16.1 Trial Information

16.1.1 Protocol and Protocol Amendments

SimpliciTB Protocol, Version 1.0, 05OCT2017

SimpliciTB Protocol, Version 2.0, 21FEB2018

SimpliciTB Protocol, Version 2.0 Summary of Changes

SimpliciTB Protocol, Version 3.0, 14JAN2019

SimpliciTB Protocol, Version 3.0 Summary of Changes

SimpliciTB Protocol, Version 4.0, 30SEP2019

SimpliciTB Protocol, Version 4.0 Summary of Changes

SimpliciTB Protocol, Memo, 17APR2020

SimpliciTB Protocol, Russia Version 1.0, 10JUL2018

SimpliciTB Protocol, Russia Version 1.0 Summary of Changes

SimpliciTB Protocol, Russia Version 2.0, 25JAN2019

SimpliciTB Protocol, Russia Version 2.0 Summary of Changes

SimpliciTB Protocol, Russia Version 3.0, 01OCT2019

SimpliciTB Protocol, Russia Version 3.0 Summary of Changes

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

SIMPLICITB

+.

Protocol Number:	NC-008 (B-Pa-M-Z)
Title:	An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).
Drug(s)/Combination(s):	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Initial Protocol Version/Date:	V1.0 / 05 October 2017
Protocol Name:	**SimpliciTB**

PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (B-Pa-M-Z)**

Protocol Date: **V1.0, 05 October 2017**

Protocol Name: **SimpliciTB**

SPONSOR: Global Alliance for TB Drug Development

I agree to the terms of this trial protocol.

DocuSigned by:
Paul Bruinenberg
Signer Name: Paul Bruinenberg
Signing Reason: I approve this document
Signing Time: 25 October 2017 | 13:48 EDT
3B496C3B3A5A4B0AAE32731255B7116B

Signature of Senior Medical Officer

Paul Bruinenberg MD, MBA

Paul Bruinenberg

Printed Name

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October 25, 2017 | 1:48 PM EDT

Date

LEAD INVESTIGATOR

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

Signature

Printed Name

Date

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (B-Pa-M-Z)**

Protocol Date: **V1.0, 05 October 2017**

Protocol Name: **SimpliciTB**

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

_____ _____
Signature Printed Name

_____
Date

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Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	ABaCavir
AE	Adverse Event
AFB	Acid-fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	ALanine aminoTransferase
AREDS2	Age Related Eye Disease Scale 2
ART	Anti-Retroviral Therapy
AST	ASpartate aminoTransferase
AUC_{τ}	Area Under Curve over a dosing interval
B	Bedaquiline
BA	Bacterial activity
BMI	Body Mass Index
BPaMZ	Combination of bedaquiline plus pretomanid plus moxifloxacin plus pyrazinamide
C	Clofazimine
CFU	Colony Forming Units
$C_{(max), (min)}$	plasma Concentration (maximum), (minimum)
CO_2	Carbon diOxide
CPK	Creatine PhosphoKinase
CYP3A4	Cytochrome P450 3A4
DMID	Division of Microbiology and Infection Disease
DNA	DeoxyriboNucleic Acid
DR-TB	drug-resistant tuberculosis For this particular protocol defined as TB participants with 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB) (participants with fluoroquinolone resistance are excluded)
DS-TB	drug-sensitive tuberculosis
DSMC	Data Safety and Monitoring Committee
E	Ethambutol
EBA	Early Bacteriocidal Activity
EC	Ethics Committee
ECG	ElectroCardioGram
EFV	EFaVirenz
(e)CRF	(electronic) Case Report Form
EMS	Early Morning Sputum
EWD	Early Withdrawal
FTC	Emtricitabine
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
H	Isoniazid
hERG	Human *Ether-à-go-go* Related Gene
HIV	Human Immunodeficiency Virus

HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
HR	Isoniazid plus rifampicin combination tablet
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent to Treat
IUATLD	International Union Against Tuberculosis and Lung Disease
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Linezolid
LH	Luteinizing hormone
LLN	Lower Limit of Normal
LPV	LoPinaVir
LTFU	Long term follow up
M	Moxifloxacin
MBD	Minimum Bactericidal Dose
MIC	Minimum Inhibitory Concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi Drug Resistant Tuberculosis
MGIT	Mycobacterial Growth Inhibiting Tube
mITT	Modified Intent To Treat
ms	millisecond
NVP	NeViraPine
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NRTI	(Triple) Nucleosidase Reverse Transcriptase Inhibitor
Pa	Pretomanid
PD	PharmacoDynamic
PP	Per Protocol
PK	PharmacoKinetic
PR	PR interval
R	Rifampicin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSCC	Serial sputum colony counting
TB	Tuberculosis
TDF	Tenofovir
TEAE	Treatment Emergent Adverse Events
TTP	Time To Positivity
ULN	Upper Limit of Normal
WHO	World Health Organization
XDR-TB	eXtensively Drug Resistant Tuberculosis
µg(/ml)	micrograms (per milliliter)
Z	pyraZinamide (tablets)

1.0 Synopsis

1.1 Synopsis Summary

Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished Products:	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Number/Title:	NC-008 / (B-Pa-M-Z)/ An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB)
Treatment Indication:	Pulmonary Tuberculosis (TB)
Trial Objective(s):	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with: **Drug Sensitive TB (DS-TB)** – BPaMZ given for 17 Weeks (4 months) – Standard HRZE/HR treatment given for 26 weeks (6 months) **Drug Resistant TB (DR-TB)** – BPaMZ given for 26 Weeks (6 months) **DR-TB Defined as participants with** 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)
Trial Design:	Phase 2c multi-center, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. All participants in the below arms will have follow-up for a period of 104 weeks (24 months) from the start of therapy. **Participants with Drug Sensitive TB (DS-TB):** Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR combination tablets daily for 26 weeks (6 months). participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation. **Participants with Drug Resistant TB (DR-TB):**

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	Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).
Patient Population:	A total of up to 450 male and female participants, diagnosed with DS-TB or DR-TB, aged 18 years and over with a target of up to 50% being HIV positive. 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation. Up to 150 DR-TB participants will be enrolled
Test product, Dose and Mode of Administration:	**The Test Treatment Regimen (BPaMZ) consists of a combination of the following products** and will be supplied as: bedaquiline 100 mg tablets (B) pretomanid 200 mg tablets (Pa) moxifloxacin 400 mg tablets (M) pyrazinamide 500 mg tablets (Z) **Instructions for Dosing of Test Regimen (BPaMZ):** Treatment will be administered orally once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months) in the following dosing schemes: **Participants with Drug Sensitive TB: (DS-TB)** Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 17 weeks (Total treatment duration 4 months) OR **Participants with Drug Resistant TB: (DR-TB)** Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 26 weeks (Total treatment duration 6 months)
Positive Control Product, Dose and Mode of Administration:	**The Control Treatment Regimen (HRZE/HR) will be supplied as:** **HRZE Tablets:** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). This combination will be given for the first 8 weeks. AND

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	HR Tablets: (isoniazid 75 mg plus rifampicin 150 mg combination tablets). This combination will be given from Weeks 9 to 26. **Instructions for Dosing Control Treatment Regimen (HRZE/HR):** To be taken with a glass of water (approximately 240 ml). HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes. Treatment will be administered orally once daily only to the "control" randomized DS-TB participants as follows: **Weeks 1-8:** HRZE tablets with the daily dose per the Participant's weight as follows: 30-37 kg: 2 tablets; 38-54 kg: 3 tablets; 55-70 kg: 4 tablets; 71 kg and over: 5 tablets; **Weeks 9-26:** HR with daily dose per the participant's weight as follows: 30-39 kg: 2 tablets; 40-54 kg: 3 tablets; 55-70 kg: 4 tablets; 71 kg and over: 5 tablets. Vitamin B6 25 mg daily supplement to be taken with the HRZE/HR treatment.
Treatment Interruptions/Pauses:	**For All Trial Regimens:** The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation, unless an interruption/pause is required urgently for a safety concern; the Medical Monitor should then be informed within 24 hours of the interruption/pause if not discussed prior to implementation. The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the investigator to identify, capture and address the cause(s) (e.g. side effects) of the non-adherence and contact the sponsor medical monitor. Action required for participants missing the following number of doses within the trial treatment regimens: • < 7 consecutive doses: restart treatment, no extension of treatment required.

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	• 7 to ≤ 21 consecutive doses: restart treatment, extend the treatment by the number of consecutive doses missed. In this case: ➢ the final treatment visit should also be pushed out to the date of last dose. ➢ it is not necessary to have an unscheduled visit at the time when the End of Treatment visit would have been. • Greater than 21 consecutive doses: discontinue treatment and withdraw participant from the trial. Any participant for whom the trial medication is discontinued (including for non-adherence) will be discussed with the sponsor medical monitor and, if applicable, the participant will be restarted on trial medication as soon as possible.

Statistical Methods:
A general description of the statistical methods planned to be used to analyze efficacy data is outlined below. Specific details will be provided in the statistical analysis plan (SAP,) which will be written and signed off prior to the first participant enrolled in the trial.

The primary analysis will be conducted using culture results from liquid culture (in the Mycobacterial Growth Indicator Tube (MGIT) system).

Criteria for Evaluation:

The primary efficacy endpoint will be time to culture negativity over 8 weeks. The primary hypothesis to be evaluated is:

In the participants with DS-TB in the experimental BPaMZ treatment regimen, the time to culture negativity by 8 weeks will be superior compared to the participants who are treated with the standard HRZE regimen.

There will be three main analyses of the primary efficacy endpoint. A modified Intent to Treat (mITT) analysis will be primary. A per-protocol (PP) analysis and an ITT analysis will also be performed for the secondary endpoint. These will be examined for consistency with the mITT analysis.

Note:
Culture conversion requires at least 2 consecutive culture negative samples, at least 7 days apart (after positive baseline confirmation).
Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered culture negative at that visit.

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Secondary Endpoints

A key secondary endpoint will be the proportion of participants experiencing bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks (12 months). The hypothesis to be evaluated for this endpoint is:

In the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen.

Other Secondary Endpoints

Efficacy:

Incidence of bacteriologic failure or relapse or clinical failure at 104 weeks from the start of therapy.
Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
Change from baseline in weight.
Change from baseline in TB symptoms.
Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.

Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
Quantitative and qualitative electrocardiogram (ECG) results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.

Changes in male reproductive hormones and lens opacities.

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [Cmin], maximum plasma concentration [Cmax], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so, too, will the effects of con-medications including antiretroviral therapy (ART), as feasible. Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy

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and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

Exploratory:
Evaluate whether any of the secondary endpoints predicts relapse free cure.
Subgroup analysis of populations by HIV status

No formal statistical comparisons will be made for the participants enrolled with DR-TB.

Sample Size
Primary endpoint: 150 participants per arm (DS-TB patients) will provide at least 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks.

Additional efficacy parameters will be evaluated including the incidence of bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks and 104 weeks from the start of therapy. Time to unfavourable outcome from assignment of trial treatment through follow-up as a function of time will be analyzed using Kaplan-Meier analysis.

Trial Duration:
Approximately 4 years (18-month enrollment period for DS-TB participants, up to 26 week-treatment, and 104-week follow-up from start of therapy. Depending on the DR-TB recruitment rate, enrollment into this arm may be continued after enrollment into the DS-TB arms is complete). The DR-TB group may still be ongoing while the DS-TB group is halted if the enrollment target is reached.

There will be 3 database locks, data analyses and trial reports generated for this trial:
When all participants have completed 8 weeks (2 months) of treatment from baseline.
When all participants have completed 52 weeks (12 months) follow-up from start of therapy.
When all participants have completed 104 weeks (24 months) follow-up from start of therapy.

1.2 Synopsis Flow Chart and Procedures

Period	Screen-ing[a]	Treatment															Follow-Up[c]					
Visit[b]	Day -9 (DS) to -1	Day 1 (Baseline)[d]	Day 7 (Week 1)	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 17 *4-month treatment*[e]	Week 17 *6-month treatment*[e]	Week 22	Week 26 *4-month treatment*[e]	Week 26 *6-month treatment*[e]	Week 39	Week 52	Week 65	Week 78	Week 104	Early Withdrawal[c]
Visit Window[v]	N/A	+/- 3 Days									+/- 5 Days						+/- 14 Days					
Written Informed Consent	X																					
Demography	X																					
Medical/Treatment/ Smoking History	X																					
Inclusion/Exclusion	X	X																				
Sputum Sampling[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Status[h] and CD4 Count[i]	X																					
Karnofsky Score	X																					
Urine Drug Screen[j]	X																					
Urine Pregnancy Test[k]	X	X								X		X	X		X	X						X
Laboratory Safety Test[l]	X	X	X	X	X	X		X		X	X	X	X		X	X						X
Male Reproductive Hormone Tests[m]	X	X											X		X		X					
12-lead ECG[n]	X	X	X	X		X				X		X	X		X	X	X					X
Chest X-Ray[o]	X																					
TB Symptoms Profile	X	X		X		X				X		X	X		X	X		X			X	X

Period	Screen-ing[a]	Treatment															Follow-Up[c]					
Visit[b]	Day -9 (DS) to -1	Day 1 (Baseline) [d]	Day 7 (Week 1)	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 17 *4-month treatment* [e]	Week 17 *6-month treatment* [e]	Week 22	Week 26 *4-month treatment* [e]	Week 26 *6-month treatment* [e]	Week 39	Week 52	Week 65	Week 78	Week 104	Early Withdrawal[c]
Patient Reported Health Status	X	X		X		X				X		X	X		X	X		X			X	X
Vital Signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination[p]	X											X	X		X	X	X					X
Physical Examination – full[q]	X	X										X				X						X
Physical Examination – limited[r]			X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Pharmacokinetic Sampling[s]		X		X						X	X	X	X				X		X	X	X	
IMP Randomization/ Assignment[t]		X																				
IMP Compliance Check[u]			X	X	X	X	X	X	X	X	X	X	X	X[e]		X						X[t]
Concomitant Medications	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
Investigator Assessment[v]																		X			X	

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

a. **Screening:** Screening assessments can occur on different days within nine days prior to Day 1 dosing (randomisation).

b. **Visit Schedule (due to unforeseen circumstances):** If the duration of treatment is extended due to dose pauses the final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time that the End of Treatment visit would have been.

c. **Follow-up Visits for Early Withdrawal Participants:** Once a participant has been permanently withdrawn from the trial, they will be required to attend Early Withdrawal, Week 52 (if not already performed) and Week 104 follow-up visits. The Week 52 and Week 104 visits will be to collect Serious Adverse Event (SAE) information (including verification of survival) and participant reported TB outcome information only and may be telephonic, a home or a site visit. They will occur at Week 52 and/or Week 104 after the participant's start of treatment date. Refer to Table 5 for additional guidance.

d. **Day 1 (Baseline):** All procedures are to be completed prior to dosing.

e. **End of Treatment Visit:** IMP Compliance Check is not performed at the Week 22 visit for participants who have completed treatment at Week 17.

f. **Sputum Sampling:** The Sputum sampling methodology/requirements and tests will be described in a separate document, the Mycobacteria Laboratory Manual.

1. Days -9 to -1 (Screening). Two spot sputum samples taken 30 minutes apart will be collected at the research site under the coaching and observation of the trial staff. The following analyses will be performed on the first of these samples:
   - Smear microscopy for acid-fast bacilli (AFB);
   - Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance;
   - Liquid Culture (MGIT) for *Mycobacterium tuberculosis* (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive.

The second sample is collected as a back-up sample to the first sample in case it is technically not possible to obtain a result/s from the first sample. If the Day (-9 to -1) (Screening) spot sputum smear shows an indeterminate result or is AFB negative, the test may be repeated on a freshly collected spot sputum/s and that result will be used.

2. All visits from Day 1 (baseline) up to and including Week 104, plus any unscheduled visits. Two sputum samples (ideally one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff; if the participant forgets to bring in the Early Morning Sputum (EMS), then two spots are to be collected at the site, at least 30 min apart, and this altered sample collection needs to be captured within case report form [CRF]). If both sputum samples at Week 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional samples or to document that the participant is not able to produce sputum. If there is a MTB confirmed positive culture at or after the end of treatment [Week 17 (4-month treatment arms)/Week 26 (6-month treatment arms)], the participant should return for an unscheduled

visit(s) to give additional sputum samples a minimum of 7 days from the previous sample or to document that the participant is not able to produce sputum. Additional samples may be required in order to define a participants' primary outcome status as described in Section 7.2. The following analyses will be performed on all sputum samples:

- Liquid Culture (MGIT) for MTB, followed by a speciation test to detect presence or absence of MTB and obtain TTP when positive.

g. **Mycobacteriology Characterisation Tests** performed on:

1. Day 1 (baseline) sputum sample (or any positive sample from screening out to Week 4 if the baseline cultures are contaminated or negative);
2. MTB confirmed positive cultures at or after Week 17 (4-month treatment arms) or Week 26 (6-month treatment arms).
3. Refer to Mycobacteria Laboratory Manual for full details.

Mycobacterial Characterization:
The MTB isolates will be processed for:

- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin;
- Drug Susceptibility Testing for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, pyrazinamide and second line TB drugs including but not limited to fluoroquinolones, and injectables using an indirect susceptibility test in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing, and comparison of sequences from baseline and relapse isolates.

h. **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 and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated as long as documentation of testing method and negative results can be provided.

i. **CD4 Count:** For all HIV-positive participants.

j. **Urine Drug Screen:** Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at **Screening only.** Investigator to utilize to determine whether participant meets Exclusion criteria 2. Positive results will not automatically exclude participant from the trial.

k. **Urine Pregnancy Test:** Women of childbearing potential only, whether they are sexually active or not.

l. **Safety Laboratory Assessments**: The Safety Laboratory sampling methodology and requirements will be described in a separate document, the laboratory manual, which will be provided prior to the trial start. The following analyses will be performed:

1. Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count).
2. Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lipase, phosphate, sodium, potassium, calcium

(corrected for albumin), chloride, magnesium, glucose, bicarbonate/carbon dioxide [CO_2], creatine phosphokinase [CPK]).

3. Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow-up to abnormal urinalysis per discretion of Investigator.

m. **Male Reproductive Hormone Tests:** Testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin B to be done on male participants in ALL treatment groups.

n. **Single 12-Lead ECG:** To every extent possible, should be performed at approximately the same time of day as the site procedures (+/-1 hour) Central ECG analysis will be performed. Results from central reading of Day -9 to -1 (screening) ECG should be used to determine eligibility.

o. **Chest X-Ray:** A chest x-ray (digital image) within 4 weeks prior to or at screening, will be obtained and read locally by Investigator or designee. Digital images will be provided to Sponsor, this process will be described in a separate document, the Radiology Manual.

p. **Slit Lamp Ophthalmic Examination** - Slit lamp will be done at EOT and at 9 month for 4 and 6-month treatment groups. An additional slit lamp at 6 months for the 4-month treatment group. Slit lamp ophthalmology examination should be performed by an Ophthalmologist with AREDS2 training. Ophthalmology examinations may occur at any time within the window period for the applicable visit i.e. do not have to be performed on the same day as the site procedures.

q. **Physical Examination – Full:** Height (m) will only be collected at Day -9 to -1 (screening).

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

s. **Pharmacokinetic Sampling:** Blood draw for PK done pre-dose (after ECGs), 1.5-3 hours post-dose (+/- 0.5 hour), and 4-6 (+/- 1 hour) hours post-dose. The dates and times of the two doses prior to the pre-dose PK sample will be collected. (PK Sampling Manual will be created). **PK Sampling:** Specific PK blood draws as follows:

   1. Day 1: pre-dose (within 2 hours prior to dosing)
   2. Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
   3. Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
   4. Week 12: pre-dose (within 2 hours prior to dosing)
   5. Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose
   6. Weeks 39, 65, 78 and 104 – PK samples are obtained when participant is in the clinic

   No PK samples will be collected for HRZE/HR treatment arm.

t. **Investigational Medicinal Product (IMP) Randomization/Assignment:** Initial randomization may occur once all the screening results are available and the investigator has determined that the participant is eligible for the trial.

u. **IMP/Compliance Check:** Trial medication administration will be supervised per local site practice to assure compliance to regimen. Performed at all visits and Early Withdrawal (EWD) if during treatment.

v. **Investigator Assessment:** Principal Investigator to review participant status and assess whether IMP or TB treatment at current visit is considered a "success" or "failure". If considered a failure, should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration. To be completed as shown on the flowchart and at any time Investigator determines that participant fulfils criteria for outcome of treatment failure.

w. **Visit Windows**: The windows noted on the flowchart for timing of visit also apply to timing *within a visit.* Procedures should be performed within +/- 3 days of scheduled visit from Day 1 to Week 8 or +/- 5 Days of scheduled visit from Week 12 to Week 26 or +/- 14 days of scheduled visit at or after Week 39. Sites should make every effort to ensure all other procedures are done on the same day when possible.

2.0 Introduction and Rationale

2.1 Tuberculosis Disease

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in the developing countries of Africa, Asia and South America. TB is currently one of the top three killer infectious diseases, 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 40 years and are relatively ineffective in controlling TB as a public health problem. 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 participants, treatment takes 6 months or more to complete. This, long duration treatment **plus side effects**, result in poor adherence which particularly occurs after the second month of treatment.

The current TB treatment regimens and treatments for drug-sensitive TB are decades old. The available treatments have a lengthy duration of treatment, involve multi-drug therapy, and require large commitments of resources and infrastructure. High rates of noncompliance are common, which often results in increased mortality and chronic, infectious, drug-resistant cases. The present TB epidemic and the challenge of current treatment options demonstrate the clear need for effective novel TB drugs and **drug regimens** that are safe for drug sensitive and drug resistant TB disease and that are well-tolerated and will shorten the current treatment duration for patients.

The full application of the Directly Observed Treatment, Short-Course strategy is becoming more and more difficult in the developing countries of the world that are also battling to control the HIV-epidemic. As a result of poor treatment adherence, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB are growing. Since the discovery of the rifamycins,[1] and their introduction into standard antituberculosis regimens, very few new classes of drugs have been evaluated with a view to their registration as antituberculosis agents. On December 28, 2012 the U.*S.* Food and Drug Administration approved bedaquiline (B) as part of combination therapy to treat adults with multi-drug resistant (MDR) pulmonary tuberculosis (TB) when other alternatives are not available. 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.

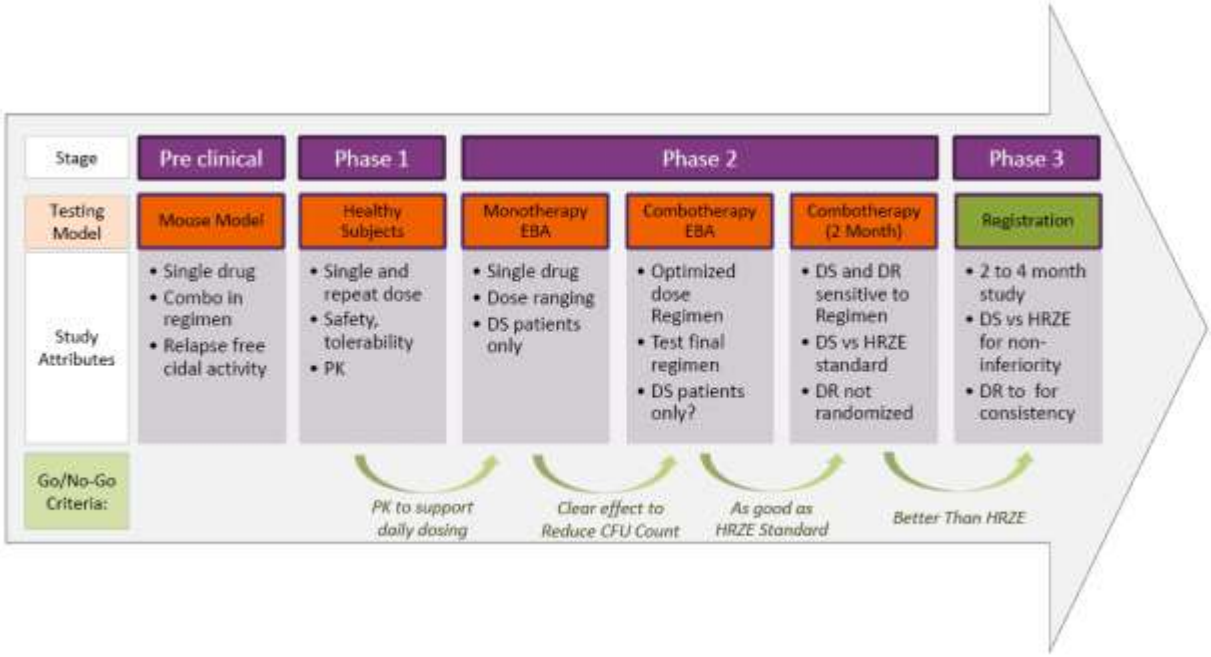
New combination regimens are desperately needed for two reasons: to shorten treatment to a duration more easily manageable by patients and public health services, and to provide more efficacious, safer and better tolerated, affordable treatments for the growing number of patients suffering from multidrug-resistant and extensively drug-resistant tuberculosis.

2.2 Tuberculosis Clinical Research

TB currently must be treated with multiple drugs to achieve maximal efficacy and prevent resistance. To transform treatment, novel TB regimens are needed. In order to telescope the time, it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm. This approach tests promising combinations of drugs together to find the most impactful treatment once the individual drug candidates have been tested in a robust pre-clinical program and the establishment of the individual drug candidates' safety and efficacy have been evaluated. It evaluates novel combinations of TB drugs — instead of single drugs — as

part of a single development program, enabling the development of novel TB drug regimens that have potential to transform treatment for drug-sensitive and drug-resistant tuberculosis. This approach offers the potential to reduce the time previously needed to develop a novel treatment regimen by up to 75%, shortening the clinical development from decades to years. The steps followed in this development model are shown in Figure 1 Between each step on the unified development pathway a decision is made as to whether to proceed.

Figure 1. Unified Drug Sensitive/Drug Resistant Regimen Development Path



Early Bactericidal Activity (EBA) Trials

EBA trials are the backbone clinical trials to quantify the bactericidal action of anti-tuberculosis agents alone or in combination by either studying the fall in the number of colony forming units (CFU) or measuring the TTP in liquid culture of *M. tuberculosis* (*MTB*) present in the sputum of participants with microscopy smear-positive pulmonary TB. EBA trials have been conducted over 2, 5, 7 and 14 days.[2]. A review of EBA trials conducted on the key anti-TB drugs has shown the value these trials offer to demonstrate the early anti-TB effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in participants.[3]

8-week Bactericidal Activity (BA) Trials

EBA methodology of quantitative colony counting on solid medium has been adapted to Phase 2, 8-week TB treatment trials based on serial sputum colony counting (SSCC) or measurement of TTP liquid culture to provide a more sensitive efficacy endpoint than the previously used binary endpoint of rate of sputum conversion measured after 8 weeks of treatment.[4-6] Such trials are conducted to provide data on which to base the selection of treatment-shortening regimens.

2.3 Trial Rationale

This proposed trial (SimpliciTB) will evaluate and support that in additional to previous studies evaluated with BPaMZ, that this drug regimen (BPaMZ) will be safe and effective, is well-tolerated and could potentially shorten the current treatment duration compared to Standard HRZE/HR treatment for patients with drug sensitive TB disease. This study will also evaluate that this drug regimen (BPaMZ) given for 6 months will be safe and effective in drug resistant TB disease.

Therefore, the study design addresses the need to find and evaluate a potential effective shorter regime compared to regimes (Standard HRZE/HR) that is current being used.

2.3.1 Trial Design Rationale

NC-008 (B-Pa-M-Z) trial - [**SimpliciTB**] - is a Phase 2c multi-center, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. This trial is to evaluate the combination regimen of **Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) plus Pyrazinamide (Z)**, (BPaMZ) in participants with pulmonary TB

All participants in the below arms will have follow-up for a period of 104 weeks (24 months) from the start of therapy.

Participants with Drug Sensitive TB (DS-TB):

participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months),

or

HRZE/HR combination tablets daily for 26 weeks (6 months). participants will be stratified for co-infection with HIV and cavitation.

Participants with Drug Resistant TB (DR-TB):

DR-TB Defined as participants with

1. mono-resistance to rifampicin or isoniazid, OR

2. resistance to both rifampicin and isoniazid (multi-drug resistant tuberculosis [MDR-TB])

Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).
Approximately 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation. Up to 150 DR-TB participants will be enrolled and assigned

The trial is sufficiently statistically powered to not only show superiority of 2 months' culture conversion but should also demonstrate non-inferiority for cure at 12 months. (This is in the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen.)

As previously discussed in order to telescope the time it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm and utilize data generated in non-clinical and clinical studies regarding combining of anti-tuberculosis agents

which could contribute significantly to the sterilization of lesions and thus treatment shortening. Therefore, the study design and proposed study regimen (**BPaMZ)** which is supported with previous non- and clinical studies as outlined below should address the need and way to evaluate an effective shorter regime compared to regimes that is current being used.

2.3.2 Trial Drug Regimen Rationale

The drug regimen **BPaMZ** has been studied singularly and in different combinations as outlined above. Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. It essentially provides protection against the development of new resistance to the B-Pa-Z drugs. Based on the exciting and promising results seen in NC-005, this regimen can be initiated in drug sensitive and drug resistant TB participants whom are sensitive to the individual drugs in the regimen (excluding extensively drug-resistant tuberculosis [XDR-TB]) and has the potential to shorten TB treatment to less than 4 months in drug sensitive TB. These are also oral regimens, removing the need for injectables as part of MDR-TB treatment and also project to be markedly less expensive than current MDR-TB therapy. Additionally, these regimens can be administered in a fixed dose for all patients, and will therefore be simpler for health systems to deliver and patients to use.

2.4 Agents used within SimpliciTB

Bedaquiline (TMC207; Sirturo™ package insert)[7] is a novel agent approved for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[9, 10]) *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. Tb* isolates,[10, 11], and is also bactericidal against non-replicating *M. Tb.*[12] In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. Tb*.[3, 4] 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.[13] 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 DS- and MDR-TB and shorten treatment duration in patients. While the combination of bedaquiline and PA-824 in the murine model of TB appeared somewhat antagonistic relative to bedaquiline alone, it was as active as the triple combination of HRZ[13] and in a subsequent trial it was more active in the mouse model than HRZ.[14] Thus, a novel regimen with a bedaquiline plus PA-824 core could be effective in the treatment of MDR-TB by providing two novel drugs for which there is no known pre-existing resistance.

Pretomanid, **PA-824** (Pa)[15] is a new agent being developed by TB alliance for TB treatment. PA-824 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] PA-824 has been under development for several years, and entered clinical trials in 2005. Several trials of PA-824 have also been conducted previously in healthy volunteers. Collectively, these trials in participants with active TB and healthy participants have defined the efficacy, safety and pharmacokinetic features of the drug. Overall, PA-824 has mycobactericidal activity in participants and is well tolerated and bioavailable after oral dosing. PA-824

demonstrated in vitro activity against both drug-sensitive (DS) and MDR-TB,[17] and in vivo activity in a mouse model of TB[17, 18] with a significant promise for shortening treatment of active TB.

Moxifloxacin (M)[19] is a microbial compound, approved in most countries around the world for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and soft tissue infections. Clinical studies have been carried out for a number of additional indications (urinary tract infections, pelvic infections, pharyngitis/tonsillitis, and tuberculosis). Moxifloxacin is an **8-methoxyquinolone** whose oral formulation (which will be used in this study) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by or induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the M. tuberculosis strain is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]" It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

Pyrazinamide (Z)[20] is a pyrazine analogue of nicotinamide and an approved anti-tuberculosis agent which is indicated for the initial treatment of active tuberculosis in adults and children when combined with other anti-tuberculosis agents and contributes significantly to the sterilization of lesions and thus treatment shortening.[21]

Control group: HRZE combination

The **HRZE/HR** combination [HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets] is approved indicated and commonly used as a 6 month treatment for drug-sensitive TB patients. Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE. Please see the HRZE package insert for more information.[22]

Additional background data supporting the combined use of new novel agents in this BPaMZ regime for the treatment of TB:

Data from preclinical studies suggest that a regimen consisting of moxifloxacin plus PA-824 plus pyrazinamide may not only be appropriate for treating both DS and MDR-TB but may also **shorten duration of therapy**. Results from an 8-week Phase 2b SSCC study, NC-002-(M-Pa-Z), showed that this **combination regimen** was effective as measured by time dependent decline of viable bacteria in participants with DS pulmonary TB. The combination was also shown to be safe and well tolerated supporting the evaluation of this combination in a Phase 3 study. In this NC-002 study 71.4% of participants with DS-TB treated with PaMZ at the 100-mg daily dose of PA-824 converted sputum to negative for *MTB* growth in liquid culture in comparison with only 37.8 % of participants treated with the HRZE control ($p<0.05$).

Studies in mice infected with *MTB* demonstrated reductions in cultured colony counts from lungs over an 8-week period when treated with the PaMZ regimen that were substantially, and

statistically significantly greater, than the reductions in mice treated with an HRZ control. Experiments in mice found that mice did not relapse with *MTB* infection when treated with PaMZ for 4 months and followed for 3 months off treatment, in comparison to mice that required 6 months of treatment with HRZ to prevent relapse.[14]

Drug Resistant TB background:

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in many countries. TB is now the world's leading infectious disease killer and is responsible for more deaths than HIV.[23] It is the leading cause of death among HIV-infected individuals, and there is more TB in the world today than at any other time in history. As a result of poor treatment adherence, in addition to primary transmission, **drug resistance** is becoming more common and fears of an epidemic with strains of extensively drug-resistant TB (XDR-TB) that is very difficult to treat are growing. Novel drugs and regimens for TB are needed for the growing number of patients with Resistant-TB.

The regulatory approvals of bedaquiline and delamanid have given hope that outcomes for patients with drug resistant TB might be improved when added to background regimens. Experience recently published from the C209 uncontrolled trial of bedaquiline given on a background of multiple drugs notes that the subset of 38 patients with XDR-TB had rates of sputum culture conversion to negative of 62.2%.[24] However, in this trial only one patient with XDR-TB was co-infected with HIV. All participants were required to have Mycobacterium tuberculosis (MTB) isolates susceptible to at least 3 drugs at enrolment, and patients had a median of only 5.4 months of treatment-free follow-up. This trial added bedaquiline for 6 months to a background regimen of many drugs given for 18 months or longer. While treatment success for MDR-TB is better than for XDR-TB, **overall success in treating MDR-TB is still approximately 50%** according to the World Health Organization 2015 Global TB Report.[23] This report presented that overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, 10% failed treatment, and for 8% there was no outcome information.

With such poor historical outcomes for patients with drug resistant-TB and with the complexity, expense and toxicity of treatments for all forms of drug resistant TB, **novel drug combinations are desperately needed to improve treatment outcomes**. Linezolid was identified in a small trial as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen[25] and this drug has increasingly been added to complex regimens to treat patients with MDR-TB.

With the current availability of the following three drugs for which there is little, if any, pre-existing resistance among strains of MTB (pretomanid [Pa], bedaquiline [B], and linezolid [L]). Mice infected with MTB had relapse-free cures with 3 months of treatment with a B-Pa-L regimen. While it is not known whether that treatment duration will translate to humans, it is hypothesized in the design of the ongoing Nix-TB clinical trial (**NiX-TB-(B-L-Pa))** that patients with pulmonary XDR-TB may have relapse-free cure after as little as 6 months' treatment with the B-Pa-L regimen. Therefore, since 2015, the TB Alliance has sponsored a trial with a 6 month treatment duration with the B-Pa-L regimen in participants with XDR-TB or MDR-TB not responsive to or intolerant to therapy (the Nix-TB trial).[26] Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. The proposed trial [SimpliciTB] allows the opportunity to assess the efficacy, safety and

tolerability of **BPaMZ** a new 6 months regimen that may be administered orally once daily to treat patients with resistant -TB (Excluding participants with XDR-TB).

Therefore, the **overall purpose** of the present proposed study **[SimpliciTB]** is to assess the efficacy, safety and tolerability of the **BPaMZ** regime after 4 months of treatment in adult participants with drug sensitive TB and after 6 months of treatment in participants with multi drug-resistant TB. The trial will also generate data of the potential for a shorted treatment duration with the **BPaMZ** regime after 4 months compared to a 6 month **HRZE/HR** (control) treatment regime in adult participants with drug sensitive TB.

This study will be conducted in accordance with the Protocol, International Good Clinical Practice (GCP) Guidelines, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirement(s).

2.5 Background of Agents to be Studied in SimpliciTB

2.5.1 Bedaquiline

Bedaquiline (formerly known as TMC-207; Sirturo™ package insert)[7] is approved agent for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[11] In vitro, bedaquiline potently inhibits both drug-sensitive and drug-resistant M. Tb isolates,[11, 12] and is also bactericidal against non-replicating M. tb.[12] 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.[27].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[27] and in a subsequent trial it was more active in the mouse model than HRZ.[28]. 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.

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as 200 mg daily for 8 weeks, followed by 100 mg daily for the remaining 17 weeks or 30 weeks if treatment is extended. This daily dosing scheme will allow more convenient dosing that should ultimately enhance patient adherence and may allow the formulation of fixed dose combinations with other drugs. This daily dosing regimen is supported by safety and efficacy demonstrated in the NC-005 trial that administered bedaquiline 200 mg daily over 8 weeks, and by pharmacokinetic modelling and simulation of the daily dosing scheme. This supportive information is detailed below.

2.5.1.1 Bedaquiline Non-clinical Studies

Full details of the preclinical studies are provided in the current bedaquiline Investigator's Brochure,[8] and Sirturo ™ label.[7] *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 International Council for Harmonisation (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.[8]

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 and ECG parameters.

Prior to the use of pretomanid in combination with bedaquiline in clinical trial NC-001, a preclinical cardiovascular safety pharmacology trial 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.[28] 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).

2.5.1.2 Bedaquiline *Clinical Studies*

In the clinical studies conducted to date, a total of approximately 645 participants (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 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001, and 45 more in trial NC-003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). Four short-term Phase 2a trials enrolled treatment-naïve participants (C202, TMC207-CL001, NC-001 and NC-003). One long-term, open-label, Phase 2 trial, in MDR-TB participants (bedaquiline-TiDP13-C209) and one long-term, Phase 2b trial, consisting of 2 different stages in participants 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,[8] and Sirturo™ label.[7].

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 participants. 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 trial, 800 mg single dose in trial 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 participants and participants 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 α 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 participants 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 trial (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 trial (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. Trial C202 was a 7-day trial of three daily doses of bedaquiline (25, 100 and 400mg) in treatment-naïve participants with MDR-TB. In this trial, the 400mg dose group

demonstrated positive EBA and was numerically superior to the 25 and 100mg doses. In trial TMC207-CL001, doses of 100, 200, 300 and 400mg daily (following a 2-day loading dose) were studied in participants 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 participants with TB and that higher doses appear to have greater efficacy.

A 14 day EBA regimen trial (TB Alliance Trial 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 participants 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 participants given bedaquiline 400 mg/d after a 2-day loading dose. In the cohort of 15 participants 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 participants 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 trial (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 participants 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 participants in the bedaquiline group became MGIT culture negative compared to 8.7% of participants 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 participants in the bedaquiline group and 65.2% of participants 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 participants 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 participants. Culture conversion rates after 2 weeks of treatment with bedaquiline as part of an individualized anti-tuberculosis regimen were higher in participants with lower extent of resistance of the M. Tb strain and in participants with no lung cavitation compared to participants with cavitations (in one or both lungs).

2.5.1.3 Bedaquiline Clinical Safety

In the clinical trials conducted to date, a total of approximately 645 participants (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 participants received bedaquiline in a monotherapy EBA trial of 14 days (trial TMC207-CL001) 45 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001 and 45 more in trial NC- 003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). In these trials, bedaquiline has been shown to be an effective treatment for participants 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 trial 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 trials, 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 participants) 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	**1 (1.3)**	**1 (1.0)**	**0**	**0**
Headache	1 (1.3)	1 (1.0)	0	0
Cardiac disorders	**0**	**0**	**0**	**0**
ECG QT Prolonged	0	0	0	0
Gastrointestinal disorders	**0**	**0**	**0**	**0**
Diarrhea	0	0	0	0
Vomiting	0	0	0	0
Hepatobiliary disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Transaminases increased [a]	2 (2.5)	2 (2.0)	0	0
Musculoskeletal and connective tissue disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Arthralgia	2 (2.5)	2 (2.0)	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 participants in the Any bedaquiline group and 5 participants 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 participants 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 participants (12.7%) compared to 3 placebo participants (3.7%). Based on the pooled results (Stage 1 and 2) while being followed in the placebo- controlled trial, 7 participants in the Any bedaquiline group and 1 Participant 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 participants 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 Participant in the bedaquiline group (pulmonary TB) and 2 participants in the Placebo group (TB-related illness and pulmonary TB) in Stage 1 died, and 4 participants in the bedaquiline group (3 participants with TB-related illness, 1 Participant motor vehicle accident) and 2 participants in the Placebo group (both TB-related illness) died after they discontinued Stage 2 of the trial. None of these participants 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 participants 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 participants 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 participants (6.9%) have died (12 participants during the trial and 4 participants 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 participants 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[7] notes that treatment initiation is not recommended in patients with:

- Heart failure;
- QTcF interval > 500 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. participants should be monitored during treatment. Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in those participants with diminished hepatic reserve.[7]

Additional safety information from a recently completed trial

In a recently completed phase I trial not yet included in the bedaquiline Investigators Brochure that evaluated drug-drug interactions between bedaquiline and either rifampin or rifabutin, 7 participants experienced SAEs. Of those participants, 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 participant 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.

2.5.2 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]

2.5.2.1 Pharmacology

Key in Vitro Evaluation of Pretomanid Bactericidal Activity

Non-clinical in vitro trials demonstrated that pretomanid was active against actively growing drug-sensitive and drug-resistant MTB strains as well as against non-replicating MTB. The minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive MTB isolates *in vitro* was shown to be similar to the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of MTB with MIC values ranging from 0.03 to 0.53 µg/mL. The Investigator's Brochure contains further information on *in vitro* bactericidal activity.[16]

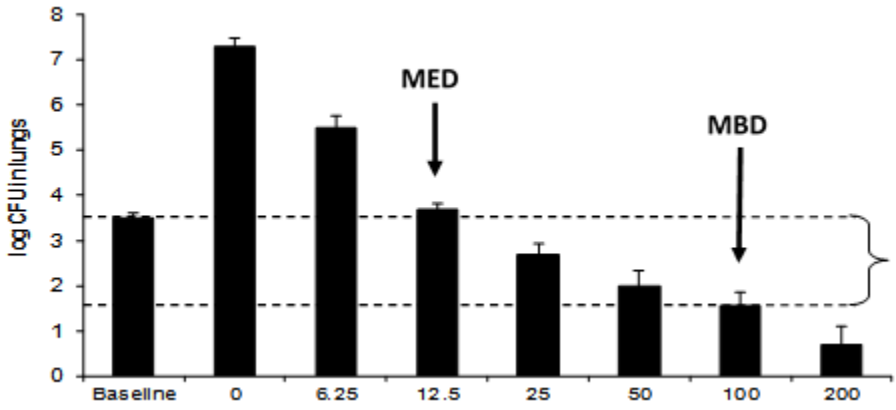
Although not thoroughly elucidated at this time, pretomanid has a novel mechanism of action that appears to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reduction of pretomanid by a deazaflavin (F420)-dependent nitroreductase has been shown to be associated with generation of reactive nitrogen species, including nitric oxide (NO),[29] although the exact target(s) of the reactive nitrogen species are not known. Transcriptional profiling trials also suggest that pretomanid affects both cell wall biosynthesis and the respiratory complex of MTB.[30, 31]

2.5.2.2 Key Non-Clinical Trials of Pretomanid

The activity of pretomanid as a single agent or as part of a multi-drug combination regimen has been examined in a number of mouse trials.[13, 14, 18, 32, 33] In a mouse model of established TB, the activity of various doses of pretomanid (given once daily, 5 days/week, for 1 month), initiated 22 days after inhalation infection with H37Rv MTB is shown in Figure 2. In this model, the minimum effective dose (MED) for pretomanid, defined as the lowest dose able to prevent the development of gross lung lesions and splenomegaly, was 12.5 mg/kg/day, while the minimum bactericidal dose (MBD), defined as the lowest dose able to reduce lung colony forming units (CFU) by 99%, was 100 mg/kg/day. Moreover, in these experiments, the activity of pretomanid at 100 mg/kg was comparable to the activity of isoniazid at 25 mg/kg.

Figure 2. Log10 CFU Counts in Lungs

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



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

2.5.2.3 Non-Clinical Toxicology and Safety

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

In the repeat-dose toxicity trials, the lowest no-observed adverse effect level (NOAELs) was 10 mg/kg/day in a 26-week trial in rats, 50 mg/kg/day in a 13-week trial in monkeys and <25 mg/kg/day (based on findings of thickening of the gastrointestinal tract at all doses) in a 9-month trial in monkeys. The major findings in safety and toxicity trials are listed below in Table 2 and are detailed in the Investigator's Brochure.[15]

Table 2. Key findings of Pretomanid in Safety and Toxicity Trials

Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behaviour at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
Testicular toxicity Although rat and rabbit embryonic development trials indicate no effects of PA-824 on fetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose toxicology trials and a Segment I fertility trial. In this fertility trial, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower dose not associated with testicular atrophy. A detailed trial in sexually mature male monkeys demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing.
Cataracts Cataracts developed in rats with prolonged daily administration of pretomanid at doses ≥100 mg/kg/day. In one 13-week trial 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 trial in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.
hERG inhibition and QT prolongation Altered ventricular repolarisation due to inhibition of hERG-mediated potassium current and manifested on the ECG as a prolonged QT interval corrected for heart rate (QTc). Pretomanid inhibited hERG current with IC50 values of approximately 6.2 µg/mL. Following a single pretomanid dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Co-administration of pretomanid with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at pretomanid doses of ≥150 mg/kg/day.

2.5.2.4 Clinical Background Information

Pretomanid has been evaluated in 8 single- and multi-dose Phase 1 trials with healthy adult male and female participants, with 163 participants receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 7 days. These Phase 1 trials have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid. Two additional Phase 1 trials sponsored by the NIH included a Thorough QT trial and a trial of drug interactions among pretomanid, efavirenz and ritonavir/lopinavir. Further details of the trials are in the Investigator's Brochure.[15]

2.5.2.5 Pharmacokinetics

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

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

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

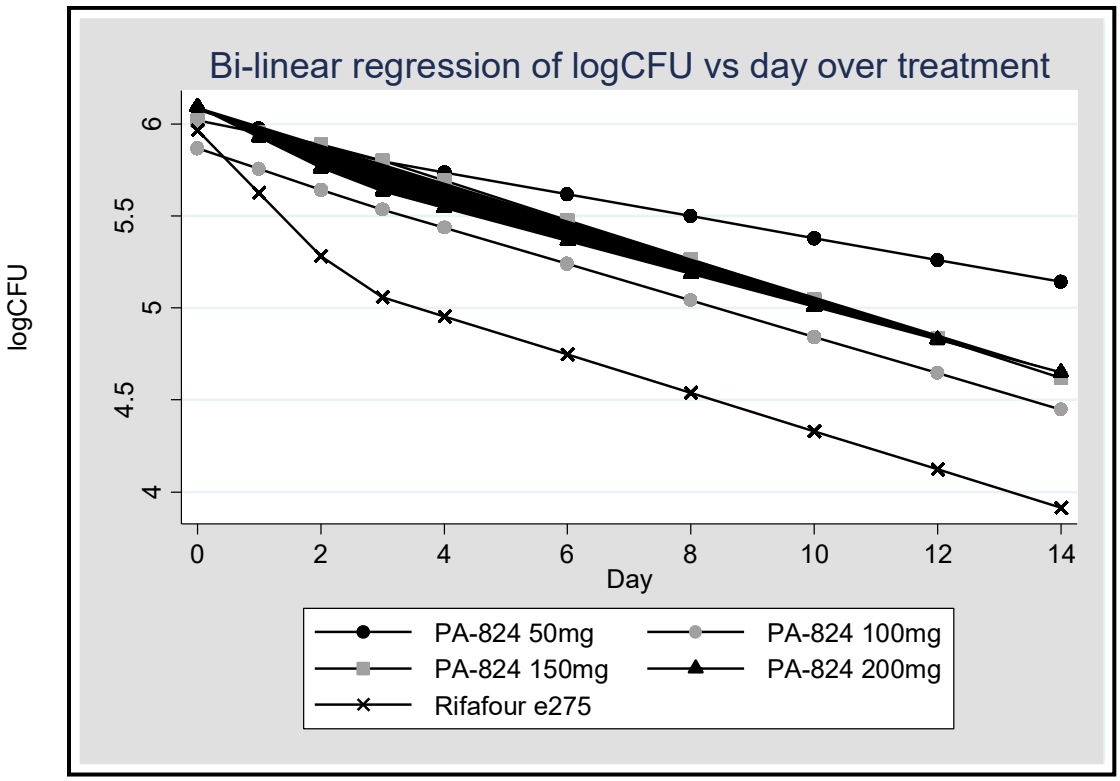
pretomanid alone from 16 PK-evaluable participants, the GMR for C_{max}, AUC_{0-24h}, and C_{min} were 0.47, 0.34, and 0.15, respectively.

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

2.5.2.6 Pretomanid Clinical Efficacy

The first two Phase 2 trials to evaluate the early bactericidal effect (EBA) of pretomanid oral monotherapy (50 to 1200 mg/day for 14 days) examined the dose-response for pretomanid in participants with newly diagnosed pulmonary TB infection. The first trial (CL-007) demonstrated good EBA, but all doses in this trial (200 to 1200 mg/day) had the same activity. The second trial (CL-010) evaluated a lower dose range (50 to 200 mg/day) and the maximum effect on EBA was seen at a dose of 100 mg/day over 14 days (Figure 3).[34]

Figure 3. Mean log Colony Forming Unit Values over Time Trial CL-010



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

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

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

2.5.2.7 Pretomanid Clinical Safety

The pretomanid Investigator's Brochure[15] provides detailed safety information.

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

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

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

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

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

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

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

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

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

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

2.5.3 Moxifloxacin (M)

Moxifloxacin (M)[19] is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by nor induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the M. tuberculosis strain is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]" It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

2.2.3.1. Moxifloxacin Clinical Trials

Moxifloxacin is commonly used as second line therapy for TB (e.g. MDR- TB), and has also been evaluated in several clinical studies of participants with TB, including four 8-week treatment period Phase 2b studies (see Table 3 below).

Table 3. Summary of Phase 2b trials in which moxifloxacin were administered as part of a four-drug regimen during the intensive phase of treatment (total treatment duration: 2 months)

Trial	Design	Objective	Participants (N)	Status
Trial 27	Randomized, double-blind, controlled	To compare the sputum culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using the standard 4-drug regimen HRZE with a standard regimen with M replacing E.	336	Completed
OFLOTUB Trial	Randomized, Open label, Controlled	To compare the bactericidal activities of regimens where gatifloxacin, M, and ofloxacin were substituted for E in the 2-month initial phase of standard TB treatment with HRZE.	217	Completed
Johns Hopkins (FDA orphan drug) Trial	Randomized, double-blind, Controlled	To compare the sputum culture conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE) with a regimen with M replacing E (HRZM).	170	Completed
Trial 28	Randomized, double-blind, Controlled	To compare the culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE 5 days per week) with a regimen with M replacing H (MRZE 5 days per week).	433	Completed

2.5.3.1 Moxifloxacin Clinical Safety

In Trial 27,[35] the moxifloxacin-containing TB regimens (HRZM) were shown to be safe and well tolerated. There was no difference in SAEs between the HRZM and HRZE treatment arms, and most SAEs were hospitalizations thought to be unrelated to the trial treatment. Participants treated with the moxifloxacin-containing regimen were more likely to report nausea (22% vs. 9%, p = 0.002), but this was generally mild and did not lead to treatment discontinuation as similar proportions of participants in both groups completed trial drug treatment (88% HRZM-treated vs. 89% HRZE-treated). The one death during the first 2 months of treatment was thought to be caused by pulmonary embolism, unrelated to tuberculosis therapy.

