any medications/substances, other than the study medications used to treat TB that may be contributing to or causing derangement of liver function tests.
- Make every effort to repeat the testing of ALT, AST, AP and bilirubin within 48 hours to confirm the abnormalities and determine if they are increasing or decreasing. Consider any additional laboratory tests that may help characterize the Subject's clinical condition. Subjects should be tested for viral hepatitis (e.g. hepatitis A and B and any other tests available of viral hepatitis). If tests for viral hepatitis are not available or done, it may still be helpful to collect an additional 10ml sample for serum for freezing (5ml yellow/SST tube x2) which may be tested later. The Subject's consent must be obtained for this.

Elevated liver enzymes considered to be of clinical significance but not accompanied by other signs and symptoms, should be reported as an adverse event and recorded as elevated liver enzymes in the eCRF. 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, 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 confirms the diagnosis of hepatitis solely 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 in the eCRF.

If ALT, AST, AP are Grade 4 per DMID (> 8x ULN):

- Contact the Subject and recall them as soon as possible. Generally, the trial medication should be stopped, but this should be discussed first with the Sponsor Medical Monitor whenever possible. Assess the subject for other signs and symptoms of more specific hepatic events, including hepatic impairment and/or hepatitis. If you are concerned, you should consider arranging for the subject to present to a medical facility (e.g. emergency department) immediately for assessment.

- Assess the clinical significance – Consider hospitalisation if the ALT is more than 10 times the ULN and/or the Subject has jaundice, a coagulation disorder or signs of hepatic encephalopathy. All study medications should be withheld pending assessment/improvement.
- Assess possible contributing factors – This should include (but is not limited to), alcohol, intra-venous and other drug use, travel, unwell contacts, any medications with known hepatotoxic potential, herbal products and dietary supplements, previous or known hepatitis infection and exposure to environmental chemical agents. Although anti-TB chemotherapy is known to cause liver function test derangement, the subject should always be assessed for other possible cause(s) or contributing factor(s).
- Make every effort to repeat the testing of ALT, AST, AP and bilirubin within 48 hours to confirm the abnormalities and determine if they are increasing or decreasing. Consider any additional laboratory tests that may help characterize the subject's clinical condition. Subjects should be tested for viral hepatitis (e.g. hepatitis A and B and any other tests available of viral hepatitis). If tests for viral hepatitis are not available or done, it may still be helpful to collect an additional 10ml sample for serum for freezing (5ml yellow/SST tube x2) which may be tested later. The Subject's consent must be obtained for this.

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General Principles for following Subjects with potential liver toxicity

The Subject should be contacted regularly depending on the Grade of LFT elevations and the magnitude of increase relative to baseline for the Subject. Initially, this should be daily and subsequently depends on clinical course/individual circumstances. Staff must ensure all Subjects know to seek medical attention urgently if they experience any evidence of worsening liver disease. Symptoms may include (but are not limited to), malaise, fever, nausea, vomiting, loss of appetite, dark urine, yellowing of the eyes or skin (jaundice).

Liver function tests 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 Subject. Manage the Subject 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 Subject is still culture positive for acid fast bacilli.

Restarting Medication

If the Investigator (after consultation with the Sponsor Medical Monitor), stops administration of the study medication, consideration may be given to re-starting the study medication. Once the liver function values have decreased substantially and symptoms have significantly improved, a decision must be made about further TB management. This will be dependent on clinical context and the decision must be made in discussion with the Sponsor Medical Monitor. 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. Subjects who permanently discontinue study medication should be managed as clinically indicated according to local National TB Programme guidelines. The Sponsor Medical Monitor can provide advice and examples of suitable treatment regimens to use if required.