In the OFLOTUB trial,[36] AEs and SAEs occurred with equal frequency in the four treatment arms. The most frequent AEs were raised amylase (in 41% of participants due to HIV infection), raised transaminase (10%), arthralgia (9%), anemia (7%), hypokalemia (6%) and vomiting (5%). No

Participant was withdrawn from the trial due to an adverse event. There were 4 deaths in the trial: 2 in the control group, 1 each in the moxifloxacin and ofloxacin arms. Importantly, participants in this trial who received moxifloxacin and pyrazinamide in addition to isoniazid and rifampin had more rapid sputum clearance than participants on the four standard first line drugs (isoniazid, rifampin, pyrazinamide and ethambutol). This difference was evident 14 days after initiation of treatment.

In the JHU trial,[37] AEs did not differ by treatment group. There were 16 SAEs (8 in each group) in 12 participants. Only 1 event was judged related to trial drug (grade 3 cutaneous reaction in the ethambutol group). Eight participants died during the trial, including 1 in each group still receiving trial phase treatment. No death was attributed to trial treatment. Only 5 participants discontinued treatment because of toxic effects; 2 participants in the moxifloxacin group stopped because of grade 2 nausea and vomiting and 1 because of grade 2 paraesthesias and ataxia. Two participants in the E group stopped because of grade 2 rash and pruritis and 1 because of grade 3 peripheral neuropathy. There was no change in the QTc interval on serial electrocardiograms taken during the trial.

In Trial 28,[38] the proportions of participants with SAEs during the intensive phase treatment were similar between arms (isoniazid 3.9% vs. moxifloxacin 4.2%; P = 0.88). Three SAEs attributed to trial treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group. Seven participants died during the trial including 3 participants receiving the moxifloxacin treatment regimen and 4 participants receiving the isoniazid treatment regimen. The 3 moxifloxacin participants died during the intensive phase of TB treatment. Two participants died from advanced pulmonary TB judged not related to trial treatment and 1 Participant (who developed diabetic ketoacidosis considered possibly related to trial treatment) died from possible acute pulmonary embolus unrelated to trial treatment. The 4 isoniazid deaths occurred during the continuation phase, and all 4 were considered unrelated to trial treatment. Nausea was more common among participants in the moxifloxacin arm than in the isoniazid arm (19.6% vs. 11.7%, respectively; P = 0.03) although similar proportions reported vomiting. However, the proportions of participants with hepatitis, defined as serum AST 3 times or greater than the upper limit of normal, were similar between treatment arms during intensive phase (isoniazid 3.4% vs. moxifloxacin 3.3%; P = 0.93). Moxifloxacin has also been evaluated in combination with PA-824 for two weeks in participants with TB (Trial NC-001) and for 8 weeks in NC002 as reviewed above in Section 2.2.3 (Trial NC-001).

For additional information on moxifloxacin, refer to the IB[39] and the manufacturer's package insert.[19]

2.5.4 Pyrazinamide (Z)

Pyrazinamide (Z) is a standard drug used as part of the four drug HRZE regimen used for the first two months of intensive therapy for drug-sensitive TB as recommended by the WHO and many National TB programs. Please see the Package Insert[20] for more detail. Z is active against TB *in vitro* and it potentiates the bactericidal and sterilizing activity of both bedaquiline and PA-824 in mouse models of TB infection.[8, 15] Pyrazinamide enhanced the bactericidal activity of both bedaquiline and PA-824 in Trial NC-001-(J-M-Pa-Z) as noted by decreases over 14 days in the CFU counts in sputum among participants.

The pyrazinamide product label notes that pyrazinamide is contraindicated in persons with severe hepatic damage, who have shown hypersensitivity to it, and with acute gout. The most serious side effect is hepatotoxicity. Its frequency appears to be dose-related and thus liver function should be assessed before and regularly during treatment with pyrazinamide. Hyperuricemia commonly occurs and is occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anemia and dysuria.

Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert. [20]

2.6 Overall Benefit/Risk Assessment

Participants with pulmonary TB in this trial will be given a **BPaMZ** regime. These drugs individually and in combination are known to have anti-tuberculosis activity and is not expected to have an adverse impact on the ultimate cure of TB in these participants. Based on NC-005 and other regimens using each of the regimen drugs in different combinations there is good evidence that this may be a highly effective therapy for both DS and MDR TB and for DS the potential for a shorter regimen than 6 months is expected to be successful based on preclinical and clinical information as listed before. Participants in this trial will have their TB infection carefully characterized, with drug sensitivity profiles established, and they will receive treatment with trial drugs that have demonstrated activity against *M. Tb*. Participants will receive individualized medical attention; this will allow a continuous monitoring of the health conditions of each participant, any of whom can be withdrawn at any stage of the study and removed from trial treatment should his/her condition suggest to the Investigator that this would be in his/her best interest. Multiple blood samples will be taken for safety laboratory studies, and ECGs will be taken at multiple time points. One concern in particular, combining two agents with known QT-prolonging effects (bedaquiline and moxifloxacin), has been addressed specifically by carefully identifying and excluding participants with risk factors that might predispose them to cardiac arrhythmias, screening all participants for evidence of existing cardiac disease and monitoring all participants with ECGs throughout the trial.

The trial drugs in the proposed regimens to be tested in this trial have all demonstrated safety and efficacy in the treatment of pulmonary tuberculosis in non-clinical and clinical studies. Specifically, the regimen B-Pa-Z was generally well-tolerated and demonstrated bactericidal activity in a 14 day EBA trial. The potential risks associated with the trial drugs and regimens has been identified as outlined below and will be monitored carefully throughout the conduct of the trial.

The BPAMZ regime is a new novel regimen treatment and is expected to be effective, safe and well-tolerated and might even shorten the current treatment duration for patients with TB. Based on data from previous trial evaluations as outlined before suggest a favourable benefit-to-risk ratio trials.Key monitoring and safety information regarding regimen agents

2.6.1 Bedaquiline

2.6.1.1 Adverse Drug Reactions for bedaquiline

Participants in the Any bedaquiline group compared to the Any Placebo group (difference > 5.0%) had headache (23.5% versus 11.4%, respectively), nausea (35.3% versus 25.7%, respectively), arthralgia (29.4% versus 20.0%, respectively), and transaminases increased (6.9% versus 1.0%, respectively).and diarrhoea (11.4% versus 5.9%, respectively).

2.6.1.2 Cardiovascular safety

During clinical studies with bedaquiline a prolongation of QTc interval was observed. An ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.

Bedaquiline 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

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.

In the MDR-TB treatment arm of the present trial, moxifloxacin will be co-administered with bedaquiline. This is to prevent the development of resistance to the other drugs in the regimen in case the participant's *M. Tb* strain is resistant to pyrazinamide. ECG assessments will be performed on all participants at baseline, each treatment visit and during the follow-up visit on Day 70.

2.6.1.3 Hepatic safety

Increases in transaminases were seen in clinical studies during administration of bedaquiline with the background regimen. Participants should be monitored during treatment.

Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in participants with diminished hepatic reserve.

2.6.2 Pretomanid

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 diarrhoea)
- Skin and subcutaneous tissue disorders

2.6.2.1 Hepatic Safety

Hepatic enzyme increases have been seen in participants treated with PA-824 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, trial NC-008 will include specific monitoring of hepatic enzymes.

For additional information refer to PA-824 IB.[15]

2.6.3 Moxifloxacin

In the usual daily doses of 400 mg/day, moxifloxacin is well tolerated. As stated in the Package Insert[19] the most frequent individual drug related AEs observed in clinical trials with 400 mg oral moxifloxacin therapy were nausea (7.5%) and diarrhoea (5.8%). Fluoroquinolones, including moxifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages.

A known but rare side effect of fluoroquinolones, including moxifloxacin is exacerbation of myasthenia gravis. In addition, moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some participants. It should be used with caution in participants being treated concomitantly with other drugs where an additive effect on the QT interval cannot be excluded.

Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, may occur after the first or subsequent doses of moxifloxacin. Also, moxifloxacin may cause peripheral neuropathy. For additional information, refer to the moxifloxacin package insert.[19]

2.6.4 Pyrazinamide

The dose of pyrazinamide that will be used in this trial is an approved dosage for the treatment of TB. The most serious side-effect of pyrazinamide is hepatotoxicity and its frequency appears to be dose-related. Hyperuricemia commonly occurs, occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side-effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria. Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert.[20]

2.6.5 HRZE/HR Control

The **HRZE** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets) combination will be given the first 8 weeks and the **HR** (isoniazid 75 mg plus rifampicin 150 mg combination tablets) combination will be given from Weeks 9 to 26.

Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE.

Please see the HRZE and HR Package Inserts[22, 40] for known and potential risks and benefits.

3.0 Trial Objectives

3.1 Primary Objectives

To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with:

Drug Sensitive TB (DS-TB)

- BPaMZ given for 17 Weeks (4 months)
- Standard HRZE/HR treatment given for 26 weeks (6 months)

Drug Resistant TB (DR-TB)

- BPaMZ given for 26 Weeks (6 months)

DR-TB Defined as participants with

1. *mono-resistance to rifampicin or isoniazid, OR*
2. *resistance to both rifampicin and isoniazid (MDR-TB)*

3.2 Secondary Objectives

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 52 (or 12 months) and 104 (or 24 months) weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
  - Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
  - Quantitative and qualitative ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones and lens opacities.

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., Cmin, Cmax, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so, too, will the effects of con-medications including antiretroviral therapy (ART), as feasible. Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

3.3 Exploratory Objectives

- Evaluate whether any of the secondary endpoints predicts relapse free cure.
- Subgroup analysis of populations by HIV status.

No formal statistical comparisons will be made for the participants enrolled with DR-TB.

4.0 Trial Design

4.1 Summary of Trial Design

This is a Phase 2c, multi-center, open-label, partially randomized clinical trial conducted in 3 treatment groups. Participants, trial investigators and staff, including laboratory staff, will not be blinded to treatment allocation during the treatment phase of the trial.

The trial will be performed globally at multiple centers located throughout all regions of the world.

A total of 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation. Up to 150 DR-TB participants will be enrolled and assigned to the treatment arm described in Table 4 below

Participants with Drug Sensitive TB (DS-TB):

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR combination tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation.

Participants with Drug Resistant TB (DR-TB):

Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).
Eligible participants who meet all of the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive. An interactive web response system (IWRS) will be used which will utilize a dynamic randomization system using cavitation with a random element to allocate participants evenly across the arms by HIV status and type of TB (DS versus DR) after they have given written, informed consent during Screening Visit (Days -9 to -1) and met all eligibility criteria

4.2 Treatment Plan: Schedule of Assessments

- Screening Period (Day -9 to Day -1)
- Treatment Period (Day 1 to Week 17 (4-month treatment); or Week 26 (6-month treatment)
- Follow-Up Period (Week 39 to Week 104)

Refer to:

- Synopsis Flow Chart and Procedures (Section 1.2; flow chart) for the timing of all procedures and laboratory samples to done at each visit.
- Trial Procedures (Section7.0, Trial Variables and Procedures) for details regarding specific procedures or laboratory tests.

Each participant will receive up to 26 weeks of treatment. The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation, in consultation with the Sponsor Medical Monitor. Participants will be followed for up to 104 weeks after the start of treatment.

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

Table 4: Treatment Groups

	Treatment Group	Treatment Duration	No of Participants
1	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily	17 weeks (4 months)	150 DS-TB
2	**HRZE Tablets:** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). **AND THEN** **HR Tablets:** (isoniazid 75 mg plus rifampicin 150 mg combination tablets) This combination will be given starting at Week 9.	First 8 weeks (2 months) then 17 weeks (4 months) Total 6 months	150 DS-TB
3	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily.	26 weeks (6 months)	Up to 150 DR-TB

5.0 Trial Population

Participant must meet all inclusion and no exclusion criteria within the screening period. Retesting for laboratory or ECG parameters is allowed within the screening period. Sponsor may consider replacement of late exclusions.

5.1 Inclusion Criteria

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

1. Signed written consent prior to undertaking any trial-related procedures.
2. Male or female, aged 18 years or over.
3. Body weight (in light clothing and no shoes) ≥ 30 kg.
4. Sputum positive for tubercule bacilli (at least 1+ on the International Union Against Tuberculosis and Lung Disease [IUATLD]/WHO scale (Appendix 1) on smear microscopy) at the trial laboratory.
5. Disease Characteristics:
   - Participants with one of the following pulmonary TB conditions:

     DS-TB treatment arm participants should be:

     a. sensitive to rifampicin and isoniazid by rapid sputum based test **AND**

     b. either newly diagnosed for TB or have a history of being untreated for at least 3 years after cure from a previous episode of TB.

     If they are entered into the trial due to being sensitive to rifampicin and isoniazid by rapid molecular sputum based test, however on receipt of the rifampicin and/or isoniazid phenotypic resistance testing in liquid culture this shows they are rifampicin or isoniazid resistant, they will be:

     a. Excluded as late exclusions;

     b. Possibly replaced as determined by the Sponsor.

     DR-TB treatment arm participants should be:

     a. Resistant to rifampicin and/or isoniazid.

   A chest x-ray which in the opinion of the investigator is compatible with pulmonary TB.

   1. Contraception:

   Be of non-childbearing potential **<u>or</u>** using effective methods of birth control, as defined below:

   Non-childbearing potential:

   a. Participant - not heterosexually active or practice sexual abstinence; or

   b. Female participant or male participants female sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or

   c. Male participant or female participants male sexual partner - vasectomised or has had a bilateral orchidectomy minimally three months prior to screening;

Effective birth control methods:

a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or

b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female participant.

c. Male participants' female sexual partner: Double barrier method or hormone-based contraceptives or an intra-uterine device for the female partner.

And both male and female participants are willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 12 weeks after the last dose of trial medication or discontinuation from trial 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 participants to prevent pregnancy).

5.2 Exclusion Criteria

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

Medical History and Concurrent Conditions:

1. Any non-TB related condition where participation in the trial, as judged by the investigator, could compromise the well-being of the participant or prevent, limit or confound protocol specified assessments.
2. Being, or about to be, treated for Malaria.
3. Is critically ill and, in the judgment of the investigator, has a diagnosis likely to result in death during the trial or the follow-up period.
4. TB meningitis or other forms of extrapulmonary tuberculosis with high risk of a poor outcome, or likely to require a longer course of therapy (such as TB of the bone or joint), as judged by the investigator.
5. History of allergy or hypersensitivity to any of the trial IMP or related substances, including known allergy to any fluoroquinolone antibiotic, history of tendinopathy associated with quinolones or suspected hypersensitivity to any rifampicin antibiotics.
6. For HIV infected participants any of the following:
    a. CD4+ count <100 cells/µL
    b. Karnofsky score <60% (Appendix 5)
    c. Received intravenous antifungal medication within the last 90 days
    d. WHO Clinical Stage 4 HIV disease (Appendix 3)
7. Participants recently started or expected to need to start ART within 1 month after randomization. Participants may be included who have been on ARTs for greater than 30 days prior to start of screening, or who are expected to start ART greater than 30 days after randomization.
8. Resistant to fluoroquinolones (rapid, sputum-based molecular screening tests).
    a. If they are entered into the trial due to being sensitive to fluoroquinolones by rapid sputum based test, however on receipt of the moxifloxacin phenotypic resistance

testing in liquid culture they are found to be fluoroquinolones resistant, they will be excluded as late exclusions;

9. Having participated in other clinical trials with investigational agents within 8 weeks prior to start of trial medication or currently enrolled in an investigational trial;
10. Participants with any of the following at screening (per measurements and reading done by ECG):
11. Cardiac arrhythmia requiring medication;
12. Prolongation of QT/QTc interval with QTcF (Fridericia correction) >450 ms;
13. History of additional risk factors for Torsade de Pointes, (e.g., heart failure, hypokalemia, family history of Long QT Syndrome);
14. Any clinically significant ECG abnormality, in the opinion of the investigator.
15. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening.

<u>Previous and Concomitant Therapy</u>

1. Previous treatment with pretomanid or bedaquiline as part of a clinical trial.
2. Previous treatment for TB which includes, but is not limited to, gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole:
3. For DS-TB treatment arms: Previous treatment for tuberculosis within 3 years prior to Day -9 to -1 (Screening). Participants who have previously received isoniazid prophylactically may be included in the trial as long as that treatment is/was discontinued at least 7 days prior to randomization into this trial.
4. For the DR-TB/MDR-TB participants: Previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB treatment regimen for no longer than 7 days at start of screening.
5. Any diseases or conditions in which the use of the standard TB drugs or any of their components is contra-indicated, including but not limited to drug allergy.
6. Use of any drug within 30 days prior to randomisation known to prolong QTc interval (including, but not limited to, amiodarone, amitriptyline, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinacrine, quinidine, sotalol, sparfloxacin, thioridazine).
7. Use of systemic glucocorticoids within one year of start of screening (inhaled or intranasal glucocorticoids are allowed) due to visual opacities or cataracts
8. For HIV infected participants, only the following types of ART are permissible:
    - Nevirapine (NVP) based regimen consisting of NVP in combination with any two nucleosidase reverse transcriptase inhibitors (NRTIs) tenofovir (TDF)/abacavir (ABC) and emtricitabine (FTC)/lamivudine (3TC).
    - Lopinavir/ritonavir based regimen consisting of lopinavir/ritonavir in combination with any two NRTI. TDF/ABC and FTC/3TC.
    - Integrase inhibitor (e.g., dolutegravir) in combination with TDF/ABC and FTC/3TC.
    - In participants who have viral load suppressed on efavirenz at the time of screening, their ART can be changed to rilpivirine in combination with TDF/ABC and FTC/3TC. If possible, the same nucleoside backbone should be used.
9. In the case where participants are randomized to a rifampicin containing regime

- EFV can be used with rifampicin.
- LPV needs to be double dosed.
- Rilpivirine cannot be given with rifampicin

Diagnostic and Laboratory Abnormalities

10. Participants with the following toxicities at screening as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November 2007) (Appendix 2) where applicable:
    - platelets grade 2 or greater (<100,000/mm3);
    - creatinine grade 2 or greater (>1.5 times upper limit of normal [ULN])
    - eGFR ≤ 60 mL/min/m^2
    - haemoglobin grade 2 or greater (≤8.0 g/dL);
    - serum potassium less than the lower limit of normal for the laboratory. This may be repeated once;
    - AST:
        - grade 3 or greater (≥3.0 x ULN) to be excluded;
        - results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor;
    - ALT:
        - grade 3 or greater (≥3.0 x ULN) to be excluded;
        - greater than ULN must be discussed with and approved by the Sponsor Medical Monitor;
    - ALP:
        - grade 3 or greater (≥3.0 x ULN) to be excluded;
        - grade 2 (2.0 – <3.0 x ULN) must be discussed with and approved by the Sponsor Medical Monitor;
    - total bilirubin:
        - >1.5 x ULN to be excluded;
        - 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor;
    - direct bilirubin:
        - greater than ULN to be excluded.

All of the inclusion and none of the exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the Investigator has reason to suspect that there might be a health problem (other than TB), enrolment should only be considered after discussing the case with the Sponsor Medical Monitor.

No waivers shall be granted

5.3 Restrictions

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

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

The following recommendations should be followed with regards to concomitant medication to avoid possible drug interaction with the IMP:

Participants on a moxifloxacin containing treatment arm: The IMP should be taken either 4 hours before or 8 hours after taking the following products:

An antacid, multivitamin, or other product that has magnesium, aluminium, iron or zinc;

Sucralfate;

Didanosine.

Participants on the HRZE/HR treatment arm: Any aluminium-containing antacids should be taken at least one hour after the IMP dose.

The following medicinal products are prohibited from Day -9 to Day -1 (Screening) and during the treatment period:

Quinolone antimalarials (e.g., chloroquine and quinacrine). Participants who have malaria at screening are to be excluded. However, if a participant develops malaria during the course of the trial, the investigator is advised to consult the Malaria Treatment Guidance document regarding the interaction between moxifloxacin and bedaquiline with anti-malarial drugs. Investigators may also contact the Sponsor medical monitor for further guidance.

Chronic systemic glucocorticoids (inhaled or intranasal glucocorticoids are allowed) due to their potential to cause visual opacities. Short term systemic glucocorticoids are allowed for emergency situations e.g for treatment of pulmonary exacerbation when Inhaled glucocorticoids is inadequate.

Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, other quinolones, thioamides, and metronidazole.

The following medicinal products should be avoided from Day 1 and during the treatment period as much as possible unless discussed with the Sponsor:

Any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). The exception is moxifloxacin and bedaquiline administered as part of the trial IMP with ECG monitoring to help ensure participant safety.

Any drug known to be hepatotoxic (including but not limited to acetaminophen/paracetamol, acetazolamide, allopurinol, amiodarone, amitriptyline, amoxicillin, amprenavir, atorvastatin, augmentin/co-amoxiclav, azathioprine, baclofen, bumetanide, captopril, carbamazepine, celecoxib, chlorpromazine, chlorpromazine, clindamycin, clopidogrel, contraceptive pill, co-

trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).

5.4 Treatment Discontinuation and/or Early Withdrawal

Any participant for whom the investigator decides to temporarily discontinue their IMP is to be discussed with the sponsor medical monitor and, if applicable, be restarted on IMP as soon as possible.

A participant must be prematurely withdrawn from the trial (during the trial treatment or follow up periods) as a result of the following:

- Withdrawal of informed consent;
- Investigator considers it for safety reasons in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment;
- Pregnancy;
- At the specific request of the sponsor or termination of the trial by the sponsor;
- Failure to comply with the protocol;
- Lost to follow-up
- Participant misses 21 or more consecutive doses of IMP;
- Drug-Sensitive TB treatment arms participants, who have been entered prior to receipt of the rapid, sputum – based molecular pyrazinamide resistance screening test result, who on receipt of the result, are found to be Z resistant.
- Drug-Sensitive TB treatment arms participants, who have been entered onto the trial as a rifampicin sensitive participant on the rapid sputum based test result, who on receipt of the rifampicin resistance testing using an indirect susceptibility test in liquid culture, this shows a rifampicin resistant result.
- Participants, who have been entered onto the trial as fluoroquinolone sensitive on the rapid sputum based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result.
- Early withdrawal due to TB (see Section 5.4.4)

A participant may withdraw from the trial at any time at his/her request (withdrawal of consent), or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or administrative issues. When a participant withdraws consent from the trial, no additional follow-up visits will be performed.

Participants who withdraw from the trial after having received IMP will not be replaced.

All participants withdrawn from trial treatment/received at least one dose of IMP will be requested to return for an early withdrawal visits and applicable safety Follow Up visits, as per flow chart (Section 1.2) Footnote c.

5.4.1 Early Withdrawal

In case of early withdrawal during the treatment or follow-up period, 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:

- Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
- Serum or Urine Pregnancy test (women of child bearing potential, whether they are sexually active or not);
- Laboratory Safety sampling (including male reproductive hormone tests);
- Single 12-lead ECG;
- TB Symptoms Profile;
- Patient Reported Health Status Questionnaire;
- Vital Signs;
- Full Physical examination including weight;
- Ophthalmology Examination if required as described in Table 5
- IMP Compliance Check (if participant on IMP);
- Concomitant Medications;
- Adverse Events.

Once a participant has been permanently withdrawn from the trial, they will be requested to attend follow-up visits as described in Table 5:

Table 5: Follow-up visits required for Early Withdrawal Participants

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

a If an additional visit is required for an ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 3 months after EWD visit date.

The Month 12 and 24 visits will be to collect SAE information (including verification of survival) and patient reported TB outcome information only and may be telephonic, a home or a site visit. They will occur at Month 12 and/or 24 after the participants' start of treatment date.

5.4.2 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.

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

- If both sputum samples (Early Morning and Spot) at Month 2 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum.
- If there is a positive culture at or after the end of treatment (Week 17 (4 month treatment arms)/Week 26 (6 month treatment arms)), the participant should return for an unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum.

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

- To be assessed on sputum culture results from:
  - End of Treatment Period (Week 17/26);
  - End of Follow-up Period (Month 12 and 24);
  - Early Withdrawal if applicable.
- Confirm whether the participant 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 Sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) a minimum of 7 days 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 is to contact the sponsor medical monitor and discuss and agree on how the patient is to be handled.

5.4.3 Lost-to-Follow-up

For Lost-to-Follow-up participants, a minimum of three contact attempts (telephonic/home visit) will be made. If these attempts are unsuccessful the participant will be considered lost to follow-up. This should be clearly documented in the participant's source documents.

5.4.4 Early Withdrawal due to TB

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

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

If the investigator decides to withdraw a participant due to TB, additional sputum samples may need to be collected in order to ensure the participant's outcome status as determined in Section 5.5.

All Early Withdrawal participants who are confirmed sputum positive (two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These participants will be referred to their applicable DS/MDR local community TB clinics for standard anti-tuberculosis chemotherapy according to National TB Guidelines. The participants will be provided with a referral letter to take with them to the TB Clinic. A follow-up call will be made by the trial site staff to the clinic to ensure the participant attended the clinic.

5.5 Participant Progress Definitions

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

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

** Early Withdrawal

5.6 Trial Stopping Rules

There are no trial specific stopping rules.

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

6.0 Treatment

6.1 IMP Administration

6.1.1 Instructions for Dosing of Test Regimen (BPaMZ):

Treatment will be administered orally once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months).

6.1.2 Instructions for Dosing Control Treatment Regimen (HRZE/HR):

To be taken with a glass of water (approximately 240 ml).

HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes.

Treatment will be administered orally once daily only to the “control” randomized DS-TB participants as follows:

Weeks 1-8: HRZE tablets with the daily dose per the Participant’s weight as follows: 30-37 kg: 2 tablets; 38-54 kg: 3 tablets; 55-70 kg: 4 tablets; 71 kg and over: 5 tablets;

Weeks 9-26: HR with daily dose per the participant's weight as follows: 30-39 kg: 2 tablets; 40-54 kg: 3 tablets; 55-70 kg: 4 tablets; 71 kg and over: 5 tablets.

Vitamin B6 25 mg daily supplement to be taken with the HRZE/HR treatment.

The daily dose of HRZE and HR combination tablets are dependent on the participant’s weight as follows:

30-37 kg: 2 tablets
38-54 kg: 3 tablets
55-70 kg: 4 tablets
>70 kg: 5 tablets

6.2 Participant Compliance

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

6.3 Treatment Modification(s)

The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the investigator to identify and address the cause(s) (e.g. side effects) of the non-adherence and contact the sponsor medical monitor within 24 hours. Participants missing:

- < 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required.

- Up to ≤ 21 consecutive doses of IMP: restart IMP, extend the IMP treatment by the number of consecutive doses missed. In this case: the final treatment visit should also be pushed out to the date of last dose.
  It is not necessary to have an unscheduled visit at the time when the End of Treatment visit would have been.
- 21 or more consecutive doses of IMP, discontinue IMP and withdraw participant from the trial.

Any participant for whom the trial medication is discontinued (including for non-adherence) will be discussed with the sponsor medical monitor and, if applicable, the participant will be restarted on trial medication as soon as possible.

6.4 IMP Packaging and Labelling

The complete formulations of the IMP, bedaquiline and pretomanid, are found in the respective Investigator Brochures.[8, 15] The complete formulations of moxifloxacin and pyrazinamide are found in the Package Inserts.[19, 20, 22, 40]

The IMP will be packaged as follows:

Treatment Group Wallet Cards

- Week 1-8 Cards
  - Bedaquiline 100 mg 14 tablets (B)
  - Pretomanid 200 mg 7 tablets (Pa)
  - Moxifloxacin 400 mg 7 tablets (M)
  - Pyrazinamide 500 mg 21 tablets (Z)

- Week 9-17/26 Cards
  - Bedaquiline 100 mg 7 tablets (B)
  - Pretomanid 200 mg 7 tablets (Pa)
  - Moxifloxacin 400 mg 7 tablets (M)
  - Pyrazinamide 500 mg 21 tablets (Z)

- Control Group Wallet Cards
  - Weight band 1 = 30-39kg
  - Weight band 2 = 40-54kg
  - Weight band 3 = 55-70kg
  - Weight band 4 = ≥71kg

- Bi-Weekly Cards (Weeks 1-8 Cards/56 days of treatment)
  - Weight Band 1 Contains: 28 tablets HRZE, 28 tablets HR
  - Weight Band 2 Contains: 42 tablets HRZE, 42 tablets HR
  - Weight Band 3 Contains: 56 tablets HRZE, 56 tablets HR
  - Weight Band 4 Contains: 70 tablets HRZE, 70 tablets HR

- B6 tablets in bottles

The IMP Treatment Arms will be packaged by individual weekly cards. The Control Arms will be supplied with bi-weekly cards and a biweekly bottle supply of B6. Contents of each weekly card is described in the IMP packaging detail listed above. The packaging of each weekly/biweekly card/bottle will be labelled with, at a minimum, the following information:

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

6.5 Blinding and Procedures for Breaking the Blind

As this is an open label trial there is no need for blinding or procedures to break the blind. The trial participants, the site staff, Sponsor, and CROs will not be blinded to treatment assignment.

6.6 Handling, Storage and Accountability

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

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

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

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

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

7.0 Trial Variables and Procedures

The Synopsis Flowchart and Procedures in Section 1.2 should be referenced for timing, sequence of assessments, and specific procedures.

7.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected:

- Written Informed Consent
- Visit Dates
- Participant Disposition
- Demography (date of birth, race and gender)
- Inclusion and Exclusion criteria
- Clinically significant medical and TB treatment history (including past and current TB diagnosis, smoking and alcohol use)
- Screening Coached Spot Sputum Sample:
  - Smear microscopy for acid-fast bacilli.
  - Gene Xpert, Hain Assay MTBDRplus or equivalent to determine MTB complex and rifamycin resistance
- Urine pregnancy test: women of childbearing potential only, whether they are sexually active or not. (Non-childbearing potential for a female participant is defined as having bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months.)
- Serology: HIV and CD4 count.
  - Where required by regulatory authorities or ethics committees:
    - Separate approval for this to be performed will be obtained from participants in the written informed consent process.
  - prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the participant, HIV counselling provided to the participant by the study site should be clearly documented in the participant's medical records/source. Participants have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the participant's medical records/source.
- Karnofsky Score (Appendix 4).
- Chest X-Ray: A Chest X-Ray digital image within 4 weeks prior to screening will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor; this process will be documented in the Radiology Manual. The Investigator is responsible for review and analysis for participant inclusion.
- Method of Birth Control: Male and Female participants and their partners.
- IMP Details: Randomization
- IMP Compliance/Actual Dosing
- Concomitant Medications

7.2 Efficacy Variables and Procedures

Two Spot Sputum Samples are collected, one Early Morning brought from home or collected in the hospital ward and one spot collected at the research site under the coaching and observation

of the trial staff or, if no early morning sample was provided, 2 samples collected on site at least 30 minutes apart. The Mycobacteriology sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start.

The following analyses will be performed:

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

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

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

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

TB Symptoms Profile:

- The TB Symptoms Profile (Appendix 6) will record participants' ratings of the severity of common TB symptoms.

Patient Reported Health Status Variables and Procedures:

- The Patient Reported Health Status variables will be collected at the time points described in the Synopsis Flow Chart (Section 1.2). Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire (Appendix 7). This descriptive system consists of five health-related quality of life dimensions, each of which will be recorded using five levels of severity. Methodology: The Patient Reported Health Status methodology and requirements will be described in a separate document/guideline which will be provided prior to the trial start.

7.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the Synopsis Flow Chart and Procedures and assessed for evaluation of the safety endpoints:

- Laboratory parameters. The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
  - Full Blood Count (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count),
  - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, ALP, AST, ALT, lipase, phosphate, sodium, potassium, calcium

(corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO_2, creatine phosphokinase (CPK).
  - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator.
- 12-lead ECG:
  - Investigator Assessment: Normal, Abnormal.
  - Central Cardiologist Assessment: Heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.
  - Methodology:
    - Timing and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start;
    - ECGs are to be recorded for 10 seconds;
    - All ECGs are to be performed in single visit.
    - ECGs should be done before any labs when both included in a visit)
    - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch).
- Vital signs:
  - Vital Signs, including weight (should be done before any labs in light clothing and with no shoes)
  - 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 (beats per minute).
  - Respiratory rate (breaths per minute)
  - Axillary body temperature (°C).
- Physical Examination:
  - Height (m) is measured at screening only.
  - Full (complete) and Limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded.
  - Weight (kg) (in light clothing and with no shoes).
  - Using the observed variables weight and height, calculated body mass index (BMI) will be derived.
- Ophthalmology Slit Lamp Examination. To be done by an Ophthalmologist trained on Age-Related Eye Disease Scale 2 (AREDS2) assessment. The ophthalmology slit lamp methodology and requirements will be described in a separate document, the Ophthalmology Guideline. The following analyses will be performed: AREDS2 opacity typing and grading.
- Ophthalmic Examination. The ophthalmic examinations can be performed by any trained study staff. The screening exams must be done by the trained study staff AND an Ophthalmologist. Methodology and requirements will be detailed in the Ophthalmology Guideline.
  - Ophthalmology History (Screening only);
  - Visual Acuity Test – Corrected. Distance Vision;
  - Colour Vision Assessment.
- Adverse Events.

- Investigator Assessment:
  - Principal Investigator to review participant status at specified visits in flow chart including any time Investigator determines that participant fulfils criteria for primary outcome of treatment failure. Investigator to assess whether TB treatment is considered a "success" or "failure". If considered a failure, should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration.

7.4 PK Variables and Procedures

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

7.5 Mycobacteriology Characterization Variable and Procedures

The following Mycobacterial Characterization variables will be collected:

Positive Culture (for MTB) from:

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

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

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

All Day 1 (baseline) MTB isolates and isolates from positive cultures to be stored at the local and central microbiology laboratories until trial closure. Extracted MTB DNA to be stored at the central microbiology laboratory until trial closure. The extracted MTB DNA and isolates will then be stored for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure. The MTB isolates will be processed at the central lab(s) for: Positive MTB at/after end of treatment: Hain MTBDR*plus* and HainMTBR*sl.*

8.0 Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

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

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

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

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

8.1.3 Attribution/Causality

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

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

Table 6: Adverse Events Attribution/Causality Ratings

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

8.1.4 Severity

Table 7: Definitions for Adverse Event Severity Gradings

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

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

8.2 Reporting

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

All Adverse events will be collected by the investigator from the time a participant signs the Informed Consent Form through to their Month 24 follow-up visit. The exception to this is Early Withdrawal participants who will only have SAEs collected from their time of Early Withdrawal to their Month 24 follow-up visit at the timepoints specified in the Flowchart (Section 1.2) and recorded in the CRF.

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

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

The sponsor/investigator/designee will inform Regulatory Authorities and/or EC/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 EC/IRB.

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

8.2.1 Follow up of Adverse Events

All AEs will be followed until:

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

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

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

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

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

8.2.2 Clinical Laboratory Adverse Events

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

8.2.3 Disease symptoms during Trial

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

worsened while the participant is in the trial; and

the investigator assesses it as clinically significant;

it will be recorded as an adverse event.

If there is:

no change; and

the investigator assesses the symptom as due to the participant's TB; and

not clinically significant;

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

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

8.2.4 Overdose

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

8.2.5 Drug Interaction

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

8.2.6 Pregnancy

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

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

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

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

Should the female partner of a male participant become pregnant during the trial or in 12 weeks after the completion of IMP and the Investigator becomes aware that this situation has occurred, the sponsor may request information from the female partner on her pregnancy history and on the current pregnancy and birth.

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

8.3 Monitoring for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in preclinical toxicity studies Investigator's Brochures[8, 15] and Package Inserts.[19, 20, 22, 40]

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

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

8.3.1 Neurological

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

8.3.2 Musculoskeletal System and Cardiac Muscle Myalgia

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

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

8.3.3 Cardiac Rhythm Disturbances

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

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

QTc prolongation

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

New left bundle branch block (LBBB) or Mobitz type 2 or complete heart block. Recordings with artifacts that interfere with the interpretation of the ECG should be repeated to confirm the findings. If the finding is from the centralized ECG machine reading the result is to be checked and confirmed by the Investigator. If this is confirmed by the Investigator, dosing is to be paused until the reading has been confirmed by the central cardiologist and the participant is to be treated per the Investigator's clinical judgment. If it is confirmed by the central cardiologist, the participant is to be withdrawn from the full regimen. Contact Sponsor Medical Monitor to review. Investigator should consider participants with confirmed Grade 3 or 4 elevations of lipase for temporary or permanent discontinuation from the full regimen.

8.4 Safety Monitoring by Data Monitoring Committee

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

9.0 Statistical Analysis

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

9.1 Analysis Populations

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

- The ITT population is defined as all randomized patients excluding late screening failures. Late screening failures are patients withdrawn from treatment because they were found to be ineligible (late exclusions from the study), based on data collected *prior to randomization*.
- The mITT population is defined as the ITT population with extra exclusions (described in the SAP).
- The PP population is defined as the mITT population with extra exclusions (described in the SAP).
- The mITT analysis will be considered primary, with consistent findings required from the other main analysis populations to support the primary conclusion.

9.2 Sample Size

For the primary endpoint, time-to-culture conversion at 8 weeks,150 participants per arm (DS-TB patients) will provide at more than 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 90% power to detect a HR of least 2. This sample size also allows for one planned interim analysis of the primary endpoint (See Section 9.4.1)

For the key secondary endpoint of clinical outcome at 12 months from randomization, 150 patients per arm will provide 74% power based on assumptions using data from the largest most recent and completed phase 3 TB treatment trial which used the same control arm.[41] That is, assuming 16% unfavourable (see Section 9.4.2) in the control arm and 13% unassessable (see Section 9.6) at 52 weeks post randomization. A 12% margin of non-inferiority was chosen to preserve at least 75% of the estimated control arm effect against placebo (estimated to be 54%)[41, 42] which is considered an acceptable proportion on which to declare non-inferiority of the test regimen.

9.3 Interim Analyses

There is no planned interim analysis in this trial.

9.4 Primary and Secondary Efficacy Endpoint Analysis

9.4.1 Primary Efficacy Endpoint, Time to Culture Conversion at 8 Weeks

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

Patients will be classified as being culture positive, culture negative, dead or unassessable at 8 weeks. The proportion culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis and groups compared using a hazard ratio and 95% confidence interval.

Non-inferiority of the key secondary endpoint of clinical outcome will be assessed using the upper bound of the one-sided 97.5% confidence interval for the difference between the proportion of patients who are classified as having an unfavourable status on the intervention less the control regimen. If the upper bound of the one-sided 97.5% confidence limit for this difference in proportions is less than 12% (the margin of inferiority) the intervention will be considered to be non-inferior to the control arm.

9.4.2 Key Secondary Efficacy Endpoint, Clinical outcome at 52 Weeks from Randomization

For the key secondary endpoint of clinical outcome (bacteriologic failure or relapse or clinical failure), patients will be classified as having a favourable, unfavourable or unassessable outcome status which will be defined in detail in the SAP. In general, participants achieving and maintaining culture negative status without any additional treatment will be considered favourable; participants who fail on treatment or relapse in follow-up will be considered unfavourable and participants who are not assessable (and who have not already been declared as unfavourable) will be considered unassessable and excluded from the analysis.

9.4.3 Other Secondary Efficacy Endpoints

The secondary efficacy endpoints and analyses are as follows are:

- Clinical outcome (bacteriologic failure or relapse or clinical failure) at 104 weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight will be summarised and presented.
- Proportion of participants experiencing a change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status will be summarised and presented.

9.5 Safety and Tolerability Assessments

- 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.

9.6 Pharmacokinetics

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., Cmin, Cmax, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on

exposure will be assessed; so, too, will the effects of con-medications including ART, as feasible. Data from other trials may be included to enhance the model-based analysis. Detailed plans for the PopPK analysis will be outlined in a separate modeling plan, and results will be reported in separate modeling report.

9.7 Pharmacokinetics/Pharmacodynamics

Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate. Planning details and results will be included in the separate modeling plan and report.

10.0 Records Management

10.1 Data Collection

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

10.2 Source Documents

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

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

10.3 File Management at the Trial Centre

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

10.4 Records Retention at the Trial Centre

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

11.0 Quality Control and Assurance

11.1 Site Procedures

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

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

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

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

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

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

11.2 Monitoring

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

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

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

11.3 Protocol Deviations

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

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

11.4 Auditing

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

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The auditors or inspectors may also review site SOPs, training records, site facilities and other trial related systems/processes.

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

12.0 Ethics and Regulatory

12.1 Basic Principles

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

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

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

12.3 Regulatory Authorities

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

12.4 Informed Consent

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

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

The trial will be included and updated in the appropriate Country registry and referenced in the informed consent forms (ICF).

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

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

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

12.5 Confidentiality

All site staff, the Sponsor, and any sponsor representatives will preserve the confidentiality of all participants taking part in the trial, in accordance with International GCP, applicable local legislation/regulations. Participant to the requirement for source data verification by the trial

personnel by reference to the participant's notes, confidentiality of all participant identities will be maintained. Unique identifiers will be used on the CRF and in all trial correspondence, as permitted. No material bearing a participant's name will be kept on file by the Sponsor. The written informed consent will contain a clause granting permission for review of the participants' source data by the sponsor or designees.

13.0 Publication Policy

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

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

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors.[43]

Because the Trial is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the Trial must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy. Specifically, (a) all peer-reviewed published research relating to the Trial must be submitted for publication by TB Alliance through the Chronos Open Access Publishing Service established by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy.

14.0 Protocol Amendment Policy

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

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

15.0 Sponsor, Financial Aspects, Insurance and Indemnity

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

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

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

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

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

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Appendices

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	scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

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

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

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of Acquired Immune Deficiency Syndrome (AIDS), NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the DMID and modified to better meet the needs of participants 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.

Appendix 3: Who Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection
Asymptomatic Acute retroviral syndrome
Clinical Stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical Stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections
Clinical Stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for >1 month Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) Persistent oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anemia (hemoglobin <8 g/dL) Neutropenia (neutrophils <500 cells/µL) Chronic thrombocytopenia (platelets <50,000 cells/µL)
Clinical Stage 4
HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Cryptococcosis, extrapulmonary (including meningitis) Disseminated nontuberculosis mycobacteria infection Progressive multifocal leukoencephalopathy Candida of the trachea, bronchi, or lungs Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)

Recurrent nontyphoidal Salmonella bacteremia
Lymphoma (cerebral or B-cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy
Symptomatic HIV-associated cardiomyopathy
Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

REF: World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children; 2007*

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: Cardiovascular Safety

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

All-important abnormalities from the ECG readings will be reported.

The percentage of participants with increases in QTc of <30, 30-60, or > 60 ms from baseline will also be tabulated at each time point.

Abnormality Code	ECG parameter			
	HR	PR	QRS	QTcorrected
Abnormalities on actual values				
“Abnormally low”	≤ 50 bpm	NAP	≤ 50 ms	-
“Abnormally high”	≥ 120 bpm	≥ 210 ms	≥ 120 ms	-
“]450 ms, 480 ms]	-	-	-	450 ms < QTc ≤ 480 ms
“]480 ms, 500 ms]	-	-	-	480 ms < QTc ≤ 500 ms
“More than 500 ms	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline				
“[30; 60] ms”	-	-	-	[30; 60] ms
“> 60 ms”	-	-	-	> 60 ms

Appendix 5: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

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

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

Appendix 6: Tuberculosis Symptoms Profile

TUBERCULOSIS SYMPTOM PROFILE (V3)

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

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

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

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

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

During the past 7 days, how would you rate your appetite?

☐ Good ☐ Fair ☐ Poor

Approved, Issued Date 09-Apr-2012

Appendix 7: Patient Reported Health Status Questionnaire

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

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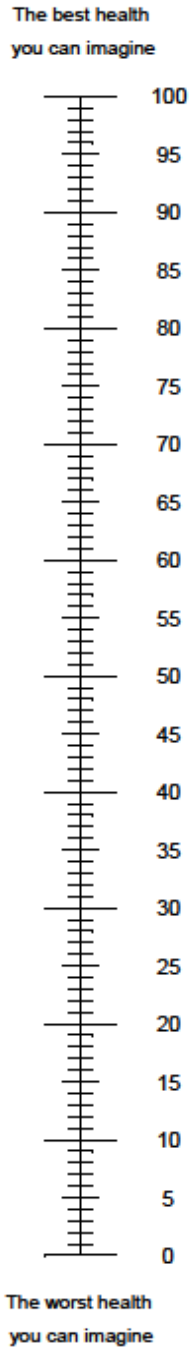
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the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

YOUR HEALTH TODAY = ☐



3

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Protocol Number:	NC-008 (B-Pa-M-Z)
Title:	An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).
Drug(s)/Combination(s):	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Amendment Version/Date:	V2.0 / 21 February 2018, Incorporating Amendment 1
Protocol Name:	**SimpliciTB**

PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (B-Pa-M-Z)**

Protocol Date: **V2.0 / 21 February 2018, Incorporating Amendment 1**

Protocol Name: **SimpliciTB**

SPONSOR: **Global Alliance for TB Drug Development**

I agree to the terms of this trial protocol.

DocuSigned by:
Paul Bruinenberg
Signer Name: Paul Bruinenberg
Signing Reason: I approve this document
Signing Time: 21 February 2018 | 06:04 PST
3B496C3B3A5A4B0AAE32731255B7116B

Signature of Senior Medical Officer

Paul Bruinenberg MD, MBA
Printed Name

February 21, 2018 | 9:04 AM EST

Date

40 Wall Street, 24th Floor
New York, NY 10005
Phone +1 646-616-8671 / +1 646-616-8629
E-mail: Paul.Bruinenberg@tballiance.org

LEAD INVESTIGATOR

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

Signature

Printed Name

Date

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (B-Pa-M-Z)**

Protocol Date: **V2.0 / 21 February 2018, Incorporating Amendment 1**

Protocol Name: **SimpliciTB**

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

_____ _____
Signature Printed Name

_____
Date

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Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AFB	Acid-fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AREDS2	Age Related Eye Disease Scale 2
ART	Anti-Retroviral Therapy
AST	Aspartate aminotransferase
AUC_{τ}	Area Under Curve over a dosing interval
B	Bedaquiline
BA	Bacterial activity
BMI	Body Mass Index
BPaMZ	Combination of bedaquiline plus pretomanid plus moxifloxacin plus pyrazinamide
C	Clofazimine
CFU	Colony Forming Units
$C_{(max), (min)}$	plasma Concentration (maximum), (minimum)
CO_2	Carbon dioxide
CPK	Creatine Phosphokinase
CYP3A4	Cytochrome P450 3A4
DMID	Division of Microbiology and Infection Disease
DNA	Deoxyribonucleic Acid
DR-TB	Drug-resistant tuberculosis For this particular protocol defined as TB participants with 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB) (participants with fluoroquinolone resistance are excluded)
DS-TB	Drug-sensitive tuberculosis
DSMC	Data Safety and Monitoring Committee
E	Ethambutol
EBA	Early Bactericidal Activity
EC	Ethics Committee
ECG	Electrocardiogram
EFV	Efavirenz
(e)CRF	(electronic) Case Report Form
EMS	Early Morning Sputum
EWD	Early Withdrawal
FTC	Emtricitabine
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
H	Isoniazid
hERG	Human *Ether-à-go-go* Related Gene
HIV	Human Immunodeficiency Virus

HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
HR	Isoniazid plus rifampicin combination tablet
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent to Treat
IUATLD	International Union Against Tuberculosis and Lung Disease
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Linezolid
LH	Luteinizing hormone
LLN	Lower Limit of Normal
LPV	Lopinavir
LTFU	Long term follow-up
M	Moxifloxacin
MBD	Minimum Bactericidal Dose
MIC	Minimum Inhibitory Concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi Drug Resistant Tuberculosis
MGIT	Mycobacterial Growth Inhibiting Tube
mITT	Modified Intent to Treat
ms	millisecond
NVP	Nevirapine
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NRTI	(Triple) Nucleosidase Reverse Transcriptase Inhibitor
Pa	Pretomanid
PD	Pharmacodynamic
PP	Per Protocol
PK	Pharmacokinetic
PR	PR interval
R	Rifampicin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSCC	Serial sputum colony counting
TB	Tuberculosis
TDF	Tenofovir
TEAE	Treatment Emergent Adverse Events
TTP	Time to Positivity
ULN	Upper Limit of Normal
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis
µg(/ml)	micrograms (per millilitre)
Z	Pyrazinamide (tablets)

1.0 Synopsis

1.1 Synopsis Summary

Synopsis	Description
Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished Products	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Number/Title	NC-008 / (B-Pa-M-Z)/ An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB)
Treatment Indication	Pulmonary Tuberculosis (TB)
Trial Objective(s)	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with: **Drug Sensitive TB (DS-TB)** – BPaMZ given for 17 Weeks (4 months), or – Standard HRZE/HR treatment given for 26 weeks (6 months) **Drug Resistant TB (DR-TB)** – BPaMZ given for 26 Weeks (6 months) **DR-TB Defined as participants with** 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)
Trial Design	Phase 2c multi-centre, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. All participants will enter post-treatment follow-up which continues until Week 104 (24 months) after start of treatment / randomisation. **Participants with Drug Sensitive TB (DS-TB):** Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR tablets daily for 26 weeks

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td></td><td>(6 months). Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation.

Participants with Drug Resistant TB (DR-TB):

Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).</td></tr>
<tr><td>Patient Population</td><td>A total of up to 450 male and female participants, diagnosed with DS-TB or DR-TB, aged 18 years and over with a target of up to 50% being HIV positive.

300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation.

Up to 150 DR-TB participants will be enrolled.</td></tr>
<tr><td>Test product, Dose and Mode of Administration</td><td>The Test Treatment Regimen (BPaMZ) consists of a combination of the following products and will be supplied as:

<table>
<tr><th>Product</th><th>Tablet Strength</th><th>Abbreviation</th></tr>
<tr><td>Bedaquiline</td><td>100 mg</td><td>(B)</td></tr>
<tr><td>Pretomanid</td><td>200 mg</td><td>(Pa)</td></tr>
<tr><td>Moxifloxacin</td><td>400 mg</td><td>(M)</td></tr>
<tr><td>Pyrazinamide</td><td>500 mg</td><td>(Z)</td></tr>
</table>

Instructions for Dosing of Test Regimen (BPaMZ):
Treatment will be administered orally once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months) in the following dosing schemes:

Participants with Drug Sensitive TB: (DS-TB)
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 17 weeks (Total treatment duration 4 months)

OR

Participants with Drug Resistant TB: (DR-TB)
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 26 weeks (Total treatment duration 6 months)</td></tr>
<tr><td>Positive Control Product, Dose and Mode of Administration</td><td>The Control Treatment Regimen (HRZE/HR) will be supplied as:</td></tr>
</table>

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td></td><td>

HRZE Tablets: (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). This combination will be given for the first 8 weeks.

AND

HR Tablets: (isoniazid 75 mg plus rifampicin 150 mg combination tablets). This combination will be given from Weeks 9 to 26.

Instructions for Dosing Control Treatment Regimen (HRZE/HR):

To be taken with a glass of water (approximately 240 ml). HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes:

Treatment will be administered orally once daily to the HRZE/HR randomized DS-TB participants as follows:

Weeks 1-26: HRZE/HR tablets daily dose per the participant's weight as follows:

<table>
<tr><th>Weight Band</th><th>Weight Range</th><th>Number of tablets</th></tr>
<tr><td>1</td><td>30-39 kg</td><td>2</td></tr>
<tr><td>2</td><td>40-54 kg</td><td>3</td></tr>
<tr><td>3</td><td>55-70 kg</td><td>4</td></tr>
<tr><td>4</td><td>≥ 71 kg</td><td>5</td></tr>
</table>

Vitamin B6 daily supplement to be taken with the HRZE/HR treatment, per each country's TB Treatment Guidelines.

</td></tr>
<tr><td>**Treatment Interruptions/Pauses**</td><td>

For All Trial Regimens:

The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical monitor prior to implementation, unless an interruption/pause is required urgently for a safety concern.

Action required for participants missing the following number of doses within the trial treatment regimens:

- Up to 7 consecutive doses: restart treatment, no extension of treatment required
- Greater than 7 and to ≤ 35 consecutive doses: restart treatment, extend the treatment by the number of consecutive doses missed, before the end of the treatment period (week 17/26). In this case, the last visit of the

</td></tr>
</table>

Synopsis	Description
	treatment period should also be pushed out to the date of the last dose • Greater than 35 consecutive doses: discontinue treatment and withdraw participant from the trial • If the participant misses a total (sum of) of 56 cumulative missed doses, discontinue IMP and withdraw participant from the trial. Any participant for whom the trial medication is discontinued (including for non-adherence) will be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial medication as soon as possible.

Statistical Methods:
A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the statistical analysis plan (SAP,) which will be written and signed off prior to the first participant enrolled in the trial.

The primary analysis will be conducted using culture results from liquid culture (in the Mycobacterial Growth Indicator Tube (MGIT) system).

Criteria for Evaluation:

The primary efficacy endpoint will be time to culture negativity over 8 weeks. The primary hypothesis to be evaluated is:

In the participants with DS-TB in the experimental BPaMZ treatment regimen, the time to culture negativity by 8 weeks will be superior, compared to the participants who are treated with the standard HRZE regimen.

There will be three main analyses. A modified Intent to Treat (mITT) analysis will be primary. A per-protocol (PP) analysis and an ITT analysis will also be performed for the secondary endpoint. These will be examined for consistency with the mITT analysis.

Note: Culture conversion requires at least 2 consecutive culture negative samples, at least 7 days apart (after positive baseline confirmation). Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered culture negative at that visit.

Secondary Endpoints

A key secondary endpoint will be the proportion of participants experiencing bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks (12 months). The hypothesis to be evaluated for this endpoint is:

Synopsis	Description

In the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen.

Other Secondary Endpoints

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 104 weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
    - Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
    - Quantitative and qualitative electrocardiogram (ECG) results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones and lens opacities.

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

Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD):
Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [Cmin], maximum plasma concentration [Cmax], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of con-medications, including antiretroviral therapy (ART), where feasible. Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

Exploratory:
Evaluate whether any of the secondary endpoints predict relapse free cure. Subgroup analysis of populations by HIV status will be performed.

Synopsis	Description
No formal statistical comparisons will be made for the participants enrolled with DR-TB. **Sample Size** Primary endpoint: 150 participants per arm (DS-TB patients) will provide at least 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. Additional efficacy parameters will be evaluated including the incidence of bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks and 104 weeks from the start of treatment. Time to unfavourable outcome from assignment of trial treatment through follow-up as a function of time will be analysed using Kaplan-Meier analysis.	
Trial Duration: Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until week 104 from start of treatment. Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms is complete. There will be 3 database locks, data analyses and trial reports generated for this trial: 1. When all participants have completed 8 weeks (2 months) of treatment from baseline. 2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy. 3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.	

1.2 Synopsis Flow Chart and Procedures

Period	Screening[a]	Treatment															Follow-Up[c]					
Visit[b]	Day -9 to -1	Day 1 (Baseline)[d]	Day 7 (Week 1)	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 17 *4-mth treatment*[e]	Week 17 *6-mth treatment*[e]	Week 22	Week 26 *4-mth treatment*[e]	Week 26 *6-mth treatment*[e]	Week 39	Week 52	Week 65	Week 78	Week 104	Early Withdrawal[c]
Visit Window[v]	N/A	+/- 3 Days									+/- 5 Days						+/- 14 Days					
Written Informed Consent	X																					
Demography	X																					
Medical/Treatment/ Smoking History	X																					
Inclusion/Exclusion	X	X																				
Sputum Sampling[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Status[h] and CD4 Count[i]	X																					
Karnofsky Score	X																					
Urine Drug Screen[j]	X																					
Urine Pregnancy Test[k]	X	X								X		X	X		X	X						X
Laboratory Safety Test[l]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X						X
Male Reproductive Hormone Tests[m]	X	X											X		X		X					
12-lead ECG[n]	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X					X
Chest X-Ray[o]	X																					
TB Symptoms Profile	X	X		X		X				X		X	X		X	X		X			X	X
Patient Reported Health Status	X	X		X		X				X		X	X		X	X		X			X	X
Vital Signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination[p]	X											X	X		X	X	X					X
Physical Examination – full[q]	X	X										X				X						X
Physical Examination – limited[r]			X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Pharmacokinetic Sampling[s]		X		X						X	X	X	X				X		X	X	X	
IMP Randomization/ Assignment[t]		X																				
IMP Compliance Check[u]			X	X	X	X	X	X	X	X	X	X	X	X[e]		X						X[t]
Concomitant Medications	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
Investigator Assessment[v]																		X			X	

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

a. **Screening:** Screening assessments can occur on different days within nine days prior to Day 1 dosing (randomisation).

b. **Visit Schedule (due to unforeseen circumstances):** If the duration of treatment is extended due to dose interruptions / pauses, the last visit of the treatment period should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time that the last visit of the treatment period would have been.

c. **Follow-up Visits for Early Withdrawal Participants:** Once a participant has been permanently withdrawn from the trial, they will be required to attend Early Withdrawal, Week 52 (if not already performed) and Week 104 follow-up visits. The Week 52 and Week 104 visits will be to collect Serious Adverse Event (SAE) information (including verification of survival) and participant reported TB outcome information only and may be telephonic, a home or a site visit. Visits will occur at Week 52 and/or Week 104 after the participant's start of treatment date. Refer to Table 5 for additional guidance.

d. **Day 1 (Baseline):** All procedures are to be completed prior to dosing.

e. **Last Visit of the Treatment Period:** Investigational Medicinal Product (IMP) Compliance Check is not performed at the Week 22 visit for participants who have completed treatment at Week 17.

f. **Sputum Sampling:** The sputum sampling methodology/requirements and tests will be described in a separate document, the Mycobacteria Laboratory Manual.
   - Days -9 to -1 (Screening). Two spot sputum samples taken 30 minutes apart will be collected at the research site under the coaching and observation of the trial staff. The following analyses will be performed on the first of these samples:
     - Smear microscopy for acid-fast bacilli (AFB);
     - Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance;
     - Liquid Culture (MGIT) for *Mycobacterium tuberculosis* (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive.
     - The second sample is collected as a back-up sample to the first sample in case it is technically not possible to obtain a result/s from the first sample. If the Day -9 to -1 (Screening) spot sputum smear shows an indeterminate result or is AFB negative, the test may be repeated on the back-up sample or on a freshly collected spot sputum/s and that result will be used.
   - Baseline to Week 104, including any unscheduled visits:
     - Two sputum samples (ideally one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff. If the participant forgets to bring in the Early Morning Sputum (EMS), then two spots are to be collected at the site, at least 30 min apart, and this altered sample collection is captured within case report form [CRF]).
     - If both sputum samples at Weeks 8, 17 (4-month treatment arm), 26 (6-month treatment arm), 52 or 104 are contaminated, the participant should return for an unscheduled visit(s) to give additional samples or to document that the

participant is not able to produce sputum. If there is a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 for the 4-month treatment arms and Week 26 for the 6-month treatment arms), the participant should return for an unscheduled visit(s) to give additional sputum samples a minimum of 7 days after the previous sample, or to document that the participant is not able to produce sputum.

- Additional samples may be required to define a participants' primary outcome status as described in Section 7.2.
- Liquid Culture (MGIT) for MTB, followed by a speciation test to detect presence or absence of MTB and obtain TTP when positive, will be performed on all samples.

g. **Mycobacteriology Characterisation Tests performed:**

- Day 1 (baseline) sputum sample (or any positive sample from screening out to Week 4 if the baseline cultures are contaminated or negative);
- MTB confirmed positive cultures at or after Week 17 (4-month treatment arms) or Week 26 (6-month treatment arms).

Refer to Mycobacteria Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates will be processed for:

- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin;
- Drug Susceptibility Testing for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, pyrazinamide and second line TB drugs including, but not limited to fluoroquinolones, and injectables using an indirect susceptibility test in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing, and comparison of sequences from baseline and relapse isolates.

h. **HIV Testing:** If HIV status is a confirmed known positive, a repeated HIV test is not needed provided that a documented HIV test result is available. If HIV status is unknown or suspected negative, a HIV test will be requested. If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated if documentation of testing method and negative HIV results can be provided. Repeated HIV testing, during the Screening period is permitted for indeterminate HIV results.

i. **CD4 Count:** Required for all HIV-positive participants.

j. **Urine Drug Screen:** Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at Screening only. Investigator to utilize this result to determine whether participant meets Exclusion criteria 2. Positive results will not automatically exclude a participant from the trial.

k. **Urine Pregnancy Test:** Women of childbearing potential only, whether they are sexually active or not.

l. **Safety Laboratory Assessments**: The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:

- Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count).

- Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/carbon dioxide [CO_2], creatine phosphokinase [CPK]). GGT is only routinely included at the Screening visit (Day -9 to -1).
- 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.
- When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

m. **Male Reproductive Hormone Tests:** Testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin B to be done on male participants in ALL treatment groups.

n. **Single 12-Lead ECG:** To every extent possible, this should be performed at approximately the same time of day as the trial procedures (+/-1 hour). Central ECG analysis will be performed. Results from central reading of Day -9 to -1 (Screening) ECG must be used to determine eligibility.

o. **Chest X-Ray:** A chest x-ray (digital image only) within 6 months prior to or at the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor and this process will be described in a separate document, the Radiology Manual.

p. **Slit Lamp Ophthalmic Examination**: Slit lamp examination will be done at the Screening visit, the last visit of the treatment period, Week 17 or 26, and at Week 39 (9 months) for both treatment groups. An additional slit lamp at 6 months will be done for the 4-month treatment group. Slit lamp ophthalmology examination will be performed by an Ophthalmologist with AREDS2 training. Ophthalmology examinations may occur at any time within the window period for the applicable visit i.e. they do not have to be performed on the same day as the trial procedures.

q. **Physical Examination – Full:** Height (m) will only be collected at Day -9 to -1 (Screening).

r. **Physical Exam – Limited:** Limited physical exams will include weight and gross neurological, pulmonary, cardiovascular and abdominal exam(s).

s. **Pharmacokinetic (PK) Sampling:** This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE-HR treatment arm. Blood draws for PK samples collected pre-dose must be done after the ECG is performed. The dates and times of the two doses of IMP taken prior to all pre-dose PK samples will be collected. Specific PK blood draws will be obtained as follows:
   - Day 1: pre-dose (within 2 hours prior to dosing)
   - Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
   - Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose

- Week 12: pre-dose (within 2 hours prior to dosing)
- Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose
- Weeks 39, 65, 78 and 104: PK samples are to be obtained at any time on the day of the scheduled visit

t. **Investigational Medicinal Product (IMP) Randomization/Assignment:** Randomization may occur once all the Screening results are available and the Investigator has determined that the participant is eligible for the trial.

u. **IMP/Compliance Check:** IMP administration will be supervised per local site practice to assure compliance to regimen. Performed at all visits and Early Withdrawal (EWD), if during the treatment period.

v. **Investigator Assessment:** Investigator to review participant status and assess whether IMP or TB treatment at current visit is considered a “success” or “failure”. If considered a failure, the Investigator should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed, as shown on the flowchart, and at any time Investigator determines that participant fulfils criteria for outcome of treatment failure.

w. **Visit Windows**: The windows noted on the flowchart for timing of visit also apply to timing *within a visit.* Procedures should be performed within +/- 3 days of scheduled visit from Day 1 to Week 8 or +/- 5 Days of scheduled visit from Week 12 to Week 26 or +/- 14 days of scheduled visit at or after Week 39. Sites should make every effort to ensure all procedures are done on the same day, when possible.

2.0 Introduction and Rationale

2.1 Tuberculosis Disease

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in the developing countries of Africa, Asia and South America. TB is currently one of the top three killer infectious diseases, 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 40 years and are relatively ineffective in controlling TB as a public health problem. 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 participants, treatment takes 6 months or more to complete. This, long duration treatment **plus side effects**, result in poor adherence which particularly occurs after the second month of treatment.

The current TB treatment regimens and treatments for drug-sensitive TB are decades old. The available treatments have a lengthy duration of treatment, involve multi-drug therapy, and require large commitments of resources and infrastructure. High rates of noncompliance are common, which often results in increased mortality and chronic, infectious, drug-resistant cases. The present TB epidemic and the challenge of current treatment options demonstrate the clear need for effective novel TB drugs and **drug regimens** that are safe for drug sensitive and drug resistant TB disease and that are well-tolerated and will shorten the current treatment duration for patients.

The full application of the Directly Observed Treatment, Short-Course strategy is becoming more and more difficult in the developing countries of the world that are also battling to control the HIV-epidemic. Because of poor treatment adherence, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB are growing. Since the discovery of the rifamycins,[1] and their introduction into standard antituberculosis regimens, very few new classes of drugs have been evaluated with a view to their registration as antituberculosis agents. On December 28, 2012 the U.*S.* Food and Drug Administration approved bedaquiline (B) as part of combination therapy to treat adults with multi-drug resistant (MDR) pulmonary tuberculosis (TB) when other alternatives are not available. 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.

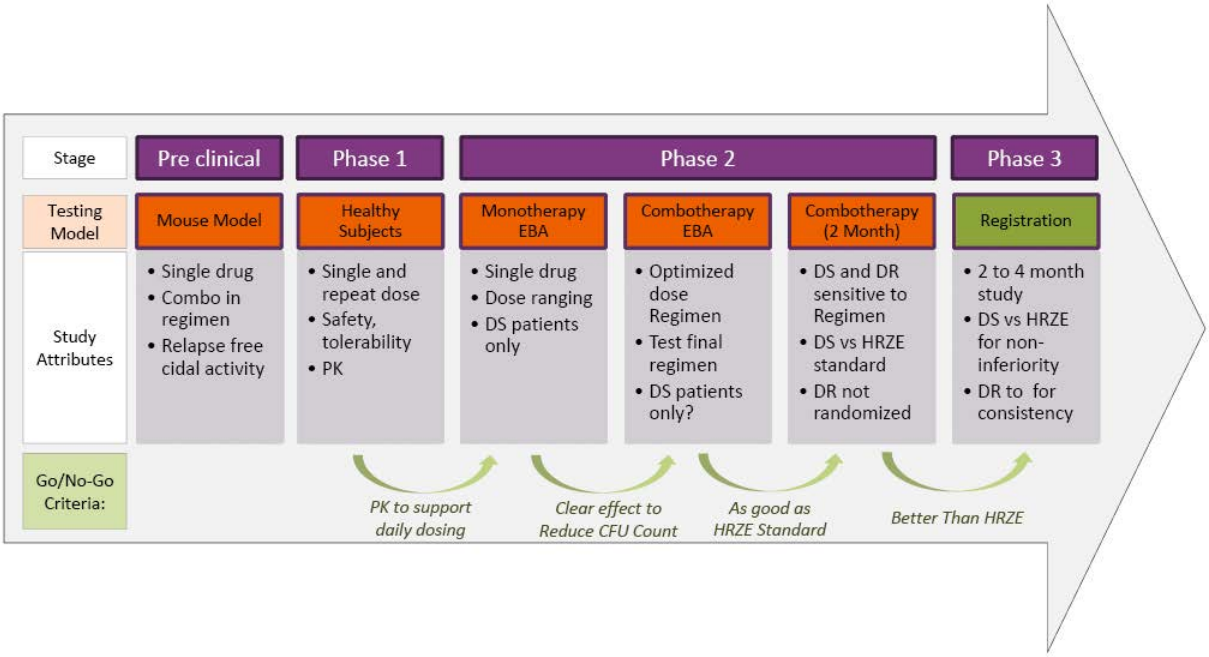
New combination regimens are desperately needed for two reasons: to shorten treatment to a duration more easily manageable by patients and public health services, and to provide more efficacious, safer and better tolerated, affordable treatments for the growing number of patients suffering from multidrug-resistant and extensively drug-resistant tuberculosis.

2.2 Tuberculosis Clinical Research

TB currently must be treated with multiple drugs to achieve maximal efficacy and prevent resistance. To transform treatment, novel TB regimens are needed. To telescope the time, it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm. This approach tests promising combinations of drugs together to find the most impactful treatment once the individual drug candidates have been tested in a robust pre-clinical program and the establishment of the individual drug candidates' safety and efficacy have been evaluated. It evaluates novel combinations of TB drugs — instead of single drugs — as part of a single development program, enabling the development of novel TB drug regimens that have

potential to transform treatment for drug-sensitive and drug-resistant tuberculosis. This approach offers the potential to reduce the time previously needed to develop a novel treatment regimen by up to 75%, shortening the clinical development from decades to years. The steps followed in this development model are shown in Figure 1 Between each step on the unified development pathway a decision is made as to whether to proceed.

Figure 1. Unified Drug Sensitive/Drug Resistant Regimen Development Path



Early Bactericidal Activity (EBA) Trials

EBA trials are the backbone clinical trials to quantify the bactericidal action of anti-tuberculosis agents alone or in combination by either trialling the fall in the number of colony forming units (CFU) or measuring the TTP in liquid culture of *M. tuberculosis* (*MTB*) present in the sputum of participants with microscopy smear-positive pulmonary TB. EBA trials have been conducted over 2, 5, 7 and 14 days.[2]. A review of EBA trials conducted on the key anti-TB drugs has shown the value these trials offer to demonstrate the early anti-TB effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in participants.[3]

8-week Bactericidal Activity (BA) Trials

EBA methodology of quantitative colony counting on solid medium has been adapted to Phase 2, 8-week TB treatment trials based on serial sputum colony counting (SSCC) or measurement of TTP liquid culture to provide a more sensitive efficacy endpoint than the previously used binary endpoint of rate of sputum conversion measured after 8 weeks of treatment.[4-6] Such trials are conducted to provide data on which to base the selection of treatment-shortening regimens.

2.3 Trial Rationale

This trial (SimpliciTB) will evaluate and support that, in additional to previous studies evaluated with BPaMZ, this drug regimen (BPaMZ) will be safe and effective, is well-tolerated and could potentially shorten the current treatment duration compared to Standard HRZE/HR treatment for patients with drug sensitive TB disease. This trial will also evaluate if this drug regimen (BPaMZ) given for 6 months will be safe and effective in drug resistant TB disease.

Therefore, the trial design addresses the need to find and evaluate a potentially effective and shorter regimen compared to regimens (Standard HRZE/HR) that are currently being used.

2.3.1 Trial Design Rationale

NC-008 (B-Pa-M-Z) trial - [**SimpliciTB**] - is a Phase 2c multi-centre, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. This trial is to evaluate the combination regimen of **Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) plus Pyrazinamide (Z)**, (BPaMZ) in participants with pulmonary TB.

All participants will enter post-treatment follow-up which continues until Week 104 (24 months) after start of treatment / randomisation.

Participants with Drug Sensitive TB (DS-TB):

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months),

or

HRZE/HR combination tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with HIV and cavitation.

Participants with Drug Resistant TB (DR-TB) are defined as:

1. mono-resistance to rifampicin or isoniazid, OR

2. resistance to both rifampicin and isoniazid (multi-drug resistant tuberculosis [MDR-TB])

Up to 150 participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months). Approximately 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation to either BPaMZ for 4 months or HRZE/HR for 6 months.

The trial is sufficiently statistically powered to not only show superiority of 2 months' culture conversion, but should also demonstrate non-inferiority for cure at 12 months. (This is in the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen).

As previously described in the background information, in order to telescope the time it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm and utilize data generated in non-clinical and clinical studies regarding combining of

anti-tuberculosis agents which could contribute significantly to the sterilization of lesions and thus treatment shortening. Therefore, the trial design and proposed trial regimen (**BPaMZ)** which is supported with previous non-clinical and clinical studies outlined below should address the need and manner of evaluating an effective shorter regimen compared to regimes that are currently being used.

2.3.2 Trial Drug Regimen Rationale

The **BPaMZ** regimen has been studied singularly and in different combinations as outlined above. Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. It essentially provides protection against the development of new resistance to the B-Pa-Z drugs. Based on the exciting and promising results seen in NC-005, this regimen can be initiated in drug sensitive and drug resistant TB participants whom are sensitive to the individual drugs in the regimen (excluding extensively drug-resistant tuberculosis [XDR-TB]) and has the potential to shorten TB treatment to less than 4 months in drug sensitive TB. These are also oral regimens, removing the need for injectables as part of MDR-TB treatment and also project to be markedly less expensive than current MDR-TB therapy. Additionally, these regimens can be administered in a fixed dose for all patients, and will therefore be simpler for health systems to deliver and patients to use.

2.4 Agents used within SimpliciTB

Bedaquiline (TMC207; Sirturo™ package insert)[7] is a novel agent approved for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[9, 10]) *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. Tb* isolates,[10, 11], and is also bactericidal against non-replicating *M. Tb.*[12] In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. Tb*.[3, 4] 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.[13] 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 DS- and MDR-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[13] and in a subsequent trial it was more active in the mouse model than HRZ.[14] Thus, a novel regimen with a 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.

Pretomanid, (Pa)[15] is a new chemical entity being developed by TB Alliance for the treatment of TB. It is 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 has been under development for several years, and entered clinical trials in 2005. Several trials of pretomanid have also been conducted previously in healthy volunteers. Collectively, these trials in participants with active TB and healthy participants have defined the efficacy, safety and pharmacokinetic features of the drug. Overall, pretomanid has mycobactericidal activity in participants and is well tolerated and bioavailable after oral dosing. Pretomanid demonstrated in

vitro activity against both drug-sensitive (DS) and MDR-TB,[17] and in vivo activity in a mouse model of TB[17, 18] with a significant promise for shortening treatment of active TB.

Moxifloxacin (M)[19] is a microbial compound, approved in most countries around the world for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and soft tissue infections. Clinical studies have been carried out for many additional indications (urinary tract infections, pelvic infections, pharyngitis/tonsillitis, and tuberculosis). Moxifloxacin is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by or induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the MTB strain is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]" It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

Pyrazinamide (Z)[20] is a pyrazine analogue of nicotinamide and an approved anti-tuberculosis agent which is indicated for the initial treatment of active tuberculosis in adults and children when combined with other anti-tuberculosis agents and contributes significantly to the sterilization of lesions and thus treatment shortening.[21]

Control Group: HRZE/HR

The **HRZE/HR** combination [HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets] is approved indicated and commonly used as a 6-month treatment for drug-sensitive TB patients. Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE. Please see the HRZE package insert for more information.[22]

Additional background data supporting the combined use of new novel agents in this BPaMZ regimen for the treatment of TB:

Data from preclinical studies suggest that a regimen consisting of moxifloxacin plus pretomanid plus pyrazinamide may not only be appropriate for treating both DS and MDR-TB but may also **shorten duration of therapy**. Results from an 8-week Phase 2b SSCC trial, NC-002-(M-Pa-Z), showed that this **combination regimen** was effective as measured by time dependent decline of viable bacteria in participants with DS pulmonary TB. The combination was also shown to be safe and well tolerated supporting the evaluation of this combination in a Phase 3 trial. In this NC-002 trial 71.4% of participants with DS-TB treated with PaMZ at the 100-mg daily dose of pretomanid converted sputum to negative for *MTB* growth in liquid culture in comparison with only 37.8 % of participants treated with the HRZE control ($p<0.05$).

Studies in mice infected with *MTB* demonstrated reductions in cultured colony counts from lungs over an 8-week period when treated with the PaMZ regimen that were substantially, and

statistically significantly greater, than the reductions in mice treated with an HRZ control. Experiments in mice found that mice did not relapse with MTB infection when treated with PaMZ for 4 months and followed for 3 months off treatment, in comparison to mice that required 6 months of treatment with HRZ to prevent relapse.[14]

Drug Resistant TB Background:

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in many countries. TB is the world's leading cause for mortality from infectious disease and is responsible for more deaths than HIV.[23] 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. Because of poor treatment adherence, in addition to primary transmission, **drug resistance** is becoming more common and fears of an epidemic with strains of extensively drug-resistant TB (XDR-TB) that is very difficult to treat are growing. Novel drugs and regimens for TB are needed for the growing number of patients with drug resistant-TB.

The regulatory approvals of bedaquiline and delamanid have given hope that outcomes for patients with drug resistant TB might be improved when added to background regimens. Experience recently published from the C209 uncontrolled trial of bedaquiline given on a background of multiple drugs notes that the subset of 38 participants with XDR-TB had rates of sputum culture conversion to negative of 62.2%.[24] However, in this trial only one participant with XDR-TB was co-infected with HIV. All participants were required to have Mycobacterium tuberculosis (MTB) isolates susceptible to at least 3 drugs at enrolment and participants had a median of only 5.4 months of treatment-free follow-up. This trial added bedaquiline for 6 months to a background regimen of many drugs given for 18 months or longer. While treatment success for MDR-TB is better than for XDR-TB, **overall success in treating MDR-TB is still approximately 50%** according to the World Health Organization 2015 Global TB Report.[23] This report presented that overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, 10% failed treatment, and for 8% there was no outcome information.

With such poor historical outcomes for patients with drug resistant-TB and with the complexity, expense and toxicity of treatments for all forms of drug resistant TB, **novel drug combinations are desperately needed to improve treatment outcomes**. Linezolid was identified in a small trial as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen[25] and this drug has increasingly been added to complex regimens to treat patients with MDR-TB.

With the current availability of the following three drugs for which there is little, if any, pre-existing resistance among strains of MTB (pretomanid [Pa], bedaquiline [B], and linezolid [L]). Mice infected with MTB had relapse-free cures with 3 months of treatment with a B-Pa-L regimen. While it is not known whether that treatment duration will translate to humans, the ongoing Nix-TB clinical trial hypothesizes patients with pulmonary XDR-TB or MDR-TB not responsive to or intolerant to therapy may have relapse-free cure after as little as 6 months' treatment with the B-Pa-L regimen.[26] Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. The proposed trial [SimpliciTB] allows the opportunity to assess the efficacy, safety and tolerability of BPaMZ, a new 6 months regimen that may be administered orally once daily to treat patients with drug resistant -TB (excluding participants with XDR-TB).

Therefore, the **overall purpose** of the present proposed trial **[SimpliciTB]** is to assess the efficacy, safety and tolerability of the **BPaMZ** regime after 4 months of treatment in adult participants with drug sensitive TB and after 6 months of treatment in participants with multi drug-resistant TB. The trial will also generate data of the potential for a shorted treatment duration with the **BPaMZ** regime after 4 months compared to a 6-month **HRZE/HR** (control) treatment regime in adult participants with drug sensitive TB.

This trial will be conducted in accordance with the Protocol, ICH Guidelines for Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirement(s).

2.5 Background of Agents to be Studied in SimpliciTB

2.5.1 Bedaquiline (B)

Bedaquiline (formerly known as TMC-207; Sirturo™ package insert[7]) is approved agent for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[11] In vitro, bedaquiline potently inhibits both drug-sensitive and drug-resistant MTB isolates,[11, 12] and is also bactericidal against non-replicating MTB[12] 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 MTB.[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.[27].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[27] and in a subsequent trial it was more active in the mouse model than HRZ.[28]. 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.

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as 200 mg daily for 8 weeks, followed by 100 mg daily for the remaining 17 weeks or 30 weeks if treatment is extended. This daily dosing scheme will allow more convenient dosing that should ultimately enhance patient adherence and may allow the formulation of fixed dose combinations with other drugs. This daily dosing regimen is supported by safety and efficacy demonstrated in the NC-005 trial that administered bedaquiline 200 mg daily over 8 weeks, and by pharmacokinetic modelling and simulation of the daily dosing scheme. This supportive information is detailed below.

2.5.1.1 Bedaquiline Non-Clinical Studies

Full details of the preclinical studies are provided in the current bedaquiline Investigator's Brochure,[8] and Sirturo ™ label.[7] *In vitro* studies have demonstrated that the range of minimum

inhibitory concentrations (MICs) for MTB 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 MTB. 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 MTB but 3-6 times less active than the parent compound bedaquiline. Bedaquiline demonstrated similar *in vitro* efficacy against MTB 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 International Council for Harmonisation (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.[8]

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 and ECG parameters.

Prior to the use of pretomanid in combination with bedaquiline in clinical trial NC-001, a preclinical cardiovascular safety pharmacology trial 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.[28] 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) Investigators Brochure for more detail.

2.5.1.2 Bedaquiline Clinical Studies

In the clinical studies conducted to date, a total of approximately 645 participants (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 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001, and 45 more in trial NC-003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). Four short-term Phase 2a trials enrolled treatment-naïve participants (C202, TMC207-CL001, NC-001 and NC-003). One long-term, open-label, Phase 2 trial, in MDR-TB participants (bedaquiline-TiDP13-C209) and one long-term, Phase 2b trial, consisting of 2 different stages in participants 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,[8] and Sirturo™ label.[7].

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 participants. 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 trial, 800 mg single dose in trial 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 participants and participants 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 α 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 participants 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 trial (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 trial (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. Trial C202 was a 7-day trial of three daily doses of bedaquiline (25, 100 and 400mg) in treatment-naïve participants with MDR-TB. In this trial, the 400mg dose group demonstrated positive EBA and was numerically superior to the 25 and 100mg doses. In trial TMC207-CL001, doses of 100, 200, 300 and 400mg daily (following a 2-day loading dose) were studied in participants 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 participants with TB and that higher doses appear to have greater efficacy.

A 14-day EBA regimen trial (TB Alliance Trial 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 participants 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 participants given bedaquiline 400 mg/d after a 2-day loading dose. In the cohort of 15 participants 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 participants 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 trial (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 participants 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 participants in the bedaquiline group became MGIT culture negative compared to 8.7% of participants 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 participants in the bedaquiline group and 65.2% of participants 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 participants 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 participants. Culture conversion rates after 2 weeks of treatment with bedaquiline as part of an individualized anti-tuberculosis regimen were higher in participants with lower extent of resistance of the M. Tb strain and in participants with no lung cavitation compared to participants with cavitations (in one or both lungs).

2.5.1.3 Bedaquiline Clinical Safety

In the clinical trials conducted to date, a total of approximately 645 participants (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 participants received bedaquiline in a monotherapy EBA trial of 14 days (trial TMC207-CL001) 45 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001 and 45 more in trial NC- 003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). In these trials, bedaquiline has been shown to be an effective treatment for participants 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 trial 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 trials, 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 participants) 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	**1 (1.3)**	**1 (1.0)**	**0**	**0**
Headache	1 (1.3)	1 (1.0)	0	0
Cardiac disorders	**0**	**0**	**0**	**0**
ECG QT Prolonged	0	0	0	0
Gastrointestinal disorders	**0**	**0**	**0**	**0**
Diarrhea	0	0	0	0
Vomiting	0	0	0	0
Hepatobiliary disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Transaminases increased [a]	2 (2.5)	2 (2.0)	0	0
Musculoskeletal and connective tissue disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Arthralgia	2 (2.5)	2 (2.0)	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 participants in the Any bedaquiline group and 5 participants 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 participants 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 participants (12.7%) compared to 3 placebo participants (3.7%). Based on the pooled results (Stage 1 and 2) while being followed in the placebo- controlled trial, 7 participants in the Any bedaquiline group and 1 Participant 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 haemoptysis. 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 participants 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 Participant in the bedaquiline group (pulmonary TB) and 2 participants in the Placebo group (TB-related illness and pulmonary TB) in Stage 1 died, and 4 participants in the bedaquiline group (3 participants with TB-related illness, 1 Participant motor vehicle accident) and 2 participants in the Placebo group (both TB-related illness) died after they discontinued Stage 2 of the trial. None of these participants 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, diarrhoea, blood uric acid increased, hypokalaemia, pruritus, injection site pain, insomnia, and tinnitus. From start of the trial up to the final analysis, 12 participants 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), haemoptysis, hypertension, and pyopneumothorax/respiratory failure. 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 participants 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 participants (6.9%) have died (12 participants during the trial and 4 participants 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 participants 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[7] notes that treatment initiation is not recommended in patients with:

- Heart failure;
- QTcF interval > 500 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).
- Hypokalaemia

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. If 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. participants should be monitored during treatment. Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in those participants with diminished hepatic reserve.[7]

Additional safety information from a recently completed trial

In a recently completed phase I trial not yet included in the bedaquiline Investigators Brochure that evaluated drug-drug interactions between bedaquiline and either rifampin or rifabutin, 7 participants experienced SAEs. Of those participants, 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 participant 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.

2.5.2 Pretomanid (P)

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]

2.5.2.1 Pharmacology

Key in Vitro Evaluation of Pretomanid Bactericidal Activity

Non-clinical in vitro trials demonstrated that pretomanid was active against actively growing drug-sensitive and drug-resistant MTB strains as well as against non-replicating MTB. The minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive MTB isolates *in vitro* was shown to be like the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of MTB with MIC values ranging from 0.03 to 0.53 µg/mL. The Investigator's Brochure contains further information on *in vitro* bactericidal activity.[16]

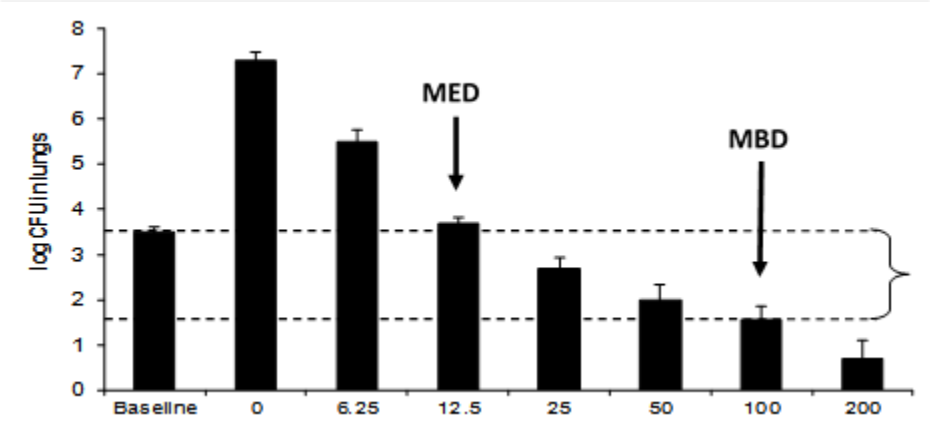
Although not thoroughly elucidated at this time, pretomanid has a novel mechanism of action that appears to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reduction of pretomanid by a deazaflavin (F420)-dependent nitroreductase has been shown to be associated with generation of reactive nitrogen species, including nitric oxide (NO),[29] although the exact target(s) of the reactive nitrogen species are not known. Transcriptional profiling trials also suggest that pretomanid affects both cell wall biosynthesis and the respiratory complex of MTB.[30, 31]

2.5.2.2 Key Non-Clinical Trials of Pretomanid

The activity of pretomanid as a single agent or as part of a multi-drug combination regimen has been examined in a number of mouse trials.[13, 14, 18, 32, 33] In a mouse model of established TB, the activity of various doses of pretomanid (given once daily, 5 days/week, for 1 month), initiated 22 days after inhalation infection with H37Rv MTB is shown in Figure 2. In this model, the minimum effective dose (MED) for pretomanid, defined as the lowest dose able to prevent the development of gross lung lesions and splenomegaly, was 12.5 mg/kg/day, while the minimum bactericidal dose (MBD), defined as the lowest dose able to reduce lung colony forming units (CFU) by 99%, was 100 mg/kg/day. Moreover, in these experiments, the activity of pretomanid at 100 mg/kg was comparable to the activity of isoniazid at 25 mg/kg.

Figure 2. Log10 CFU Counts in Lungs

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



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

2.5.2.3 Non-Clinical Toxicology and Safety

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

In the repeat-dose toxicity trials, the lowest no-observed adverse effect level (NOAELs) was 10 mg/kg/day in a 26-week trial in rats, 50 mg/kg/day in a 13-week trial in monkeys and <25 mg/kg/day (based on findings of thickening of the gastrointestinal tract at all doses) in a 9-month trial in monkeys. The major findings in safety and toxicity trials are listed below in Table 2 and are detailed in the Investigator's Brochure.[15]

Table 2. Key findings of Pretomanid in Safety and Toxicity Trials

Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behaviour at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
Testicular toxicity Although rat and rabbit embryonic development trials indicate no effects of pretomanid on foetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose toxicology trials and a Segment I fertility trial. In this fertility trial, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower dose not associated with testicular atrophy. A detailed trial in sexually mature male monkeys demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing.
Cataracts Cataracts developed in rats with prolonged daily administration of pretomanid at doses ≥100 mg/kg/day. In one 13-week trial 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 trial in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.
hERG inhibition and QT prolongation Altered ventricular repolarisation due to inhibition of hERG-mediated potassium current and manifested on the ECG as a prolonged QT interval corrected for heart rate (QTc). Pretomanid inhibited hERG current with IC50 values of approximately 6.2 µg/mL. Following a single pretomanid dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Co-administration of pretomanid with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at pretomanid doses of ≥150 mg/kg/day.

2.5.2.4 Clinical Background Information

Pretomanid has been evaluated in 8 single- and multi-dose Phase 1 trials with healthy adult male and female participants, with 163 participants receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 7 days. These Phase 1 trials have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid. Two additional Phase 1 trials Sponsored by the NIH included a Thorough QT trial and a trial of drug interactions among pretomanid, efavirenz and ritonavir/lopinavir. Further details of the trials are in the Investigator's Brochure.[15]

2.5.2.5 Pharmacokinetics

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

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

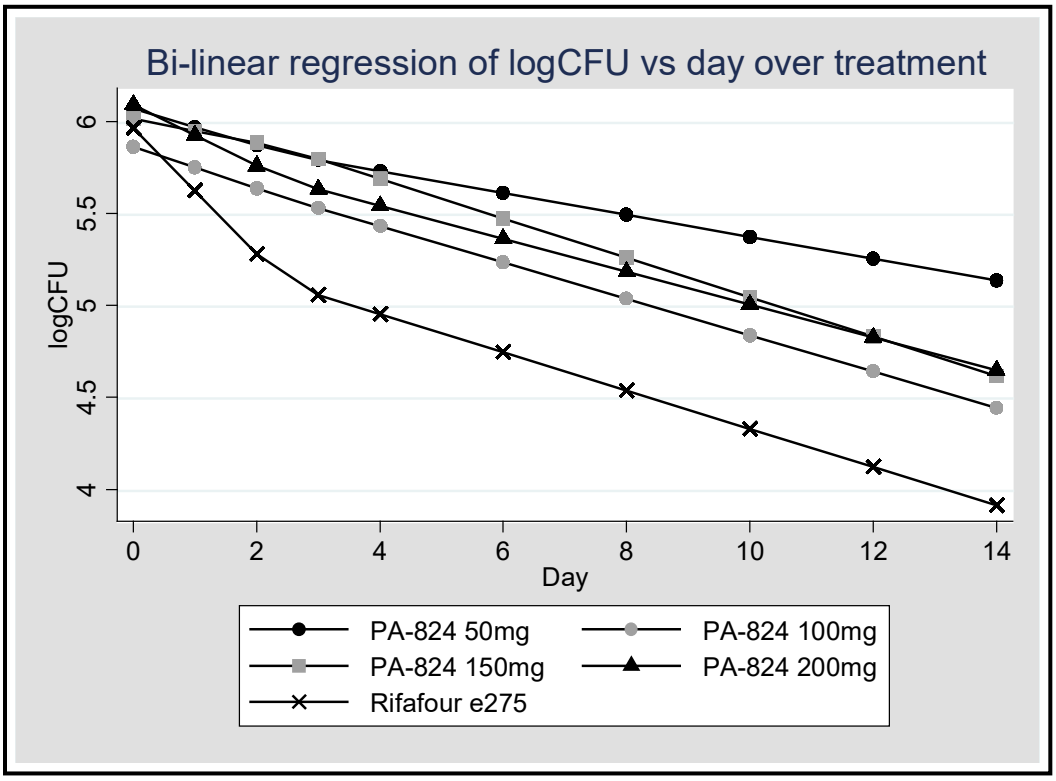
Drug interaction with efavirenz, ritonavir/lopinavir, and rifampicin: The US NIH Sponsored this drug interaction trial with rifampicin, a known hepatic enzyme inducer, and with the antiretroviral drugs efavirenz and ritonavir/lopinavir (LPV/r) in healthy participants. Participants in Arm 1 were randomised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

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

2.5.2.6 Pretomanid Clinical Efficacy

The first two Phase 2 trials to evaluate the early bactericidal effect (EBA) of pretomanid oral monotherapy (50 to 1200 mg/day for 14 days) examined the dose-response for pretomanid in participants with newly diagnosed pulmonary TB infection. The first trial (CL-007) demonstrated good EBA, but all doses in this trial (200 to 1200 mg/day) had the same activity. The second trial (CL-010) evaluated a lower dose range (50 to 200 mg/day) and the maximum effect on EBA was seen at a dose of 100 mg/day over 14 days (Figure 3).[34]

Figure 3. Mean log Colony Forming Unit Values over Time Trial CL-010



CFU = colony-forming unit; PRETOMANID = pretomanid

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

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

2.5.2.7 Pretomanid Clinical Safety

The pretomanid Investigator's Brochure[15] provides detailed safety information.

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

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

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

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

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

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

- Ophthalmologic Evaluations – while the detailed examinations in Phase 2 have not raised concern for humans, ophthalmologic examinations, with slit lamp exam and grading of lens opacities, will continue in all human trials that involve exposure to pretomanid longer than 14 days. These examinations will be conducted at baseline, near the end of the dosing period

and 3 months after the end of trial drug exposure. These examinations are to follow up on the finding of cataracts in rats exposed to pretomanid in clinical trials.

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

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

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

2.5.3 Moxifloxacin (M)

Moxifloxacin (M)[19] is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by nor induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the strain of MTB is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]" It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

2.2.3.1. Moxifloxacin Clinical Trials

Moxifloxacin is commonly used as second line therapy for TB (e.g. MDR- TB), and has also been evaluated in several clinical studies of participants with TB, including four 8-week treatment period Phase 2b studies (see Table 3 below).

Table 3. Summary of Phase 2b trials in which moxifloxacin were administered as part of a four-drug regimen during the intensive phase of treatment (total treatment duration: 2 months)

Trial	Design	Objective	Participants (N)	Status
Trial 27	Randomized, double-blind, controlled	To compare the sputum culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using the standard 4-drug regimen HRZE with a standard regimen with M replacing E.	336	Completed
OFLOTUB Trial	Randomized, Open label, Controlled	To compare the bactericidal activities of regimens where gatifloxacin, M, and ofloxacin were substituted for E in the 2-month initial phase of standard TB treatment with HRZE.	217	Completed
Johns Hopkins (FDA orphan drug) Trial	Randomized, double-blind, Controlled	To compare the sputum culture conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE) with a regimen with M replacing E (HRZM).	170	Completed
Trial 28	Randomized, double-blind, Controlled	To compare the culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE 5 days per week) with a regimen with M replacing H (MRZE 5 days per week).	433	Completed

2.5.3.1 Moxifloxacin Clinical Safety

In Trial 27,[35] the moxifloxacin-containing TB regimens (HRZM) were shown to be safe and well tolerated. There was no difference in SAEs between the HRZM and HRZE treatment arms, and most SAEs were hospitalizations thought to be unrelated to the trial treatment. Participants treated with the moxifloxacin-containing regimen were more likely to report nausea (22% vs. 9%, p = 0.002), but this was generally mild and did not lead to treatment discontinuation as similar proportions of participants in both groups completed trial drug treatment (88% HRZM-treated vs. 89% HRZE-treated). The one death during the first 2 months of treatment was thought to be caused by a pulmonary embolism unrelated to tuberculosis therapy.

In the OFLOTUB trial,[36] AEs and SAEs occurred with equal frequency in the four treatment arms. The most frequent AEs were raised amylase (in 41% of participants due to HIV infection), raised transaminase (10%), arthralgia (9%), anaemia (7%), hypokalaemia (6%) and vomiting (5%). No Participant was withdrawn from the trial due to an adverse event. There were 4 deaths in the trial: 2 in the control group, 1 each in the moxifloxacin and ofloxacin arms. Importantly, participants in this trial who received moxifloxacin and pyrazinamide in addition to isoniazid and rifampin had more rapid sputum clearance than participants on the four standard first line drugs

(isoniazid, rifampin, pyrazinamide and ethambutol). This difference was evident 14 days after initiation of treatment.

In the JHU trial,[37] AEs did not differ by treatment group. There were 16 SAEs (8 in each group) in 12 participants. Only 1 event was judged related to trial drug (grade 3 cutaneous reaction in the ethambutol group). Eight participants died during the trial, including 1 in each group still receiving trial phase treatment. No death was attributed to trial treatment. Only 5 participants discontinued treatment because of toxic effects; 2 participants in the moxifloxacin group stopped because of grade 2 nausea and vomiting and 1 because of grade 2 paraesthesia's and ataxia. Two participants in the E group stopped because of grade 2 rash and pruritus and 1 because of grade 3 peripheral neuropathy. There was no change in the QTc interval on serial electrocardiograms taken during the trial.

In Trial 28,[38] the proportions of participants with SAEs during the intensive phase treatment were similar between arms (isoniazid 3.9% vs. moxifloxacin 4.2%; P = 0.88). Three SAEs attributed to trial treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group. Seven participants died during the trial including 3 participants receiving the moxifloxacin treatment regimen and 4 participants receiving the isoniazid treatment regimen. The 3 moxifloxacin participants died during the intensive phase of TB treatment. Two participants died from advanced pulmonary TB judged not related to trial treatment and 1 Participant (who developed diabetic ketoacidosis considered possibly related to trial treatment) died from possible acute pulmonary embolus unrelated to trial treatment. The 4 isoniazid deaths occurred during the continuation phase, and all 4 were considered unrelated to trial treatment. Nausea was more common among participants in the moxifloxacin arm than in the isoniazid arm (19.6% vs. 11.7%, respectively; P = 0.03) although similar proportions reported vomiting. However, the proportions of participants with hepatitis, defined as serum AST 3 times or greater than the upper limit of normal, were similar between treatment arms during intensive phase (isoniazid 3.4% vs. moxifloxacin 3.3%; P = 0.93). Moxifloxacin has also been evaluated in combination with pretomanid for two weeks in participants with TB (Trial NC-001) and for 8 weeks in NC002 as reviewed above in Section 2.2.3 (Trial NC-001).

For additional information on moxifloxacin, refer to the IB[39] and the manufacturer's package insert.[19]

2.5.4 Pyrazinamide (Z)

Pyrazinamide (Z) is a standard drug used as part of the four drug HRZE regimen used for the first two months of intensive therapy for drug-sensitive TB as recommended by the WHO and many National TB programs. Please see the Package Insert[20] for more detail. Z is active against TB *in vitro* and it potentiates the bactericidal and sterilizing activity of both bedaquiline and pretomanid in mouse models of TB infection.[8, 15] Pyrazinamide enhanced the bactericidal activity of both bedaquiline and pretomanid in Trial NC-001-(J-M-Pa-Z) as noted by decreases over 14 days in the CFU counts in sputum among participants.

The pyrazinamide product label notes that pyrazinamide is contraindicated in persons with severe hepatic damage, who have shown hypersensitivity to it, and with acute gout. The most serious side effect is hepatotoxicity. Its frequency appears to be dose-related and thus liver function should be assessed before and regularly during treatment with pyrazinamide. Hyperuricemia commonly occurs and is occasionally accompanied by arthralgia and may lead to attacks of gout.

Photosensitivity and skin rash have been reported less frequently. Other side effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria.

Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert. [20]

2.6 Overall Benefit/Risk Assessment

Some participants with pulmonary TB in this trial will be given a regimen of **BPaMZ**. These drugs individually and in combination are known to have anti-tuberculosis activity and is not expected to have an adverse impact on the ultimate cure of TB in these participants. Based on NC-005 and other regimens using each of the regimen drugs in different combinations there is good evidence that this may be a highly effective therapy for both DS-TB and DR-TB.

For DS-TB the potential for a shorter regimen than 6 months is expected to be successful based on preclinical and clinical information as listed before. Participants in this trial will have their TB infection carefully characterized, with drug sensitivity profiles established, and they will receive treatment with trial drugs that have demonstrated activity against MTB.

Participants will receive individualized medical attention; this will allow a continuous monitoring of the health conditions of each participant, any of whom can be withdrawn at any stage of the trial and removed from trial treatment should his/her condition suggest to the Investigator that this would be in his/her best interest. Multiple blood samples will be taken for safety laboratory studies, and ECGs will be taken at multiple time points.

One concern in particular, the combination of two agents with known QT-prolonging effects (bedaquiline and moxifloxacin), has been addressed specifically by carefully identifying and excluding participants with risk factors that might predispose them to cardiac arrhythmias, screening all participants for evidence of existing cardiac disease and monitoring all participants with ECGs throughout the trial.

The trial drugs in the proposed regimens to be tested in this trial have all demonstrated safety and efficacy in the treatment of pulmonary tuberculosis in non-clinical and clinical studies. Specifically, the regimen B-Pa-Z was generally well-tolerated and demonstrated bactericidal activity in a 14-day EBA trial. The potential risks associated with the trial drugs and regimens has been identified as outlined below and will be monitored carefully throughout the conduct of the trial.

The BPaMZ regimen is a novel regimen treatment expected to be effective, safe and well-tolerated and might even shorten the current treatment duration for patients with TB. Based on data from previous trial evaluations of key monitoring and safety information as outlined before suggests a favourable benefit-to-risk ratio trials.

Key Monitoring and Safety Information Regarding Regimen Agents

2.6.1 Bedaquiline (B)

2.6.1.1 Adverse Drug Reactions for bedaquiline

Participants in the Any bedaquiline group compared to the Any Placebo group (difference > 5.0%) had headache (23.5% versus 11.4%, respectively), nausea (35.3% versus 25.7%, respectively),

arthralgia (29.4% versus 20.0%, respectively), and transaminases increased (6.9% versus 1.0%, respectively).and diarrhoea (11.4% versus 5.9%, respectively).

2.6.1.2 Cardiovascular safety

During clinical studies with bedaquiline a prolongation of QTc interval was observed. An ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.

Bedaquiline 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

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. If co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

In the DR-TB treatment arm of the present trial, moxifloxacin will be co-administered with bedaquiline. This is to prevent the development of resistance to the other drugs in the regimen in case the participant's strain of MTB is resistant to pyrazinamide. ECG assessments will be performed on all participants at screening, baseline, and at treatment visits specified in the flow chart.

2.6.1.3 Hepatic safety

Increases in transaminases were seen in clinical studies during administration of bedaquiline with the background regimen. Participants should be monitored during treatment.

Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in participants with diminished hepatic reserve.

2.6.2 Pretomanid (P)

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 diarrhoea)
- Skin and subcutaneous tissue disorders

2.6.2.1 Hepatic Safety

Hepatic enzyme increases have been seen in participants 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 NC-008 trial will include specific monitoring of hepatic enzymes.

For additional information refer to pretomanid IB.[15]

2.6.3 Moxifloxacin (M)

In the usual daily doses of 400 mg/day, moxifloxacin is well tolerated. As stated in the Package Insert[19] the most frequent individual drug related AEs observed in clinical trials with 400 mg oral moxifloxacin therapy were nausea (7.5%) and diarrhoea (5.8%). Fluoroquinolones, including moxifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages.

A known but rare side effect of fluoroquinolones, including moxifloxacin is exacerbation of myasthenia gravis. In addition, moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some participants. It should be used with caution in participants being treated concomitantly with other drugs where an additive effect on the QT interval cannot be excluded.

Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, as well as peripheral neuropathy may occur after the first or subsequent doses of moxifloxacin. For additional information, refer to the moxifloxacin package insert.[19]

2.6.4 Pyrazinamide (Z)

The dose of pyrazinamide that will be used in this trial is an approved dosage for the treatment of TB. The most serious side-effect of pyrazinamide is hepatotoxicity and its frequency appears to be dose-related. Hyperuricemia commonly occurs, occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side-effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria. Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert.[20]

2.6.5 HRZE/HR Control

The **HRZE** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets) combination will be given the first 8 weeks and the **HR** (isoniazid 75 mg plus rifampicin 150 mg combination tablets) combination will be given from Weeks 9 to 26.

Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE.

Please see the HRZE and HR Package Inserts[22, 40] for known and potential risks and benefits.

3.0 Trial Objectives

3.1 Primary Objectives

To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with:

Drug Sensitive TB (DS-TB)

- BPaMZ given for 17 Weeks (4 months)
- Standard HRZE/HR treatment given for 26 weeks (6 months)

Drug Resistant TB (DR-TB)

- BPaMZ given for 26 Weeks (6 months)

DR-TB are defined as participants with:

1. *mono-resistance to rifampicin or isoniazid, OR*
2. *resistance to both rifampicin and isoniazid (DR-TB)*

3.2 Secondary Objectives

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 52 weeks (or 12 months) and 104 weeks (or 24 months) weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
  - Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
  - Quantitative and qualitative ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones and lens opacities.

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., Cmin, Cmax, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of con-medications including antiretroviral therapy (ART), as feasible.

Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

3.3 Exploratory Objectives

- Evaluate whether any of the secondary endpoints predicts relapse free cure.
- Subgroup analysis of populations by HIV status.

No formal statistical comparisons will be made for the participants enrolled with DR-TB.

4.0 Trial Design

4.1 Summary of Trial Design

This is a Phase 2c, multi-centre, open-label, partially randomized clinical trial conducted in 3 treatment groups. Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment allocation during the treatment phase of the trial.

The trial will be performed globally at multiple centres located throughout all regions of the world.

A total of 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation. Up to 150 DR-TB participants will be enrolled and assigned to the treatment arm described in Table 4 below.

Participants with Drug Sensitive TB (DS-TB):

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR combination tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation.

Participants with Drug Resistant TB (DR-TB):

Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).

Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive. An interactive web response system (IWRS) will be used which will utilize a dynamic randomization system using cavitation with a random element to allocate participants evenly across the arms by HIV status and type of TB (DS versus DR) after they have given written, informed consent during the Screening Visit (Days -9 to -1) and met all eligibility criteria.

4.2 Treatment Plan: Schedule of Assessments

- Screening Period (Day -9 to Day -1)
- Treatment Period (Day 1 to Week 17 (4-month treatment); or Week 26 (6-month treatment))
- Follow-Up Period (Week 39 to Week 104)

Refer to:

- Synopsis Flow Chart and Procedures (Section 1.2; flow chart) for the timing of all procedures and laboratory samples to done at each visit.
- Trial Procedures (Section 7.0, Trial Variables and Procedures) for details regarding specific procedures or laboratory tests.

Each participant will receive up to 26 weeks of treatment. The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation unless an interruption/pause is required urgently for a safety concern.

All participants will enter post-treatment follow-up which continues until Week 104 (24 months) after start of treatment / randomisation.

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

Table 4: Treatment Groups

	Treatment Group	Treatment Duration	No of Participants
1	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily	17 weeks (4 months)	150 DS-TB
2	**HRZE Tablets (Weeks 1-8):** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). Followed by **HR Tablets (Weeks 9-26):** (isoniazid 75 mg plus rifampicin 150 mg combination tablets).	First 8 weeks (2 months) then 17 weeks (4 months) Total 6 months	150 DS-TB
3	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily.	26 weeks (6 months)	Up to 150 DR-TB

5.0 Trial Population

The participant must meet all inclusion and no exclusion criteria within the screening period. Retesting for any laboratory or ECG parameters is allowed within the screening period. Sponsor may consider replacement of late exclusions.

5.1 Inclusion Criteria

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

1. Signed written consent prior to undertaking any trial-related procedures.

2. Male or female, aged 18 years or over.
3. Body weight (in light clothing and no shoes) ≥ 30 kg.
4. Sputum positive for tubercule bacilli (at least 1+ on the International Union Against Tuberculosis and Lung Disease [IUATLD]/WHO scale (Appendix 1) on smear microscopy) at the trial laboratory.
5. Disease Characteristics:
   - Participants with one of the following pulmonary TB conditions:

     DS-TB treatment arm participants should be:

     a. sensitive to rifampicin and isoniazid by rapid sputum based test **AND**

     b. either newly diagnosed for TB or have a history of being untreated for at least 3 years after cure from a previous episode of TB.

     If they are randomised into the trial due to being sensitive to rifampicin and isoniazid by rapid molecular sputum based test, however on receipt of the rifampicin and/or isoniazid phenotypic resistance testing in liquid culture this shows they are rifampicin or isoniazid resistant, they will be:

     a. Excluded as late exclusions;

     b. Possibly replaced as determined by the Sponsor.

     DR-TB treatment arm participants should be:

     a. Resistant to rifampicin and/or isoniazid.

     b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 7 days at start of screening.

6. A chest x-ray, within 6 months prior to or during the Screening visit, which in the opinion of the Investigator is compatible with pulmonary TB.
7. Contraception:

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

   Non-childbearing potential:

   a. Participant - not heterosexually active or practice sexual abstinence; or

   b. Female participant or male participants female sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or

   c. Male participant or female participants male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening;

Effective birth control methods:

a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or

b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female participant.

c. Male participants' female sexual partner: Double barrier method or hormone-based contraceptives or an intra-uterine device for the female partner.

Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 12 weeks after the last dose of trial medication or discontinuation from trial 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 participants to prevent pregnancy.

5.2 Exclusion Criteria

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

Medical History and Concurrent Conditions:

1. Any non-TB related condition where participation in the trial, as judged by the Investigator, could compromise the well-being of the participant or prevent, limit or confound protocol specified assessments.
2. Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
3. Being, or about to be, treated for malaria.
4. Is critically ill and, in the judgment of the Investigator, has a diagnosis likely to result in death during the trial or the follow-up period.
5. TB meningitis or other forms of extrapulmonary tuberculosis with high risk of a poor outcome, or likely to require a longer course of therapy (such as TB of the bone or joint), as judged by the Investigator.
6. History of allergy or hypersensitivity to any of the trial IMP or related substances, including known allergy to any fluoroquinolone antibiotic, history of tendinopathy associated with quinolones or suspected hypersensitivity to any rifampicin antibiotics.
7. For HIV infected participants any of the following:

    a. CD4+ count <100 cells/µL
    b. Karnofsky score <60% (Appendix 5)
    c. Received intravenous antifungal medication within the last 90 days
    d. WHO Clinical Stage 4 HIV disease (Appendix 3)

8. Participants who recently started or expected to need to start ART within 1 month after randomization. Participants who have been on ARTs for more than 30 days prior to start

of the Screening visit, or expected to start ART greater than 30 days after randomization may be included.

9. Resistant to fluoroquinolones (rapid, sputum-based molecular screening tests)

    a. If they are randomised into the trial due to being sensitive to fluoroquinolones by rapid sputum based test, however on receipt of the moxifloxacin phenotypic resistance testing in liquid culture they are found to be fluoroquinolones resistant, they will be excluded as late exclusions.

10. Having participated in other clinical trials with investigational agents within 8 weeks prior to start of trial medication or currently enrolled in an investigational trial.
11. Participants with any of the following at the Screening visit (per measurements and reading done by ECG):

    a. QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with the Sponsor Medical Monitor before enrolment.
    b. Heart failure
    c. A personal or family history of congenital QT prolongation
    d. A history of or known, untreated, ongoing hypothyroidism
    e. A history of or ongoing bradyarrhythmia
    f. A history of Torsade de Pointe

12. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening.
13. Females who have a positive pregnancy test at the Screening visit or already known to be pregnant, breast-feeding, or planning to conceive a child during the trial or within 6 months of stopping treatment. Males planning to conceive a child during the trial or within 6 months of stopping treatment.

<u>Previous and Concomitant Therapy</u>

14. Previous treatment with pretomanid or bedaquiline.
15. Previous treatment for TB which includes, but is not limited to, gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.
16. For DS-TB participants: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days prior to randomization.
17. For the DR-TB participants: Previous treatment for DR-TB/MDR-TB, although may have been on a DR/MDR-TB treatment regimen for no longer than 7 days at start of screening.
18. Any diseases or conditions in which the use of the standard TB drugs or any of their components is contra-indicated, including but not limited to drug allergy.
19. Use of any drug within 30 days prior to randomisation known to prolong QTc interval (including, but not limited to, amiodarone, amitriptyline, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinacrine, quinidine, sotalol, sparfloxacin, thioridazine).

20. Use of systemic glucocorticoids within one year of start of screening (topical, inhaled or intranasal glucocorticoids are allowed) due to visual opacities or cataracts.
21. For HIV infected participants, only the following types of ART are permissible:

    a. Lopinavir/ritonavir based regimen consisting of lopinavir/ritonavir in combination with any two NRTI. TDF/ABC and FTC/3TC.
    b. Integrase inhibitor (e.g., dolutegravir) in combination with TDF/ABC and FTC/3TC.
    c. In participants who have viral load suppressed on efavirenz at the time of screening, their ART can be changed to rilpivirine in combination with TDF/ABC and FTC/3TC. If possible, the same nucleoside backbone should be used.
    d. Nevirapine (NVP) based regimen consisting of NVP in combination with any two nucleosidase reverse transcriptase inhibitors (NRTIs) tenofovir (TDF)/abacavir (ABC) and emtricitabine (FTC)/lamivudine (3TC).

22. In the case where participants are randomized to a rifampicin containing regime:

    a. EFV can be used with rifampicin.
    b. LPV needs to be double dosed.
    c. Rilpivirine cannot be given with rifampicin

<u>Diagnostic and Laboratory Abnormalities</u>

23. Participants with the following toxicities at screening as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (Draft November 2007) (Appendix 2) where applicable:

    a. platelets grade 2 or greater (<100,000/mm^3)
    b. creatinine grade 2 or greater (>1.5 times upper limit of normal [ULN])
    c. eGFR ≤ 60 mL/min/m^2
    d. haemoglobin grade 2 or greater (≤8.0 g/dL)
    e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once
    f. GGT: greater than 3 x ULN
    g. AST:
        - grade 3 or greater (≥3.0 x ULN) to be excluded;
        - results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor
    h. ALT:
        - grade 3 or greater (≥3.0 x ULN) to be excluded
        - greater than ULN must be discussed with and approved by the Sponsor Medical Monitor
    i. ALP:
        - grade 3 or greater (≥3.0 x ULN) to be excluded
        - grade 2 (2.0 – <3.0 x ULN) must be discussed with and approved by the Sponsor Medical Monitor
    j. Total bilirubin:
        - >1.5 x ULN to be excluded;
        - 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor

k. Direct bilirubin:
   - greater than 1x ULN to be excluded

All the inclusion and none of the exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the Investigator has reason to suspect that there might be a health problem (other than TB), enrolment should only be considered after discussing the case with the Sponsor Medical monitor.

No protocol waivers will be granted by the TB Alliance.

5.3 Restrictions

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

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

The following recommendations should be followed with regards to concomitant medication to avoid possible drug interaction with the IMP:

Participants on a **moxifloxacin** containing treatment arm: The IMP should be taken either 4 hours before or 8 hours after taking the following products:

- An antacid, multivitamin, or other product that has magnesium, aluminium, iron or zinc
- Sucralfate
- Didanosine

Participants on the **HRZE/HR** treatment arm:

- Any aluminium-containing antacids should be taken at least one hour after the IMP dose.

The following medicinal products are prohibited from Day -9 to Day -1 (Screening) and during the treatment period:

- Quinolone antimalarial (e.g., chloroquine and quinacrine). Participants who have malaria at screening are to be excluded. However, if a participant develops malaria during the trial, the Investigator is advised to consult the Malaria Treatment Guidance document regarding the interaction between moxifloxacin and bedaquiline with anti-

malarial drugs. Investigators may also contact the Sponsor Medical Monitor for further guidance.

- Chronic systemic glucocorticoids (topical, inhaled or intranasal glucocorticoids are allowed) due to their potential to cause visual opacities. Short term systemic glucocorticoids are allowed for emergency situations (e.g. for treatment of pulmonary exacerbation when Inhaled glucocorticoids is inadequate).
- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, other quinolones, thioamides, and metronidazole.

The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible unless discussed with the Sponsor Medical Monitor:

- Any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). The exception is moxifloxacin and bedaquiline administered as part of the trial IMP, with ECG monitoring, to help ensure participant safety.
- Any drug known to be hepatotoxic (including but not limited to acetaminophen/paracetamol, acetazolamide, allopurinol, amiodarone, amitriptyline, amoxicillin, amprenavir, atorvastatin, augmentin/co-amoxiclav, azathioprine, baclofen, bumetanide, captopril, carbamazepine, celecoxib, chlorpromazine, chlorpromazine, clindamycin, clopidogrel, contraceptive pill, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).

5.4 Treatment Discontinuation and/or Early Withdrawal

Any participant for whom the Investigator decides to temporarily discontinue their IMP is to be discussed with the Sponsor Medical Monitor and, if applicable, be restarted on IMP as soon as possible.

A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following:

- Withdrawal of informed consent
- Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment.

- Pregnancy
- At the specific request of the Sponsor or termination of the trial by the Sponsor.
- Lost to follow-up
- Drug-Sensitive TB treatment arms: participants, who have been randomised onto the trial as a rifampicin sensitive participant on the rapid sputum based test result, who on receipt of the rifampicin resistance testing using an indirect susceptibility test in liquid culture, shows a rifampicin resistant result.
- Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result.
- Early withdrawal due to TB (see Section 5.4.4)

A participant may withdraw from the trial at any time at his/her request (withdrawal of consent), or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative issues. When a participant withdraws consent from the trial, no additional follow-up visits will be performed.

Participants who withdraw from the trial after having received IMP will not be replaced.

All participants withdrawn from trial and who received at least one dose of IMP will be requested to return for an Early Withdrawal visit and the applicable safety Follow-Up visits, as per the Synopsis Flow Chart and Procedures (Section 1.2 footnote c), as well as Table 5.

5.4.1 Early Withdrawal

In case of early withdrawal during the treatment or follow-up period, 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:

- Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff). If no early morning sputum sample was provided by the participant, 2 samples may be collected at the site, at least 30 minutes apart.
- Urine pregnancy test (women of child bearing potential, whether they are sexually active or not)
- Laboratory safety sampling (including male reproductive hormone tests);
- Single 12-lead ECG
- TB Symptoms Profile
- Patient Reported Health Status Questionnaire
- Vital signs
- Full physical examination, including weight
- Ophthalmology examination, if required as described in Table 5
- IMP compliance check (if participant on IMP)
- Concomitant medications
- Adverse events

Once a participant has been withdrawn early from the trial, they will be requested to attend follow-up visits as described in Table 5:

Table 5: Follow-up Visits Required for Early Withdrawal Participants

Treatment Duration at EWD visit	Ophthalmology Examination at EWD[a]	Ophthalmology Examination Visit 3 months after EWD Visit[a]	Week 52 (Month12) Follow-up Visit	Week 104 (Month 24) Follow-up Visit
≤ 14 days	Not required	Not required	Required	Required
15 days to ≤ 12 weeks	Not required	Required	Required	Required
> 12 weeks	Required	Required	Required, if not already performed	Required

a. If an additional visit is required for an ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 3 months after the EWD visit date.

The Weeks 52 and 104 (Month 12 and 24) visits will be performed to collect SAE information (including verification of survival) and participant reported TB outcome information. This visit may be telephonic, a home or a site visit at Weeks 52 (Month 12) and/or Week 104 (Month 24) after the participants' start of treatment date.

5.4.2 Unscheduled Visits

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

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

- If both sputum samples (Early Morning and Spot) at Week 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum.
- If there is a MTB confirmed positive culture at or after the end of treatment at Week 17 (4-month treatment) or Week 26 (6-month treatment), the participant should return for an Unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum. If no early morning sputum sample was provided by the participant, 2 samples may be collected at the site, at least 30 minutes apart.

To be able to define a participant's primary outcome status it may be necessary in certain situations to contact a participant and request they visit the site to collect additional sputum samples at unscheduled visits, as follows:

- To be assessed on sputum culture results from:
  - End of Treatment Period (Week 17 or 26)
  - End of Follow-up Period (Month 12 and 24)
  - Early Withdrawal, if applicable

- To confirm whether the participant 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, two sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) should be taken at least 7 days apart until they fall into one of the above categories. If no early morning sputum sample was provided by the participant, 2 samples may be collected on site at least 30 minutes apart.

If the Investigator is unsure of the outcome in any of the above scenarios the Investigator is to contact the Sponsor Medical Monitor and discuss and agree on how the participant is to be managed.

5.4.3 Lost-to-Follow-up

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

5.4.4 Early Withdrawal due to TB

Ultimately it is the Investigator's decision whether a participant requires early withdrawal from the trial due to a concern that the participant has symptomatic worsening of TB and/or bacteriological failure/relapse.

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

If the Investigator decides to withdraw a participant due to TB, additional sputum samples may need to be collected to ensure the participant's outcome status as determined in Section 5.5.

All early withdrawn participants who are confirmed sputum positive (two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These participants will be referred to their applicable DS/DR local community TB clinics for standard anti-tuberculosis chemotherapy according to National TB Treatment Guidelines. The participants will be provided with a referral letter from the Investigator to take with them to the TB clinic. A follow-up call will be made by the trial site staff to the clinic to ensure the participant attended the clinic.

5.5 Participant Progress Definitions

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

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

** Early Withdrawal

5.6 Trial Stopping Rules

There are no trial specific stopping rules.

The trial or parts of the trial can be stopped by the Sponsor on advice from the Data Safety and Monitoring Committee (DSMC) after their review of applicable trial data. In addition, the Sponsor has the right to stop the trial or a specific trial site at any time, although this should only occur after consultation between the involved parties. Should this occur, the local and central Ethics Committee/Institutional Review Board (EC/IRB) and Regulatory Authorities will be informed.

Should a trial site be closed prematurely, all trial materials (except documentation that must remain at the site) will be returned to the Sponsor or vendor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Participants currently on treatment will receive an appropriate regimen and all participants will be referred to their applicable DS-TB/DR-TB National Treatment Program.

6.0 Treatment

6.1 IMP Administration

6.1.1 Instructions for Dosing of Test Regimen (BPaMZ):

- Treatment will be orally administered once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months).

6.1.2 Instructions for Dosing Control Treatment Regimen (HRZE/HR):

- To be taken with a glass of water (approximately 240 ml).
- HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes.

HRZE/HR treatment will be administered orally once daily to DS-TB participants as follows:

Weight Band	Weight Range	Number of tablets per weight band
1	30-39 kg	2
2	40-54 kg	3
3	55-70 kg	4
4	≥ 71 kg	5

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

6.2 Participant Compliance

During site clinic visits, the IMP will be administered by the Investigator(s)/designated site personnel and when possible, the check for IMP compliance via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the participant has swallowed the IMP). During the trial, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how the IMP is to be taken as well as check cards for unused tablets in the containers at each visit during the treatment phase.

6.3 Treatment Modification(s)

The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the Investigator to identify and address the cause(s) (e.g. side effects).

Participants that do not take:

- Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required.
- Greater than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been.
- Greater than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial.

- If the participant misses a total (sum) of 56 cumulative missed doses, discontinue IMP and withdraw participant from the trial.

Any participant for whom the trial medication is discontinued (including for non-adherence) will be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial medication as soon as possible.

6.4 IMP Packaging and Labelling

The complete formulations of the IMP, bedaquiline and pretomanid, are found in the respective Investigator Brochures.[8, 15] The complete formulations of moxifloxacin, pyrazinamide, HRZE/HR are found in the Package Inserts.[19, 20, 22, 40]

The IMP will be packaged in weekly or bi-weekly cards as follows:

Week 1 to 8 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	14	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Week 9 to 17/26 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	7	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Control (HRZE/HR) Group: Dispensed *Bi-weekly*			
Weight Band	**Weight Range**	**Number of tablets per weight band**	**Number of tablets in each card**
1	30-39 kg	2	28
2	40-54 kg	3	42
3	55-70 kg	4	56
4	≥71 kg	5	70

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

The packaging of each weekly and biweekly cards will be labelled with, at a minimum, the following information:

- Name of Sponsor
- Name of medication
- Dosage, quantity and method of administration
- Reference/lot number
- The statement "For Clinical Trial Use Only"

- Space for completion of name of Investigator and site number
- MedID: medication identification number
- Storage conditions
- Period of use
- The statement "Keep out of reach of children"
- Expiry date
- Directions for use
- Space for completion of participant number and visit/date dispensed

6.5 Blinding and Procedures for Breaking the Blind

As this is an open label trial there is no need for blinding or procedures to break the blind. The trial participants, the site staff, Sponsor, and CROs will not be blinded to treatment assignment.

6.6 Handling, Storage and Accountability

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

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

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

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

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

7.0 Trial Variables and Procedures

The Synopsis Flowchart and Procedures in Section 1.2 should be referenced for timing, sequence of assessments, and specific procedures.

7.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected:

- Written Informed Consent
- Visit dates
- Participant disposition

- Demography (date of birth, race and gender)
- Inclusion and exclusion criteria
- Clinically significant medical and TB treatment history (including past and current TB diagnosis, smoking and alcohol use)
- Screening coached spot sputum samples:
  - Smear microscopy for acid-fast bacilli
  - Gene Xpert, Hain Assay MTBDRplus or equivalent to determine MTB complex and rifamycin resistance
- Urine pregnancy test: women of childbearing potential only, whether they are sexually active or not (Non-childbearing potential for a female participant is defined as having bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months).
- Serology: HIV and CD4 count. Where required by regulatory authorities or ethics committees, a separate (EC/IRB approved) HIV informed consent form will be obtained from participants:
  - Prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the participant, HIV counselling that is provided to the participant by the trial site should be clearly documented in the participant's medical records/source. Participants have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the participant's medical records/source.
- Karnofsky Score (Appendix 4)
- Chest X-Ray: A chest X-ray digital image within 6 months prior to or during the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor; this process will be documented in the Radiology Manual. The investigator is responsible for review and analysis of the chest X-ray for participant's inclusion.
- Method of birth control: male and female participants and their partners
- IMP details: randomization
- IMP compliance and actual dosing
- Concomitant medications

7.2 Efficacy Variables and Procedures

Two spot sputum samples are collected, one early morning brought from home or collected in the hospital ward (only if the participant is hospitalised) and one spot sputum sample collected at the research site under the coaching and observation of the trial staff or, if no early morning sputum sample was provided by the participant, 2 samples may be collected on site at least 30 minutes apart. The mycobacteriology sampling methodology and requirements will be described in a separate document, the Mycobacteriology Laboratory Manual, which will be provided prior to the trial start. Sputum samples may not be obtained by induction.

The following analyses will be performed:

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

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

- Bacteriologic failure/relapse
- Time to sputum culture conversion
- Number of participants with sputum culture conversion

Every effort must 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 participant who never achieves culture negative status due to the inability to produce sputum, but has completed Week 26 (6 months) post treatment completion follow-up and is without clinical or biological evidence of relapse, will be considered to have a favourable outcome.

TB Symptoms Profile:

- The TB Symptoms Profile (Appendix 6) will record participants' ratings of the severity of common TB symptoms.

Patient Reported Health Status Variables and Procedures:

- The Patient Reported Health Status variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2). Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire (Appendix 7). This descriptive system consists of five health-related quality of life dimensions, each of which will be recorded using five levels of severity.

Methodology: The Patient Reported Health Status methodology and requirements will be described in a separate document/guideline which will be provided prior to the trial start.

7.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the Synopsis Flow Chart and Procedures 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 Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
    - Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count)
    - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, ALP, AST, ALT, lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO_2, creatine phosphokinase (CPK). GGT is only routinely included at the Screening visit (Day -9 to -1).
    - When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

  - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator
- 12-lead ECG:
  - Investigator assessment: normal or abnormal
  - Central cardiologist assessment: heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.
  - Methodology:
    - Timing and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start
    - ECGs are to be recorded for 10 seconds
    - ECGs are to be performed during a single visit
    - ECGs should be done before any phlebotomy when both included in a visit
    - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch)
- Vital signs:
  - Vital signs (should be done before any phlebotomy in light clothing and with no shoes)
  - Systolic and diastolic blood pressure (mmHg) to be measured in a supine position (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 (beats per minute)
  - Respiratory rate (breaths per minute)
  - Axillary body temperature (°C)
- Physical Examination:
  - Height (m) is measured at the screening visit only
  - Full (complete) and limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded
  - Weight (kg) (in light clothing and with no shoes)
  - Using the variables of weight and height, the body mass index (BMI) will be calculated
- Ophthalmology Slit Lamp Examination:
  - To be done by an Ophthalmologist trained on Age-Related Eye Disease Scale 2 (AREDS2) assessment. The ophthalmology slit lamp methodology and requirements will be described in a separate document, the Ophthalmology Guideline. The following analyses will be performed: AREDS2 opacity typing and grading.
- Adverse events
- Investigator assessment:
  - The Investigator will review the participant status at specified visits in the Synopsis Flow Chart and Procedures, including any time the Investigator determines that the participant fulfils the criteria for the primary outcome of treatment failure. The Investigator will assess whether TB treatment is considered a “success” or “failure”. If it is considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration.

7.4 PK Variables and Procedures

Plasma concentrations from sparse sampling (see Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, and linezolid to further evaluate the effects of covariates on model parameters in this trial population.

PK data from the current trial may be combined with prior data (e.g., from the NiX-TB trial) to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{min}, C_{max}, AUC_{τ}, C_{mean}, and time above minimum inhibitory concentration) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

7.5 Mycobacteriology Characterization Variable and Procedures

The following Mycobacterial Characterization variables will be collected:

Positive Culture (for MTB) from:

- Day 1 or if Day 1 is not available, first positive result between screening through Week 4
- Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be sub-cultured and sent to the central microbiology laboratory from the applicable local microbiology laboratory, for relevant participants / no positive cultures from screening through week 4
- When applicable, at last visit of the treatment period (Week 17 for the 4-month treatment arm and Week 26 for the 6-month treatment arm) or visits with positive cultures, during the post-treatment follow-up period

The MTB isolates will be processed at the central microbiology laboratory for:

- MIC against bedaquiline, pretomanid and moxifloxacin
- Drug Susceptibility Testing in liquid culture for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide, and second line TB drugs including but not limited to fluoroquinolones, and injectables
- Extraction of organismal (MTB) DNA for whole genome sequencing, and the comparison of sequences from baseline and relapse isolates.

All Day 1 (Baseline) MTB isolates and isolates from positive cultures to be stored at the local and central microbiology laboratories, until trial closure. Extracted MTB DNA to be stored at the central microbiology laboratory until trial closure. The extracted MTB DNA and isolates will then be stored for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure.

The MTB isolates will be processed at the trial microbiology laboratories for positive MTB complex at/after the last visit of the treatment period (Week 17 for the 4-month treatment arm and Week 26 for the 6-month treatment arm) via Hain MTBDR*plus* and HainMTBR*sl.*

8.0 Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

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

symptom, or disease (new or exacerbated) temporally associated with the use of a trial treatment, whether or not related to the trial treatment.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

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

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse. A "suspected transmission of infectious agent by a medicinal product" is also considered a serious adverse event under the SAE criterion "Other medically important condition".

8.1.3 Attribution/Causality

- The Investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE
- The Investigator will use clinical judgment to determine the relationship
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment

- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor/designee. However, it is very important that the Investigator always assesses causality for every event before the initial transmission of the SAE data to the Sponsor/designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment

Table 6: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An AE, which is not related to the use of the drug.
Unlikely	An AE 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 AE, 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 AE, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by de-challenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An AE, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

8.1.4 Severity

Table 7: Definitions for Adverse Event Severity Gradings

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

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

8.2 Reporting

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

All AEs will be collected by the Investigator from the time a participant signs the Informed Consent Form through to their Week 104 (Month 24) follow-up visit. The exception to this is early withdrawal participants who will only have SAEs collected from their time of early withdrawal to their Week 104 (Month 24) follow-up visit at the timepoints specified in the Synopsis Flow Chart and Procedures (Section 1.2) and recorded in the CRF.

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

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

The Sponsor/Investigator/designee will inform Regulatory Authorities and/or EC/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 EC/IRB.

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

8.2.1 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- The end of the follow-up period; and
- 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 Investigator. However, this will have to be agreed upon with the Sponsor Medical Monitor.

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with

other health care professionals. The Investigator should contact the Sponsor/designee to discuss appropriate medical follow-up if consultation is required.

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

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

8.2.2 Clinical Laboratory Adverse Events

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

8.2.3 Disease Symptoms During Trial

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

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

it will be recorded as an adverse event. If there is:

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

it will not be recorded as an AE and this will be noted in the participant's source documentation. All TB related symptoms that meet SAE criteria will be recorded and reported as a SAE.

8.2.4 Overdose

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

8.2.5 Drug Interaction

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

8.2.6 Pregnancy

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

- Any time during the trial
- Within 6 months after the last dose of IMP

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

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

8.3 Monitoring for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in the preclinical toxicity studies of the Investigator's Brochures[8, 15] and Package Inserts.[19, 20, 22, 40]

AEs still ongoing at the end of the treatment period in the trial will be followed until satisfactory clinical resolution or stabilization, or until the end of the follow-up period and until all queries on these AEs have been resolved.

Grade 3 and Grade 4 laboratory abnormalities, and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.

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

8.3.1 ALT, AST and Bilirubin Elevations

The Investigator should refer to Appendix 8 Liver Toxicity Management, to appropriately monitor significant elevations of AST, ALT or Bilirubin. A separate Hepatoxicity Management Guideline document has been developed to aid investigators in the management of participants.

When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase

(GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

8.3.2 Lipase

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

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

8.3.3 Neurological

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

8.3.4 Musculoskeletal System and Cardiac Muscle Myalgia

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

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

8.3.5 Cardiac Rhythm Disturbances

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

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

<u>QTc prolongation</u>

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

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

8.4 Safety Monitoring by Data Monitoring Committee

A Data Safety Monitoring Committee (DSMC) will be appointed for the trial. The primary responsibility of the DSMC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial participants by monitoring participant safety, assess participant risk versus benefit, and assess data quality and general evaluation of the trial progress. Its activities will be delineated in a DSMC charter that will define the membership, responsibilities and the scope and frequency of data reviews.

The DSMC will operate on a conflict-free basis independently of the Sponsor and the trial team. It will comprise at least 3 voting members that include at least 2 clinicians and one statistician.

The DSMC may have an organizational meeting prior to commencement of the trial. The DSMC will have meetings where it will review unblinded data during a closed session. These meetings will be planned at regular intervals.

The Sponsor or the DSMC may convene ad hoc meetings based on rates of SAEs and/or to review results of the futility analysis, or if safety concerns arise during the trial. After its assessment, the DSMC will recommend to the Sponsor continuation, modification or termination of the clinical trial.

9.0 Statistical Analysis

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

9.1 Analysis Populations

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

- The ITT population is defined as all randomized participants excluding late screening failures. Late screening failures are participants withdrawn from treatment because they were found to be ineligible (late exclusions from the trial), based on data collected *prior to randomization*.
- The mITT population is defined as the ITT population with extra exclusions (described in the SAP).
- The PP population is defined as the mITT population with extra exclusions (described in the SAP).
- The mITT analysis will be considered primary, with consistent findings required from the other main analysis populations to support the primary conclusion.

9.2 Sample Size

For the primary endpoint, time-to-culture conversion at 8 weeks,150 participants per arm (DS-TB participants) will provide at more than 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 90% power to detect a HR of least 2. This sample size also allows for one planned interim analysis of the primary endpoint (See Section 9.4.1)

For the key secondary endpoint of clinical outcome at 12 months from randomization, 150 patients per arm will provide 74% power based on assumptions using data from the largest most recent and completed phase 3 TB treatment trial which used the same control arm.[41] That is, assuming 16% unfavourable (see Section 9.4.2) in the control arm and 13% unassessable (see Section 9.6) at 52 weeks post randomization. A 12% margin of non-inferiority was chosen to preserve at least 75% of the estimated control arm effect against placebo (estimated to be 54%)[41, 42] which is considered an acceptable proportion on which to declare non-inferiority of the test regimen.

9.3 Interim Analyses

There is no planned interim analysis in this trial.

9.4 Primary and Secondary Efficacy Endpoint Analysis

9.4.1 Primary Efficacy Endpoint, Time to Culture Conversion at 8 Weeks

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

Participants will be classified as being culture positive, culture negative, dead or unassessable at 8 weeks. The proportion culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis and groups compared using a hazard ratio and 95% confidence interval.

Non-inferiority of the key secondary endpoint of clinical outcome will be assessed using the upper bound of the one-sided 97.5% confidence interval for the difference between the proportion of participants who are classified as having an unfavourable status on the intervention less the control regimen. If the upper bound of the one-sided 97.5% confidence limit for this difference in proportions is less than 12% (the margin of inferiority) the intervention will be non-inferior to the control arm.

9.4.2 Key Secondary Efficacy Endpoint, Clinical Outcome at 52 Weeks from Randomization

For the key secondary endpoint of clinical outcome (bacteriologic failure or relapse or clinical failure), participants will be classified as having a favourable, unfavourable or unassessable outcome status which will be defined in detail in the SAP. In general, participants achieving and maintaining culture negative status without any additional treatment will be considered favourable; participants who fail on treatment or relapse in follow-up will be considered unfavourable and participants who are not assessable (and who have not already been declared as unfavourable) will be considered unassessable and excluded from the analysis.

9.4.3 Other Secondary Efficacy Endpoints

The secondary efficacy endpoints and analyses are as follows are:

- Clinical outcome (bacteriologic failure or relapse or clinical failure) at 104 weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.

- Change from baseline in weight will be summarised and presented.
- Proportion of participants experiencing a change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status will be summarised and presented.

9.5 Safety and Tolerability Assessments

- 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.

9.6 Pharmacokinetics

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., C_{min}, C_{ma}x, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so, too, will the effects of concomitant medications including ART, as feasible. Data from other trials may be included to enhance the model-based analysis.

Detailed plans for the PopPK analysis will be outlined in a separate modelling plan, and results will be reported in separate modelling report.

9.7 Pharmacokinetics/Pharmacodynamics

Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate. Planning details and results will be included in the separate modelling plan and report.

10.0 Records Management

10.1 Data Collection

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

10.2 Source Documents

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

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

10.3 File Management at the Trial Centre

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

10.4 Records Retention at the Trial Centre

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

11.0 Quality Control and Assurance

11.1 Site Procedures

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

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

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

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

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

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

11.2 Monitoring

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

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

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

11.3 Protocol Deviations

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

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

11.4 Auditing

For 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 about accuracy, adequacy and consistency, and to assure that trials are in accordance with the guidelines. Having the highest quality data from trials is an essential aspect of drug development.

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The auditors or inspectors may also review site SOPs, training records, site facilities and other trial related systems/processes.

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

12.0 Ethics and Regulatory

12.1 Basic Principles

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

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

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

12.3 Regulatory Authorities

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

12.4 Informed Consent

Written informed consent will be obtained from all participants (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment

procedures) are performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for 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 part of the research.

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

The trial will be included and updated in the appropriate Country registry and referenced in the informed consent forms (ICF).

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

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

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

12.5 Confidentiality

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

13.0 Publication Policy

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

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

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory Investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors.[43]

Because the Trial is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the Trial must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy. Specifically, (a) all peer-reviewed published research relating to the Trial must be submitted for publication by TB Alliance through the Chronos Open Access Publishing Service established by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy.

14.0 Protocol Amendment Policy

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

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

15.0 Sponsor, Financial Aspects, Insurance and Indemnity

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

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

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

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

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

16.0 References

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Appendices

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	scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

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

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

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

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

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

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

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

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

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

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	Subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia

Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint 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: Who Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection
Asymptomatic Acute retroviral syndrome
Clinical Stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical Stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections
Clinical Stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for >1 month Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) Persistent oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anemia (hemoglobin <8 g/dL) Neutropenia (neutrophils <500 cells/µL) Chronic thrombocytopenia (platelets <50,000 cells/µL)
Clinical Stage 4
HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Cryptococcosis, extrapulmonary (including meningitis) Disseminated nontuberculosis mycobacteria infection Progressive multifocal leukoencephalopathy Candida of the trachea, bronchi, or lungs Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)

Recurrent nontyphoidal Salmonella bacteremia
Lymphoma (cerebral or B-cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy
Symptomatic HIV-associated cardiomyopathy
Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

REF: World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children; 2007*

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: Cardiovascular Safety

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

All-important abnormalities from the ECG readings will be reported.

The percentage of participants with increases in QTc of <30, 30-60, or > 60 ms from baseline will also be tabulated at each time point.

Abnormality Code	ECG parameter			
	HR	PR	QRS	QTcorrected
Abnormalities on actual values				
“Abnormally low”	≤ 50 bpm	NAP	≤ 50 ms	-
“Abnormally high”	≥ 120 bpm	≥ 210 ms	≥ 120 ms	-
“]450 ms, 480 ms]	-	-	-	450 ms < QTc ≤ 480 ms
“]480 ms, 500 ms]	-	-	-	480 ms < QTc ≤ 500 ms
“More than 500 ms	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline				
“[30; 60] ms”	-	-	-	[30; 60] ms
“> 60 ms”	-	-	-	> 60 ms

Appendix 5: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

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

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

Appendix 6: Tuberculosis Symptoms Profile

TUBERCULOSIS SYMPTOM PROFILE (V3)

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

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

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

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

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

Approved, Issued Date 09-Apr-2012

Appendix 7: Patient Reported Health Status Questionnaire

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

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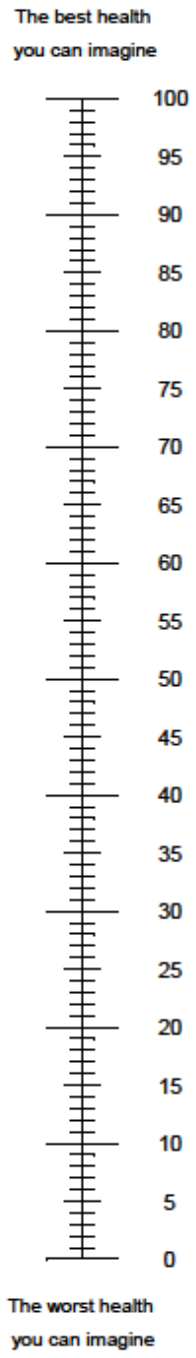
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the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

YOUR HEALTH TODAY = ☐



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Appendix 8: Liver Toxicity Management

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

In pre-marketing clinical trials of new drugs and regimens it is especially important to identify and carefully manage any trial participants who are at risk of progression to serious liver injury. The observation of altered liver function to a degree that has a high risk of progressing to liver failure as been referred to informally as Hy's Law;[44, 45]; this reflects that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components:

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

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

Procedure

Blood tests for liver function will be taken routinely at screening (Day -9 to -1) and at the specific time points designated in the protocol, and at Early Withdrawal. If at any other visit the clinician suspects derangement of liver function, e.g. the participant describes nausea and vomiting, right upper abdominal pain or is jaundiced, blood should be taken for liver function tests and the participant comprehensively assessed for evidence of hepatitis or hepatic impairment and any potentially contributing causes.

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

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

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

Temporarily Stopping and Restarting Trial Medication

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

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

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

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

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Protocol Amendment

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

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

Reasons for Protocol Amendment:	
1	**Change** of HRZE weight band 1 and 2 in compliance with the HRZE and HR Package Inserts (Synopsis and Section 6.1.2 Instructions for Dosing Control Treatment Regime HRZE/HR)
2	**Removal** of Vitamin B6 from Synopsis and IMP Section 6 Treatment, and clarified that 'a daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline'
3	**Removal** of reporting non-adherence to the Sponsor Medical Monitor from the Synopsis and from Section 6.3 Treatment Modification(s) as it is sufficient to state that 'Non-adherence should prompt the Investigator to identify and addresses the cause(s) – this is to prevent over-reporting of inappropriate protocol non-compliances by the participant.
4	**Change** the number of consecutive missed doses in the Synopsis and Section 6.3 Treatment Modifications, from 7 to ≤ **21**, to 7 to ≤ **35** and stated that no more than 56 cumulative (sum of) consecutive doses may be missed before the IMP is stopped and the participant is withdrawn from the trial (consistent with ZeNix).
5	**Addition** of safety laboratory assessments at weeks 5 and 7 (Section 1.2 Synopsis Flow Chart and Procedures)
6	**Addition** of ECG assessments included at weeks 3, 6, 7 and 8 (Section 1.2 Synopsis Flow Chart and Procedures)
7	**Clarified** that if the Screening (Day-9 to -1) spot sputum smear shows an indeterminate result or is AFB negative that a test may be repeated on a back-up sample or a freshly collected spot sputum sample (Section 1.2 Synopsis Flow Chart and Procedures, Item f).
8	**Clarified** that if both sputum samples at Weeks 8, 17 (4-month treatment arm), 26 (6-month treatment arm), 52 or 104 are contaminated, the participant should return for an unscheduled visit(s) to give additional samples.
9	**Clarified** that if HIV status is a confirmed known positive, a repeated HIV test is not needed provided that a documented HIV test result is available, and that a HIV re-test of an indeterminate result can be done within the Screening period (Section 1.2 Synopsis Flow Chart and Procedures, Item h.)
10	**Addition** of GGT assessment to the clinical chemistry assessments at Screening and Unscheduled visits (only) in the Synopsis Flow Chart Item l, and added to Exclusion Criteria #23: f) a GGT greater than 3x ULN (will be excluded at the Screening visit); updated Section 7.3 Safety and Tolerability Assessments

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11	**Change** of the timing of the chest x-ray from 4 weeks prior to or at the Screening visit, to 6 weeks prior to or at the Screening visit (Section 1.2 Synopsis Flow Chart and Procedures, and Inclusion Criteria #6, Section 7.1 Demographic and Background Variables and Procedures)
12	**Clarified** that the Slit Lamp Ophthalmic Examination will also be performed at the Screening visit (Section 1.2 Synopsis Flow Chart and Procedures Item p.), as reflected in the actual flow chart.
13	**Clarified** the timing of PK sampling at Weeks 39, 65, 78 and 104 to indicate that the samples can be taken at any time during the specified visits, as this was not previously stated (Section 1.2 Synopsis Flow Chart and Procedures, Item s.)
14	**Clarified** that the DR-TB participants should not have had previous treatment for DR-TB/MDR-TB, although may have been on a MDR-TB/MDR-TB treatment regimen for no longer than 7 days at start of screening (Inclusion criteria #5)
15	**Addition** of Exclusion criteria #2, 'Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations' for safety reasons.
16	**Change of** the Exclusion Criteria # 11 by increasing the QTcF interval from >450 to >500 msec and specified the following additional exclusionary criteria: heart failure, a personal or family history of congenital QT prolongation, history of or known, untreated, ongoing hypothyroidism, a history of or ongoing bradyarrhythmia, a history of Torsade de Pointe (consistent with ZeNix)
17	**Addition** of Exclusion criteria #15, Females who have a positive pregnancy test at the Screening visit or already known to be pregnant, breast-feeding, or planning to conceive a child during the trial or within 6 months of stopping treatment. Males planning to conceive a child during the trial or within 6 months of stopping treatment' for safety reasons.
18	**Addition** of topical steroids to Exclusion Criteria #20 and Section 5.3 Restrictions, as this was previous limited only to inhaled or intranasal glucocorticoids
19	**Removal** of 'Failure to comply with the protocol' from Section 5.4 Treatment Discontinuation and/or Early Withdrawal to prevent unnecessary or inappropriate withdrawal of participants from the study.
20	**Removal** of the optional serum pregnancy assessment from Section 5.4.1 Early Withdrawal visit, as urine pregnancy test confirmation is sufficient
21	**Removal** of the requirement in Section 6.2 Participant Compliance, of checking IMP compliance with the support of the National TB Treatment Program personnel (DOTS)
22	**Removal** of the address and telephone number of the sponsor from Section 6.4 IMP Packaging and Labelling, as this is not required or documented on the approved IMP labels
23	**Removal** of the ophthalmic examination from Section 7.3 Safety and Tolerability (consistent with 1.2 Synopsis Flow Chart and Procedures) as only ophthalmology slit lamp examination by (AREDS2 trained) ophthalmologist is required
24	**Clarified** in Section 7.5 Mycobacteriology Characterisation Variable and Procedures that 'extraction of organismal (MTB) DNA for whole genome sequencing, and the comparison of sequences from baseline and relapse isolates' to be documented in this section (consistent with wording in Section 1.2 Synopsis Flow Chart and Procedures, Item g.) instead of only 'genotyping'.
25	**Removal** of the paragraph referring to 'female partners of male participants', from Section 8.2.6 Pregnancy, as information from female partners of male participants who may become pregnant during the trial, will not be collected

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26	**Addition** of additional laboratory parameters that require monitoring, in Section 8.3, that were not previously listed, for safety reasons.
27	**Addition** of References #44 and 45 Hy's Law, as referenced in Appendix #8)
28	**Addition** of DMID reference tables to Appendix 2 (previously missing)
29	**Addition** of Liver Toxicity Management, Appendix 8
30	Administrative changes, including spelling, grammar and format changes have been applied to the entire document. Refer to the 'tracked changes' (V1.1 and V1.2 for details of changes made)

<table>
<tr><th>#</th><th>Section</th><th>Previous Text
Version 1.0 dated 05-Oct-17</th><th>Amended Text
Version 2.0 dated 16-Feb-18
~~Additional text - bold font. Deleted text – strike through.~~</th><th>Reason for Change
Insert reason # from table above</th></tr>
<tr><td>1</td><td>Synopsis and Section 6.1.2</td><td>Weeks 1-8: HRZE tablets with the daily dose per the participant's weight as follows: 30-37 kg: 2 tablets; 38-54 kg: 3 tablets; 55-70 kg: 4 tablets; ≥ 71 kg: 5 tablets

Weeks 9-26: HR tablets with the daily dose per the participant's weight as follows: 30-39 kg: 2 tablets; 40-54 kg: 3 tablets; 55-70 kg: 4 tablets; ≥ 71 kg: 5 tablets</td><td>Weeks 1-26 HRZE/HR tables daily dose per the participant's weight as follows:
<table>
<tr><th>Weight Band</th><th>Weight Range</th><th>Number of tablets</th></tr>
<tr><td>1</td><td>30-39 kg</td><td>2</td></tr>
<tr><td>2</td><td>40-54 kg</td><td>3</td></tr>
<tr><td>3</td><td>55-70 kg</td><td>4</td></tr>
<tr><td>4</td><td>≥ 71 kg</td><td>5</td></tr>
</table></td><td>1</td></tr>
<tr><td>2</td><td>Synopsis and Section 6 Treatment</td><td>Vitamin B6 25 mg daily supplement to be taken with the HRZE/HR treatment.</td><td>Vitamin B6 daily supplement to be taken with the HRZE/HR treatment, per each country's TB Treatment Guidelines.</td><td>2</td></tr>
</table>

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#	Section	Previous Text Version 1.0 dated 05-Oct-17	Amended Text Version 2.0 dated 16-Feb-18 ~~Additional text - bold font. Deleted text – strike-through.~~	Reason for Change Insert reason # from table above
3	Synopsis and Section 6.3 Treatment Modification(s)	The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation, unless an interruption/pause is required urgently for a safety concern; the Medical Monitor should then be informed within 24 hours of the interruption/pause if not discussed prior to implementation. The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the investigator to identify, capture and address the cause(s) (e.g. side effects) of the non-adherence and contact the sponsor medical monitor.	The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical monitor prior to implementation, unless an interruption/pause is required urgently for a safety concern.	3

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4	Synopsis and Section 3.3 Treatment Modifications	• Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required. • Greater than 7 to ≤ 21 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been. • Greater than 21 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial.	• Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required. • Greater than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been. • Greater than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial. • If the participant misses a total (sum of) 56 cumulative missed doses, discontinue IMP and withdraw participant from the trial.	4
5	Synopsis Flow Chart and Procedures	Safety laboratory assessment previously not performed at weeks 5 and 7	Safety laboratory assessment performed at weeks 5 and 7 (i.e. will be performed weekly, from Baseline to Week 8)	5
6	Synopsis Flow Chart and Procedures	ECGs not previously performed at weeks 3, 5, 6 and 7	ECGs will be performed weekly from Day 1 (Baseline) to Week 8	6

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7	Synopsis Flow Chart and Procedures, Item f.	• The second sample is collected as a back-up sample to the first sample in case it is technically not possible to obtain a result/s from the first sample. If the Day -9 to -1 (Screening) spot sputum smear shows an indeterminate result or is AFB negative, the test may be repeated on a freshly collected spot sputum/s and that result will be used.	• The second sample is collected as a back-up sample to the first sample in case it is technically not possible to obtain a result/s from the first sample. If the Day -9 to -1 (Screening) spot sputum smear shows an indeterminate result or is AFB negative, the test may be **repeated on the back-up sample or** a freshly collected spot sputum/s and that result will be used.	7
8	Synopsis Flow Chart and Procedures, Item f.	• If both sputum samples at Weeks 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional samples or it must be documented that the participant is not able to produce sputum.	• If both sputum samples at Weeks **8, 17 (4-month treatment arm), 26 (6-month treatment arm), 52 or 104** are contaminated, the participant should return for an unscheduled visit(s) to give additional samples or it must be documented that the participant is not able to produce sputum.	8
9	Synopsis Flow Chart and Procedures, Item h.	If HIV status is a confirmed known positive, repeated HIV test is not needed, provided documentation is available.	• If HIV status is a confirmed known positive, a repeated HIV test is not needed **provided that a documented HIV test result is available.** • Repeated HIV testing, during the Screening period is permitted for indeterminate HIV results.	9

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10	1.2 Synopsis Flow Chart and Procedures, Item l. and Exclusion Criteria #23 and Section 7.3 Safety and Tolerability assessments	**1.2 Synopsis Flow Chart and Procedures, Item l** Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/carbon dioxide [CO_2], creatine phosphokinase [CPK]). **Exclusion Criteria #23** Addition of item f. not previously present **7.3 Safety and Tolerability Assessments** 3rd bullet in this section not previously present	**1.2 Synopsis Flow Chart and Procedures, Item l** Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/carbon dioxide [CO_2], creatine phosphokinase [CPK]). **GGT is only routinely included at the Screening visit (Day -9 to -1).** **Exclusion Criteria #23** f. GGT: great than 3 x ULN **7.3 Safety and Tolerability Assessments** When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].	10

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11	1.2 Synopsis Flow Chart and Procedures, Item o., Inclusion Criteria #6 and Section 7.1 Demographic and Background Variables and Procedures	A chest x-ray (digital image) within 4 weeks prior to or at screening	A chest x-ray (digital image) **within 6 months** prior to or at screening	11
12	Synopsis Flow Chart and Procedures, Item p.	Slit lamp will be done at EOT and at 9 month for 4 and 6-month treatment groups.	Slit lamp examination will be done at the **Screening visit, the last visit of the treatment period, Week 17 or 26, and at Week 39 (9 months) for both treatment groups.**	12
13	Synopsis Flow Chart and Procedures, Item s.	6. Weeks 39, 65, 78 and 104 – PK samples are obtained when participant is in the clinic	6. Weeks 39, 65, 78 and 104: PK samples to be obtained **at any time on the day of the scheduled visit.**	13
14	Section 5.1 Inclusion Criteria #5	**DR-TB treatment arm participants should be:** a. Resistant to rifampicin and/or isoniazid.	**DR-TB treatment arm participants should be:** a. Resistant to rifampicin and/or isoniazid. b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 7 days at start of screening.	14

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15	Section 5.2 Exclusion Criteria #2	Not previously stated.	2. Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.	15
16	Section 5.2 Exclusion Criteria #11	10. Participants with any of the following at screening (per measurements and reading done by ECG): 11. Cardiac arrhythmia requiring medication; 12. Prolongation of QT/QTc interval with QTcF (Fridericia correction) >450 ms; 13. History of additional risk factors for Torsade de Pointes, (e.g., heart failure, hypokalemia, family history of Long QT Syndrome); 14. Any clinically significant ECG abnormality, in the opinion of the investigator.	11. Participants with any of the following at the Screening visit (per measurements and reading done by ECG): a. QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with the Sponsor Medical Monitor before enrolment. b. Heart failure c. A personal or family history of congenital QT prolongation d. A history of or known, untreated, ongoing hypothyroidism e. A history of or ongoing bradyarrhythmia f. A history of Torsade de Pointe	16

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17	Section 5.2 Exclusion Criteria #13	Not previously stated.	13. Females who have a positive pregnancy test at the Screening visit or already known to be pregnant, breast-feeding, or planning to conceive a child during the trial or within 6 months of stopping treatment. Males planning to conceive a child during the trial or within 6 months of stopping treatment.	17
18	Section 5.2 Exclusion Criteria #20 and Section 5.3 Restrictions	7. Use of systemic glucocorticoids within one year of start of screening (inhaled or intranasal glucocorticoids are allowed) due to visual opacities or cataracts **Section 5.3 Restrictions** Chronic systemic glucocorticoids (inhaled or intranasal glucocorticoids are allowed) due to their potential to cause visual opacities. Short term systemic glucocorticoids are allowed for emergency situations e.g for treatment of pulmonary exacerbation when Inhaled glucocorticoids is inadequate.	20. Use of systemic glucocorticoids within one year of start of screening (topical, inhaled or intranasal glucocorticoids are allowed) due to visual opacities or cataracts. **Section 5.3 Restrictions** Chronic systemic glucocorticoids (**topical**, inhaled or intranasal glucocorticoids are allowed) due to their potential to cause visual opacities. Short term systemic glucocorticoids are allowed for emergency situations (e.g. for treatment of pulmonary exacerbation when Inhaled glucocorticoids is inadequate).	18
19	Section 5.4 Treatment Discontinuation and/or Early Withdrawal	Failure to comply with the protocol (5th bullet)	Removal of this reason to withdraw the participant early.	19

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#	Section	Previous Text Version 1.0 dated 05-Oct-17	Amended Text Version 2.0 dated 16-Feb-18 ~~Additional text - bold font. Deleted text – strike-through.~~	Reason for Change Insert reason # from table above
20	Section 5.4.1 Early Withdrawal	Serum or Urine Pregnancy test (women of child bearing potential, whether they are sexually active or not);	Urine Pregnancy test (women of child bearing potential, whether they are sexually active or not);	20
21	Section 6.2 Participant Compliance	During site clinic visits, the IMP will be administered by the Investigator/designated site personnel. During the trial, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how IMP is to be taken. When possible, participants will be checked for IMP compliance by the Investigators or trial personnel/National TB Treatment Program personnel via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the participant has swallowed the IMP). Additionally, participant cards will be checked for unused tablets in the blisters at each visit during the treatment phase.	During site clinic visits, the IMP will be administered by the Investigator(s)/designated site personnel and when possible, the check for IMP compliance via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the participant has swallowed the IMP). During the trial, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how the IMP is to be taken as well as check cards for unused tablets in the containers at each visit during the treatment phase.	21
22	Section 6.4 IMP Packaging and Labelling	Name, address and telephone number of Sponsor.	Name of Sponsor.	22

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23	Section 7.3 Safety and Tolerability Assessments	• Ophthalmic Examination. The ophthalmic examinations can be performed by any trained study staff. The screening exams must be done by the trained study staff AND an Ophthalmologist. Methodology and requirements will be detailed in the Ophthalmology Guideline. o Ophthalmology History (Screening only); o Visual Acuity Test – Corrected. Distance Vision; o Colour Vision Assessment.	Removed – not required. Only the ophthalmology slit lamp examination is required and remains in Section 7.3	23
24	Section 7.5 Mycobacteriology Characterisation Variable and Procedures	The MTB isolates will be processed at the central lab(s) for: • MIC against bedaquiline, pretomanid and moxifloxacin; • Drug Susceptibility Testing in liquid culture for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide, and second line TB drugs including but not limited to fluoroquinolones, and injectables; • Genotyping.	The MTB isolates will be processed at the central microbiology laboratory for: • MIC against bedaquiline, pretomanid and moxifloxacin • Drug Susceptibility Testing in liquid culture for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide, and second line TB drugs including but not limited to fluoroquinolones, and injectables • **Extraction of organismal (MTB) DNA for whole genome sequencing, and the comparison of sequences from baseline and relapse isolates.**	24

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25	8.2.6 Pregnancy	Should the female partner of a male participant become pregnant during the trial or in 12 weeks after the completion of IMP and the Investigator becomes aware that this situation has occurred, the sponsor may request information from the female partner on her pregnancy history and on the current pregnancy and birth.	Paragraph removed from this section.	25

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#	Section	Previous Text Version 1.0 dated 05-Oct-17	Amended Text Version 2.0 dated 16-Feb-18 ~~Additional text - bold font. Deleted text – strike-through.~~	Reason for Change Insert reason # from table above
26	Section 8.3 Monitoring for Specific Toxicities	Not previously listed in this section.	**8.3.1 ALT, AST and Bilirubin Elevations** The Investigator should refer to Appendix 8 Liver Toxicity Management, to appropriately monitor significant elevations of AST, ALT or Bilirubin. A separate Hepatoxicity Management Guideline document has been developed to aid investigators in the management of participants. When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)]. **8.3.2 Lipase** Grade 3 (> 2.0 to ≤ 5.0 x ULN) or Grade 4 (> 5.0 x ULN): • Contact the Sponsor Medical Monitor to review. Participants with confirmed Grade 3 or 4 elevations of lipase, the Investigator should consider pausing the full regimen, pending further evaluation.	26

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27	Section 16.0 References	Not previously listed	44. Reuben A (2004). "Hy's Law". Landmarks in Hepatology 39(2): 574-578. 45. Temple RJ (2006). "Hy's Law: predicting serious hepatotoxicity". Pharmacoepidemoiology and Drug Safety 15: 241-243.	27
28	Appendix 2	DMID tables tot previously listed	Refer to tables in Appendix 2	28
29	Appendix 8	Not previously present	Refer to Appendix 8	29
30	Entire Document	Administrative changes, including spelling, grammar and format changes have been applied to the entire document. Refer to the 'tracked changes' (V1.1 and V1.2 for details of changes made)		30

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Protocol Amendment

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Sponsor

I agree to the terms of this protocol amendment

DocuSigned by:
Paul Bruinenberg
Signer Name: Paul Bruinenberg
Signing Reason: I approve this document
Signing Time: 21 February 2018 | 06:06 PST
3B496C3B3A5A4B0AAE32731255B7116B

Signature of Senior Medical Officer	Printed name	Date
	Paul Bruinenberg	February 21, 2018 | 9:06 AM EST

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Protocol Amendment

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Principal Investigator

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

Signature of Principal Investigator	Printed name	Date

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Protocol Number:	NC-008 (BPaMZ)
Title:	An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).
Drug(s)/Combination(s):	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Version/Date:	V3.0 / 14 January 2019, Incorporating Amendments 1 and 2
Protocol Name:	SimpliciTB

PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (BPaMZ)**

Protocol Date: **V3.0 / 14 January 2019, Incorporating Amendments 1 and 2**

Protocol Name: **SimpliciTB**

Sponsor: **TB Alliance**

I agree to the terms of this trial protocol.

DocuSigned by:
Morounfolu Olugbosi
Signer Name: Morounfolu Olugbosi
Signing Reason: I approve this document
Signing Time: 14 January 2019 | 07:22 PST
3DABF6C3410E4B8F85E1D6E511FA5A5F

Signature of Study Physician

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PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (BPaMZ)**

Protocol Date: **V3.0 / 14 January 2019, Incorporating Amendments 1 and 2**

Protocol Name: **SimpliciTB**

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

_____ _____
Signature Printed Name

_____
Date

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Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AFB	Acid-fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AREDS2	Age Related Eye Disease Scale 2
ART	Anti-Retroviral Therapy
AST	Aspartate aminotransferase
AUC_{τ}	Area Under Curve over a dosing interval
B	Bedaquiline
BA	Bacterial activity
BMI	Body Mass Index
BPaMZ	Combination of bedaquiline plus pretomanid plus moxifloxacin plus pyrazinamide
C	Clofazimine
CFU	Colony Forming Units
$C_{(max), (min)}$	plasma Concentration (maximum), (minimum)
CO_2	Carbon dioxide
CPK	Creatine Phosphokinase
CYP3A4	Cytochrome P450 3A4
DMID	Division of Microbiology and Infection Disease
DNA	Deoxyribonucleic Acid
DR-TB	Drug-resistant tuberculosis For this particular protocol defined as TB participants with 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB) (participants with fluoroquinolone resistance are excluded)
DS-TB	Drug-sensitive tuberculosis
DSMC	Data Safety and Monitoring Committee
DST	Drug Susceptibility Testing
E	Ethambutol
EBA	Early Bactericidal Activity
EC	Ethics Committee
ECG	Electrocardiogram
EFV	Efavirenz
(e)CRF	(electronic) Case Report Form
EMS	Early Morning Sputum
EWD	Early Withdrawal
FTC	Emtricitabine
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
H	Isoniazid
HR	Hazard Ratio

hERG	Human *Ether-à-go-go* Related Gene
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
HR	Isoniazid plus rifampicin combination tablet
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent to Treat
IUATLD	International Union Against Tuberculosis and Lung Disease
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Linezolid
LH	Luteinizing hormone
LLN	Lower Limit of Normal
LPV	Lopinavir
LTFU	Lost to follow-up
M	Moxifloxacin
MBD	Minimum Bactericidal Dose
MIC	Minimum Inhibitory Concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi Drug Resistant Tuberculosis
MGIT	Mycobacterial Growth Inhibiting Tube
mITT	Modified Intent to Treat
ms	millisecond
NVP	Nevirapine
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NRTI	(Triple) Nucleosidase Reverse Transcriptase Inhibitor
Pa	Pretomanid
PD	Pharmacodynamic
PP	Per Protocol
PK	Pharmacokinetic
PR	PR interval
R	Rifampicin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSCC	Serial sputum colony counting
TB	Tuberculosis
TDF	Tenofovir
TEAE	Treatment Emergent Adverse Events
TTP	Time to Positivity
ULN	Upper Limit of Normal
WGS	Whole Genome Sequencing
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis
µg(/ml)	micrograms (per millilitre)
Z	Pyrazinamide (tablets)

1.0 Synopsis

1.1 Synopsis Summary

Synopsis	Description
Name of Sponsor/Company	TB Alliance
Name of Finished Products	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Number/Title	NC-008 (BPaMZ) An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB)
Treatment Indication	Pulmonary Tuberculosis (TB)
Trial Objective(s)	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the treatment regimens in participants with Drug Sensitive TB (DS-TB) and Drug Resistant TB (DR-TB). DR-TB is defined as participants with: 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)
Trial Design	Phase 2c multi-centre, open-label, partially randomized clinical trial in Drug Sensitive-TB (DS-TB) and Drug Resistant-TB (DR-TB) participants. All participants will enter post-treatment follow-up which continues until Week 104 from start of treatment / randomisation. **Participants with DS-TB:** Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation. **Participants with DR-TB:**

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td></td><td>Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).</td></tr>
<tr><td>Participant Population</td><td>Up to 450 male and female participants, diagnosed with DS-TB or DR-TB, aged 18 years and over with a target of up to 50% being HIV positive.

300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation.

Up to 150 DR-TB participants will be enrolled.</td></tr>
<tr><td>Test Product, Dose and Mode of Administration</td><td>The Test Product (BPaMZ) consists of a combination of the following products and will be supplied as:
<table>
<tr><th>Product</th><th>Tablet Strength</th><th>Abbreviation</th></tr>
<tr><td>Bedaquiline</td><td>100 mg</td><td>(B)</td></tr>
<tr><td>Pretomanid</td><td>200 mg</td><td>(Pa)</td></tr>
<tr><td>Moxifloxacin</td><td>400 mg</td><td>(M)</td></tr>
<tr><td>Pyrazinamide</td><td>500 mg</td><td>(Z)</td></tr>
</table>
Instructions for Dosing of BPaMZ

Investigational Medicinal Product (IMP) will be administered orally once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months) in the following dosing schemes:

Participants with DS-TB:
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 17 weeks (total treatment duration 4 months)

OR

Participants with DR-TB:
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 26 weeks (Total treatment duration 6 months).</td></tr>
<tr><td>Positive Control Product, Dose and Mode of Administration</td><td>The Control Treatment Regimen (HRZE/HR) will be supplied as:

HRZE Tablets: isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets. This combination will be given for the first 8 weeks.

AND</td></tr>
</table>

Synopsis	Description
	HR Tablets: isoniazid 75 mg plus rifampicin 150 mg combination tablets. This combination will be given from Weeks 9 to 26. **Instructions for Dosing Control Treatment Regimen** To be taken with a glass of water (approximately 240 ml). HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes: Treatment will be administered orally once daily to the HRZE/HR randomized DS-TB participants as follows: **Weeks 1-26:** HRZE/HR tablets daily dose per the participant's weight as follows: **Weight Band** / **Weight Range** / **Number of tablets** 1 / 30-39 kg / 2 2 / 40-54 kg / 3 3 / 55-70 kg / 4 4 / ≥ 71 kg / 5 The participant's weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and HRZE and HR dose to administer. Vitamin B6 daily supplement to be taken with the HRZE/HR treatment, as per each country's TB Treatment Guidelines.
Treatment Interruptions/Pauses	**For All Trial Regimens** The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation, unless an interruption/pause is required urgently for a safety concern. Action required for participants missing the following number of doses within the trial treatment regimens: • Up to 7 consecutive doses: restart treatment, no extension of treatment required. • If more than 7 and to ≤ 35 consecutive doses missed, before the end of the treatment period (Week 17/26): restart treatment, extend the treatment by the number of consecutive doses missed. In this case, the last visit of the treatment period should also be pushed out to the date of the last dose.

Synopsis	Description
	• If more than 35 consecutive doses: discontinue treatment and withdraw participant from the trial. • If the participant misses a total of 56 cumulative missed doses, discontinue the IMP and withdraw the participant from the trial. • If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose, that was missed. Any participant for whom the trial IMP is discontinued (including for non-adherence) should be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial IMP as soon as possible.
Statistical Methods	A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP) which will be written and signed off prior to the interim analysis. **Criteria for Evaluation** **Primary Endpoint** The primary efficacy endpoint will be time to culture negativity over 8 weeks. The primary hypothesis to be evaluated is: • In the participants with DS-TB in the experimental BPaMZ treatment regimen, the time to culture negativity by 8 weeks will be superior, compared to the participants who are treated with the standard HRZE/HR regimen. **Secondary Endpoints** • A key secondary efficacy endpoint will be the proportion of participants experiencing bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks. The hypothesis to be evaluated for this endpoint is: • In the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen. <u>Abbreviated Definitions, full definitions will be described in the Statistical Analysis Plan (SAP)</u>:

Synopsis	Description
	• Bacteriologic failure: During the treatment period, failure to attain or maintain culture conversion to negative. • Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status, with culture conversion to positive status with a strain of *Mycobacterium tuberculosis* (MTB) genetically identical to the infecting strain at baseline. • Clinical failure: A change from protocol-specified TB treatment to a new regimen before end of protocol specified treatment due to treatment failure, retreatment for TB during follow up, or TB-related death. <u>Note</u>: o Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart. o Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit. **Other Secondary Endpoints** <u>Efficacy</u>: • Incidence of bacteriologic failure or relapse or clinical failure at 104 weeks from the start of treatment. • Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of treatment. • Change from baseline in weight. • Change from baseline in TB symptoms. • Change from baseline in Participant Reported Health Status. <u>Safety and Tolerability:</u> • Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death. • Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline. • Quantitative and qualitative electrocardiogram (ECG) results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read. • Changes in male reproductive hormones.

Synopsis	Description
	• Changes in lens opacities. These data will be presented as descriptive analyses, and no inferential tests will be carried out. <u>Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD):</u> Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [C_{min}], maximum plasma concentration [C_{max}], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of concomitant medications, including antiretroviral therapy (ART), where feasible. Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate. <u>Exploratory Objectives:</u> Evaluate whether any of the secondary endpoints predict relapse free cure. Subgroup analysis of populations by HIV status will be performed. No formal statistical comparisons will be made for the participants enrolled with DR-TB. **Sample Size** <u>Primary endpoint</u>: 150 participants per arm (DS-TB patients) will provide at least 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. Additional efficacy parameters will be evaluated including the incidence of bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks and 104 weeks from the start of treatment. Time to unfavourable outcome from assignment of trial treatment through follow-up as a function of time will be analysed using Kaplan-Meier analysis.

Synopsis	Description
	Interim Analysis There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size: If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows: • **Primary Objective** *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.* • **Secondary Objective** *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.* All other trial objectives will remain unchanged. To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46, 47, 48] and full details are provided in the Statistical Analysis Plan.
Trial Duration	Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until 104 weeks from start of treatment). Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms are complete.

1.2 Synopsis Flow Chart and Procedures

Period	Screening[a]	Treatment															Follow-Up[c]					
Visit[b]	Day -9 to -1	Day 1 (Baseline)[d]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 17 *4-mth treatment*[e]	Week 17 *6-mth treatment*[e]	Week 22	Week 26 *4-mth treatment*[e]	Week 26 *6-mth treatment*[e]	Week 39	Week 52	Week 65	Week 78	Week 104	Early Withdrawal[c]
Visit Window[v]	N/A	+/- 3 Days									+/- 5 Days						+/- 14 Days					
Written Informed Consent	X																					
Demography	X																					
Medical/Treatment/ Smoking History	X																					
Inclusion/Exclusion	X	X																				
Sputum Sampling[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Status[h] and CD4 Count[i]	X																					
Karnofsky Score[x]	X																					
Urine Drug Screen[j]	X																					
Urine Pregnancy Test[k]	X	X								X		X	X		X	X						X
Laboratory Safety Test[l]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X						X
Male Reproductive Hormone Tests[m]	X	X											X		X		X					
12-lead ECG[n]	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X					X
Chest X-Ray[o]	X																					
TB Symptoms Profile	X	X		X		X				X		X	X		X	X		X			X	X
Patient Reported Health Status	X	X		X		X				X		X	X		X	X		X			X	X
Vital Signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination[p]	X											X	X		X	X	X					X
Physical Examination – full[q]	X	X										X				X						X
Physical Examination – limited[r]			X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Pharmacokinetic Sampling[s]		X		X						X	X	X	X				X		X	X	X	
IMP Randomization/ Assignment[t]		X																				
IMP Compliance Check[u]			X	X	X	X	X	X	X	X	X	X	X	X[e]		X						X[t]
Concomitant Medications	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
Investigator Assessment[v]																		X			X	

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

a. **Screening:** Screening assessments can occur on different days, within nine days before Day 1 (Baseline).

b. **Visit Schedule (due to unforeseen circumstances):** If the duration of treatment is extended due to dose interruptions / pauses (7 to ≤ 35 consecutive doses), the last visit of the corresponding treatment period should also be pushed out to the date of the last dose. It is not necessary to have an unscheduled visit at the time that the last visit of the treatment period would have been scheduled on.

c. **Follow-up Visits for Early Withdrawal Participants:** Once a participant has been permanently withdrawn from the trial, they will be required to attend an Early Withdrawal visit (Week 52, if not already performed) and Week 104 follow-up visits. The Week 52 and Week 104 visits will be performed to collect Serious Adverse Event (SAE) information (including verification of survival) and the participant reported TB outcome information only, and may be performed telephonically, at home or a site visit. Visits will occur at Week 52 and/or Week 104 after the participant's start of treatment date. Refer to Table 5 for additional guidance.

d. **Day 1 (Baseline):** All procedures are to be completed before dosing.

e. **Last Visit of the Treatment Period:** Investigational Medicinal Product (IMP) Compliance Check is not performed at the Week 22 visit for participants who have completed treatment at Week 17.

f. **Sputum Sampling:** The sputum sampling methodology, requirements and tests will be described in a separate document, the Mycobacteriology Laboratory Manual.

- Screening (Days -9 to -1). Two spot sputum samples taken 30 minutes apart will be collected at the research site under the coaching and observation of the trial staff. The following analyses will be performed on the first of these samples:
  - Smear microscopy for acid-fast bacilli (AFB);
  - Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance (Hain MTBDRplus and Hain MTBRsl);
  - Liquid Culture (MGIT) for *Mycobacterium tuberculosis* (MTB), followed by a speciation test to detect the presence or absence of MTB and obtain the time to positivity (TTP) when positive.
  - The second sample is collected as a back-up sample to the first sample in case it is technically not possible to obtain a result/s from the first sample. If the Screening spot sputum smear shows an indeterminate result or is AFB negative, the test may be repeated on the back-up sample or on a freshly collected spot sputum, and then that result will be used.
- Day 1 (Baseline) to Week 104 and Unscheduled visits for additional sputum samples:
  - Two sputum samples are collected, ideally one Early Morning Sputum (EMS) brought from home and one spot sputum sample at the research site, under the coaching and observation of the trial staff. If the participant forgets to

bring in the EMS, then two spot sputum samples are to be collected at the site, at least 30 min apart, and this altered sample collection is captured within case report form (CRF).
    - If both sputum cultures at Week 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional sputum samples or to document that the participant is not able to produce a sputum sample.
- If after having converted to culture negative, and the participant has a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 or Week 26), the participant should return for unscheduled visit/s to provide additional sputum samples, at a minimum of 7 days apart, or to document that the participant is not able to produce a sputum sample.
- Additional samples may be required to define a participants' primary outcome status as described in Sections 5.4.2 and 7.2.
- Liquid Culture (MGIT) for MTB, followed by a speciation test to detect the presence or absence of MTB and obtain TTP when positive, will be performed on all samples.

g. **Mycobacteriology Characterisation Tests Performed:**

- Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative);
- MTB confirmed positive cultures (after the participant has previously converted to culture negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.
- Refer to the Mycobacteriology Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for:

- Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);
- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin;
- Drug Susceptibility Testing (DST) for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing (WGS), and comparison of sequences from baseline and relapse isolates.

h. **HIV Testing:** If HIV status is a confirmed known positive, a repeated HIV test is not needed provided that a documented HIV test result (ELISA, Western Blot or Electro-Chemiluminescence) is available. If the HIV status is unknown or suspected negative, a HIV test will be requested. If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated if documentation of testing method and negative HIV results can be provided. Repeated HIV testing, during the Screening period is permitted for indeterminate HIV results.

i. **CD4 Count:** Required for all HIV-positive participants.

j. **Urine Drug Screen:** Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at Screening only. Investigator to utilize this result to determine whether participant meets Exclusion Criteria 2. Positive results will not automatically exclude a participant from the trial.

k. **Urine Pregnancy Test:** Women of childbearing potential only, whether they are sexually active or not.

l. **Safety Laboratory Assessments**: The safety laboratory sampling methodology and requirements will be described in a separate document, the Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:

- Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count).
- Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/carbon dioxide [CO_2], creatine phosphokinase [CPK]). GGT is only routinely included at the Screening visit (Day -9 to -1).
- 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.
- When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

m. **Male Reproductive Hormone Tests:** Testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin B to be done on male participants in ALL treatment groups.

n. **Single 12-Lead ECG:** ECGs to be performed prior to pre- and post-dose PK sampling as described below:

- Day 1: pre-dose (within 2 hours prior to dosing)
- Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 12: pre-dose (within 2 hours prior to dosing)
- Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose

Central ECG analysis will be performed. Results from central reading of Screening ECG must be used to determine eligibility.

o. **Chest X-Ray:** A chest x-ray (digital image only) within 6 months prior to or at the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor and this process will be described in a separate document, the Radiology Manual.

p. **Slit Lamp Ophthalmic Examination**: Slit lamp examination will be done at the Screening visit, the last visit of the treatment period (Week 17 or 26) and at Week 39 for both treatment groups. An additional slit lamp at Week 26 will be done for the 4-month treatment group. Slit lamp ophthalmology examination will be performed by an

Ophthalmologist with AREDS2 training. Ophthalmology examinations may occur at any time within the window period for the applicable visit i.e. they do not have to be performed on the same day as the trial procedures.

q. **Physical Examination, Full:** Height (m) will only be collected at Screening.

r. **Physical Exam, Limited:** Limited physical exams will include weight and gross neurological, pulmonary, cardiovascular and abdominal exam(s).

s. **Pharmacokinetic (PK) Sampling:** This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE/HR treatment arm. Blood draws for PK samples collected pre- and post-dose must be done after the ECG is performed. The dates and times of IMP taken prior to all pre-dose PK samples will be collected. Specific PK blood draws will be obtained as follows:

- Day 1: pre-dose (within 2 hours prior to dosing)
- Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 12: pre-dose (within 2 hours prior to dosing)
- Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose
- Weeks 39, 65, 78 and 104: PK samples are to be obtained at any time on the day of the scheduled visit.

Only bedaquiline and M2 will be measured.

If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.

t. **Investigational Medicinal Product (IMP) Randomization/Assignment:** Randomization/Assignment may occur once all the Screening results are available and the Investigator has determined that the participant is eligible for the trial.

u. **IMP/Compliance Check:** IMP administration will be supervised per local site practice to assure compliance to the regimen. Performed at all visits and Early Withdrawal (EWD), if during the treatment period.

v. **Investigator Assessment:** Investigator to review the participant status and assess whether IMP or TB treatment at Week 52 and 104 is considered a “success” or “failure”. If considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed, at Week 52 and 104, <u>and at any time</u> the Investigator determines that the participant fulfils the criteria for outcome of treatment failure.

w. **Visit Windows**: The windows noted on the flowchart for timing of visit also apply to the timing *within a visit.* Procedures should be performed within +/- 3 days of scheduled visit from Day 1 to Week 8 or +/- 5 Days of scheduled visit from Week 12 to Week 26 or +/- 14 days of scheduled visit at or after Week 39. Sites should make every effort to ensure all procedures are done on the same day, when possible.

x. **Karnofsky Score**: Only to be performed on HIV+ participants.

2.0 Introduction and Rationale

2.1 Tuberculosis Disease

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in the developing countries of Africa, Asia and South America. TB is currently one of the top three killer infectious diseases, 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 40 years and are relatively ineffective in controlling TB as a public health problem. 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 participants, treatment takes 6 months or more to complete. This, long duration treatment **plus side effects**, result in poor adherence which particularly occurs after the second month of treatment.

The current TB treatment regimens and treatments for drug-sensitive TB are decades old. The available treatments have a lengthy duration of treatment, involve multi-drug therapy, and require large commitments of resources and infrastructure. High rates of noncompliance are common, which often results in increased mortality and chronic, infectious, drug-resistant cases. The present TB epidemic and the challenge of current treatment options demonstrate the clear need for effective novel TB drugs and **drug regimens** that are safe for drug sensitive and drug resistant TB disease and that are well-tolerated and will shorten the current treatment duration for patients.

The full application of the Directly Observed Treatment, Short-Course strategy is becoming more and more difficult in the developing countries of the world that are also battling to control the HIV-epidemic. Because of poor treatment adherence, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB are growing. Since the discovery of the rifamycins,[1] and their introduction into standard antituberculosis regimens, very few new classes of drugs have been evaluated with a view to their registration as antituberculosis agents. On December 28, 2012 the U.*S.* Food and Drug Administration approved bedaquiline (B) as part of combination therapy to treat adults with multi-drug resistant (MDR) pulmonary tuberculosis (TB) when other alternatives are not available. 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.

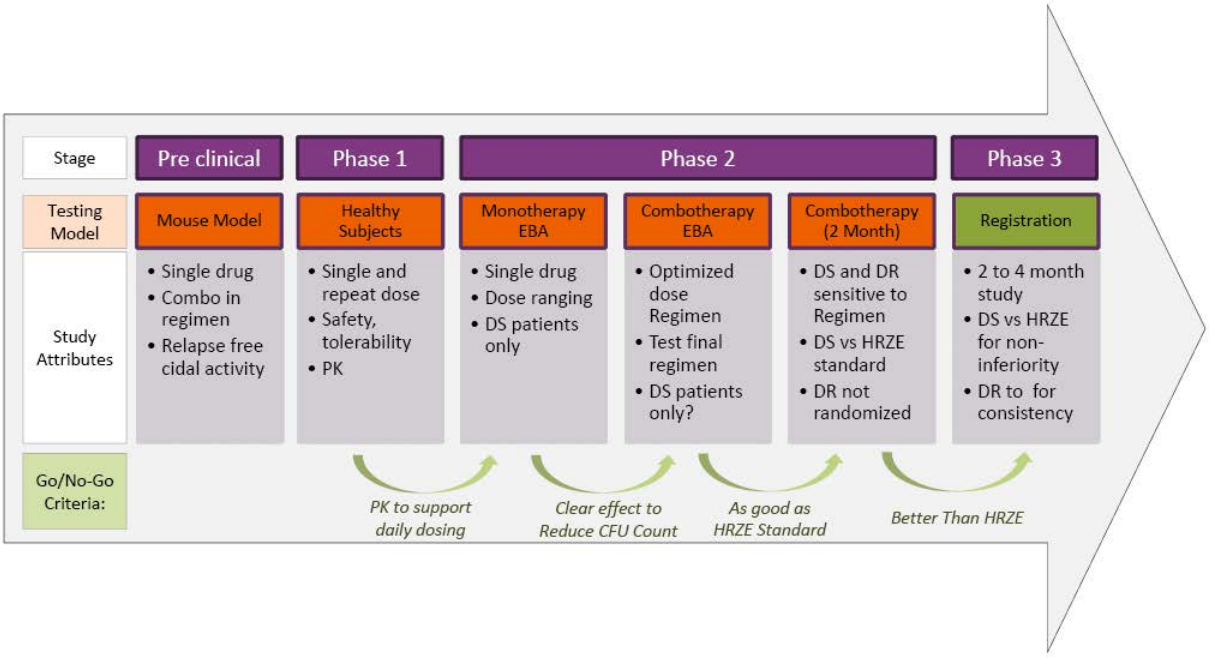
New combination regimens are desperately needed for two reasons: to shorten treatment to a duration more easily manageable by patients and public health services, and to provide more efficacious, safer and better tolerated, affordable treatments for the growing number of patients suffering from multidrug-resistant and extensively drug-resistant tuberculosis.

2.2 Tuberculosis Clinical Research

TB currently must be treated with multiple drugs to achieve maximal efficacy and prevent resistance. To transform treatment, novel TB regimens are needed. To telescope the time, it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm. This approach tests promising combinations of drugs together to find the most impactful treatment once the individual drug candidates have been tested in a robust pre-clinical program and the establishment of the individual drug candidates' safety and efficacy have been evaluated. It evaluates novel combinations of TB drugs — instead of single drugs — as part of a single development program, enabling the development of novel TB drug regimens that have

potential to transform treatment for drug-sensitive and drug-resistant tuberculosis. This approach offers the potential to reduce the time previously needed to develop a novel treatment regimen by up to 75%, shortening the clinical development from decades to years. The steps followed in this development model are shown in Figure 1 Between each step on the unified development pathway a decision is made as to whether to proceed.

Figure 1. Unified Drug Sensitive/Drug Resistant Regimen Development Path



Early Bactericidal Activity (EBA) Trials

EBA trials are the backbone clinical trials to quantify the bactericidal action of anti-tuberculosis agents alone or in combination by either trialling the fall in the number of colony forming units (CFU) or measuring the TTP in liquid culture of *M. tuberculosis* (*MTB*) present in the sputum of participants with microscopy smear-positive pulmonary TB. EBA trials have been conducted over 2, 5, 7 and 14 days.[2]. A review of EBA trials conducted on the key anti-TB drugs has shown the value these trials offer to demonstrate the early anti-TB effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in participants.[3]

8-week Bactericidal Activity (BA) Trials

EBA methodology of quantitative colony counting on solid medium has been adapted to Phase 2, 8-week TB treatment trials based on serial sputum colony counting (SSCC) or measurement of TTP liquid culture to provide a more sensitive efficacy endpoint than the previously used binary endpoint of rate of sputum conversion measured after 8 weeks of treatment.[4-6] Such trials are conducted to provide data on which to base the selection of treatment-shortening regimens.

2.3 Trial Rationale

The SimpliciTB NC-008 (BPaMZ) trial will evaluate and support that, in addition to previous studies evaluated with BPaMZ, this drug regimen will be safe and effective, is well-tolerated and could potentially shorten the current treatment duration compared to the standard HRZE/HR treatment for patients with drug sensitive TB disease. This trial will also evaluate if the BPaMZ drug regimen given for 6 months will be safe and effective in drug resistant TB disease.

Therefore, the trial design addresses the need to find and evaluate a potentially effective and shorter regimen compared to regimens (standard HRZE/HR) that are currently being used.

2.3.1 Trial Design Rationale

The SimpliciTB NC-008 (BPaMZ) trial is a Phase 2c multi-centre, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. This trial is to evaluate the combination regimen of **Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) plus Pyrazinamide (Z)** (BPaMZ), in participants with pulmonary TB.

All participants will enter post-treatment follow-up which continues until Week 104 after start of treatment / randomisation.

Participants with DS-TB:

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either:

- BPaMZ daily for 17 weeks (4 months),

OR

- HRZE/HR combination tablets daily for 26 weeks (6 months).

Participants will be stratified for co-infection with HIV and cavitation.

Participants with DR-TB are defined as:

1. mono-resistance to rifampicin or isoniazid, OR
2. resistance to both rifampicin and isoniazid (multi-drug resistant tuberculosis [MDR-TB])

Up to 150 participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months). Approximately 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation to either BPaMZ for 4 months or HRZE/HR for 6 months.

The trial is sufficiently statistically powered to not only show superiority of 8 Weeks culture conversion but should also demonstrate non-inferiority for cure at 52 Weeks (this is in the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen).

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary

endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

  *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objectives**

  *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46, 47, 48] and full details are provided in the Statistical Analysis Plan.

As previously described in the background information, in order to telescope the time it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm and utilize data generated in non-clinical and clinical studies regarding combining of anti-tuberculosis agents which could contribute significantly to the sterilization of lesions and thus treatment shortening. Therefore, the trial design and proposed trial regimen (BPaMZ) which is supported with previous non-clinical and clinical studies outlined below should address the need and manner of evaluating an effective shorter regimen compared to regimes that are currently being used.

2.3.2 Trial Drug Regimen Rationale

The BPaMZ regimen has been studied singularly and in different combinations as outlined above. Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. It essentially provides protection against the development of new resistance to the B-Pa-Z drugs. Based on the exciting and promising results seen in NC-005, this regimen can be initiated in drug sensitive and drug resistant TB participants whom are sensitive to the individual drugs in the regimen (excluding extensively drug-resistant tuberculosis [XDR-TB] and Pre-XDR tuberculosis) and has the potential to shorten TB treatment to less than 4 months in drug sensitive TB. These are also oral regimens, removing the need for injectables as part of MDR-TB treatment, and also project to be markedly less expensive than current MDR-TB therapy. Additionally, these regimens can be administered in a fixed dose for all patients and will therefore be simpler for health systems to deliver and patients to use.

2.4 Agents used within SimpliciTB

Bedaquiline (TMC207; Sirturo™ package insert)[7] is a novel agent approved for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[9, 10]) *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. Tb* isolates,[10, 11], and is also bactericidal against non-replicating *M. Tb.*[12] In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. Tb*.[3, 4] 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.[13] 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 DS- and MDR-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[13] and in a subsequent trial it was more active in the mouse model than HRZ.[14] Thus, a novel regimen with a 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.

Pretomanid, (Pa)[15] is a new chemical entity being developed by TB Alliance for the treatment of TB. It is 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 has been under development for several years and entered clinical trials in 2005. Several trials of pretomanid have also been conducted previously in healthy volunteers. Collectively, these trials in participants with active TB and healthy participants have defined the efficacy, safety and pharmacokinetic features of the drug. Overall, pretomanid has mycobactericidal activity in participants and is well tolerated and bioavailable after oral dosing. Pretomanid demonstrated in vitro activity against both drug-sensitive (DS) and MDR-TB,[17] and in vivo activity in a mouse model of TB[17, 18] with a significant promise for shortening treatment of active TB.

Moxifloxacin (M)[19] is a microbial compound, approved in most countries around the world for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and soft tissue infections. Clinical studies have been carried out for many additional indications (urinary tract infections, pelvic infections, pharyngitis/tonsillitis, and tuberculosis). Moxifloxacin is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by or induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the MTB strain is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]" It is currently in late stage clinical

development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

Pyrazinamide (Z)[20] is a pyrazine analogue of nicotinamide and an approved anti-tuberculosis agent which is indicated for the initial treatment of active tuberculosis in adults and children when combined with other anti-tuberculosis agents and contributes significantly to the sterilization of lesions and thus treatment shortening.[21]

Control Group: HRZE/HR

The **HRZE/HR** combination [HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets] is approved indicated and commonly used as a 6-month treatment for drug-sensitive TB patients. Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE. Please see the HRZE package insert for more information.[22]

Additional background data supporting the combined use of new novel agents in this BPaMZ regimen for the treatment of TB:

Data from preclinical studies suggest that a regimen consisting of moxifloxacin plus pretomanid plus pyrazinamide may not only be appropriate for treating both DS and MDR-TB but may also **shorten duration of therapy**. Results from an 8-week Phase 2b SSCC trial, NC-002-(M-Pa-Z), showed that this **combination regimen** was effective as measured by time dependent decline of viable bacteria in participants with DS pulmonary TB. The combination was also shown to be safe and well tolerated supporting the evaluation of this combination in a Phase 3 trial. In this NC-002 trial 71.4% of participants with DS-TB treated with PaMZ at the 100-mg daily dose of pretomanid converted sputum to negative for *MTB* growth in liquid culture in comparison with only 37.8 % of participants treated with the HRZE control ($p<0.05$).

Studies in mice infected with *MTB* demonstrated reductions in cultured colony counts from lungs over an 8-week period when treated with the PaMZ regimen that were substantially, and statistically significantly greater, than the reductions in mice treated with an HRZ control. Experiments in mice found that mice did not relapse with MTB infection when treated with PaMZ for 4 months and followed for 3 months off treatment, in comparison to mice that required 6 months of treatment with HRZ to prevent relapse.[14]

Drug Resistant TB Background:

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in many countries. TB is the world's leading cause for mortality from infectious disease and is responsible for more deaths than HIV.[23] 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. Because of poor treatment adherence, in addition to primary transmission, **drug resistance** is becoming more common and fears of an epidemic with strains of extensively drug-resistant TB (XDR-TB) that is very difficult to treat are growing. Novel drugs and regimens for TB are needed for the growing number of patients with drug resistant-TB.

The regulatory approvals of bedaquiline and delamanid have given hope that outcomes for patients with drug resistant TB might be improved when added to background regimens. Experience recently published from the C209 uncontrolled trial of bedaquiline given on a

background of multiple drugs notes that the subset of 38 participants with XDR-TB had rates of sputum culture conversion to negative of 62.2%.[24] However, in this trial only one participant with XDR-TB was co-infected with HIV. All participants were required to have Mycobacterium tuberculosis (MTB) isolates susceptible to at least 3 drugs at enrolment and participants had a median of only 5.4 months of treatment-free follow-up. This trial added bedaquiline for 6 months to a background regimen of many drugs given for 18 months or longer. While treatment success for MDR-TB is better than for XDR-TB, **overall success in treating MDR-TB is still approximately 50%** according to the World Health Organization 2015 Global TB Report.[23] This report presented that overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, 10% failed treatment, and for 8% there was no outcome information.

With such poor historical outcomes for patients with drug resistant-TB and with the complexity, expense and toxicity of treatments for all forms of drug resistant TB, **novel drug combinations are desperately needed to improve treatment outcomes**. Linezolid was identified in a small trial as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen[25] and this drug has increasingly been added to complex regimens to treat patients with MDR-TB.

With the current availability of the following three drugs for which there is little, if any, pre-existing resistance among strains of MTB (pretomanid [Pa], bedaquiline [B], and linezolid [L]). Mice infected with MTB had relapse-free cures with 3 months of treatment with a B-Pa-L regimen. While it is not known whether that treatment duration will translate to humans, the ongoing Nix-TB clinical trial hypothesizes patients with pulmonary XDR-TB or MDR-TB not responsive to or intolerant to therapy may have relapse-free cure after as little as 6 months' treatment with the B-Pa-L regimen.[26] Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. The proposed trial [SimpliciTB] allows the opportunity to assess the efficacy, safety and tolerability of BPaMZ, a new 6 months regimen that may be administered orally once daily to treat patients with drug resistant -TB (excluding participants with XDR-TB).

Therefore, the **overall purpose** of the present proposed trial **[SimpliciTB]** is to assess the efficacy, safety and tolerability of the **BPaMZ** regime after 4 months of treatment in adult participants with drug sensitive TB and after 6 months of treatment in participants with multi drug-resistant TB. The trial will also generate data of the potential for a shorted treatment duration with the **BPaMZ** regime after 4 months compared to a 6-month **HRZE/HR** (control) treatment regime in adult participants with drug sensitive TB.

This trial will be conducted in accordance with the Protocol, ICH Guidelines for Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirement(s).

2.5 Background of Agents to be Studied in SimpliciTB

2.5.1 Bedaquiline (B)

Bedaquiline (formerly known as TMC-207; Sirturo™ package insert[7]) is approved agent for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[11] In vitro, bedaquiline potently inhibits both drug-sensitive and

drug-resistant MTB isolates,[11, 12] and is also bactericidal against non-replicating MTB[12] 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 MTB.[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.[27].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[27] and in a subsequent trial it was more active in the mouse model than HRZ.[28]. 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.

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as 200 mg daily for 8 weeks, followed by 100 mg daily for the remaining 17 weeks or 30 weeks if treatment is extended. This daily dosing scheme will allow more convenient dosing that should ultimately enhance patient adherence and may allow the formulation of fixed dose combinations with other drugs. This daily dosing regimen is supported by safety and efficacy demonstrated in the NC-005 trial that administered bedaquiline 200 mg daily over 8 weeks, and by pharmacokinetic modelling and simulation of the daily dosing scheme. This supportive information is detailed below.

2.5.1.1 Bedaquiline Non-Clinical Studies

Full details of the preclinical studies are provided in the current bedaquiline Investigator's Brochure,[8] and Sirturo ™ label.[7] *In vitro* studies have demonstrated that the range of minimum inhibitory concentrations (MICs) for MTB 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 MTB. 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 MTB but 3-6 times less active than the parent compound bedaquiline. Bedaquiline demonstrated similar *in vitro* efficacy against MTB 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 International Council for Harmonisation (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.[8]

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 and ECG parameters.

Prior to the use of pretomanid in combination with bedaquiline in clinical trial NC-001, a preclinical cardiovascular safety pharmacology trial 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.[28] 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) Investigators Brochure for more detail.

2.5.1.2 Bedaquiline Clinical Studies

In the clinical studies conducted to date, a total of approximately 645 participants (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 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001, and 45 more in trial NC-003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). Four short-term Phase 2a trials enrolled treatment-naïve participants (C202, TMC207-CL001, NC-001 and NC-003). One long-term, open-label, Phase 2 trial, in MDR-TB participants (bedaquiline-TiDP13-C209) and one long-term, Phase 2b trial, consisting of 2 different stages in participants 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,[8] and Sirturo™ label.[7].

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

participants. 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 trial, 800 mg single dose in trial 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 participants and participants 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 ȧ 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 participants 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 trial (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 trial (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. Trial C202 was a 7-day trial of three daily doses of bedaquiline (25, 100 and 400mg) in treatment-naïve participants with MDR-TB. In this trial, the 400mg dose group demonstrated positive EBA and was numerically superior to the 25 and 100mg doses. In trial TMC207-CL001, doses of 100, 200, 300 and 400mg daily (following a 2-day loading dose) were studied in participants 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 participants with TB and that higher doses appear to have greater efficacy.

A 14-day EBA regimen trial (TB Alliance Trial 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 participants 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 participants given bedaquiline 400 mg/d after a 2-day loading dose. In the cohort of 15 participants 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 participants 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 trial (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 participants 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 participants in the bedaquiline group became MGIT culture negative compared to 8.7% of participants 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 participants in the bedaquiline group and 65.2% of participants 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 participants 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 participants. Culture conversion rates after 2 weeks of treatment with bedaquiline as part of an individualized anti-tuberculosis regimen were higher in participants with lower extent of resistance of the M. Tb strain and in participants with no lung cavitation compared to participants with cavitations (in one or both lungs).

2.5.1.3 Bedaquiline Clinical Safety

In the clinical trials conducted to date, a total of approximately 645 participants (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 participants received bedaquiline in a monotherapy EBA trial of 14 days (trial TMC207-CL001) 45 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001 and 45 more in trial NC- 003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). In these trials, bedaquiline has been shown to be an effective treatment for participants 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 trial 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 trials, 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 participants) 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

SOC ADR (Grouped term), n (%)	Investigational Treatment Phase Controlled Trials TMC207 24 Weeks N = 79	 Any N = 102	 Placebo 24 Weeks N = 81	 Any N = 105
At least grade 3 ADR	*5 (6.3)*	*5 (4.9)*	*0*	*0*
Nervous system disorders	**1 (1.3)**	**1 (1.0)**	**0**	**0**
Headache	1 (1.3)	1 (1.0)	0	0
Cardiac disorders	**0**	**0**	**0**	**0**
ECG QT Prolonged	0	0	0	0
Gastrointestinal disorders	**0**	**0**	**0**	**0**
Diarrhea	0	0	0	0
Vomiting	0	0	0	0
Hepatobiliary disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Transaminases increased [a]	2 (2.5)	2 (2.0)	0	0
Musculoskeletal and connective tissue disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Arthralgia	2 (2.5)	2 (2.0)	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 participants in the Any bedaquiline group and 5 participants 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 participants 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 participants (12.7%) compared to 3 placebo participants (3.7%). Based on the pooled results (Stage 1 and 2) while being followed in the placebo- controlled trial, 7 participants in the Any bedaquiline group and 1 Participant 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 haemoptysis. 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 participants 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 Participant in the bedaquiline group (pulmonary TB) and 2 participants in the Placebo group (TB-related illness and pulmonary TB) in Stage 1 died, and 4 participants in the bedaquiline group (3 participants with TB-related illness, 1 Participant motor vehicle accident) and 2 participants in the Placebo group (both TB-related illness) died after they discontinued Stage 2 of the trial. None of these participants 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, diarrhoea, blood uric acid increased, hypokalaemia, pruritus, injection site pain, insomnia, and tinnitus. From start of the trial up to the final analysis, 12 participants 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), haemoptysis, hypertension, and pyopneumothorax/respiratory failure. 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 participants 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 participants (6.9%) have died (12 participants during the trial and 4 participants 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 participants 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[7] notes that treatment initiation is not recommended in patients with:

- Heart failure;
- QTcF interval > 500 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).
- Hypokalaemia

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. If 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. participants should be monitored during treatment. Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in those participants with diminished hepatic reserve.[7]

Additional safety information from a recently completed trial

In a recently completed phase I trial not yet included in the bedaquiline Investigators Brochure that evaluated drug-drug interactions between bedaquiline and either rifampin or rifabutin, 7

participants experienced SAEs. Of those participants, 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 participant 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.

2.5.2 Pretomanid (P)

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]

2.5.2.1 Pharmacology

Key in Vitro Evaluation of Pretomanid Bactericidal Activity

Non-clinical in vitro trials demonstrated that pretomanid was active against actively growing drug-sensitive and drug-resistant MTB strains as well as against non-replicating MTB. The minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive MTB isolates *in vitro* was shown to be like the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of MTB with MIC values ranging from 0.03 to 0.53 µg/mL. The Investigator's Brochure contains further information on *in vitro* bactericidal activity.[16]

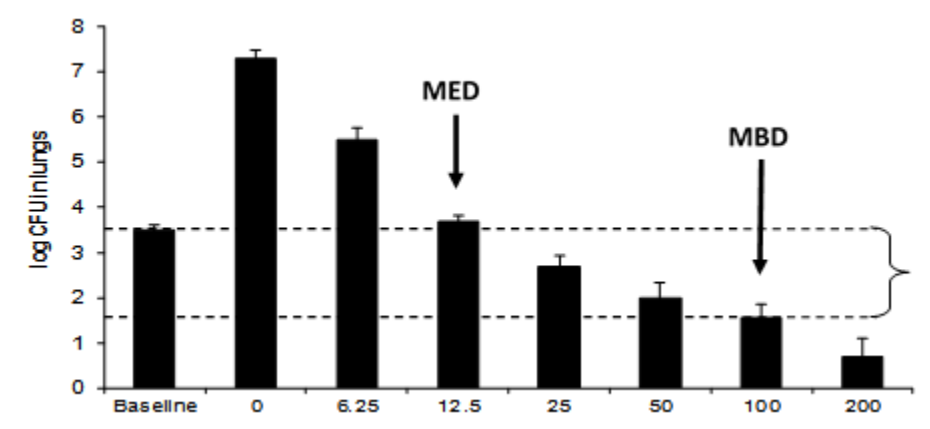
Although not thoroughly elucidated at this time, pretomanid has a novel mechanism of action that appears to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reduction of pretomanid by a deazaflavin (F420)-dependent nitroreductase has been shown to be associated with generation of reactive nitrogen species, including nitric oxide (NO),[29] although the exact target(s) of the reactive nitrogen species are not known. Transcriptional profiling trials also suggest that pretomanid affects both cell wall biosynthesis and the respiratory complex of MTB.[30, 31]

2.5.2.2 Key Non-Clinical Trials of Pretomanid

The activity of pretomanid as a single agent or as part of a multi-drug combination regimen has been examined in a number of mouse trials.[13, 14, 18, 32, 33] In a mouse model of established TB, the activity of various doses of pretomanid (given once daily, 5 days/week, for 1 month), initiated 22 days after inhalation infection with H37Rv MTB is shown in Figure 2. In this model, the minimum effective dose (MED) for pretomanid, defined as the lowest dose able to prevent the development of gross lung lesions and splenomegaly, was 12.5 mg/kg/day, while the minimum bactericidal dose (MBD), defined as the lowest dose able to reduce lung colony forming units (CFU) by 99%, was 100 mg/kg/day. Moreover, in these experiments, the activity of pretomanid at 100 mg/kg was comparable to the activity of isoniazid at 25 mg/kg.

Figure 2. Log10 CFU Counts in Lungs

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



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

2.5.2.3 Non-Clinical Toxicology and Safety

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

In the repeat-dose toxicity trials, the lowest no-observed adverse effect level (NOAELs) was 10 mg/kg/day in a 26-week trial in rats, 50 mg/kg/day in a 13-week trial in monkeys and <25 mg/kg/day (based on findings of thickening of the gastrointestinal tract at all doses) in a 9-month trial in monkeys. The major findings in safety and toxicity trials are listed below in Table 2 and are detailed in the Investigator's Brochure.[15]

Table 2. Key findings of Pretomanid in Safety and Toxicity Trials

Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behaviour at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
Testicular toxicity Although rat and rabbit embryonic development trials indicate no effects of pretomanid on foetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose toxicology trials and a Segment I fertility trial. In this fertility trial, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower

dose not associated with testicular atrophy. A detailed trial in sexually mature male monkeys demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing.
Cataracts Cataracts developed in rats with prolonged daily administration of pretomanid at doses ≥100 mg/kg/day. In one 13-week trial 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 trial in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.
hERG inhibition and QT prolongation Altered ventricular repolarisation due to inhibition of hERG-mediated potassium current and manifested on the ECG as a prolonged QT interval corrected for heart rate (QTc). Pretomanid inhibited hERG current with IC50 values of approximately 6.2 µg/mL. Following a single pretomanid dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Co-administration of pretomanid with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at pretomanid doses of ≥150 mg/kg/day.

2.5.2.4 Clinical Background Information

Pretomanid has been evaluated in 8 single- and multi-dose Phase 1 trials with healthy adult male and female participants, with 163 participants receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 7 days. These Phase 1 trials have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid. Two additional Phase 1 trials Sponsored by the NIH included a Thorough QT trial and a trial of drug interactions among pretomanid, efavirenz and ritonavir/lopinavir. Further details of the trials are in the Investigator's Brochure.[15]

2.5.2.5 Pharmacokinetics

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

Drug interaction with midazolam: Trial CL-006 was an open-label, fixed-sequence drug-drug interaction trial to evaluate the effects of multiple-dose administration of pretomanid on the PK of midazolam, a sensitive probe substrate and representative compound for drugs metabolised by CYP3A enzymes. Dosing with pretomanid at 400 mg/day for 14 days (to steady state) had minimal effect on the PK of midazolam and its 1-hydroxy metabolite as assessed by measurement of the Day 17: Day 1 ratios of maximum concentration (C_{max}, AUC_{0-t}, and AUC_{0-inf}. The C_{max} and AUC values for midazolam after co-administration with pretomanid were approximately 85% of those

observed after treatment with midazolam alone. Furthermore, midazolam and 1-hydroxy midazolam time to maximum concentration (T_{max}) and half-life ($t_{1/2}$) values were not different in the presence or absence of pretomanid. Therefore, 14 days' dosing with 400 mg/day pretomanid does not appear to significantly inhibit CYP3A4 in humans.

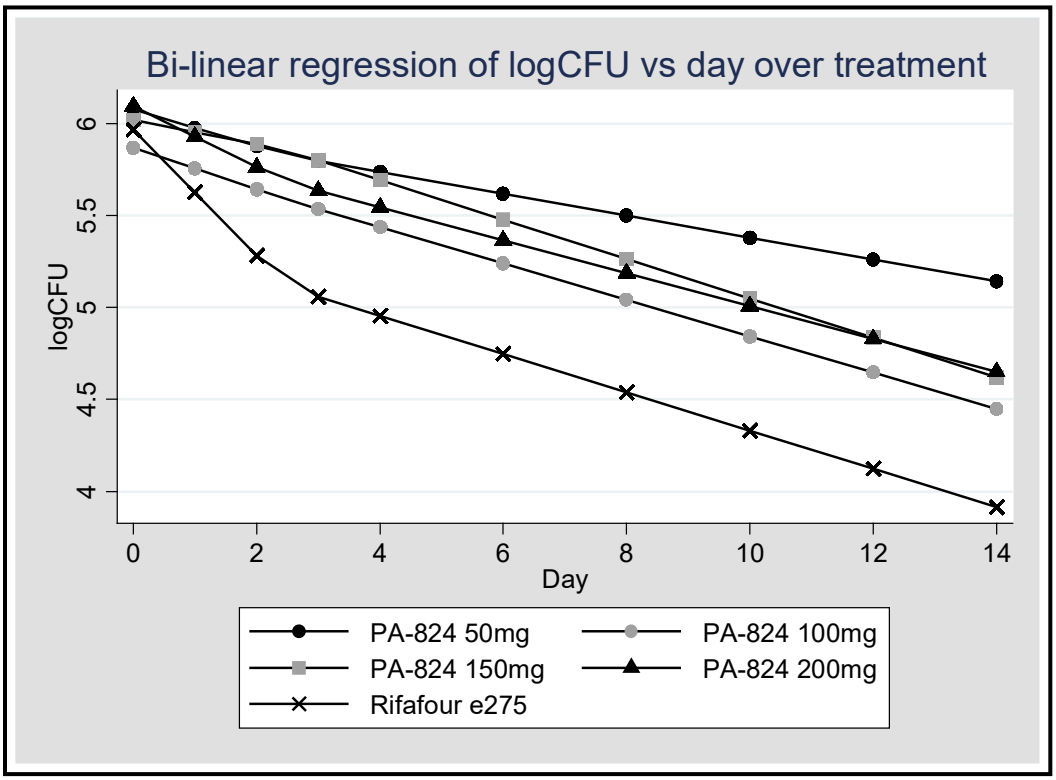
Drug interaction with efavirenz, ritonavir/lopinavir, and rifampicin: The US NIH Sponsored this drug interaction trial with rifampicin, a known hepatic enzyme inducer, and with the antiretroviral drugs efavirenz and ritonavir/lopinavir (LPV/r) in healthy participants. Participants in Arm 1 were randomised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

In conclusion, compared to pretomanid alone, plasma pretomanid values (based on geometric mean ratios) for C_{max}, $AUC_{0\text{-}24h}$, and C_{min} were reduced 28%, 35%, and 46% with efavirenz; 13%, 17%, and 21% with LPV/r; and 53%, 66%, and 85% with rifampicin, respectively.

2.5.2.6 Pretomanid Clinical Efficacy

The first two Phase 2 trials to evaluate the early bactericidal effect (EBA) of pretomanid oral monotherapy (50 to 1200 mg/day for 14 days) examined the dose-response for pretomanid in participants with newly diagnosed pulmonary TB infection. The first trial (CL-007) demonstrated good EBA, but all doses in this trial (200 to 1200 mg/day) had the same activity. The second trial (CL-010) evaluated a lower dose range (50 to 200 mg/day) and the maximum effect on EBA was seen at a dose of 100 mg/day over 14 days (Figure 3).[34]

Figure 3. Mean log Colony Forming Unit Values over Time Trial CL-010



CFU = colony-forming unit; PRETOMANID = pretomanid

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

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

2.5.2.7 Pretomanid Clinical Safety

The pretomanid Investigator's Brochure[15] provides detailed safety information.

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

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

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

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

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

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

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

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

- Central Nervous System Safety –While pretomanid alone or combined in various regimens has been well tolerated overall, one participant in Trial NC-002 of the Pa-M-Z regimen had a seizure without any prior seizure history, and some animals in toxicology trials have had

seizures at high drug exposures. Consequently, close surveillance will be made of participants in the Phase 3 trial for seizures or any central nervous system adverse events of potential concern.

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

2.5.3 Moxifloxacin (M)

Moxifloxacin (M)[19] is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by nor induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that “all patients [with MDR-TB] should receive a Group 3 medication if the strain of MTB is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]” It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

2.5.3.1 Moxifloxacin Clinical Trials

Moxifloxacin is commonly used as second line therapy for TB (e.g. MDR- TB) and has also been evaluated in several clinical studies of participants with TB, including four 8-week treatment period Phase 2b studies (see Table 3 below).

Table 3. Summary of Phase 2b trials in which moxifloxacin were administered as part of a four-drug regimen during the intensive phase of treatment (total treatment duration: 2 months)

Trial	Design	Objective	Participants (N)	Status
Trial 27	Randomized, double-blind, controlled	To compare the sputum culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using the standard 4-drug regimen HRZE with a standard regimen with M replacing E.	336	Completed
OFLOTUB Trial	Randomized, Open label, Controlled	To compare the bactericidal activities of regimens where gatifloxacin, M, and ofloxacin were substituted for E in the 2-month initial phase of standard TB treatment with HRZE.	217	Completed
Johns Hopkins (FDA orphan drug) Trial	Randomized, double-blind, Controlled	To compare the sputum culture conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE) with a regimen with M replacing E (HRZM).	170	Completed
Trial 28	Randomized, double-blind, Controlled	To compare the culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE 5 days per week) with a regimen with M replacing H (MRZE 5 days per week).	433	Completed

2.5.3.2 Moxifloxacin Clinical Safety

In Trial 27,[35] the moxifloxacin-containing TB regimens (HRZM) were shown to be safe and well tolerated. There was no difference in SAEs between the HRZM and HRZE treatment arms, and most SAEs were hospitalizations thought to be unrelated to the trial treatment. Participants treated with the moxifloxacin-containing regimen were more likely to report nausea (22% vs. 9%, p = 0.002), but this was generally mild and did not lead to treatment discontinuation as similar proportions of participants in both groups completed trial drug treatment (88% HRZM-treated vs. 89% HRZE-treated). The one death during the first 2 months of treatment was thought to be caused by a pulmonary embolism unrelated to tuberculosis therapy.

In the OFLOTUB trial,[36] AEs and SAEs occurred with equal frequency in the four treatment arms. The most frequent AEs were raised amylase (in 41% of participants due to HIV infection), raised transaminase (10%), arthralgia (9%), anaemia (7%), hypokalaemia (6%) and vomiting (5%). No Participant was withdrawn from the trial due to an adverse event. There were 4 deaths in the trial: 2 in the control group, 1 each in the moxifloxacin and ofloxacin arms. Importantly, participants in this trial who received moxifloxacin and pyrazinamide in addition to isoniazid and rifampin had more rapid sputum clearance than participants on the four standard first line drugs

(isoniazid, rifampin, pyrazinamide and ethambutol). This difference was evident 14 days after initiation of treatment.

In the JHU trial,[37] AEs did not differ by treatment group. There were 16 SAEs (8 in each group) in 12 participants. Only 1 event was judged related to trial drug (grade 3 cutaneous reaction in the ethambutol group). Eight participants died during the trial, including 1 in each group still receiving trial phase treatment. No death was attributed to trial treatment. Only 5 participants discontinued treatment because of toxic effects; 2 participants in the moxifloxacin group stopped because of grade 2 nausea and vomiting and 1 because of grade 2 paraesthesia's and ataxia. Two participants in the E group stopped because of grade 2 rash and pruritus and 1 because of grade 3 peripheral neuropathy. There was no change in the QTc interval on serial electrocardiograms taken during the trial.

In Trial 28,[38] the proportions of participants with SAEs during the intensive phase treatment were similar between arms (isoniazid 3.9% vs. moxifloxacin 4.2%; P = 0.88). Three SAEs attributed to trial treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group. Seven participants died during the trial including 3 participants receiving the moxifloxacin treatment regimen and 4 participants receiving the isoniazid treatment regimen. The 3 moxifloxacin participants died during the intensive phase of TB treatment. Two participants died from advanced pulmonary TB judged not related to trial treatment and 1 Participant (who developed diabetic ketoacidosis considered possibly related to trial treatment) died from possible acute pulmonary embolus unrelated to trial treatment. The 4 isoniazid deaths occurred during the continuation phase, and all 4 were considered unrelated to trial treatment. Nausea was more common among participants in the moxifloxacin arm than in the isoniazid arm (19.6% vs. 11.7%, respectively; P = 0.03) although similar proportions reported vomiting. However, the proportions of participants with hepatitis, defined as serum AST 3 times or greater than the upper limit of normal, were similar between treatment arms during intensive phase (isoniazid 3.4% vs. moxifloxacin 3.3%; P = 0.93). Moxifloxacin has also been evaluated in combination with pretomanid for two weeks in participants with TB (Trial NC-001) and for 8 weeks in NC-002 (as reviewed above).

For additional information on moxifloxacin, refer to the IB[39] and the manufacturer's package insert.[19]

2.5.4 Pyrazinamide (Z)

Pyrazinamide (Z) is a standard drug used as part of the four drug HRZE regimen used for the first two months of intensive therapy for drug-sensitive TB as recommended by the WHO and many National TB programs. Please see the Package Insert[20] for more detail. Z is active against TB *in vitro* and it potentiates the bactericidal and sterilizing activity of both bedaquiline and pretomanid in mouse models of TB infection.[8, 15] Pyrazinamide enhanced the bactericidal activity of both bedaquiline and pretomanid in Trial NC-001-(J-M-Pa-Z) as noted by decreases over 14 days in the CFU counts in sputum among participants.

The pyrazinamide product label notes that pyrazinamide is contraindicated in persons with severe hepatic damage, who have shown hypersensitivity to it, and with acute gout. The most serious side effect is hepatotoxicity. Its frequency appears to be dose-related and thus liver function should be assessed before and regularly during treatment with pyrazinamide. Hyperuricemia commonly occurs and is occasionally accompanied by arthralgia and may lead to attacks of gout.

Photosensitivity and skin rash have been reported less frequently. Other side effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria.

Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert. [20]

2.6 Overall Benefit/Risk Assessment

Some participants with pulmonary TB in this trial will be given a regimen of **BPaMZ**. These drugs individually and in combination are known to have anti-tuberculosis activity and is not expected to have an adverse impact on the ultimate cure of TB in these participants. Based on NC-005 and other regimens using each of the regimen drugs in different combinations there is good evidence that this may be a highly effective therapy for both DS-TB and DR-TB.

For DS-TB the potential for a shorter regimen than 6 months is expected to be successful based on preclinical and clinical information as listed before. Participants in this trial will have their TB infection carefully characterized, with drug sensitivity profiles established, and they will receive treatment with trial drugs that have demonstrated activity against MTB.

Participants will receive individualized medical attention; this will allow a continuous monitoring of the health conditions of each participant, any of whom can be withdrawn at any stage of the trial and removed from trial treatment should his/her condition suggest to the Investigator that this would be in his/her best interest. Multiple blood samples will be taken for safety laboratory studies, and ECGs will be taken at multiple time points.

One concern, the combination of two agents with known QT-prolonging effects (bedaquiline and moxifloxacin), has been addressed specifically by carefully identifying and excluding participants with risk factors that might predispose them to cardiac arrhythmias, screening all participants for evidence of existing cardiac disease and monitoring all participants with ECGs throughout the trial.

The trial drugs in the proposed regimens to be tested in this trial have all demonstrated safety and efficacy in the treatment of pulmonary tuberculosis in non-clinical and clinical studies. Specifically, the regimen B-Pa-Z was generally well-tolerated and demonstrated bactericidal activity in a 14-day EBA trial. The potential risks associated with the trial drugs and regimens has been identified as outlined below and will be monitored carefully throughout the conduct of the trial.

The BPaMZ regimen is a novel regimen treatment expected to be effective, safe and well-tolerated and might even shorten the current treatment duration for patients with TB. Based on data from previous trial evaluations of key monitoring and safety information as outlined before suggests a favourable benefit-to-risk ratio trials.

Key Monitoring and Safety Information Regarding Regimen Agents

2.6.1 Bedaquiline (B)

2.6.1.1 Adverse Drug Reactions for bedaquiline

Participants in the Any bedaquiline group compared to the Any Placebo group (difference > 5.0%) had headache (23.5% versus 11.4%, respectively), nausea (35.3% versus 25.7%, respectively),

arthralgia (29.4% versus 20.0%, respectively), and transaminases increased (6.9% versus 1.0%, respectively).and diarrhoea (11.4% versus 5.9%, respectively).

2.6.1.2 Cardiovascular safety

During clinical studies with bedaquiline a prolongation of QTc interval was observed. An ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.

Bedaquiline 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

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. If co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

In the DR-TB treatment arm of the present trial, moxifloxacin will be co-administered with bedaquiline. This is to prevent the development of resistance to the other drugs in the regimen in case the participant's strain of MTB is resistant to pyrazinamide. ECG assessments will be performed on all participants at screening, baseline, and at treatment visits specified in the flow chart.

2.6.1.3 Hepatic safety

Increases in transaminases were seen in clinical studies during administration of bedaquiline with the background regimen. Participants should be monitored during treatment.

Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in participants with diminished hepatic reserve.

2.6.2 Pretomanid (P)

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 diarrhoea)
- Skin and subcutaneous tissue disorders

2.6.2.1 Hepatic Safety

Hepatic enzyme increases have been seen in participants 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 NC-008 trial will include specific monitoring of hepatic enzymes.

For additional information refer to pretomanid IB.[15]

2.6.3 Moxifloxacin (M)

In the usual daily doses of 400 mg/day, moxifloxacin is well tolerated. As stated in the Package Insert[19] the most frequent individual drug related AEs observed in clinical trials with 400 mg oral moxifloxacin therapy were nausea (7.5%) and diarrhoea (5.8%). Fluoroquinolones, including moxifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages.

A known but rare side effect of fluoroquinolones, including moxifloxacin is exacerbation of myasthenia gravis. In addition, moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some participants. It should be used with caution in participants being treated concomitantly with other drugs where an additive effect on the QT interval cannot be excluded.

Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, as well as peripheral neuropathy may occur after the first or subsequent doses of moxifloxacin. For additional information, refer to the moxifloxacin package insert.[19]

2.6.4 Pyrazinamide (Z)

The dose of pyrazinamide that will be used in this trial is an approved dosage for the treatment of TB. The most serious side-effect of pyrazinamide is hepatotoxicity and its frequency appears to be dose-related. Hyperuricemia commonly occurs, occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side-effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria. Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert.[20]

2.6.5 HRZE/HR Control

The **HRZE** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets) combination will be given the first 8 weeks and the **HR** (isoniazid 75 mg plus rifampicin 150 mg combination tablets) combination will be given from Weeks 9 to 26.

Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE.

Please see the HRZE and HR Package Inserts[22, 40] for known and potential risks and benefits.

3.0 Trial Objectives

3.1 Primary Endpoint

To evaluate the time to culture negativity over 8 weeks from the start of the treatment regimens in participants with:

- Drug Sensitive TB (DS-TB)

- Drug Resistant TB (DR-TB)

DR-TB are defined as participants with:

1. *mono-resistance to rifampicin or isoniazid, OR*
2. *resistance to both rifampicin and isoniazid (DR-TB)*

3.2 Secondary Endpoints

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 52 weeks (12 months) and 104 weeks (or 24 months) weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
  - Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
  - Quantitative and qualitative ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones
- Changes in lens opacities.

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [C_{min}], maximum plasma concentration [C_{max}], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of concomitant medications, including antiretroviral therapy (ART), where feasible.

Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

3.3 Exploratory Objectives

- Evaluate whether any of the secondary endpoints predicts relapse free cure.
- Subgroup analysis of populations by HIV status.

4.0 Trial Design

4.1 Summary of Trial Design

This is a Phase 2c, multi-centre, open-label, partially randomized clinical trial conducted in 3 treatment groups. Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment randomisation and allocation during the treatment phase of the trial.

The trial will be performed globally at multiple centres located throughout the world.

A total of 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation, with a target of 50% of the participants being HIV positive. Up to 150 DR-TB participants will be enrolled and assigned to the treatment arm described in Table 4 below.

Refer to Section 3.0 Trial Objectives above and Section 9.3 Interim Analysis for details of the planned interim analysis and potential updates to the trial objectives and sample size.

Participants with Drug Sensitive TB (DS-TB):

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 Weeks, or HRZE/HR combination tablets daily for 26 Weeks. Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation.

Participants with Drug Resistant TB (DR-TB):

Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).

Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive.

DR participants will be treated with 6 months of BPaMZ. DS participants will be randomised using an interactive web response system (IWRS) stratifying for cavitation and HIV status to allocate participants evenly across the arms after they have given written, informed consent during the Screening visit (Days -9 to -1).

4.2 Treatment Plan: Schedule of Assessments

- Screening Period (Day -9 to Day -1)
- Treatment Period (Day 1 to Week 17 / Week 26)
- Follow-Up Period (Week 39 to Week 104)

Refer to:

- Synopsis Flow Chart and Procedures (Section 1.2) for the timing of all procedures and laboratory samples to done at each visit.

- Trial Procedures (Section 7.0 Trial Variables and Procedures) for details regarding specific procedures or laboratory tests.

Each participant will receive up to 26 weeks of treatment. The trial IMP regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation unless an interruption/pause is required urgently for a safety concern.

All participants will enter post-treatment follow-up which continues until Week 104 after start of treatment / randomisation.

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

Table 4: Treatment Groups

	Treatment Group	Treatment Duration	No of Participants
1	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily	17 weeks (4 months)	150 DS-TB
2	**HRZE Tablets (Weeks 1-8):** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). Followed by, **HR Tablets (Weeks 9-26):** (isoniazid 75 mg plus rifampicin 150 mg combination tablets).	First 8 weeks (2 months) then 17 weeks (4 months) Total 6 months	150 DS-TB
3	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily.	26 weeks (6 months)	Up to 150 DR-TB

5.0 Trial Population

The participant must meet all inclusion and no exclusion criteria within the screening period. Retesting for any laboratory or ECG parameters is allowed within the screening period. Sponsor may consider replacement of late exclusions.

5.1 Inclusion Criteria

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

1. Signed written consent prior to undertaking any trial-related procedures.
2. Male or female, aged 18 years or over.

3. Body weight (in light clothing and no shoes) ≥ 30 kg.
4. Sputum positive for tubercule bacilli (at least 1+ on the International Union Against Tuberculosis and Lung Disease [IUATLD]/WHO scale (Appendix 1) on smear microscopy) at the trial laboratory.
5. Disease Characteristics - Participants with one of the following pulmonary TB conditions:

DS-TB treatment arm participants should be:

a. sensitive to rifampicin, isoniazid and fluoroquinolones by rapid sputum-based test **AND**

b. either newly diagnosed for TB or have a history of being untreated for at least 3 years after cure from a previous episode of TB.

DR-TB treatment arm participants should be:

a. Resistant to rifampicin and/or isoniazid; but sensitive to fluoroquinolones by rapid sputum-based test **AND**

b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 3 days at start of screening.

c. Participants with resistance to injectables by rapid sputum-based test are allowed in the trial.

When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.

6. A chest x-ray, within 6 months prior to or during the Screening visit, which in the opinion of the Investigator is compatible with pulmonary TB.
7. Contraception:

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

Non-childbearing potential:

a. Participant - not heterosexually active or practice sexual abstinence; or

b. Female participant or male participants female sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or

c. Male participant or female participants male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening;

Effective birth control methods:

a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or

b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device.

c. Male participants' female sexual partner: Barrier method combined with hormone-based contraceptives or an intra-uterine device.

Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 6 months after the last dose of trial IMP or discontinuation from trial IMP 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 participants to prevent pregnancy.

5.2 Exclusion Criteria

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

Medical History and Concurrent Conditions:

1. Any non-TB related condition where participation in the trial, as judged by the Investigator, could compromise the well-being of the participant or prevent, limit or confound protocol specified assessments.
2. Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
3. Historical and or current use of local traditional medications/herbs which in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
4. Being, or about to be, treated for malaria.
5. Is critically ill and, in the judgment of the Investigator, has a diagnosis likely to result in death during the trial or the follow-up period.
6. TB meningitis or other forms of extrapulmonary tuberculosis with high risk of a poor outcome, or likely to require a longer course of therapy (such as TB of the bone or joint), as judged by the Investigator.
7. History of allergy or hypersensitivity to any of the trial IMP or related substances, including known allergy to any fluoroquinolone antibiotic, history of tendinopathy associated with quinolones or suspected hypersensitivity to any rifampicin antibiotics.
8. For HIV infected participants any of the following:

    a. CD4+ count <100 cells/µL
    b. Karnofsky score <60% (Appendix 5)
    c. Received intravenous antifungal medication within the last 90 days
    d. WHO Clinical Stage 4 HIV disease (Appendix 3)

9. Participants who recently started or expected to need to start ART within 1 month after randomization. Participants who have been on ARTs for more than 30 days prior to start of the Screening visit or expected to start ART greater than 30 days after randomization may be included.
10. Having participated in other clinical trials with investigational agents within 8 weeks prior to start of trial IMP or currently enrolled in an investigational trial.
11. Participants with any of the following at the Screening visit (per measurements and reading done by ECG):

    a. QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with the Sponsor Medical Monitor before enrolment.
    b. Heart failure
    c. A personal or family history of congenital QT prolongation
    d. A history of or known, untreated, ongoing hypothyroidism
    e. A history of or ongoing bradyarrhythmia
    f. A history of Torsade de Pointe

12. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening.
13. Females who have a positive pregnancy test at the Screening visit or already known to be pregnant, breast-feeding, or planning to conceive a child during the trial or within 6 months of stopping treatment. Males planning to conceive a child during the trial or within 6 months of stopping treatment.

<u>Previous and Concomitant Therapy</u>

14. Previous treatment for TB:

    - <u>For DS-TB participants</u>: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days at the start of the Screening visit.
    - <u>For the DR-TB participants</u>: Previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 3 days at the start of the Screening visit.

15. Any diseases or conditions in which the use of the standard TB drugs or any of their components is contra-indicated, including but not limited to drug allergy.
16. Use of any drug within 30 days prior to randomisation known to prolong QTc interval (including, but not limited to, amiodarone, amitriptyline, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinacrine, quinidine, sotalol, sparfloxacin, thioridazine).
17. Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), as they can lead to visual opacities or cataracts.
18. For HIV infected participants:

a. The following antiretroviral therapy (ART) should not be used with either (BPaMZ and HRZE/HR) trial regimen:

   1. Stavudine
   2. Didanosine
   3. Triple NRTI regimen is not considered optimal for HIV treatment (poor efficacy)

b. In the case where participants are randomized to HRZE arm, rilpivirine and etravirine cannot be given with rifampicin due to drug-drug interactions. A standard NRTI backbone may be used in combination with one of the following:

   1. Efavirenz requires no dose adjustment
   2. Dolutegravir dose adjustment is required – double dose when co-prescribed with rifampicin.
   3. Raltegravir requires no dose adjustment
   4. Lopinavir/r dose adjustment is required – double dose when co-prescribed with rifampicin
   5. Nevirapine requires no dose adjustment, however, please note that nevirapine based regimens are associated with higher ART failure in participants having or known to have a previous viral load more than or equal to 100,000/ mL

c. In the case where participants are randomized to the BPaMZ trial regimen, a standard NRTI backbone may be combined with the following:

   1. Rilpivirine
   2. Dolutegravir
   3. Raltegravir
   4. Nevirapine
   5. Lopinavir/r
   6. Participants who are on efavirenz, atazanavir/r or darunavir/r at the time of screening and have an undetectable viral load, should have their ART switched to one of the agents listed above (1-5). It would be preferable to switch to another permissible ARV within the same class accompanied by the same nucleoside backbone.

d. ART regimen choice should be discussed with the Sponsor Medical Monitors if there are any concerns.

Confirmed plans to use Isoniazid prophylaxis for HIV positive participants during the treatment and follow up period is not permitted.

Diagnostic and Laboratory Abnormalities

19. Participants with the following toxicities at screening as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (Draft November 2007) (Appendix 2) where applicable:

a. platelets <75,000/mm^3
b. creatinine >1.5 times upper limit of normal (ULN)
c. eGFR ≤ 60 mL/min
d. haemoglobin <8.0 g/dL
e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once
f. GGT: greater than 3 x ULN
g. AST:
   - ≥3.0 x ULN to be excluded;
   - results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor
h. ALT:
   - ≥3.0 x ULN to be excluded
   - greater than ULN must be discussed with and approved by the Sponsor Medical Monitor
i. ALP:
   - ≥3.0 x ULN to be excluded
   - 2.0 – <3.0 x ULN must be discussed with and approved by the Sponsor Medical Monitor
j. Total bilirubin:
   - >1.5 x ULN to be excluded;
   - greater than 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor
k. Direct bilirubin:
   - greater than 1x ULN to be excluded

All the inclusion and none of the exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the Investigator has reason to suspect that there might be a health problem (other than TB), enrolment should only be considered after discussing the case with the Sponsor Medical Monitor.

No protocol waivers will be granted by the TB Alliance.

5.3 Restrictions

Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are necessary for the participant's welfare, 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 reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected to prevent any potentially serious and/or life-threatening drug interactions.

The following recommendations should be followed with regards to concomitant medication to avoid possible drug interaction with the IMP:

Participants on a **moxifloxacin** containing treatment arm: The IMP should be taken either 4 hours before or 8 hours after taking the following products:

- An antacid, multivitamin, or other product that has magnesium, aluminium, iron or zinc
- Sucralfate
- Didanosine

Participants on the **HRZE/HR** treatment arm:

- Any aluminium-containing antacids should be taken at least one hour after the IMP dose.

The following medicinal products are prohibited from the Screening visit and during the treatment period:

- Quinolone antimalarial (e.g., chloroquine and quinacrine). Participants who have malaria at screening are to be excluded. However, if a participant develops malaria during the trial, the Investigator is advised to consult the Malaria Treatment Guidance document regarding the interaction between moxifloxacin and bedaquiline with anti-malarial drugs. Investigators may also contact the Sponsor Medical Monitor for further guidance.
- Chronic systemic glucocorticoids (topical, inhaled or intranasal glucocorticoids are allowed) due to their potential to cause visual opacities. Short term systemic glucocorticoids are allowed for emergency situations (e.g. for treatment of pulmonary exacerbation when inhaled glucocorticoids is inadequate).
- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, other quinolones, thioamides, and metronidazole.

The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible (unless this is required for emergency management of the participant). Investigators may also contact the Sponsor Medical Monitor for further guidance.

- Any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). The exception is moxifloxacin and bedaquiline administered as part of the trial IMP, with ECG monitoring, to help ensure participant safety.
- Any drug known to be hepatotoxic (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, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines,

phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).

5.4 Treatment Discontinuation and/or Early Withdrawal

Any participant for whom the Investigator decides to temporarily discontinue their IMP is to be discussed with the Sponsor Medical Monitor and, if applicable, be restarted on IMP as soon as possible.

A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following:

- Withdrawal of informed consent
- Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment
- Pregnancy
- At the specific request of the Sponsor or termination of the trial by the Sponsor
- Lost to follow-up
- When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.

A participant may withdraw from the trial at any time at his/her request (withdrawal of consent) or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative issues.

When a participant withdraws consent from the trial, no additional follow-up visits will be performed.

Participants who withdraw from the trial after having received IMP will not be replaced.

All participants withdrawn from trial and who received at least one dose of IMP will be requested to return for an Early Withdrawal visit and the applicable safety Follow-Up visits, as per the Synopsis Flow Chart and Procedures (Section 1.2 footnote c), as well as Table 5.

5.4.1 Early Withdrawal

In case of early withdrawal during the treatment or follow-up period, 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:

- Sputum sample collection x 2 (one EMS brought from home and one spot at the research site under the coaching and observation of the trial staff). If no EMS was provided by the participant, 2 spot samples may be collected at the site, at least 30 minutes apart.

- Urine pregnancy test (women of child bearing potential, whether they are sexually active or not)
- Laboratory safety sampling (including male reproductive hormone tests);
- Single 12-lead ECG
- TB Symptoms Profile
- Patient Reported Health Status Questionnaire
- Vital signs
- Full physical examination, including weight
- Ophthalmology examination, if required as described in Table 5
- IMP compliance check (if participant on IMP)
- Concomitant medications
- Adverse events

Once a participant has been withdrawn early from the trial, they will be requested to attend follow-up visits as described in Table 5:

Table 5: Follow-up Visits Required for Early Withdrawal Participants

Treatment Duration at EWD visit	**Ophthalmology Examination at EWD[a]**	**Ophthalmology Examination** **Visit 3 months after EWD Visit[a]**	**Week 52** (Month12) **Follow-up Visit**	**Week 104** (Month 24) **Follow-up Visit**
≤ 14 days	Not required	Not required	Required	Required
15 days to ≤ 12 weeks	Not required	Required	Required	Required
> 12 weeks	Required	Required	Required, if not already performed	Required

a. If an additional visit is required for an ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 3 months after the EWD visit date.

The Weeks 52 and 104 visits will be performed to collect SAE information (including verification of survival) and participant reported TB outcome information. This visit may be telephonic, a home or a site visit at Weeks 52) and/or Week 104 after the participants' start of treatment date.

5.4.2 Unscheduled Visits

Any visit which is conducted in addition to those required by the Synopsis Flow Chart and Procedures (Section 1.2), should be considered unscheduled regardless of the reason for the visit. The assessments which are undertaken as part of an Unscheduled visit should be as clinically indicated.

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

- For any medical reason, as determined by the Investigator or participant.
- If both sputum samples (EMS and spot) at Week 8 or later are contaminated, the participant should return for an unscheduled visit/s to give additional sputum samples or to document that the participant is not able to produce sputum.

- If after having converted to culture negative, the participant has a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 or Week 26), the participant should return for unscheduled visit/s to provide additional sputum samples, at a minimum of 7 days apart, or to document that the participant is not able to produce a sputum sample.

Determination of the participant's primary outcome status requires sputum culture results at the following time-points during the trial:

- End of Follow-up Period (Week 52 and 104)
- Early Withdrawal, if applicable

At least one of the following criteria should be met at these time-points to confirm a participant's primary outcome status:

- 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 the participant is clinically asymptomatic

Should the participant's primary outcome not meet any of the above criteria, the Investigator should continue to recall the participant for an Unscheduled visit to collect sputum samples until the criteria is met and the primary outcome can be determined.

Additional sputum samples: Two samples at each visit – ideally, one EMS and one spot sputum sample at the research site under the coaching and observation of the trial staff). If no EMS was provided by the participant, 2 spot sputum samples may be collected on site, at least 30 minutes apart. Additional sputum samples should be collected at least 7 days after the previous sample.

Table 6: Summary of Scenarios Requiring Unscheduled Visits for Mycobacteriology Testing

Time-point	Scenario	Unscheduled Visit/s Required?	Comment
Week 8 or later	Both sputum cultures are contaminated	Yes	Provide additional samples until a positive or negative result is reported, or it is confirmed that the participant is unable to produce sputum
At or after the last treatment visit (Week 17 or Week 26)	Previously converted to culture negative but now has an MTB-positive culture	Yes	Provide additional samples at least 7 days after the previous sample until the result is confirmed, or it is confirmed that the participant is unable to produce sputum.

End of Follow-up Period (Week 52 and 104) Early Withdrawal, if applicable	Participant's primary outcome status cannot be confirmed by: 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	Yes	Provide additional samples at least 7 days after the previous sample until one of the criteria is met and the primary outcome status can be determined.

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

5.4.3 Lost-to-Follow-up

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

5.4.4 Early Withdrawal due to TB

Ultimately it is the Investigator's decision whether a participant requires early withdrawal from the trial due to a concern that the participant has symptomatic worsening of TB and/or bacteriological failure/relapse.

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

If the Investigator decides to withdraw a participant due to TB, additional sputum samples may need to be collected to ensure the participant's outcome status as determined in Section 5.5.

All early withdrawn participants who are confirmed sputum positive (two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These

participants will be referred to their applicable DS/DR local community TB clinics for standard anti-tuberculosis chemotherapy according to National TB Treatment Guidelines.

The participant will be provided with a referral letter from the Investigator to take with them to their National Treatment Program (NTP) clinic and the referral letter, at a minimum, should include all treatment received by the participant and information about any suspected/confirmed adverse event/reaction related to any of the trial IMP's and or concomitant medications. A follow-up call should be made by the trial site staff to the clinic to ensure the participant attended the NTP clinic.

5.5 Participant Progress Definitions

Table 7: Participant Progress Definitions

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

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

** Early Withdrawal

5.6 Trial Stopping Rules

There are no trial specific stopping rules.

The trial or parts of the trial can be stopped by the Sponsor on advice from the Data Safety and Monitoring Committee (DSMC) after their review of applicable trial data. In addition, the Sponsor has the right to stop the trial or a specific trial site at any time, although this should only occur

after consultation between the involved parties. Should this occur, the local and central Ethics Committee/Institutional Review Board (EC/IRB) and Regulatory Authorities will be informed.

Should a trial site be closed prematurely, all trial materials (except source documentation that must remain at the site) will be returned to the Sponsor or applicable vendor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Participants currently on trial IMP will receive an appropriate regimen and all participants will be referred to their applicable DS-TB/DR-TB NTP clinic.

6.0 Treatment

6.1 IMP Administration

6.1.1 Instructions for Dosing of Test Regimen (BPaMZ)

- Treatment will be orally administered once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months).

6.1.2 Instructions for Dosing Control Treatment Regimen (HRZE/HR)

- To be taken with a glass of water (approximately 240 ml).
- HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes.

HRZE/HR treatment will be administered orally once daily to DS-TB participants as follows:

Weight Band	Weight Range	Number of tablets per weight band
1	30-39 kg	2
2	40-54 kg	3
3	55-70 kg	4
4	≥ 71 kg	5

The participant's weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and dose to administer.

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

6.2 Participant Compliance

During site clinic visits, the IMP will be administered by the Investigator(s)/designated site personnel and when possible, the check for IMP compliance via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the participant has swallowed the IMP). During the trial, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how the IMP is to be taken, as well as to check the IMP cards for unused tablets in the containers at each visit during the treatment phase.

6.3 Treatment Modification(s)

The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the Investigator to identify and address the cause(s) (e.g. side effects).

Participants that do not take:

- Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required.
- If more than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been.
- If more than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial.
- If the participant misses a total (sum) of 56 cumulative missed doses, discontinue the IMP and withdraw the participant from the trial.
- If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose that was missed.

Any participant for whom the trial IMP is discontinued (including for non-adherence) will be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial IMP as soon as possible.

6.4 IMP Packaging and Labelling

The complete formulations of the IMP, bedaquiline and pretomanid, are found in the respective Investigator Brochures.[8, 15] The complete formulations of moxifloxacin, pyrazinamide, HRZE/HR are found in the Package Inserts.[19, 20, 22, 40]

The IMP will be packaged in weekly or bi-weekly cards as follows:

Week 1 to 8 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	14	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Week 9 to 17/26 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	7	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Control (HRZE/HR) Group: Dispensed *Bi-weekly*			
Weight Band	**Weight Range**	**Number of tablets per weight band**	**Number of tablets in each card**
1	30-39 kg	2	28
2	40-54 kg	3	42
3	55-70 kg	4	56
4	≥71 kg	5	70

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

The packaging of each weekly and biweekly cards will be labelled with, at a minimum, the following information:

- Name of Sponsor
- Name of medication
- Dosage, quantity and method of administration
- Reference/lot number
- The statement "For Clinical Trial Use Only"
- Space for completion of name of Investigator and site number
- MedID: medication identification number
- Storage conditions
- Period of use
- The statement "Keep out of reach of children"
- Expiry date
- Directions for use
- Space for completion of participant number and visit/date dispensed

6.5 Blinding and Procedures for Breaking the Blind

As this is an open label trial there is no need for blinding or procedures to break the blind. The trial participants, the site staff, Sponsor, and CROs will not be blinded to treatment assignment.

6.6 Handling, Storage and Accountability

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

Only participants randomised in the trial may receive trial IMP and only authorized site staff may supply or administer trial IMP. All trial IMP's must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

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

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

Further guidance and information for the handling, storage, accountability and final disposition of unused trial IMPs are provided in the Pharmacy Manual.

7.0 Trial Variables and Procedures

The Synopsis Flowchart and Procedures (Section 1.2) should be referenced for timing, sequence of assessments, and specific procedures.

7.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected:

- Written Informed Consent
- Visit dates
- Participant disposition
- Demography (date of birth, race and gender)
- Inclusion and exclusion criteria
- Clinically significant medical and TB treatment history (including past and current TB diagnosis, smoking and alcohol use)
- Screening coached spot sputum samples:
  - Smear microscopy for acid-fast bacilli
  - Rapid molecular tests for isoniazid, rifampicin, fluoroquinolones resistance (Hain MTBDRplus and HainMTBRsl)
  - Liquid Culture (MGIT) for Mycobacterium tuberculosis (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive.
- Urine pregnancy test: women of childbearing potential only, whether they are sexually active or not (non-childbearing potential for a female participant is defined as having bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months).
- Serology: HIV and CD4 count. Where required by regulatory authorities or ethics committees, a separate (EC/IRB approved) HIV informed consent form will be obtained from participants:
  - Prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the participant, HIV counselling that is provided to the participant by the trial site should be clearly documented in the participant's medical records/source. Participants have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the participant's medical records/source.
- Karnofsky Score (Appendix 5). Only for HIV positive participants.
- Chest X-Ray: A chest X-ray digital image within 6 months prior to or during the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor; this process will be documented in the Chest X-Ray / Radiology Manual. The investigator is responsible for review and analysis of the chest X-ray for participant's inclusion.
- Method of birth control: male and female participants and their sexual partners
- IMP details: randomization
- IMP compliance and actual dosing
- Concomitant medications

7.2 Efficacy Variables and Procedures

Two spot sputum samples are collected, one EMS brought from home or collected in the hospital ward (only if the participant is hospitalised) and one spot sputum sample collected at the research site under the coaching and observation of the trial staff or, if no EMS sample was provided by the participant, 2 samples may be collected on site at least 30 minutes apart. The mycobacteriology sampling methodology and requirements will be described in a separate document, the Mycobacteriology Laboratory Manual, which will be provided prior to the trial start. Sputum samples may not be obtained by induction.

The following analyses will be performed:

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

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

- Bacteriologic failure/relapse
- Time to sputum culture conversion
- Number of participants with sputum culture conversion

Every effort must 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 participant who never achieves culture negative status due to the inability to produce sputum but has completed Week 17 or Week 26 and post treatment follow-up (Weeks 39 to 104) and is without clinical or biological evidence of relapse, will be considered to have a favourable outcome.

TB Symptoms Profile:

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

Patient Reported Health Status Variables and Procedures:

- The Patient Reported Health Status variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2). Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire. 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 trial Participant Questionnaires Guideline, which will be provided prior to the trial start.

7.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2) and assessed for evaluation of the safety endpoints:

- The safety laboratory sampling methodology and requirements will be described in a separate document, the Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
    - Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count)
    - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, ALP, AST, ALT, lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO_2, creatine phosphokinase (CPK). GGT is only routinely included at the Screening visit (Day -9 to -1).
    - When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].
    - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator
- 12-lead ECG:
    - Investigator assessment: normal or abnormal
    - Central cardiologist assessment: heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.
    - Methodology:
        - Timing (Synopsis Flow Chart and Procedures, Section 1.2) and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start
        - ECGs are to be recorded for 10 seconds
        - ECGs are to be performed during a single visit
        - ECGs should be done before any phlebotomy when both included in a visit
        - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch)
    - ECGs to be performed prior to pre- and post-dose PK sampling as described below:
        - Day 1: pre-dose (within 2 hours prior to dosing)
        - Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
        - Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
        - Week 12: pre-dose (within 2 hours prior to dosing)
        - Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose
- Vital signs:
    - Vital signs (should be done before any phlebotomy in light clothing and with no shoes)
    - Systolic and diastolic blood pressure (mmHg) to be measured in a supine position (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 (beats per minute)

  - Respiratory rate (breaths per minute)
  - Axillary body temperature (°C)
- Physical Examination:
  - Height (m) is measured at the screening visit only
  - Full (complete) and limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded
  - Weight (kg) (in light clothing and with no shoes)
  - Using the variables of weight and height, the body mass index (BMI) will be calculated
- Ophthalmology Slit Lamp Examination:
  - To be done by an Ophthalmologist trained on Age-Related Eye Disease Scale 2 (AREDS2) assessment. The ophthalmology slit lamp methodology and requirements will be described in a separate document, the Ophthalmology Guideline. The following analyses will be performed: AREDS2 opacity typing and grading.
- Adverse events
- Investigator assessment:
  - The Investigator will review the participant status at specified visits in the Synopsis Flow Chart and Procedures (Section 1.2), including any time the Investigator determines that the participant fulfils the criteria for the primary outcome of treatment failure. The Investigator will assess whether TB treatment is considered a “success” or “failure”. If it is considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration.

7.4 PK Variables and Procedures

Plasma concentrations from sparse sampling (Synopsis Flow Chart and Procedures, Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid to further evaluate the effects of covariates on model parameters in this trial population.

PK data from the current trial may be combined with prior data to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{min}, C_{max}, AUC_{τ}, C_{mean}, and time above minimum inhibitory concentration) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.

7.5 Mycobacteriology Characterization Variable and Procedures

- Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative);
- MTB confirmed positive cultures (after the participant has previously converted to negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.
- Refer to the Mycobacteriology Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for:

- Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);
- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin;
- Drug Susceptibility Testing for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing (WGS), and comparison of sequences from baseline and relapse isolates.

If the participant's culture converts to negative and has a MTB positive culture at or after the last visit of the treatment period (Week 17 and Week 26), the MTB cultures will be tested at the trial mycobacteriology laboratories using Hain MTBDR*plus* and HainMTBR*sl* to detect resistance to isoniazid, rifampicin, fluoroquinolones and injectables.

All MTB isolates must be stored at the local mycobacteriology laboratories, until trial closure. In addition, MTB isolates as well as extracted MTB DNA from the applicable baseline and follow-up cultures will be stored at the central mycobacteriology laboratory for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure.

8.0 Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

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

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening (any event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation; in general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred, or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity; the term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition

is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect; or
- Is a medically important event

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse. A “suspected transmission of infectious agent by a medicinal product” is also considered a serious adverse event under the SAE criterion “Other medically important condition”.

8.1.3 Attribution/Causality

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

Table 8: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An AE, which is not related to the use of the drug.
Unlikely	An AE 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 AE, 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 AE, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by de-challenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An AE, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

8.1.4 Severity

Table 9: Definitions for Adverse Event Severity Gradings

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

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

8.2 Reporting

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

All AEs will be collected by the Investigator from the time a participant signs the Informed Consent Form through to their Week 104 follow-up visit. The exception to this is early withdrawal participants who will only have SAEs collected from their time of early withdrawal to their Week

104 follow-up visit at the timepoints specified in the Synopsis Flow Chart and Procedures (Section 1.2) and recorded in the CRF.

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

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

The Sponsor/Investigator/designee will inform Regulatory Authorities and/or EC/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 EC/IRB.

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

8.2.1 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- The end of the follow-up period; and
- 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 Investigator. However, this will have to be agreed upon with the Sponsor Medical Monitor.

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

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

New or updated SAE information will be recorded in the originally completed CRF and submitted to the Sponsor within 24 hours of receipt, per the eCRF completion guideline.

8.2.2 Clinical Laboratory Adverse Events

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

8.2.3 Disease Symptoms During Trial

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

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

it will be recorded as an adverse event. If there is:

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

it will not be recorded as an AE and this will be noted in the participant's source documentation. All TB related symptoms that meet SAE criteria will be recorded and reported as a SAE.

8.2.4 Overdose

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

8.2.5 Drug Interaction

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

8.2.6 Pregnancy

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

If a pregnancy is suspected while the participant is receiving IMP, the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner, the participant withdrawn from the trial and referred to the NTP for further management.

Protocol-required procedures for trial discontinuation and follow-up will be performed unless contraindicated by the pregnancy.

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

8.3 Monitoring for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in the preclinical toxicity studies of the Investigator's Brochures[8, 15] and Package Inserts.[19, 20, 22, 40]

AEs still ongoing at the end of the treatment period in the trial will be followed until satisfactory clinical resolution or stabilization, or until the end of the follow-up period and until all queries on these AEs have been resolved.

Grade 3 and Grade 4 laboratory abnormalities, and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.

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

8.3.1 ALT, AST and Bilirubin Elevations

The Investigator should refer to the Hepatoxicity Management Guideline, to appropriately monitor significant elevations of AST, ALT or Bilirubin. A separate Hepatoxicity Management Guideline document has been developed to aid investigators in the management of participants.

When managing participants with elevated liver enzymes at an Unscheduled visit, the Investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

8.3.2 Lipase

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

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

8.3.3 Musculoskeletal System and Cardiac Muscle Myalgia

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

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

8.3.4 Cardiac Rhythm Disturbances

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

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

<u>QTc prolongation</u>

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

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

8.4 Safety Monitoring by Data Monitoring Committee

A Data Safety Monitoring Committee (DSMC) will be appointed for the trial. The primary responsibility of the DSMC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial participants by monitoring participant safety, assess participant risk versus benefit, and assess data quality and general evaluation of the trial progress. Its activities will be delineated in a DSMC Charter that will define the membership, responsibilities and the scope and frequency of data reviews.

The DSMC will operate on a conflict-free basis independently of the Sponsor and the trial team. It will comprise at least 3 voting members that include at least 2 clinicians and one statistician.

The DSMC may have an organizational meeting prior to commencement of the trial. The DSMC will have meetings where it will review unblinded data during a closed session. These meetings will be planned at regular intervals.

The Sponsor or the DSMC may convene ad hoc meetings based on rates of SAEs and/or to review results of the futility analysis, or if safety concerns arise during the trial. After its assessment, the DSMC will recommend to the Sponsor continuation, modification or termination of the clinical trial.

9.0 Statistical Analysis

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

There will be 3 data analyses and trial reports generated for this trial:

1. When all participants have completed 8 weeks (2 months) of treatment from baseline.
2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy.
3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.

9.1 Analysis Populations

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

- The ITT population is defined as all randomized participants excluding late screening failures. Late screening failures are participants withdrawn from treatment because they were found to be ineligible (late exclusions from the trial), based on data collected *prior to randomization*.
- The mITT population is defined as the ITT population with extra exclusions (described in the SAP).
- The PP population is defined as the mITT population with extra exclusions (described in the SAP).
- The mITT analysis will be considered primary, with consistent findings required from the other main analysis populations to support the primary conclusion.

9.2 Sample Size

For the primary endpoint, time-to-culture conversion at 8 weeks,150 participants per arm (DS-TB participants) will provide at more than 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 90% power to detect a HR of least 2. This sample size also allows for one planned interim analysis of the primary endpoint (See Section 9.4.1)

For the key secondary endpoint of clinical outcome at 12 months from randomization, 150 patients per arm will provide 74% power based on assumptions using data from the largest most recent and completed phase 3 TB treatment trial which used the same control arm.[41] That is, assuming 16% unfavourable (see Section 9.4.2) in the control arm and 13% unassessable (see Section 9.6) at 52 weeks post randomization. A 12% margin of non-inferiority was chosen to preserve at least 75% of the estimated control arm effect against placebo (estimated to be 54%)[41, 42] which is considered an acceptable proportion on which to declare non-inferiority of the test regimen.

9.3 Interim Analyses

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard

ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

  *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objectives**

  *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46, 47, 48] and full details are provided in the Statistical Analysis Plan.

9.4 Primary and Secondary Efficacy Endpoint Analysis

9.4.1 Primary Efficacy Endpoint, Time to Culture Conversion at 8 Weeks

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

Participants will be classified as being culture positive, culture negative, dead or unassessable at 8 weeks. The proportion culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis and groups compared using a hazard ratio and 95% confidence interval.

Non-inferiority of the key secondary endpoint of clinical outcome will be assessed using the upper bound of the one-sided 97.5% confidence interval for the difference between the proportion of participants who are classified as having an unfavourable status on the intervention less the control regimen. If the upper bound of the one-sided 97.5% confidence limit for this difference in proportions is less than 12% (the margin of inferiority) the intervention will be non-inferior to the control arm.

9.4.2 Key Secondary Efficacy Endpoint, Clinical Outcome at 52 Weeks from Randomization

For the key secondary endpoint of clinical outcome (bacteriologic failure or relapse or clinical failure), participants will be classified as having a favourable, unfavourable or unassessable outcome status which will be defined in detail in the SAP. In general, participants achieving and maintaining culture negative status without any additional treatment will be considered favourable;

participants who fail on treatment or relapse in follow-up will be considered unfavourable and participants who are not assessable (and who have not already been declared as unfavourable) will be considered unassessable and excluded from the analysis.

9.4.3 Other Secondary Efficacy Endpoints

The secondary efficacy endpoints and analyses are as follows are:

- Clinical outcome (bacteriologic failure or relapse or clinical failure) at 104 weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight will be summarised and presented.
- Proportion of participants experiencing a change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status will be summarised and presented.

9.5 Safety and Tolerability Assessments

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.

9.6 Pharmacokinetics

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., C_{min}, C_{max}, AUC) for bedaquiline and its M2 metabolite,

pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so, too, will the effects of concomitant medications including ART, as feasible. Data from other trials may be included to enhance the model-based analysis.

Detailed plans for the PopPK analysis will be outlined in a separate modelling plan, and results will be reported in separate modelling report.

9.7 Pharmacokinetics/Pharmacodynamics

Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate. Planning details and results will be included in the separate modelling plan and report.

10.0 Records Management

10.1 Data Collection

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

10.2 Source Documents

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

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

10.3 File Management at the Trial Centre

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

10.4 Records Retention at the Trial Centre

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

11.0 Quality Control and Assurance

11.1 Site Procedures

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

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

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

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

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

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

11.2 Monitoring

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

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

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

11.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol and GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the trial site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly.

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

11.4 Auditing

For 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 about accuracy, adequacy and consistency, and to assure that trials are in accordance with the guidelines. Having the highest quality data from trials is an essential aspect of drug development.

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The auditors or inspectors may also review site SOPs, training records, site facilities and other trial related systems/processes.

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

12.0 Ethics and Regulatory

12.1 Basic Principles

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

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

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

12.3 Regulatory Authorities

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

12.4 Informed Consent

Written informed consent will be obtained from all participants (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment procedures) are performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for 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 part of the research.

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

The trial will be included and updated in the appropriate Country registry and referenced in the informed consent forms (ICF).

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

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

The monitor will inspect the original completed ICFs for all participants.

12.5 Confidentiality

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

informed consent will contain a clause granting permission for review of the participants' source data by the Sponsor or designees.

13.0 Publication Policy

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

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

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory Investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors.[43]

Because the trial is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the Trial must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy. Specifically, (a) all peer-reviewed published research relating to the trial must be submitted for publication by TB Alliance through the Chronos Open Access Publishing Service established by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy.

14.0 Protocol Amendment Policy

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

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

15.0 Sponsor, Financial Aspects, Insurance and Indemnity

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

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

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

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

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

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Appendices

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	scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

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

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

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

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

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

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

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

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

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

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	Subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia

Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint 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: Who Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection
Asymptomatic Acute retroviral syndrome
Clinical Stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical Stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections
Clinical Stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for >1 month Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) Persistent oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anemia (hemoglobin <8 g/dL) Neutropenia (neutrophils <500 cells/µL) Chronic thrombocytopenia (platelets <50,000 cells/µL)
Clinical Stage 4
HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Cryptococcosis, extrapulmonary (including meningitis) Disseminated nontuberculosis mycobacteria infection Progressive multifocal leukoencephalopathy Candida of the trachea, bronchi, or lungs Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)

Recurrent nontyphoidal Salmonella bacteremia
Lymphoma (cerebral or B-cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy
Symptomatic HIV-associated cardiomyopathy
Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

REF: World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children; 2007*

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: Cardiovascular Safety

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

All-important abnormalities from the ECG readings will be reported.

The percentage of participants with increases in QTc of <30, 30-60, or > 60 ms from baseline will also be tabulated at each time point.

Abnormality Code	ECG parameter			
	HR	PR	QRS	QTcorrected
Abnormalities on actual values				
“Abnormally low”	≤ 50 bpm	NAP	≤ 50 ms	-
“Abnormally high”	≥ 120 bpm	≥ 210 ms	≥ 120 ms	-
“]450 ms, 480 ms]	-	-	-	450 ms < QTc ≤ 480 ms
“]480 ms, 500 ms]	-	-	-	480 ms < QTc ≤ 500 ms
“More than 500 ms	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline				
“[30; 60] ms”	-	-	-	[30; 60] ms
“> 60 ms”	-	-	-	> 60 ms

Appendix 5: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

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

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

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Protocol Amendment or Administrative Change

Lead Trial Number	Trial Name
NC-008	SimpliciTB

x Protocol Amendment Number 2, Dated 14/JAN/2019
☐ Protocol Administrative Change Number _ _, Dated _ _/_ _ _/_ _ _ _

Summary - Protocol section changed		Does amendment / administrative change affect any of the elements listed?	
		YES	NO
A	Purpose of trial	☐	x
B	Design of trial	☐	x
C	Informed consent	x	☐
D	Recruitment procedure	☐	x
E	Measures of efficacy	☐	x
F	Schedule of samples	☐	x
G	Addition or deletion of tests or measures	x	☐
H	Number of participants	x	☐
I	Age range of participants	☐	x
J	Inclusion criteria	x	☐
K	Exclusion criteria	x	☐
L	Safety monitoring	x	☐
M	Duration of exposure to the investigational medicinal product(s)	☐	x
N	Change of posology of the investigational medicinal product(s)	☐	x
O	Change of comparator	☐	x
P	Statistical analysis	x	☐

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**Protocol Amendment
or Administrative Change**

Reasons for Protocol Amendment or Administrative Change:

1	**Change:** All references to The Global Alliance for TB Drug Development have been changed to TB Alliance (TBA). The correct and current TBA logo has been placed into the header of the protocol, on the cover page.
2	**Delete:** Lead Investigator signature filed, as there has not been in the past and won't be in the future, a SimpliciTB Lead Investigator. This is to prevent unnecessary RA and EC queries, as experienced with the review and approval cycles of the prior Protocol Versions 1.0 and 2.0.
3	**Add:** Abbreviations and Definition of Terms - DST, Drug Susceptibility Testing
4	**Add:** Abbreviations and Definition of Terms - HR, Hazard Ratio
5	**Change:** Abbreviations and Definition of Terms - LTFU, previously described as Long-Term Follow-up, changed to Lost to Follow-up in the section
6	**Add**: Abbreviations and Definition of Terms - WGS, Whole Genome Sequencing.
7	**Delete:** 1.1 Synopsis Summary, Section Trial Objective(s) - description and treatment duration from the as it is not applicable to this section.
8	**Add:** 1.1 Synopsis Summary, Statistical Methods – description of abbreviated definitions from the SAP to provide further clarity
9	**Clarify:** 1.1 Synopsis Summary and Protocol Section 6.1.2 Instructions for Dosing Control Treatment Regimen (HRZE/HR) - The participants weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and HRZE and HR does to administer, to ensure optimal dosing at these 2 time-points when changing from HRZE to HR.
10	**Clarify:** 1.1 Synopsis Summary and Protocol Section 6.3 Treatment Modification(s) – If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose that was missed, as the Bedaquiline dose (BPaMZ treatment regime) changes from 200mg to 100 mg at Week 9, and from HRZE to HR at Week 9 (HRZE/HR treatment regime). The term 'greater than' has been replaced with 'if more than' for clarity.
11	**Change:** 1.1 Synopsis, Statistical Methods and Protocol Section 9.0 Statistical Analysis - the Statistical Analysis Plan (SAP) will be written and signed of prior to the interim analysis.
12	**Change:** 1.1 Synopsis, Statistical Methods and Protocol Section 9.3 Interim Analysis - There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size: If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the study on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The study efficacy objectives will be updated as follows: - **Primary Objective:** *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.* - **Secondary Objective:** *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

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	To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework and full details are provided in the Statistical Analysis Plan.
13	**Delete:** Synopsis, Trial Duration – removed reference to 3 database locks as it is not applicable to the trial duration.
14	**Clarify:** 1.2 Synopsis Flow Chart and Procedures - Week 1 occurs on Day 8 and not Day 7 (Day 7 deleted), as per Protocol Memo 1 dated 11 May 2018, to ensure that 7 days of IMP are administered to the participant between Day 1 / Baseline and Week 1.
15	**Change:** 1.2 Synopsis and Flow Chart (foot note) General: vital signs and blood draws (removed ECGs) are to be performed before dosing, unless otherwise specified. Vital signs and or ECGs should be done before blood draws (safety and PK) on days with those assessments.
16	**Change:** Synopsis and Flow Chart (foot note, a) – Screening assessments must occur during the Screening period (Day -9 to -1) before Day 1 (Baseline). This has been amended for clarity.
17	**Clarify:** 1.2 Synopsis and Flow Chart (foot note, f) that rifampicin resistance testing includes Hain MTBDRPlus and Hain MTBRsl.
18	**Clarify:** 1.2 Synopsis and Flow Chart (foot note, f) that unscheduled visits referenced in this section, are for the collection of additional sputum samples.
19	**Change:** 1.2 Synopsis and Flow Chart (foot note, f) if sputum samples collected at Week 8 or later (remove reference to Weeks 17, 26, 52 and 104) are contaminated the participant return for an unscheduled visit.
20	**Change:** 1.2 Synopsis and Flow Chart (foot note, g) Rapid molecular tests will be done for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period) and Drug Susceptibility Testing will be done for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide only, in liquid culture
21	**Add:** 1.2 Synopsis and Flow Chart (foot note, n) – Additional single 12-lead ECGs to be performed prior to pre- and post-dose PK sampling to observe the cardiac safety profile at defined timepoints after dosing, over time, on these days (weeks 2, 8 and 17).
22	**Add:** 1.2 Synopsis and Flow Chart (foot note, s) Blood draws for PK samples collected pre and post-dose must be done after the ECG is performed, as previously ECG's were only performed pre-dose.
23	**Add:** 1.2 Synopsis and Flow Chart (foot note, s) PK samples at Weeks 39, 65, 78 and 104 are to be obtained at any time on the day of the scheduled visit, and only bedaquiline and M2 will be measured.
24	**Add:** 1.2 Synopsis and Flow Chart (foot note, s) and Protocol Section 7.4 PK Variables and Procedures - If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.
25	**Clarify:** 1.2 Synopsis and Flow Chart (foot note, v) the Investigator Assessment, per the Synopsis and Flow Chart, is only performed at Week 52 and 104 or anytime the Investigator determines that the participant fulfills the criteria for outcome of treatment failure.
26	**Add:** 1.2 Synopsis and Flow Chart (additional foot note, x) and Protocol Section 7.1 Demographic and Background Variables and Procedures - The Karnofsky Score is only to be performed on HIV+ participants.
27	**Clarify:** Protocol Section 3.1 Primary Endpoint - To evaluate the time to culture negativity over 8 weeks from the start of the following treatment regimens in participants with: Drug Sensitive TB (DS-TB) and Drug Resistant TB (DR-TB). DR-TB are defined as participants with: mono-resistance to rifampicin or isoniazid, OR resistance to both rifampicin and isoniazid (DR-TB). The treatment allocation descriptions have been removed as they are irrelevant to this section.

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Protocol Amendment or Administrative Change

28	**Clarify:** Protocol Section 3.2 Secondary Endpoints, PK and PD - Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., **minimum plasma concentration** [Cmin], **maximum plasma concentration** [Cmax], **area under curve** over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide.
29	**Clarify:** Protocol Section 4.1 Summary of Trial Design - Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment **randomisation** and allocation (as all DR-TB participants are allocated and not randomised, to only receive 6 months BPaMZ) during the treatment phase of the trial.
30	**Clarify:** Protocol Section 4.1 has been re-written to state that DS participants will be randomized (either to HRZE/HR or 4 months BPaMZ) and all DR participants will be allocated and not randomized to 6 months BPaMZ.
31	**Change:** Protocol Section 5.1 Inclusion Criteria #5 has been changed to the following for the DS-TB treatment arm participants: sensitive to rifampicin, isoniazid **and fluoroquinolones** by rapid sputum-based test.
32	**Change:** Protocol Section 5.1 Inclusion Criteria #5 has been changed to not (late) exclude DS-TB participants who are randomized to the trial due to being sensitive to rifampicin and isoniazid by rapid molecular sputum-based test, however on receipt of the rifampicin and or isoniazid phenotypic resistance testing in liquid culture this shows they are rifampicin or isoniazid resistant.
33	Change: Protocol Section 5.1 Inclusion Criteria #5 has been changed for the DR-TB treatment arm participants, as follows: - Resistant to rifampicin and/or isoniazid; **but sensitive to fluoroquinolones by rapid sputum-based test AND** - Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than **3 days** (previously, was 7 days) at start of screening. - **Participants with resistance to injectables by rapid sputum-based test are allowed in the trial**. - When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.
34	**Change:** Protocol Section 5.1 Inclusion Criteria #7, Contraception **–** Contraception has been updated to require that both the female trial participants and the male trial participants' female sexual partners, use the same type of contraception: Barrier method combined with hormone-based contraceptives or an intra-uterine device. Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 6 months (previously stated in this section as 3 months) after the last dose of trial IMP or discontinuation from trial IMP in case of premature discontinuation, to ensure consistency throughout the protocol, as per Section 5.2 Exclusion Criteria #13 that also references a period of 6 months.
35	**Add:** Protocol Section 5.2 Exclusion Criteria #3 - Historical and or current use of local traditional medications/herbs which in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
36	**Delete:** Protocol Section 5.2 Exclusion Criteria #9 - Resistant to fluoroquinolones (rapid, sputum-based molecular screening tests). If they are randomised into the trial due to being sensitive to fluoroquinolones by rapid sputum-based test, however on receipt of the moxifloxacin phenotypic resistance testing in liquid culture they are found to be fluoroquinolones resistant, they will be excluded as late exclusions. This criterion is already stipulated in the updated Inclusion Criteria #5.

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37	**Change:** Protocol Section 5.2 Exclusion Criteria #14, 15, 16 and 17, as these criteria are consolidated and described more specifically in the updated Exclusion Criteria #14, including an update to a limit of **3 days** previous DR-TB/MDR-TB treatment regimen for the DR-TB participants.
38	**Clarify:** Protocol Section 5.2 Exclusion Criteria #17 (previously #20) has been corrected, as follows: Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), **as they can lead to** visual opacities or cataracts.
39	**Add:** Protocol Section 5.2 Exclusion Criteria #18 (previously #21) has been extended to provide additional instructions wrt ART for HIV infected participants.
40	**Delete:** Protocol Section 5.2 Exclusion Criteria #19 (previously #22) has been updated to remove the DMID grade for platelets, haemoglobin, AST, ALT, ALP and total bilirubin to provide clarity and remove ambiguity. The actual values of these laboratory results remain unchanged.
41	**Delete:** Protocol Section 5.3 Restrictions – 1st paragraph, 2nd sentence has been updated to be keep the participant's welfare as the primary concern: However, if concomitant medications are necessary for the participant's welfare, they may be given at the discretion of the Investigator.
42	**Clarify:** Protocol Section 5.3 Restrictions – The section that describes medications that should be avoided has been updated to state the following: The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible (**unless this is required for emergency management of the participant**). Investigators may also contact the Sponsor Medical Monitor for further guidance.
43	**Delete:** Protocol Section 5.3 Restrictions – 'contraceptive pill' has been deleted from the list of medications to be avoided, since it is a contraceptive requirement (Inclusion Criteria #7) to participate in this trial.
44	**Change:** Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal, as the criteria for late exclusion based on phenotypic DST and whole genome sequencing has been amended.
45	**Delete:** Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal – the following 2 reasons for withdrawal have been removed, due to the updated Inclusion Criteria #5: - Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum-based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result. - Early withdrawal due to TB (removed as this is now detailed in the additional criteria listed in item #44 above)
46	**Clarify:** Protocol Section 5.4.2 Unscheduled Visits has been updated to provide additional clarity, as follows: - Addition of the following reason: For any medical reason, as determined by the Investigator or participant. - End of Treatment Period (Week 17 or 26) has been removed from the timepoint at which sputum cultures are assessed for the primary outcome status, as this was incorrectly stated in the previous protocol - General rewording of this section to provide clarity to the Investigator on when Unscheduled Assessments should occur - Addition of Table 6: Summary of Scenarios Requiring Unscheduled Visit for Mycobacteriology Testing to aid the Investigator's understanding of the Unscheduled Assessment requirements. - Last sentence has been updated to indicate that the …'Investigator **should** (previously documented as, 'is to') contact the Sponsor Medical Monitor to discuss'…
47	**Clarify:** Protocol Section 5.4.4 Early Withdrawal due to TB – last paragraph has been updated to ensure that the Investigator provides a referral letter and at a minimum should include all treatment received by the participant and information about any suspected/confirmed adverse event/reaction related to any of the trial IMP's and or concomitant medications. A follow-up call **should** (previously stated as 'will') be made by the trial site staff to the clinic to ensure the participant attended the NTP clinic.

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48	**Clarify:** Protocol Section 7.1 Demographic and Background Variables and Procedures – The following 2 descriptions of testing as documented in Section 7.5 Mycobacteriology Characterization Variable and Procedures: - Rapid molecular tests for isoniazid, rifampicin, fluoroquinolones resistance (Hain MTBDRplus and HainMTBRsl) - Liquid Culture (MGIT) for Mycobacterium tuberculosis (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive. **Delete:** Protocol Section 7.1 Demographic and Background Variables and Procedures - Gene Xpert, as this was incorrectly included in the previous version of the protocol.
49	**Clarify:** Protocol Section 7.1 Demographic and Background Variables and Procedures – method of birth control: make and female participants and their **sexual** partners
50	**Delete:** Protocol Section 7.4 PK Variables and Procedures – references to linezolid and the NiX-TB trial, as these were incorrectly included in the previous version of the protocol.
51	**Clarify:** Protocol Section 7.5 Mycobacteriology Characterization Variable and Procedures – exact wording documented in 1.2 Synopsis and Flowchart (footnote, g) to ensure consistency of procedure description. **Delete:** 'Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be sub-cultured and sent to the central microbiology laboratory from the applicable local microbiology laboratory, for relevant participants / no positive cultures from screening through week 4', because only assessments perform from the Screening visit will be used for this trial. **Change:** Protocol Section 7.5 Mycobacteriology Characterization Variable and Procedures – all MTB isolates (not just those obtained at Baseline / Day 1, as previously documented) must be stored…
52	**Clarify:** Protocol Section 8.2.1 Follow-up of Adverse Events – reference to the reporting requirements is now referenced as the eCRF Guidelines (incorrectly referenced as SAE Completion Guidelines, in the previous version of the protocol).
53	**Clarify:** Protocol Section 8.2.6 Pregnancy – reporting required at any time during the trial.
54	**Delete:** Protocol Section 8.3 Monitoring for Specific Toxicities – 16.3.3 Neurological, has been removed, as it is not a requirement given the safety profiles of the BPaMZ and or HRZE/HR trial regimens.
55	**Add:** (moved from the Synopsis): Protocol Section 9.0 Statistical Analysis – added the following: There will be 3 data analyses and trial reports generated for this trial: - When all participants have completed 8 weeks (2 months) of treatment from baseline. - When all participants have completed 52 weeks (12 months) follow-up from start of therapy. - When all participants have completed 104 weeks (24 months) follow-up from start of therapy.
56	**Delete:** Protocol Section 11.3 Protocol Deviations – reference to the Monitoring Plan has been removed as the Investigator is not provided with this plan, and therefore would not deviate from this plan.
57	**Delete:** Removal of the following appendixes and references in the protocol, as these appendixes are now included in separate trial documents, and provided to the Investigator: - Appendix 6 TB Symptom Profile is documented in the 'Participant Questionnaires Guideline'

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	- Appendix 7 Patient Reported Health Status is documented in the 'Participant Questionnaires Guideline' - Appendix 8 Liver Toxicity Management documented in 'Hepatoxicity Management Guideline'
58	**Clarify:** Protocol Section 5.2 Exclusion Criteria – with the addition of criteria #3, deletion of #9, 14, 15 the numbering of the Exclusion Criteria has had to change.
59	**Change:** Tables – with the addition of Table #5, Tables 5 to 7 become Tables 6 to 8
60	**Change:** all references to the 2 treatment periods of Week 17 (4-month treatment arm) and Week 26 (6-month treatment arm) are stated as either Week 17 or Week 26, only.
61	**Change:** all references to 'study' have been changed to 'trial' for consistency.
62	**Change:** all references to 'patient' (where applicable) have been changed to 'participant' for consistency.
63	**Change:** all references to B-Pa-M-Z have been changed to BPaMZ.
64	**Change:** all references to 'therapy' has been changed to 'treatment' for consistency.
65	**Change:** all references to early morning sample or early morning sputum, has been changed to EMS, Early Morning Sputum, per the 'Abbreviations and Definition of Terms'.
66	**Change:** all references to Drug Resistant TB (DR-TB) and Drug Sensitive TB (DS-TB), are documented as either DS-TB or DR TB, per the 'Abbreviations and Definition of Terms'.
67	**Change:** all references to trial medication and or study medication, has been changed to 'trial IMP' where appropriate, per the 'Abbreviations and Definition of Terms'.
68	**Delete:** all references to study time points in 'months'. All study time points are only referenced in weeks.
69	Administrative changes, including spelling, grammar, format, use of 'Abbreviations and Definition of Terms' in the protocol body, have been implemented and updated throughout the entire document.

#	Section	Previous Text Version 2.0 dated 21-Feb-18	Amended Text Version 3.0 dated 14-Jan-19 Additional text - bold font. Deleted text – strike-through.	Reason for Change Insert reason # from table above
1	Cover Page	Global Alliance for TB Drug Development TB ALLIANCE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT	TB Alliance TB ALLIANCE	1

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2	Protocol signature page	**LEAD INVESTIGATOR** I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations. Signature Printed Name Date	~~**LEAD INVESTIGATOR**~~ ~~I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations.~~ ~~Signature~~ ~~Printed Name~~ ~~Date~~	2
3	Abbreviations and Definitions of Terms	No previous text	**DST Drug Susceptibility Testing**	3
4	Abbreviations and Definitions of Terms	No previous text	**HR Hazard Ratio**	4
5	Abbreviations and Definitions of Terms	LTFU Long term follow-up	**LTFU Lost to Follow-up**	5
6	Abbreviations and Definitions of Terms	No previous text	**WGS Whole Genome Sequencing**	6

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7	1.1 Synopsis Summary, Trial Objectives	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with: **Drug Sensitive TB (DS-TB)** – BPaMZ given for 17 Weeks (4 months), or – Standard HRZE/HR treatment given for 26 weeks (6 months) **Drug Resistant TB (DR-TB)** – BPaMZ given for 26 Weeks (6 months) **DR-TB Defined as participants with** 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with: Drug Sensitive TB (DS-TB) – ~~BPaMZ given for 17 Weeks (4 months), or~~ – ~~Standard HRZE/HR treatment given for 26 weeks (6 months)~~ Drug Resistant TB (DR-TB) – ~~BPaMZ given for 26 Weeks (6 months)~~ DR-TB Defined as participants with 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)	7

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8	1.1 Synopsis Summary, Statistical Methods	No previous text to describe the abbreviated SAP definitions	**Abbreviated Definitions, full definitions will be described in the Statistical Analysis Plan (SAP):** • **Bacteriologic failure: During the treatment period, failure to attain or maintain culture conversion to negative.** • **Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status, with culture conversion to positive status with a strain of *Mycobacterium tuberculosis* (MTB) genetically identical to the infecting strain at baseline.** • **Clinical failure: A change from protocol-specified TB treatment to a new regimen before end of protocol specified treatment due to treatment failure, retreatment for TB during follow up, or TB-related death.** **Note:** ○ **Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.** ○ **Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit.**	8

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9	1.1 Synopsis Summary, Positive Control Product, Dose and Mode of Administration and Protocol Section 6.1.2	No previous text	**The participant's weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and HRZE and HR dose to administer.**	9
10	1.1 Synopsis Summary, Treatment Interruptions /Pauses and Protocol Section 6.3	• Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required. • Greater than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been. • Greater than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial. • If the participant misses a total (sum) of 56 cumulative missed doses, discontinue the IMP and withdraw participant from the trial.	• Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required. • ~~Greater~~ **If more** than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been. • ~~Greater~~ **If more** than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial. • If the participant misses a total (sum) of 56 cumulative missed doses, discontinue the IMP and withdraw **the** participant from the trial. **If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose that was missed.**	10

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11	1.1 Synopsis, Statistical Methods and Protocol Section 9.0 Statistical Analysis	A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the statistical analysis plan (SAP,) which will be written and signed off prior to the first participant enrolled in the trial.	A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP) which will be written and signed off **prior to the interim analysis.**	11

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12	1.1 Synopsis, Statistical Methods and Protocol Sections 2.3.1 Trial Design Rationale, and 9.3 Interim Analysis	No previous text	**<u>Interim Analysis</u>** **There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:** **If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the study on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The study efficacy objectives will be updated as follows:** - **Primary Objective** ***To determine the incidence of bacteriologic failure or relapse or clinical failure at 52 weeks from the start of treatment / randomisation.*** - **Secondary Objective** ***To evaluate the time to culture negativity over 8 weeks, from the start of treatment / randomisation.*** **All other study objectives will remain unchanged.**	12

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			To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework and full details are provided in the Statistical Analysis Plan.	
13	1.1 Synopsis, Trial Duration	Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until week 104 from start of treatment. Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms is complete. There will be 3 database locks, data analyses and trial reports generated for this trial: 1. When all participants have completed 8 weeks (2 months) of treatment from baseline. 2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy. 3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.	Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until week 104 from start of treatment. Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms is complete. ~~There will be 3 database locks, data analyses and trial reports generated for this trial:~~ ~~1. When all participants have completed 8 weeks (2 months) of treatment from baseline.~~ ~~2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy.~~ ~~3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.~~	13
14	1.2 Synopsis Flow Chart and Procedures	1.2 Synopsis Flow Chart and Procedures Period: Screen-ing[a]; Treatment Visit[b]: Day -9 to -1; Day 1 (Baseline)[d]; Day 7 (Week 1); Week 2; Week 3; Week 4; Week 5; Week 6; Week 7; Week 8; Week 12	1.2 Synopsis Flow Chart and Procedures Period: Screen-ing[a]; Treatment Visit[b]: Day -9 to -1; Day 1 (Baseline)[d]; Week 1; Week 2; Week 3; Week 4; Week 5; Week 6; Week 7; Week 8; Week 12	14

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15	1.2 Synopsis Flow Chart and Procedures (foot notes), General	GENERAL: Vital signs, ECGs and blood draws are to be performed pre-dosing unless otherwise specified. Vital signs and/or ECGs should be done prior to blood draws (safety and PK) on days with those assessments.	GENERAL: Vital signs~~, ECGs~~ and blood draws are to be performed **before** dosing unless otherwise specified. Vital signs and/or ECGs should be done **before** blood draws (safety and PK) on days with those assessments.	15
16	1.2 Synopsis Flow Chart and Procedures (foot note a)	Screening: Screening assessments can occur on different days, within nine days before Day 1 dosing (randomisation).	Screening: Screening assessments can occur on different days, within nine days before Day 1 ~~dosing~~ **(**~~randomisation~~ **Baseline).**	16
17	1.2 Synopsis Flow Chart and Procedures (foot notes, f)	Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance	Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance **(Hain MTBDRplus and Hain MTBRsl);**	17
18	1.2 Synopsis Flow Chart and Procedures (foot notes, f)	Baseline to Week 104, including any Unscheduled visits:	**Day 1 (**Baseline**)** to Week 104 **and** ~~including any~~ Unscheduled visits **for additional sputum samples:**	18
19	1.2 Synopsis Flow Chart and Procedures (foot notes, f)	If both sputum samples at Weeks 8, 17 (4-month treatment arm), 26 (6-month treatment arm), 52 or 104 are contaminated, the participant should return for an unscheduled visit(s) to give additional samples or to document that the participant is not able to produce sputum.	If both sputum samples at Weeks 8 **or later**~~, 17 (4-month treatment arm), 26 (6-month treatment arm), 52 or 104~~ are contaminated, the participant should return for an unscheduled visit(s) to give additional samples or to document that the participant is not able to produce sputum.	19

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20	1.2 Synopsis Flow Chart and Procedures (foot notes, g)	Mycobacterial Characterization - MTB isolates will be processed for: - Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin; - Drug Susceptibility Testing for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, pyrazinamide and second line TB drugs including, but not limited to fluoroquinolones, and injectables using an indirect susceptibility test in liquid culture; - Extraction of organismal (MTB) DNA for whole genome sequencing, and comparison of sequences from baseline and relapse isolates.	Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for: - **Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);** - Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin; - Drug Susceptibility Testing (DST) for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, ~~and second line TB drugs including, but not limited to fluoroquinolones, and injectables using an indirect susceptibility test in pyrazinamide~~ in liquid culture; - Extraction of organismal (MTB) DNA for whole genome sequencing **(WGS),** and comparison of sequences from baseline and relapse isolates.	20
21	1.2 Synopsis Flow Chart and Procedures (foot notes, n) and Protocol Section 7.3 Safety and Tolerability Assessments	Single 12-Lead ECG: To every extent possible, this should be performed at approximately the same time of day as the trial procedures (+/-1 hour). Central ECG analysis will be performed. Results from central reading of Day -9 to -1 (Screening) ECG must be used to determine eligibility.	Single 12-Lead ECG: **ECGs to be performed prior to pre- and post-dose PK sampling as described below:** • **Day 1: pre-dose (within 2 hours prior to dosing)** • **Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose** • **Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose** • **Week 12: pre-dose (within 2 hours prior to dosing)** • **Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose** Central ECG analysis will be performed. Results from central reading of ~~Day -9 to -1 (Screening)~~ Screening ECG must be used to determine eligibility.	21

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22	1.2 Synopsis Flow Chart and Procedures (foot notes, s)	Pharmacokinetic (PK) Sampling: This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE-HR treatment arm. Blood draws for PK samples collected pre-dose must be done after the ECG is performed.	Pharmacokinetic (PK) Sampling: This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE/HR treatment arm. Blood draws for PK samples collected pre- **and post-dose** must be done after the ECG is performed.	22
23	1.2 Synopsis Flow Chart and Procedures (foot notes, s)	Weeks 39, 65, 78 and 104: PK samples are to be obtained at any time on the day of the scheduled visit.	Weeks 39, 65, 78 and 104: PK samples are to be obtained at any time on the day of the scheduled visit, **and only bedaquiline and M2 will be measured**.	23
24	1.2 Synopsis Flow Chart and Procedures (foot notes, s) and Protocol Section 7.4 PK Variables and Procedures	No previous text	**If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.**	24
25	1.2 Synopsis Flow Chart and Procedures (foot notes, v)	Investigator Assessment: Investigator to review participant status and assess whether IMP or TB treatment at current visit is considered a “success” or “failure”. If considered a failure, the Investigator should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed, as shown on the flowchart, and at any time Investigator determines that participant fulfils criteria for outcome of treatment failure.	Investigator Assessment: Investigator to review the participant status and assess whether IMP or TB treatment at ~~current visit~~ **Week 52 and 104** is considered a “success” or “failure”. If considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed~~, as shown on the flowchart,~~ **at Week 52 and 104, <u>and at any time</u>** the Investigator determines that the participant fulfils the criteria for outcome of treatment failure.	25

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26	1.2 Synopsis Flow Chart and Procedures (foot notes, x), and Protocol section 7.1	No previous text	**Karnofsky Score: Only to be performed on HIV+ participants.**	26
27	Protocol Section 3.1 Primary Objective	Primary Objectives To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with: Drug Sensitive TB (DS-TB) – BPaMZ given for 17 Weeks (4 months) – Standard HRZE/HR treatment given for 26 weeks (6 months) Drug Resistant TB (DR-TB) – BPaMZ given for 26 Weeks (6 months) DR-TB are defined as participants with: 1. *mono-resistance to rifampicin or isoniazid, OR* 2. *resistance to both rifampicin and isoniazid (DR-TB)*	Primary **Endpoints** To evaluate **the time to culture negativity over 8 weeks from the start of the following treatment regimens in participants with** ~~the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with~~: - Drug Sensitive TB (DS-TB) ~~– BPaMZ given for 17 Weeks (4 months)~~ ~~– Standard HRZE/HR treatment given for 26 weeks (6 months)~~ - Drug Resistant TB (DR-TB) ~~– BPaMZ given for 26 Weeks (6 months)~~ DR-TB are defined as participants with: 2. *mono-resistance to rifampicin or isoniazid, OR* 2. *resistance to both rifampicin and isoniazid (DR-TB)*	27

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28	Protocol Section 3.2 Secondary Objectives, PK and PD	Secondary Objectives Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., Cmin, Cmax, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide.	Secondary **Endpoints** Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., **minimum plasma concentration** [Cmin], **maximum plasma concentration** [Cmax], **area under curve over a dosing interval** [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide.	28
29	Protocol Section 4.1 Summary of Trial Design	Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment allocation during the treatment phase of the trial.	Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment **randomisation and** allocation during the treatment phase of the trial.	29

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30	Protocol Section 4.1 Summary of Trial Design, 6th paragraph	Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive. An interactive web response system (IWRS) will be used which will utilize a dynamic randomization system using cavitation with a random element to allocate participants evenly across the arms by HIV status and type of TB (DS versus DR) after they have given written, informed consent during the Screening Visit (Days -9 to -1) and met all eligibility criteria.	Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive. ~~An interactive web response system (IWRS) will be used which will utilize a dynamic randomization system using cavitation with a random element to allocate participants evenly across the arms by HIV status and type of TB (DS versus DR) after they have given written, informed consent during the Screening Visit (Days -9 to -1) and met all eligibility criteria.~~ **DR participants will be treated with 6 months of BPaMZ**. **DS participants will be randomised** using ~~a~~ **an interactive web response system (IWRS) stratifying for cavitation and HIV status to allocate participants evenly across the arms after they have given written, informed consent during the Screening Visit (Days -9 to -1).**	30
31	Protocol Section 5.1, Inclusion Criteria #5	DS-TB treatment arm participants should be: sensitive to rifampicin and isoniazid by rapid sputum-based test	DS-TB treatment arm participants should be: sensitive to rifampicin, isoniazid **and fluoroquinolones** by rapid sputum-based test.	31
32	Protocol Section 5.1, Inclusion Criteria #5	If they are randomised into the trial due to being sensitive to rifampicin and isoniazid by rapid molecular sputum-based test, however on receipt of the rifampicin and/or isoniazid phenotypic resistance testing in liquid culture this shows they are rifampicin or isoniazid resistant, they will be: - Excluded as late exclusions; - Possibly replaced as determined by the Sponsor.	~~If they are randomised into the trial due to being sensitive to rifampicin and isoniazid by rapid molecular sputum-based test, however on receipt of the rifampicin and/or isoniazid phenotypic resistance testing in liquid culture this shows they are rifampicin or isoniazid resistant, they will be:~~ ~~- Excluded as late exclusions;~~ ~~- Possibly replaced as determined by the Sponsor.~~	32

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33	Protocol Section 5.1, Inclusion Criteria #5	DR-TB treatment arm participants should be: a. Resistant to rifampicin and/or isoniazid. b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 7 days at start of screening.	DR-TB treatment arm participants should be: a. Resistant to rifampicin and/or isoniazid; **but sensitive to fluoroquinolones by rapid sputum-based test AND** b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than ~~7~~ **3** days at start of screening. c. **Participants with resistance to injectables by rapid sputum-based test are allowed in the trial.** **When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.**	33

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34	Protocol Section 5.1 Inclusion Criteria #7, Contraception	Effective birth control methods: a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female participant. c. Male participants' female sexual partner: Double barrier method or hormone-based contraceptives or an intra-uterine device for the female partner. Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 12 weeks after the last dose of trial medication or discontinuation from trial medication in case of premature discontinuation.	Effective birth control methods: a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device ~~for the female participant~~. c. Male participants' female sexual partner: ~~Double~~ Barrier method **combined with** hormone-based contraceptives or an intra-uterine device ~~for the female partner~~. Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for **6 months** ~~12 weeks~~ after the last dose of trial IMP or discontinuation from trial IMP in case of premature discontinuation.	34
35	Protocol Section 5.2 Exclusion Criteria #3	No previous text	**Historical and or current use of local traditional medications/herbs which in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.**	35

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36	Protocol Section 5.2 Exclusion Criteria #9 (previous protocol)	Resistant to fluoroquinolones (rapid, sputum-based molecular screening tests) - If they are randomised into the trial due to being sensitive to fluoroquinolones by rapid sputum-based test, however on receipt of the moxifloxacin phenotypic resistance testing in liquid culture they are found to be fluoroquinolones resistant, they will be excluded as late exclusions.	~~Resistant to fluoroquinolones (rapid, sputum-based molecular screening tests)~~ ~~- If they are randomised into the trial due to being sensitive to fluoroquinolones by rapid sputum-based test, however on receipt of the moxifloxacin phenotypic resistance testing in liquid culture they are found to be fluoroquinolones resistant, they will be excluded as late exclusions.~~	36
37	Protocol Section 5.2 Exclusion Criteria #14, 15, 16, 17 (previous protocol)	14. Previous treatment with pretomanid or bedaquiline. 15. Previous treatment for TB which includes, but is not limited to, gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole. 16. For DS-TB participants: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days prior to randomization 17. For the DR-TB participants: Previous treatment for DR-TB/MDR-TB, although may have been on a DR/MDR-TB treatment regimen for no longer than 7 days at start of screening.	~~Previous treatment with pretomanid or bedaquiline.~~ ~~Previous treatment for TB which includes, but is not limited to, gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.~~ **14. Previous treatment for TB:** <u>For DS-TB participants</u>: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days at the start of the Screening visit. <u>For the DR-TB participants</u>: Previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than **3** days at the start of the Screening visit.	37

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38	Protocol Section 5.2 Exclusion Criteria # 17	Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), due to visual opacities or cataracts.	Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), ~~due to~~ **as they can lead to** visual opacities or cataracts.	38

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39	Protocol Section 5.2 Exclusion Criteria # 18	For HIV infected participants, only the following types of ART are permissible: a. Lopinavir/ritonavir-based regimen consisting of lopinavir/ritonavir in combination with any two NRTI. TDF/ABC and FTC/3TC. b. Integrase inhibitor (e.g., dolutegravir) in combination with TDF/ABC and FTC/3TC. c. In participants who have viral load suppressed on efavirenz at the time of screening, their ART can be changed to rilpivirine in combination with TDF/ABC and FTC/3TC. If possible, the same nucleoside backbone should be used. d. Nevirapine (NVP) based regimen consisting of NVP in combination with any two nucleosidase reverse transcriptase inhibitors (NRTIs) tenofovir (TDF)/abacavir (ABC) and emtricitabine (FTC)/lamivudine (3TC). In the case where participants are randomized to a rifampicin containing regime: a. EFV can be used with rifampicin. b. LPV needs to be double dosed. c. Rilpivirine cannot be given with rifampicin	For HIV infected participants ~~only the following types of ART are permissible~~: **a. The following antiretroviral therapy (ART) should not be used with either (BPaMZ and HRZE/HR) trial regimen:** **1. Stavudine** **2. Didanosine** **3. Triple NRTI regimen is not considered optimal for HIV treatment (poor efficacy)** **b.** In the case where participants are randomised to HRZE arm, **<u>rilpivirine and etravirine cannot be given</u> with rifampicin due to drug-drug interactions. A standard NRTI backbone may be used in combination with one of the following:** **1. Efavirenz requires no dose adjustment** **2. Dolutegravir dose adjustment is required – double dose when co-prescribed with rifampicin.** **3. Raltegravir requires no dose adjustment** **4. Lopinavir/r dose adjustment is required – double dose when co-prescribed with rifampicin** **5. Nevirapine requires no dose adjustment, however please note that nevirapine based regimens are associated with higher ART failure in participants having or known to have a previous viral load more than or equal to 100,000/ mL** **c. In the case where participants are randomized to the BPaMZ trial regimen, a standard NRTI backbone may be combined with the following:**	39

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			1. Rilpivirine **2. Dolutegravir** **3. Raltegravir** **4. Nevirapine** **5. Lopinavir/r** **6. Participants who are on efavirenz, atazanavir/r or darunavir/r at the time of screening and have an undetectable viral load, should have their ART switched to one of the agents listed above (1-5). It would be preferable to switch to another permissible ARV within the same class accompanied by the same nucleoside backbone.** **d. ART regimen choice should be discussed with the Sponsor Medical Monitors if there are any concerns.** **Confirmed plans to use Isoniazid prophylaxis for HIV positive participants during the treatment and follow up period is not permitted.**	

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40	Protocol Section 5.2 Exclusion Criteria, Diagnostic and Laboratory Abnormalities, Item #19 (Previously #22)	a. platelets grade 2 or greater (<100,000/mm^3) b. creatinine grade 2 or greater (>1.5 times upper limit of normal [ULN]) c. eGFR ≤ 60 mL/min/m^2 d. haemoglobin grade 2 or greater (≤8.0 g/dL) e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once f. GGT: greater than 3 x ULN g. AST: • grade 3 or greater (≥3.0 x ULN) to be excluded; • results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor h. ALT: • grade 3 or greater (≥3.0 x ULN) to be excluded • greater than ULN must be discussed with and approved by the Sponsor Medical Monitor i. ALP: • grade 3 or greater (≥3.0 x ULN) to be excluded • grade 2 (2.0 – <3.0 x ULN) must be discussed with and approved by the Sponsor Medical Monitor j. Total bilirubin: • >1.5 x ULN to be excluded; • 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor k. Direct bilirubin: • greater than 1x ULN to be excluded	a. platelets ~~grade 2 or greater (<100~~<75,000/mm^3~~)~~ b. creatinine ~~grade 2 or greater (~~>1.5 times upper limit of normal (~~[~~ULN~~]~~) c. eGFR ≤ 60 mL/min~~/m^2~~ d. haemoglobin ~~grade 2 or greater (≤~~<8.0 g/dL~~)~~ e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once f. GGT: greater than 3 x ULN g. AST: • ~~grade 3 or greater (~~≥3.0 x ULN~~)~~ to be excluded; • results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor h. ALT: • ~~grade 3 or greater (~~≥3.0 x ULN~~)~~ to be excluded • greater than ULN must be discussed with and approved by the Sponsor Medical Monitor i. ALP: • ~~grade 3 or greater (~~≥3.0 x ULN~~)~~ to be excluded • ~~grade 2 (~~2.0 – <3.0 x ULN~~)~~ must be discussed with and approved by the Sponsor Medical Monitor j. Total bilirubin: • >1.5 x ULN to be excluded; • **greater than** 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor k. Direct bilirubin: • greater than 1x ULN to be excluded	40
41	Protocol Section 5.3 Restrictions	Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are necessary for the participant's welfare and are unlikely to	Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are necessary for the participant's welfare ~~and are unlikely to~~	41

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		interfere with the IMP, they may be given at the discretion of the Investigator.	~~interfere with the IMP~~, they may be given at the discretion of the Investigator.	
42	Protocol Section 5.3 Restrictions	The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible unless discussed with the Sponsor Medical Monitor:	The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible **(unless this is required for emergency management of the participant**~~) unless discussed with the Sponsor Medical Monitor~~**. Investigators may also contact the Sponsor Medical Monitor for further guidance.**	42
43	Protocol Section 5.3 Restrictions	Any drug known to be hepatotoxic (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…	Any drug known to be hepatotoxic (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~~…	43

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44	Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal	A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following: • Withdrawal of informed consent • Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment. • Pregnancy • At the specific request of the Sponsor or termination of the trial by the Sponsor. • Lost to follow-up • Drug-Sensitive TB treatment arms: participants, who have been randomised onto the trial as a rifampicin sensitive participant on the rapid sputum based test result, who on receipt of the rifampicin resistance testing using an indirect susceptibility test in liquid culture, shows a rifampicin resistant result. • Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result.	A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following: • Withdrawal of informed consent • Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment • Pregnancy • At the specific request of the Sponsor or termination of the trial by the Sponsor • Lost to follow-up • ~~Drug-Sensitive TB treatment arms: participants, who have been randomised onto the trial as a rifampicin sensitive participant on the rapid sputum based test result, who on receipt of the rifampicin resistance testing using an indirect susceptibility test in liquid culture, shows a rifampicin resistant result.~~ • ~~Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result.~~ • **When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that**	44

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			participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.	
45	Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal	- Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum-based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result. - Early withdrawal due to TB (see Section 5.4.4)	~~- Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum-based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result.~~ ~~- Early withdrawal due to TB (see Section5.4.4)~~	45

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<table>
<tr>
<td>46</td>
<td>Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal</td>
<td>The following situation/s would require an unscheduled visit/s:

- If both sputum samples (Early Morning and Spot) at Week 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum.
- If there is a MTB confirmed positive culture at or after the end of treatment at Week 17 (4-month treatment) or Week 26 (6-month treatment), the participant should return for an Unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum. If no early morning sputum sample was provided by the participant, 2 samples may be collected at the site, at least 30 minutes apart.

Table 6 is a new table and did not previously exist in Protocol V2.0.

If the Investigator is unsure of the outcome in any of the above scenarios the Investigator is to contact the Sponsor Medical Monitor and discuss and agree on how the participant is to be managed.</td>
<td>The following situation/s would require an unscheduled visit/s:

- For any medical reason, as determined by the Investigator or participant.
- If both sputum samples (EMS and spot sputum sample) at Week 8 or later are contaminated, the participant should return for an unscheduled visit/s to give 2 (EMS and spot sputum sample, at each visit ~~under the coaching and observation of the trial staff~~) additional sputum samples or to document that the participant is not able to produce sputum.
- ~~If there is a MTB confirmed positive culture~~ If after having converted to culture negative, the participant has a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 or Week 26) ~~Week 17 (4-month treatment) or Week 26 (6-month treatment)~~, the participant should return for Unscheduled visit/s to provide 2 (EMS and spot sputum sample, at each visit) additional sputum samples ~~under the coaching and observation of the trial staff~~), at a minimum of 7 days apart, or to document that the participant is not able to produce a sputum sample.

Table 6: Summary of Scenarios Requiring Unscheduled Visits for Mycobacteriology Testing
<table>
<tr><th>Time-point</th><th>Scenario</th><th>Unscheduled Visit/s Required?</th><th>Comment</th></tr>
<tr><td>Week 8 or later</td><td>Both sputum cultures are contaminated</td><td>Yes</td><td>Provide additional samples until a positive or negative result is reported, or it is confirmed that the participant is unable to produce sputum</td></tr>
<tr><td>At or after the last treatment visit (Week 17 or Week 26)</td><td>Previously converted to culture negative but now has an MTB-positive culture</td><td>Yes</td><td>Provide additional samples at least 7 days after the previous sample until the result is confirmed, or it is confirmed that the</td></tr>
</table>
</td>
<td>46</td>
</tr>
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<table>
<tr><th>#</th><th>Section</th><th>Previous Text
Version 2.0 dated 21-Feb-18</th><th>Amended Text
Version 3.0 dated 14-Jan-19
Additional text - bold font. Deleted text – strike-through.</th><th>Reason for Change
Insert reason # from table above</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td></td><td></td><td>participant is unable to produce sputum.</td></tr>
<tr><td>End of Follow-up Period (Week 52 and 104) Early Withdrawal, if applicable</td><td>Participant's primary outcome status cannot be confirmed by: 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</td><td>Yes</td><td>Provide additional samples at least 7 days after the previous sample until one of the criteria is met and the primary outcome status can be determined.</td></tr>
</table>

If the Investigator is unsure of the outcome in any of the above scenarios, the Investigator should ~~is to~~ contact the Sponsor Medical Monitor to discuss and agree on how the participant is to be managed.</td><td></td></tr>
<tr><td>47</td><td>Protocol Section 5.4.4 Early Withdrawal due to TB</td><td>The participants will be provided with a referral letter from the Investigator to take with them to the TB clinic. A follow-up call will be made by the trial site staff to the clinic to ensure the participant attended the clinic.</td><td>The participant will be provided with a referral letter from the Investigator to take with them ~~to the TB clinic~~ their National Treatment Program (NTP) clinic and the referral letter, at a minimum, should include all treatment received by the participant and information about any suspected/confirmed adverse event/reaction related to any of the trial IMP's and or concomitant medications. A follow-up call ~~will~~ should be made by the trial site staff to the clinic to ensure the participant attended the NTP clinic.</td><td>47</td></tr>
</table>

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48	Protocol Section 7.1 Demographic and Background Variables and Procedures	Screening coached spot sputum samples: ○ Smear microscopy for acid-fast bacilli ○ Gene Xpert, Hain Assay MTBDRplus or equivalent to determine MTB complex and rifamycin resistance	Screening coached spot sputum samples: ○ Smear microscopy for acid-fast bacilli ○ ~~Gene Xpert~~ **Rapid molecular tests for isoniazid, rifampicin, fluoroquinolones resistance** (Hain MTBDRplus and **HainMTBRsl**) ○ **Liquid Culture (MGIT) for Mycobacterium tuberculosis (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive.**	48
49	Protocol Section 7.1 Demographic and Background Variables and Procedures	Method of birth control: male and female participants and their partners	Method of birth control: male and female participants and their **sexual** partners	49
50	Protocol Section 7.4 PK Variables and Procedures	Plasma concentrations from sparse sampling (see Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, and linezolid to further evaluate the effects of covariates on model parameters in this trial population. PK data from the current trial may be combined with prior data (e.g., from the NiX-TB trial) to enhance this population PK analysis.	Plasma concentrations from sparse sampling (see Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite pretomanid, ~~and linezolid~~ to further evaluate the effects of covariates on model parameters in this trial population. PK data from the current trial may be combined with prior data ~~(e.g., from the NiX-TB trial)~~ to enhance this population PK analysis.	50

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51	Protocol Section 7.5 Mycobacteriology Characterisation Variable and Procedures	Mycobacteriology Characterization Variable and Procedures The following Mycobacterial Characterization variables will be collected: Positive Culture (for MTB) from: • Day 1 or if Day 1 is not available, first positive result between screening through Week 4 • Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be sub-cultured and sent to the central microbiology laboratory from the applicable local microbiology laboratory, for relevant participants / no positive cultures from screening through week 4 • When applicable, at last visit of the treatment period (Week 17 for the 4-month treatment arm and Week 26 for the 6-month treatment arm) or visits with positive cultures, during the post-treatment follow-up period The MTB isolates will be processed at the central microbiology laboratory for: • MIC against bedaquiline, pretomanid and moxifloxacin • Drug Susceptibility Testing in liquid culture for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide, and second line TB drugs including but not limited to fluoroquinolones, and injectables • Extraction of organismal (MTB) DNA for whole genome sequencing, and the comparison of sequences from baseline and relapse isolates.	Mycobacteriology Characterization Variable and Procedures ~~The following Mycobacterial Characterization variables will be collected:~~ ~~Positive Culture (for MTB) from:~~ • **Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative).** • ~~Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be sub-cultured and sent to the central microbiology laboratory from the applicable local microbiology laboratory, for relevant participants / no positive cultures from screening through week 4~~ • **MTB confirmed positive cultures (after the participant has previously converted to negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.** • **Refer to the Mycobacteriology Laboratory Manual for full details.** **Mycobacterial Characterization** - MTB isolates **(from the first MTB positive culture)** will be processed for: • **Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);** • **Minimum Inhibitory Concentration** (MIC) against bedaquiline, pretomanid, and moxifloxacin; • DST ~~in liquid culture~~ for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, and	51

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		All Day 1 (Baseline) MTB isolates and isolates from positive cultures to be stored at the local and central microbiology laboratories, until trial closure. Extracted MTB DNA to be stored at the central microbiology laboratory until trial closure. The extracted MTB DNA and isolates will then be stored for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure. The MTB isolates will be processed at the trial microbiology laboratories for positive MTB complex at/after the last visit of the treatment period (Week 17 for the 4-month treatment arm and Week 26 for the 6-month treatment arm) via Hain MTBDR*plus* and HainMTBR*sl*.	pyrazinamide, ~~and second line TB drugs including but not limited to fluoroquinolones, and injectables~~ **in liquid culture**; • Extraction of organismal (MTB) DNA for whole genome sequencing **(WGS),** and comparison of sequences from baseline and relapse isolates. **If the participant's culture converts to negative and has a MTB positive culture at or after the last visit of the treatment period (Week 17 and Week 26), the MTB cultures** ~~isolates will be processed~~ **will be tested at the trial mycobacteriology laboratories** ~~for positive MTB complex~~ **using Hain MTBDR*plus* and HainMTBR*sl* to detect resistance to isoniazid, rifampicin, fluoroquinolones and injectables.** All ~~Day 1 (Baseline)~~ MTB isolates and isolates from positive cultures to must be stored at the local mycobacteriology laboratories, until trial closure. **In addition**, MTB ~~DNA~~ **isolates as well as extracted MTB DNA from the applicable baseline and follow-up cultures** will be stored at the central mycobacteriology laboratory for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure.	
52	Protocol Section 8.2.1 Follow-up of Adverse Events	New or updated information will be recorded in the originally completed CRF and submitted to the Sponsor within 24 hours of receipt, per SAE reporting guidelines.	New or updated SAE information will be recorded in the originally completed CRF and submitted to the Sponsor within 24 hours of receipt, per the ~~SAE~~ **eCRF Completion Guideline.**	52

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53	Protocol Section 8.2.6 Pregnancy	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: • Any time during the trial • Within 6 months after the last dose of IMP	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) **at any time during the trial.** ~~for the following time-periods:~~ ~~• Any time during the trial~~ ~~• Within 6 months after the last dose of IMP~~	53
54	Protocol Section 8.3 Monitoring for Specific Toxicities	Neurological Participants co-administration with a serotonergic agent, including anti-depressants, should be monitored closely for signs of serotonin syndrome. The Investigator should determine whether the full regimen or the concomitant agent should be discontinued for those who experience signs or symptoms of serotonin syndrome such as cognitive dysfunction, hyperrexia, hyperreflexia and incoordination.	~~Neurological~~ ~~Participants co-administration with a serotonergic agent, including anti-depressants, should be monitored closely for signs of serotonin syndrome. The Investigator should determine whether the full regimen or the concomitant agent should be discontinued for those who experience signs or symptoms of serotonin syndrome such as cognitive dysfunction, hyperrexia, hyperreflexia and incoordination.~~	54
55	Protocol Section 9.0 Statistical Analysis	Statistical Analysis The statistical analysis plan (SAP), which will contain details of the analyses specified in this section, will be written and signed off prior to first patient randomized.	Statistical Analysis The statistical analysis plan (SAP), which will contain details of the analyses specified in this section, will be written and signed off prior to **the interim analysis.** **There will be 3 data analyses and trial reports generated for this trial:** **- When all participants have completed 8 weeks (2 months) of treatment from baseline.** **- When all participants have completed 52 weeks (12 months) follow-up from start of therapy.** **- When all participants have completed 104 weeks (24 months) follow-up from start of therapy.**	55

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56	Protocol Section 11.3 Protocol Deviations	A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Monitoring Plan requirements.	A protocol deviation is any noncompliance with the clinical trial protocol **and** GCP ~~or Monitoring Plan requirements~~.	56
57	Appendix 6 Appendix 7 Appendix 8	TB Symptom Profile **TUBERCULOSIS SYMPTOM PROFILE (V3)** This questionnaire asks about symptoms that patients with tuberculosis may or may not experience. Please read each symptom carefully and think about your experience **during the past 7 days** when you make your response. Then tick (☑) one box for each symptom. If you **did not** experience the symptom **during the past 7 days**, please tick (☑) "None" for that symptom. If you **did** experience the symptom **during the past 7 days**, please tick (☑) whether the intensity of the symptom you experienced was "Mild", "Moderate" or "Severe". **TB Symptom** — **Rate your experience of each symptom over the past 7 days.** Feeling feverish: ☐ None ☐ Mild ☐ Moderate ☐ Severe Feeling chills: ☐ None ☐ Mild ☐ Moderate ☐ Severe Excessive sweating: ☐ None ☐ Mild ☐ Moderate ☐ Severe Shortness of breath: ☐ None ☐ Mild ☐ Moderate ☐ Severe Chest pain: ☐ None ☐ Mild ☐ Moderate ☐ Severe Feeling unwell: ☐ None ☐ Mild ☐ Moderate ☐ Severe Tiredness/weakness: ☐ None ☐ Mild ☐ Moderate ☐ Severe Cough: ☐ None ☐ Mild ☐ Moderate ☐ Severe Coughing up mucus: ☐ None ☐ Mild ☐ Moderate ☐ Severe Coughing up blood: ☐ None ☐ Mild ☐ Moderate ☐ Severe **During the past 7 days**, how would you rate your appetite? ☐ Good ☐ Fair ☐ Poor Approved, Issued Date 09-Apr-2012 Patient Reported Health Status Questionnaire	~~TB Symptom Profile~~ ~~Patient Reported Health Status Questionnaire~~	57

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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 ❑

2

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		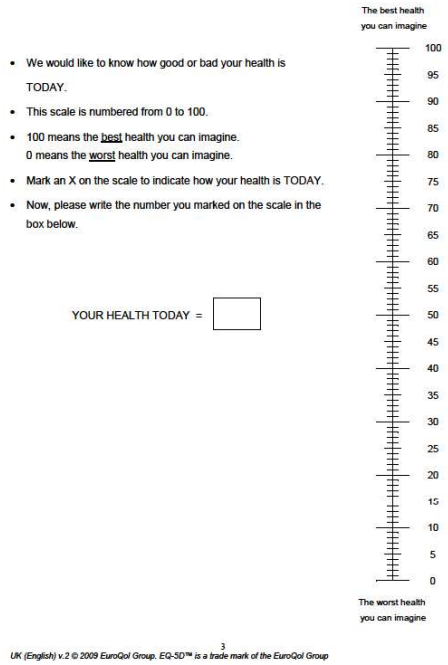 The best health you can imagine 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 The worst health you can imagine • We would like to know how good or bad your health is TODAY. • This scale is numbered from 0 to 100. • 100 means the best health you can imagine. 0 means the worst health you 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 = 3 UK (English) v.2 © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group Liver Toxicity Management Standard anti-TB chemotherapy is known to cause derangement of liver function tests in a substantial number of patients. In many cases this will be asymptomatic and self-limiting. In some cases, severe hepatitis and even fulminant liver failure and death can occur. In pre-marketing clinical trials of new drugs and regimens it is especially important to identify and carefully manage	~~Liver Toxicity Management~~ ~~Standard anti-TB chemotherapy is known to cause derangement of liver function tests in a substantial number of patients. In many cases this will be asymptomatic and self-limiting. In some cases, severe hepatitis and even fulminant liver failure and death can occur.~~ ~~In pre-marketing clinical trials of new drugs and regimens it is especially important to identify and carefully manage any trial participants who are at risk of progression to~~	

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		any trial participants who are at risk of progression to serious liver injury. The observation of altered liver function to a degree that has a high risk of progressing to liver failure as been referred to informally as Hy's Law;[44, 45]; this reflects that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components: 1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo. 2. Among trial participants showing such aminotransferase (AT) elevations, often with ATs much greater than 3x ULN, one or more also show elevation of serum total bilirubin (TBL) to >2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase (ALP)). 3. No other reason can be found to explain the combination of increased AT and total bilirubin level (TBL), such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury. During the trial, liver function will be monitored regularly with clinical assessment and blood tests in trial participants and this will assist in follow up laboratory measurements that can document either resolution of abnormalities or signal the potential for drug-induced liver injury (DILI). In a clinical trial of new drugs and combinations it is especially important for Investigators to follow closely any participants who have evidence of hepatic inflammation or potential toxicity. The	~~serious liver injury. The observation of altered liver function to a degree that has a high risk of progressing to liver failure as been referred to informally as Hy's Law;[44, 45]; this reflects that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components:~~ ~~4. 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.~~ ~~5. Among trial participants showing such aminotransferase (AT) elevations, often with ATs much greater than 3x ULN, one or more also show elevation of serum total bilirubin (TBL) to >2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase (ALP)).~~ ~~6. No other reason can be found to explain the combination of increased AT and total bilirubin level (TBL), such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.~~ ~~During the trial, liver function will be monitored regularly with clinical assessment and blood tests in trial participants and this will assist in follow up laboratory measurements that can document either resolution of abnormalities or signal the potential for drug-induced liver injury (DILI). In a clinical trial of new drugs and combinations it is especially important for Investigators to follow closely any participants who have evidence of hepatic inflammation or potential toxicity. The following procedure describes the management of~~	

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		following procedure describes the management of deranged liver function tests in trial participants. Procedure Blood tests for liver function will be taken routinely at screening (Day -9 to -1) and at the specific time points designated in the protocol, and at Early Withdrawal. If at any other visit the clinician suspects derangement of liver function, e.g. the participant describes nausea and vomiting, right upper abdominal pain or is jaundiced, blood should be taken for liver function tests and the participant comprehensively assessed for evidence of hepatitis or hepatic impairment and any potentially contributing causes. Suspected liver toxicity (or elevated liver enzymes detected in the absence of symptoms) must be taken seriously and detailed guidance will be provided in a separate document, Management of Hepatotoxicity Guideline. Investigators should refer to this document as a guide to management in cases of suspected or proven liver toxicity. Importantly, the Sponsor Medical Monitor is available to provide further assistance if there is any uncertainty or additional questions. The laboratory source (print-out of any results) should be stored alongside or transcribed into the clinical source document. Each abnormal value should be marked as clinically significant (CS) or non-clinically significant (NCS); the assessment of significance is at the discretion of the Investigator. All clinically significant abnormal results must be recorded as Adverse Events in the eCRF and graded clinically as per the DMID adult toxicity table grading, (Appendix 2). Assessments and decision making for elevations in aminotransferase values	~~deranged liver function tests in trial participants.~~ ~~Procedure~~ ~~Blood tests for liver function will be taken routinely at screening (Day -9 to -1) and at the specific time points designated in the protocol, and at Early Withdrawal. If at any other visit the clinician suspects derangement of liver function, e.g. the participant describes nausea and vomiting, right upper abdominal pain or is jaundiced, blood should be taken for liver function tests and the participant comprehensively assessed for evidence of hepatitis or hepatic impairment and any potentially contributing causes.~~ ~~Suspected liver toxicity (or elevated liver enzymes detected in the absence of symptoms) must be taken seriously and detailed guidance will be provided in a separate document, Management of Hepatotoxicity Guideline. Investigators should refer to this document as a guide to management in cases of suspected or proven liver toxicity. Importantly, the Sponsor Medical Monitor is available to provide further assistance if there is any uncertainty or additional questions.~~ ~~The laboratory source (print-out of any results) should be stored alongside or transcribed into the clinical source document. Each abnormal value should be marked as clinically significant (CS) or non-clinically significant (NCS); the assessment of significance is at the discretion of the Investigator. All clinically significant abnormal results must be recorded as Adverse Events in the eCRF and graded clinically as per the DMID adult toxicity table grading, (Appendix 2). Assessments and decision making for elevations in aminotransferase values~~	

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		or bilirubin of various levels of concern are detailed below: Elevated liver enzymes considered of clinical significance, but not accompanied by other signs and symptoms, should be reported as an adverse event and should usually be recorded as elevated liver enzymes. If the term "hepatitis" is used, the Safety Data Manager will question the site for additional evidence to support the diagnosis, such as clinical signs and serological or biopsy data. While a liver biopsy is not required to make a diagnosis of hepatitis, the term "hepatitis" should be reserved in most instances for cases where there is supportive evidence beyond a liver enzyme abnormality. However, if the Investigator will confirm the diagnosis of hepatitis just on the basis of clinical signs and laboratory values the diagnosis will be accepted. Should other symptoms or signs be present, these should also be recorded as adverse events. Temporarily Stopping and Restarting Trial Medication Liver function tests that are improving should be repeated regularly, such as every 3 days for the first week then once a week until they return to near baseline values for the participant. Manage the participant symptomatically as required using medications that are not potentially hepatotoxic and discontinue any concomitant drugs, if clinically warranted, that may be hepatotoxic. Infection control issues must be carefully managed whilst TB medications are being withheld, especially if the participant is still culture positive for acid fast bacilli. If trial medication has been temporarily stopped, once the liver function values have decreased	~~or bilirubin of various levels of concern are detailed below:~~ ~~Elevated liver enzymes considered of clinical significance, but not accompanied by other signs and symptoms, should be reported as an adverse event and should usually be recorded as elevated liver enzymes. If the term "hepatitis" is used, the Safety Data Manager will question the site for additional evidence to support the diagnosis, such as clinical signs and serological or biopsy data. While a liver biopsy is not required to make a diagnosis of hepatitis, the term "hepatitis" should be reserved in most instances for cases where there is supportive evidence beyond a liver enzyme abnormality. However, if the Investigator will confirm the diagnosis of hepatitis just on the basis of clinical signs and laboratory values the diagnosis will be accepted. Should other symptoms or signs be present, these should also be recorded as adverse events.~~ ~~Temporarily Stopping and Restarting Trial Medication~~ ~~Liver function tests that are improving should be repeated regularly, such as every 3 days for the first week then once a week until they return to near baseline values for the participant. Manage the participant symptomatically as required using medications that are not potentially hepatotoxic and discontinue any concomitant drugs, if clinically warranted, that may be hepatotoxic. Infection control issues must be carefully managed whilst TB medications are being withheld, especially if the participant is still culture positive for acid fast bacilli.~~ ~~If trial medication has been temporarily stopped, once the liver function values have decreased~~	

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		substantially a decision must be made about further TB management. This will be dependent on the clinical context and a decision must be made in discussion with the Sponsor Medical Monitor. Investigational treatment can only be restarted if the Sponsor Medical Monitor is in agreement with the plan. In all cases treatment should be recommenced under close supervision for any evidence of recurrent liver function abnormalities. If there is a further significant elevation of hepatic enzymes or bilirubin or symptoms of clinical concern after resumption of trial medication, the trial medication should be withdrawn permanently. Participants who permanently discontinue trial medication should be managed as clinically indicated according to local National TB Programme guidelines. The Sponsor Medical Monitor can be contacted for further advice when referring to the National Treatment Program. The Sponsor Medical Monitor is available to assist the Investigators in both the management of liver toxicity and decisions regarding the holding or re-introduction of trial medication. Investigators must involve the Sponsor Medical Monitor in any decisions regarding medication hold or re-start, and there should always be a low threshold for contacting the Sponsor Medical Monitor in cases of elevated liver enzymes.	~~substantially a decision must be made about further TB management. This will be dependent on the clinical context and a decision must be made in discussion with the Sponsor Medical Monitor. Investigational treatment can only be restarted if the Sponsor Medical Monitor is in agreement with the plan. In all cases treatment should be recommenced under close supervision for any evidence of recurrent liver function abnormalities.~~ ~~If there is a further significant elevation of hepatic enzymes or bilirubin or symptoms of clinical concern after resumption of trial medication, the trial medication should be withdrawn permanently. Participants who permanently discontinue trial medication should be managed as clinically indicated according to local National TB Programme guidelines. The Sponsor Medical Monitor can be contacted for further advice when referring to the National Treatment Program.~~ ~~The Sponsor Medical Monitor is available to assist the Investigators in both the management of liver toxicity and decisions regarding the holding or re-introduction of trial medication. Investigators must involve the Sponsor Medical Monitor in any decisions regarding medication hold or re-start, and there should always be a low threshold for contacting the Sponsor Medical Monitor in cases of elevated liver enzymes.~~	

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Sponsor

I agree to the terms of this Protocol Amendment #2.

DocuSigned by:
Morounfolu Olugbosi
Signer Name: Morounfolu Olugbosi
Signing Reason: I approve this document
Signing Time: 14 January 2019 | 07:25 PST
3DABF6C3410E4B8F85E1D6E511FA5A5F

Signature of Study Physician	Morounfolu Olugbosi Printed name	January 14, 2019 | 7:25 AM PST Date

Principal Investigator

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

Signature of Principal Investigator	Printed name	Date

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Envelope Summary Events	Status	Timestamps
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Required hardware and software

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

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Protocol Number:	NC-008 (BPaMZ)
Title:	An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).
Drug(s)/Combination(s):	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Version/Date:	V4.0 / 30 September 2019, Incorporating Amendments 1, 2 and 3
Protocol Name:	SimpliciTB

PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (BPaMZ)**

Protocol Date: **V4.0 / 30 September 2019, Incorporating Amendments 1, 2 and 3**

Protocol Name: **SimpliciTB**

Sponsor: **TB Alliance**

I agree to the terms of this trial protocol.

DocuSigned by:
Morounfolu Olugbosi
Signer Name: Morounfolu Olugbosi
Signing Reason: I approve this document
Signing Time: October 1, 2019 | 5:46 AM PDT
3DABF6C3410E4B8F85E1D6E511FA5A5F

Signature of Study Physician

Morounfolu Olugbosi
Printed Name

October 1, 2019 | 5:46 AM PDT
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PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (BPaMZ)**

Protocol Date: **V4.0 / 30 September 2019, Incorporating Amendments 1, 2 and 3**

Protocol Name: **SimpliciTB**

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

_____ _____
Signature Printed Name

_____
Date

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Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AFB	Acid-fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AREDS2	Age Related Eye Disease Scale 2
ART	Anti-Retroviral Therapy
AST	Aspartate aminotransferase
AUC_{τ}	Area Under Curve over a dosing interval
B	Bedaquiline
BA	Bacterial activity
BMI	Body Mass Index
BPaMZ	Combination of bedaquiline plus pretomanid plus moxifloxacin plus pyrazinamide
C	Clofazimine
CFU	Colony Forming Units
$C_{(max), (min)}$	plasma Concentration (maximum), (minimum)
CO_2	Carbon dioxide
CPK	Creatine Phosphokinase
CYP3A4	Cytochrome P450 3A4
DMID	Division of Microbiology and Infection Disease
DNA	Deoxyribonucleic Acid
DR-TB	Drug-resistant tuberculosis For this particular protocol defined as TB participants with 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB) (participants with fluoroquinolone resistance are excluded)
DS-TB	Drug-sensitive tuberculosis
DSMC	Data Safety and Monitoring Committee
DST	Drug Susceptibility Testing
E	Ethambutol
EBA	Early Bactericidal Activity
EC	Ethics Committee
ECG	Electrocardiogram
EFV	Efavirenz
(e)CRF	(electronic) Case Report Form
EMS	Early Morning Sputum
EWD	Early Withdrawal
FTC	Emtricitabine
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
H	Isoniazid
HR	Hazard Ratio

hERG	Human *Ether-à-go-go* Related Gene
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
HR	Isoniazid plus rifampicin combination tablet
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent to Treat
IUATLD	International Union Against Tuberculosis and Lung Disease
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Linezolid
LH	Luteinizing hormone
LLN	Lower Limit of Normal
LPV	Lopinavir
LTFU	Lost to follow-up
M	Moxifloxacin
MBD	Minimum Bactericidal Dose
MIC	Minimum Inhibitory Concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi Drug Resistant Tuberculosis
MGIT	Mycobacterial Growth Inhibiting Tube
mITT	Modified Intent to Treat
ms	Millisecond
NVP	Nevirapine
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NRTI	(Triple) Nucleosidase Reverse Transcriptase Inhibitor
Pa	Pretomanid
PD	Pharmacodynamic
PP	Per Protocol
PK	Pharmacokinetic
PR	PR interval
R	Rifampicin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSCC	Serial sputum colony counting
TB	Tuberculosis
TDF	Tenofovir
TEAE	Treatment Emergent Adverse Events
TTP	Time to Positivity
ULN	Upper Limit of Normal
WGS	Whole Genome Sequencing
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis
µg(/ml)	micrograms (per millilitre)
Z	Pyrazinamide (tablets)

1.0 Synopsis

1.1 Synopsis Summary

Synopsis	Description
Name of Sponsor/Company	TB Alliance
Name of Finished Products	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Number/Title	NC-008 (BPaMZ) An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB)
Treatment Indication	Pulmonary Tuberculosis (TB)
Trial Objective(s)	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the treatment regimens in participants with Drug Sensitive TB (DS-TB) and Drug Resistant TB (DR-TB). DR-TB is defined as participants with: 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)
Trial Design	Phase 2c multi-centre, open-label, partially randomized clinical trial in Drug Sensitive-TB (DS-TB) and Drug Resistant-TB (DR-TB) participants. All participants will enter post-treatment follow-up which continues until Week 104 from start of treatment / randomisation. **Participants with DS-TB:** Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation. **Participants with DR-TB:**

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td></td><td>Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).</td></tr>
<tr><td>Participant Population</td><td>Up to 450 male and female participants, diagnosed with DS-TB or DR-TB, aged 18 years and over with a target of up to 50% being HIV positive.

300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation.

Up to 150 DR-TB participants will be enrolled.</td></tr>
<tr><td>Test Product, Dose and Mode of Administration</td><td>The Test Product (BPaMZ) consists of a combination of the following products and will be supplied as:
<table>
<tr><th>Product</th><th>Tablet Strength</th><th>Abbreviation</th></tr>
<tr><td>Bedaquiline</td><td>100 mg</td><td>(B)</td></tr>
<tr><td>Pretomanid</td><td>200 mg</td><td>(Pa)</td></tr>
<tr><td>Moxifloxacin</td><td>400 mg</td><td>(M)</td></tr>
<tr><td>Pyrazinamide</td><td>500 mg</td><td>(Z)</td></tr>
</table>
Instructions for Dosing of BPaMZ

Investigational Medicinal Product (IMP) will be administered orally once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months) in the following dosing schemes:

Participants with DS-TB:
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 17 weeks (total treatment duration 4 months)

OR

Participants with DR-TB:
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 26 weeks (Total treatment duration 6 months).</td></tr>
<tr><td>Positive Control Product, Dose and Mode of Administration</td><td>The Control Treatment Regimen (HRZE/HR) will be supplied as:

HRZE Tablets: isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets. This combination will be given for the first 8 weeks.

AND</td></tr>
</table>

Synopsis	Description
	HR Tablets: isoniazid 75 mg plus rifampicin 150 mg combination tablets. This combination will be given from Weeks 9 to 26. **Instructions for Dosing Control Treatment Regimen** To be taken with a glass of water (approximately 240 ml). HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes: Treatment will be administered orally once daily to the HRZE/HR randomized DS-TB participants as follows: **Weeks 1-26:** HRZE/HR tablets daily dose per the participant's weight as follows: **Weight Band** / **Weight Range** / **Number of tablets** 1 / 30-39 kg / 2 2 / 40-54 kg / 3 3 / 55-70 kg / 4 4 / ≥ 71 kg / 5 The participant's weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and HRZE and HR dose to administer. Vitamin B6 daily supplement to be taken with the HRZE/HR treatment, as per each country's TB Treatment Guidelines.
Treatment Interruptions/Pauses	**For All Trial Regimens** The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation, unless an interruption/pause is required urgently for a safety concern. Action required for participants missing the following number of doses within the trial treatment regimens: • Up to 7 consecutive doses: restart treatment, no extension of treatment required. • If more than 7 and to ≤ 35 consecutive doses missed, before the end of the treatment period (Week 17/26): restart treatment, extend the treatment by the number of consecutive doses missed. In this case, the last visit of the treatment period should also be pushed out to the date of the last dose.

Synopsis	Description
	• If more than 35 consecutive doses: discontinue treatment and withdraw participant from the trial. • If the participant misses a total of 56 cumulative missed doses, discontinue the IMP and withdraw the participant from the trial. • If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose, that was missed. Any participant for whom the trial IMP is discontinued (including for non-adherence) should be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial IMP as soon as possible.
Statistical Methods	A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP) which will be written and signed off prior to the interim analysis. **Criteria for Evaluation** **Primary Endpoint** The primary efficacy endpoint will be time to culture negativity over 8 weeks. The primary hypothesis to be evaluated is: • In the participants with DS-TB in the experimental BPaMZ treatment regimen, the time to culture negativity by 8 weeks will be superior, compared to the participants who are treated with the standard HRZE/HR regimen. **Secondary Endpoints** • A key secondary efficacy endpoint will be the proportion of participants experiencing bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks. The hypothesis to be evaluated for this endpoint is: • In the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen. <u>Abbreviated Definitions, full definitions will be described in the Statistical Analysis Plan (SAP)</u>:

Synopsis	Description
	• Bacteriologic failure: During the treatment period, failure to attain or maintain culture conversion to negative. • Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status, with culture conversion to positive status with a strain of *Mycobacterium tuberculosis* (MTB) genetically identical to the infecting strain at baseline. • Clinical failure: A change from protocol-specified TB treatment to a new regimen before end of protocol specified treatment due to treatment failure, retreatment for TB during follow up, or TB-related death. <u>Note</u>: o Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart. o Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit. **Other Secondary Endpoints** <u>Efficacy</u>: • Incidence of bacteriologic failure or relapse or clinical failure at 104 weeks from the start of treatment. • Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of treatment. • Change from baseline in weight. • Change from baseline in TB symptoms. • Change from baseline in Participant Reported Health Status. <u>Safety and Tolerability:</u> • Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death. • Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline. • Quantitative and qualitative electrocardiogram (ECG) results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read. • Changes in male reproductive hormones.

Synopsis	Description
	• Changes in lens opacities. These data will be presented as descriptive analyses, and no inferential tests will be carried out. <u>Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD):</u> Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [C_{min}], maximum plasma concentration [C_{max}], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of concomitant medications, including antiretroviral therapy (ART), where feasible. Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate. <u>Exploratory Objectives:</u> Evaluate whether any of the secondary endpoints predict relapse free cure. Subgroup analysis of populations by HIV status will be performed. No formal statistical comparisons will be made for the participants enrolled with DR-TB. **Sample Size** <u>Primary endpoint</u>: 150 participants per arm (DS-TB patients) will provide at least 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. Additional efficacy parameters will be evaluated including the incidence of bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks and 104 weeks from the start of treatment. Time to unfavourable outcome from assignment of trial treatment through follow-up as a function of time will be analysed using Kaplan-Meier analysis.

Synopsis	Description
	Interim Analysis There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size: If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows: • **Primary Objective** *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.* • **Secondary Objective** *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.* All other trial objectives will remain unchanged. To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46, 47, 48] and full details are provided in the Statistical Analysis Plan.
Trial Duration	Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until 104 weeks from start of treatment). Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms are complete.

1.2 Synopsis Flow Chart and Procedures

Period	Screen-ing[a]	Treatment															Follow-Up[c]					
Visit[b]	Day -9 to -1	Day 1 (Baseline)[d]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 17 *4-mth treatment*[e]	Week 17 *6-mth treatment*[e]	Week 22	Week 26 *4-mth treatment*[e]	Week 26 *6-mth treatment*[e]	Week 39	Week 52	Week 65	Week 78	Week 104	Early Withdrawal[c]
Visit Window[v]	N/A	+/- 3 Days									+/- 5 Days						+/- 14 Days					
Written Informed Consent	X																					
Demography	X																					
Medical/Treatment/ Smoking History	X																					
Inclusion/Exclusion	X	X																				
Sputum Sampling[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Status[h] and CD4 Count[i]	X																					
Karnofsky Score[x]	X																					
Urine Drug Screen[j]	X																					
Urine Pregnancy Test[k]	X	X								X		X	X		X	X						X
Laboratory Safety Test[l]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X						X
Male Reproductive Hormone Tests[m]	X	X										X				X	X					X
12-lead ECG[n]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X					X
Chest X-Ray[o]	X																					
TB Symptoms Profile	X	X		X		X				X		X	X		X	X		X			X	X
Patient Reported Health Status	X	X		X		X				X		X	X		X	X		X			X	X
Vital Signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination[p]	X											X			X	X	X					X
Physical Examination – full[q]	X	X										X				X						X
Physical Examination – limited[r]			X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Pharmacokinetic Sampling[s]		X		X						X	X	X	X				X		X	X	X	
IMP Randomization/ Assignment[t]		X																				
IMP Compliance Check[u]			X	X	X	X	X	X	X	X	X	X	X	X[e]		X						X[t]
Concomitant Medications	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
Investigator Assessment[v]																		X			X	

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

a. **Screening:** Screening assessments can occur on different days, within nine days before Day 1 (Baseline).

b. **Visit Schedule (due to unforeseen circumstances):** If the duration of treatment is extended due to dose interruptions / pauses (7 to ≤ 35 consecutive doses), the last visit of the corresponding treatment period should also be pushed out to the date of the last dose. It is not necessary to have an unscheduled visit at the time that the last visit of the treatment period would have been scheduled on.

c. **Follow-up Visits for Early Withdrawal Participants:** Once a participant has been permanently withdrawn from the trial, they will be required to attend an Early Withdrawal visit (Week 52, if not already performed) and Week 104 follow-up visits. The Week 52 and Week 104 visits will be performed to collect Serious Adverse Event (SAE) information (including verification of survival) and the participant reported TB outcome information only, and may be performed telephonically, at home or a site visit. Visits will occur at Week 52 and/or Week 104 after the participant's start of treatment date. Refer to Table 5 for additional guidance.

d. **Day 1 (Baseline):** All procedures are to be completed before dosing.

e. **Last Visit of the Treatment Period:** Investigational Medicinal Product (IMP) Compliance Check is not performed at the Week 22 visit for participants who have completed treatment at Week 17.

f. **Sputum Sampling:** The sputum sampling methodology, requirements and tests will be described in a separate document, the Mycobacteriology Laboratory Manual.

- Screening (Days -9 to -1). Two spot sputum samples taken 30 minutes apart will be collected at the research site under the coaching and observation of the trial staff. The following analyses will be performed on the first of these samples:
  - Smear microscopy for acid-fast bacilli (AFB);
  - Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance (Hain MTBDRplus and Hain MTBRsl);
  - Liquid Culture (MGIT) for *Mycobacterium tuberculosis* (MTB), followed by a speciation test to detect the presence or absence of MTB and obtain the time to positivity (TTP) when positive.
  - The second sample is collected as a back-up sample to the first sample in case it is technically not possible to obtain a result/s from the first sample. If the Screening spot sputum smear shows an indeterminate result or is AFB negative, the test may be repeated on the back-up sample or on a freshly collected spot sputum, and then that result will be used.
- Day 1 (Baseline) to Week 104 and Unscheduled visits for additional sputum samples:
  - Two sputum samples are collected, ideally one Early Morning Sputum (EMS) brought from home and one spot sputum sample at the research site, under the coaching and observation of the trial staff. If the participant forgets to bring in the EMS, then two spot sputum samples are to be collected at the site, at least 30 min apart, and this altered sample collection is captured within case report form (CRF).
  - If both sputum cultures at Week 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional sputum samples or to document that the participant is not able to produce a sputum sample.

- If after having converted to culture negative, and the participant has a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 or Week 26), the participant should return for unscheduled visit/s to provide additional sputum samples, at a minimum of 7 days apart, or to document that the participant is not able to produce a sputum sample.
- Additional samples may be required to define a participants' primary outcome status as described in Sections 5.4.2 and 7.2.
- Liquid Culture (MGIT) for MTB, followed by a speciation test to detect the presence or absence of MTB and obtain TTP when positive, will be performed on all samples.

g. **Mycobacteriology Characterisation Tests Performed:**

- Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative);
- MTB confirmed positive cultures (after the participant has previously converted to culture negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.
- Refer to the Mycobacteriology Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for:

- Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);
- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin;
- Drug Susceptibility Testing (DST) for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing (WGS), and comparison of sequences from baseline and relapse isolates.

h. **HIV Testing:** If HIV status is a confirmed known positive, a repeated HIV test is not needed provided that a documented HIV test result (ELISA, Western Blot or Electro-Chemiluminescence) is available. If the HIV status is unknown or suspected negative, a HIV test will be requested. If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated if documentation of testing method and negative HIV results can be provided. Repeated HIV testing, during the Screening period is permitted for indeterminate HIV results.

i. **CD4 Count:** Required for all HIV-positive participants.

j. **Urine Drug Screen:** Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at Screening only. Investigator to utilize this result to determine whether participant meets Exclusion Criteria 2. Positive results will not automatically exclude a participant from the trial.

k. **Urine Pregnancy Test:** Women of childbearing potential only, whether they are sexually active or not.

l. **Safety Laboratory Assessments**: The safety laboratory sampling methodology and requirements will be described in a separate document, the Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:

- Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count).

- Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/carbon dioxide [CO_2], creatine phosphokinase [CPK]). GGT is only routinely included at the Screening visit (Day -9 to -1).
- 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.
- When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator should request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].
- Hepatitis A, B and C serology test to be performed at Day 1 (baseline) or where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Protocol V4.0.

m. **Male Reproductive Hormone Tests:** Testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin B to be done on male participants in ALL treatment groups.

n. **Single 12-Lead ECG:** ECGs to be performed prior to pre- and post-dose PK sampling as described below:

- Day 1: pre-dose (within 2 hours prior to dosing)
- Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 12: pre-dose (within 2 hours prior to dosing)
- Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose

Central ECG analysis will be performed. Results from central reading of Screening ECG must be used to determine eligibility.

o. **Chest X-Ray:** A chest x-ray (digital image only) within 6 months prior to or at the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor and this process will be described in a separate document, the Radiology Manual.

p. **Slit Lamp Ophthalmic Examination**: Slit lamp examination will be done at the Screening visit, the last visit of the treatment period (Week 17 or 26) and at Week 39 for both treatment groups. An additional slit lamp at Week 26 will be done for the 4-month treatment group. Slit lamp ophthalmology examination will be performed by an Ophthalmologist with AREDS2 training. Ophthalmology examinations may occur at any time within the window period for the applicable visit i.e. they do not have to be performed on the same day as the trial procedures.

q. **Physical Examination, Full:** Height (m) will only be collected at Screening.

r. **Physical Exam, Limited:** Limited physical exams will include weight and gross neurological, pulmonary, cardiovascular and abdominal exam(s).

s. **Pharmacokinetic (PK) Sampling:** This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE/HR treatment arm. Blood draws for PK samples collected pre- and post-dose must be done after the ECG is

performed. The dates and times of IMP taken prior to all pre-dose PK samples will be collected. Specific PK blood draws will be obtained as follows:

- *Day 1: pre-dose (within 2 hours prior to dosing)
- Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 12: pre-dose (within 2 hours prior to dosing)
- Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose
- Weeks 39, 65, 78 and 104: PK samples are to be obtained at any time on the day of the scheduled visit.

Only bedaquiline and M2 will be measured.

If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.

* Where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Protocol V4.0.

t. **Investigational Medicinal Product (IMP) Randomization/Assignment:** Randomization/Assignment may occur once all the Screening results are available and the Investigator has determined that the participant is eligible for the trial.

u. **IMP/Compliance Check:** IMP administration will be supervised per local site practice to assure compliance to the regimen. Performed at all visits and Early Withdrawal (EWD), if during the treatment period.

v. **Investigator Assessment:** Investigator to review the participant status and assess whether IMP or TB treatment at Week 52 and 104 is considered a “success” or “failure”. If considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed, at Week 52 and 104, <u>and at any time</u> the Investigator determines that the participant fulfils the criteria for outcome of treatment failure.

w. **Visit Windows**: The windows noted on the flowchart for timing of visit also apply to the timing *within a visit.* Procedures should be performed within +/- 3 days of scheduled visit from Day 1 to Week 8 or +/- 5 Days of scheduled visit from Week 12 to Week 26 or +/- 14 days of scheduled visit at or after Week 39. Sites should make every effort to ensure all procedures are done on the same day, when possible.

x. **Karnofsky Score**: Only to be performed on HIV+ participants.

2.0 Introduction and Rationale

2.1 Tuberculosis Disease

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in the developing countries of Africa, Asia and South America. TB is currently one of the top three killer infectious diseases, 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 40 years and are relatively ineffective in controlling TB as a public health problem. 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 participants, treatment takes 6 months or more to complete. This, long duration treatment **plus side effects**, result in poor adherence which particularly occurs after the second month of treatment.

The current TB treatment regimens and treatments for drug-sensitive TB are decades old. The available treatments have a lengthy duration of treatment, involve multi-drug therapy, and require large commitments of resources and infrastructure. High rates of noncompliance are common, which often results in increased mortality and chronic, infectious, drug-resistant cases. The present TB epidemic and the challenge of current treatment options demonstrate the clear need for effective novel TB drugs and **drug regimens** that are safe for drug sensitive and drug resistant TB disease and that are well-tolerated and will shorten the current treatment duration for patients.

The full application of the Directly Observed Treatment, Short-Course strategy is becoming more and more difficult in the developing countries of the world that are also battling to control the HIV-epidemic. Because of poor treatment adherence, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB are growing. Since the discovery of the rifamycins,[1] and their introduction into standard antituberculosis regimens, very few new classes of drugs have been evaluated with a view to their registration as antituberculosis agents. On December 28, 2012 the U.*S.* Food and Drug Administration approved bedaquiline (B) as part of combination therapy to treat adults with multi-drug resistant (MDR) pulmonary tuberculosis (TB) when other alternatives are not available. 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.

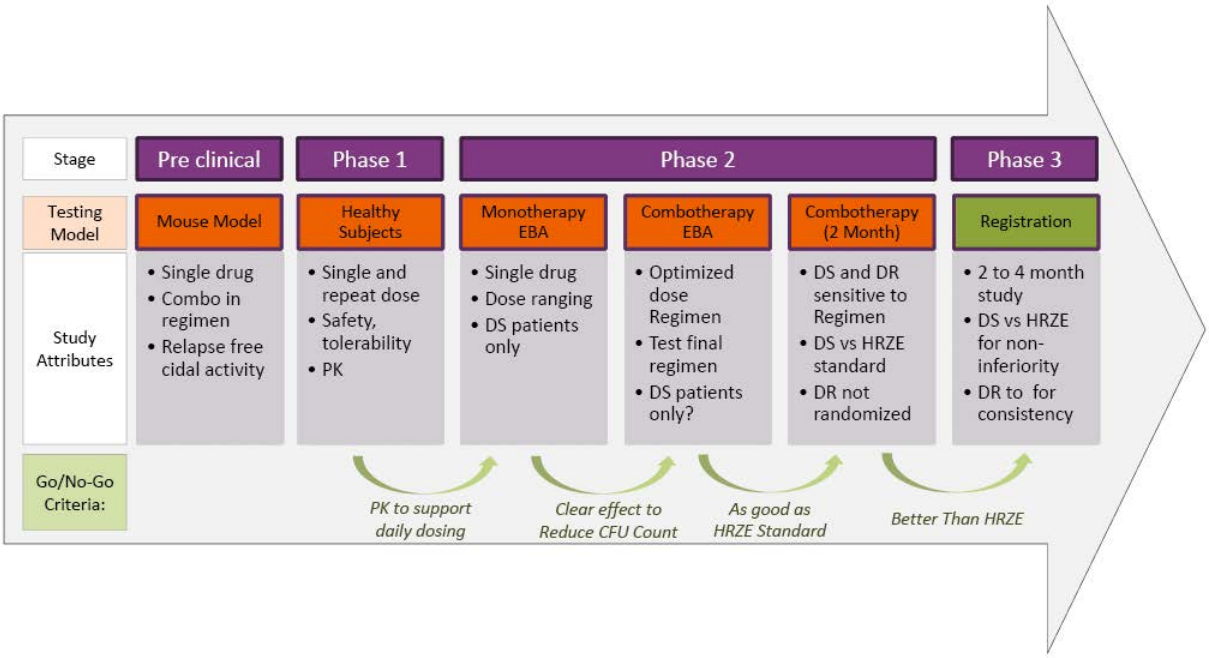
New combination regimens are desperately needed for two reasons: to shorten treatment to a duration more easily manageable by patients and public health services, and to provide more efficacious, safer and better tolerated, affordable treatments for the growing number of patients suffering from multidrug-resistant and extensively drug-resistant tuberculosis.

2.2 Tuberculosis Clinical Research

TB currently must be treated with multiple drugs to achieve maximal efficacy and prevent resistance. To transform treatment, novel TB regimens are needed. To telescope the time, it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm. This approach tests promising combinations of drugs together to find the most impactful treatment once the individual drug candidates have been tested in a robust pre-clinical program and the establishment of the individual drug candidates' safety and efficacy have been evaluated. It evaluates novel combinations of TB drugs — instead of single drugs — as part of a

single development program, enabling the development of novel TB drug regimens that have potential to transform treatment for drug-sensitive and drug-resistant tuberculosis. This approach offers the potential to reduce the time previously needed to develop a novel treatment regimen by up to 75%, shortening the clinical development from decades to years. The steps followed in this development model are shown in Figure 1 Between each step on the unified development pathway a decision is made as to whether to proceed.

Figure 1. Unified Drug Sensitive/Drug Resistant Regimen Development Path



Early Bactericidal Activity (EBA) Trials

EBA trials are the backbone clinical trials to quantify the bactericidal action of anti-tuberculosis agents alone or in combination by either trialling the fall in the number of colony forming units (CFU) or measuring the TTP in liquid culture of *M. tuberculosis* (*MTB*) present in the sputum of participants with microscopy smear-positive pulmonary TB. EBA trials have been conducted over 2, 5, 7 and 14 days.[2]. A review of EBA trials conducted on the key anti-TB drugs has shown the value these trials offer to demonstrate the early anti-TB effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in participants.[3]

8-week Bactericidal Activity (BA) Trials

EBA methodology of quantitative colony counting on solid medium has been adapted to Phase 2, 8-week TB treatment trials based on serial sputum colony counting (SSCC) or measurement of TTP liquid culture to provide a more sensitive efficacy endpoint than the previously used binary endpoint of rate of sputum conversion measured after 8 weeks of treatment.[4-6] Such trials are conducted to provide data on which to base the selection of treatment-shortening regimens.

2.3 Trial Rationale

The SimpliciTB NC-008 (BPaMZ) trial will evaluate and support that, in addition to previous studies evaluated with BPaMZ, this drug regimen will be safe and effective, is well-tolerated and could potentially shorten the current treatment duration compared to the standard HRZE/HR treatment for patients with drug sensitive TB disease. This trial will also evaluate if the BPaMZ drug regimen given for 6 months will be safe and effective in drug resistant TB disease.

Therefore, the trial design addresses the need to find and evaluate a potentially effective and shorter regimen compared to regimens (standard HRZE/HR) that are currently being used.

2.3.1 Trial Design Rationale

The SimpliciTB NC-008 (BPaMZ) trial is a Phase 2c multi-centre, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. This trial is to evaluate the combination regimen of **Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) plus Pyrazinamide (Z)** (BPaMZ), in participants with pulmonary TB.

All participants will enter post-treatment follow-up which continues until Week 104 after start of treatment / randomisation.

Participants with DS-TB:

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either:

- BPaMZ daily for 17 weeks (4 months),

OR

- HRZE/HR combination tablets daily for 26 weeks (6 months).

Participants will be stratified for co-infection with HIV and cavitation.

Participants with DR-TB are defined as:

1. mono-resistance to rifampicin or isoniazid, OR
2. resistance to both rifampicin and isoniazid (multi-drug resistant tuberculosis [MDR-TB])

Up to 150 participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months). Approximately 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation to either BPaMZ for 4 months or HRZE/HR for 6 months.

The trial is sufficiently statistically powered to not only show superiority of 8 Weeks culture conversion but should also demonstrate non-inferiority for cure at 52 Weeks (this is in the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen).

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary

endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

  *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objectives**

  *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46, 47, 48] and full details are provided in the Statistical Analysis Plan.

As previously described in the background information, in order to telescope the time it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm and utilize data generated in non-clinical and clinical studies regarding combining of anti-tuberculosis agents which could contribute significantly to the sterilization of lesions and thus treatment shortening. Therefore, the trial design and proposed trial regimen (BPaMZ) which is supported with previous non-clinical and clinical studies outlined below should address the need and manner of evaluating an effective shorter regimen compared to regimes that are currently being used.

2.3.2 Trial Drug Regimen Rationale

The BPaMZ regimen has been studied singularly and in different combinations as outlined above. Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. It essentially provides protection against the development of new resistance to the B-Pa-Z drugs. Based on the exciting and promising results seen in NC-005, this regimen can be initiated in drug sensitive and drug resistant TB participants whom are sensitive to the individual drugs in the regimen (excluding extensively drug-resistant tuberculosis [XDR-TB] and Pre-XDR tuberculosis) and has the potential to shorten TB treatment to less than 4 months in drug sensitive TB. These are also oral regimens, removing the need for injectables as part of MDR-TB treatment, and also project to be markedly less expensive than current MDR-TB therapy. Additionally, these regimens can be administered in a fixed dose for all patients and will therefore be simpler for health systems to deliver and patients to use.

2.4 Agents used within SimpliciTB

Bedaquiline (TMC207; Sirturo™ package insert)[7] is a novel agent approved for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[9, 10]) *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. Tb* isolates,[10, 11], and is also bactericidal against non-replicating *M. Tb.*[12] In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. Tb*.[3, 4] 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.[13] 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 DS- and MDR-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[13] and in a subsequent trial it was more active in the mouse model than HRZ.[14] Thus, a novel regimen with a 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.

Pretomanid, (Pa)[15] is a new chemical entity being developed by TB Alliance for the treatment of TB. It is 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 has been under development for several years and entered clinical trials in 2005. Several trials of pretomanid have also been conducted previously in healthy volunteers. Collectively, these trials in participants with active TB and healthy participants have defined the efficacy, safety and pharmacokinetic features of the drug. Overall, pretomanid has mycobactericidal activity in participants and is well tolerated and bioavailable after oral dosing. Pretomanid demonstrated in vitro activity against both drug-sensitive (DS) and MDR-TB,[17] and in vivo activity in a mouse model of TB[17, 18] with a significant promise for shortening treatment of active TB.

Moxifloxacin (M)[19] is a microbial compound, approved in most countries around the world for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and soft tissue infections. Clinical studies have been carried out for many additional indications (urinary tract infections, pelvic infections, pharyngitis/tonsillitis, and tuberculosis). Moxifloxacin is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by or induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the MTB strain is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]" It is currently in late stage clinical

development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

Pyrazinamide (Z)[20] is a pyrazine analogue of nicotinamide and an approved anti-tuberculosis agent which is indicated for the initial treatment of active tuberculosis in adults and children when combined with other anti-tuberculosis agents and contributes significantly to the sterilization of lesions and thus treatment shortening.[21]

Control Group: HRZE/HR

The **HRZE/HR** combination [HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets] is approved indicated and commonly used as a 6-month treatment for drug-sensitive TB patients. Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE. Please see the HRZE package insert for more information.[22]

Additional background data supporting the combined use of new novel agents in this BPaMZ regimen for the treatment of TB:

Data from preclinical studies suggest that a regimen consisting of moxifloxacin plus pretomanid plus pyrazinamide may not only be appropriate for treating both DS and MDR-TB but may also **shorten duration of therapy**. Results from an 8-week Phase 2b SSCC trial, NC-002-(M-Pa-Z), showed that this **combination regimen** was effective as measured by time dependent decline of viable bacteria in participants with DS pulmonary TB. The combination was also shown to be safe and well tolerated supporting the evaluation of this combination in a Phase 3 trial. In this NC-002 trial 71.4% of participants with DS-TB treated with PaMZ at the 100-mg daily dose of pretomanid converted sputum to negative for *MTB* growth in liquid culture in comparison with only 37.8 % of participants treated with the HRZE control ($p<0.05$).

Studies in mice infected with *MTB* demonstrated reductions in cultured colony counts from lungs over an 8-week period when treated with the PaMZ regimen that were substantially, and statistically significantly greater, than the reductions in mice treated with an HRZ control. Experiments in mice found that mice did not relapse with MTB infection when treated with PaMZ for 4 months and followed for 3 months off treatment, in comparison to mice that required 6 months of treatment with HRZ to prevent relapse.[14]

Drug Resistant TB Background:

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in many countries. TB is the world's leading cause for mortality from infectious disease and is responsible for more deaths than HIV.[23] 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. Because of poor treatment adherence, in addition to primary transmission, **drug resistance** is becoming more common and fears of an epidemic with strains of extensively drug-resistant TB (XDR-TB) that is very difficult to treat are growing. Novel drugs and regimens for TB are needed for the growing number of patients with drug resistant-TB.

The regulatory approvals of bedaquiline and delamanid have given hope that outcomes for patients with drug resistant TB might be improved when added to background regimens. Experience recently published from the C209 uncontrolled trial of bedaquiline given on a

background of multiple drugs notes that the subset of 38 participants with XDR-TB had rates of sputum culture conversion to negative of 62.2%.[24] However, in this trial only one participant with XDR-TB was co-infected with HIV. All participants were required to have Mycobacterium tuberculosis (MTB) isolates susceptible to at least 3 drugs at enrolment and participants had a median of only 5.4 months of treatment-free follow-up. This trial added bedaquiline for 6 months to a background regimen of many drugs given for 18 months or longer. While treatment success for MDR-TB is better than for XDR-TB, **overall success in treating MDR-TB is still approximately 50%** according to the World Health Organization 2015 Global TB Report.[23] This report presented that overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, 10% failed treatment, and for 8% there was no outcome information.

With such poor historical outcomes for patients with drug resistant-TB and with the complexity, expense and toxicity of treatments for all forms of drug resistant TB, **novel drug combinations are desperately needed to improve treatment outcomes**. Linezolid was identified in a small trial as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen[25] and this drug has increasingly been added to complex regimens to treat patients with MDR-TB.

With the current availability of the following three drugs for which there is little, if any, pre-existing resistance among strains of MTB (pretomanid [Pa], bedaquiline [B], and linezolid [L]). Mice infected with MTB had relapse-free cures with 3 months of treatment with a B-Pa-L regimen. While it is not known whether that treatment duration will translate to humans, the ongoing Nix-TB clinical trial hypothesizes patients with pulmonary XDR-TB or MDR-TB not responsive to or intolerant to therapy may have relapse-free cure after as little as 6 months' treatment with the B-Pa-L regimen.[26] Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. The proposed trial [SimpliciTB] allows the opportunity to assess the efficacy, safety and tolerability of BPaMZ, a new 6 months regimen that may be administered orally once daily to treat patients with drug resistant -TB (excluding participants with XDR-TB).

Therefore, the **overall purpose** of the present proposed trial **[SimpliciTB]** is to assess the efficacy, safety and tolerability of the **BPaMZ** regime after 4 months of treatment in adult participants with drug sensitive TB and after 6 months of treatment in participants with multi drug-resistant TB. The trial will also generate data of the potential for a shorted treatment duration with the **BPaMZ** regime after 4 months compared to a 6-month **HRZE/HR** (control) treatment regime in adult participants with drug sensitive TB.

This trial will be conducted in accordance with the Protocol, ICH Guidelines for Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirement(s).

2.5 Background of Agents to be Studied in SimpliciTB

2.5.1 Bedaquiline (B)

Bedaquiline (formerly known as TMC-207; Sirturo™ package insert[7]) is approved agent for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[11] In vitro, bedaquiline potently inhibits both drug-sensitive and

drug-resistant MTB isolates,[11, 12] and is also bactericidal against non-replicating MTB[12] 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 MTB.[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.[27].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[27] and in a subsequent trial it was more active in the mouse model than HRZ.[28]. 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.

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as 200 mg daily for 8 weeks, followed by 100 mg daily for the remaining 17 weeks or 30 weeks if treatment is extended. This daily dosing scheme will allow more convenient dosing that should ultimately enhance patient adherence and may allow the formulation of fixed dose combinations with other drugs. This daily dosing regimen is supported by safety and efficacy demonstrated in the NC-005 trial that administered bedaquiline 200 mg daily over 8 weeks, and by pharmacokinetic modelling and simulation of the daily dosing scheme. This supportive information is detailed below.

2.5.1.1 Bedaquiline Non-Clinical Studies

Full details of the preclinical studies are provided in the current bedaquiline Investigator's Brochure,[8] and Sirturo ™ label.[7] *In vitro* studies have demonstrated that the range of minimum inhibitory concentrations (MICs) for MTB 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 MTB. 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 MTB but 3-6 times less active than the parent compound bedaquiline. Bedaquiline demonstrated similar *in vitro* efficacy against MTB 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 International Council for Harmonisation (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.[8]

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 and ECG parameters.

Prior to the use of pretomanid in combination with bedaquiline in clinical trial NC-001, a preclinical cardiovascular safety pharmacology trial 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.[28] 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) Investigators Brochure for more detail.

2.5.1.2 Bedaquiline Clinical Studies

In the clinical studies conducted to date, a total of approximately 645 participants (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 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001, and 45 more in trial NC-003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). Four short-term Phase 2a trials enrolled treatment-naïve participants (C202, TMC207-CL001, NC-001 and NC-003). One long-term, open-label, Phase 2 trial, in MDR-TB participants (bedaquiline-TiDP13-C209) and one long-term, Phase 2b trial, consisting of 2 different stages in participants 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,[8] and Sirturo™ label.[7].

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

participants. 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 trial, 800 mg single dose in trial 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 participants and participants 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 ȧ 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 participants 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 trial (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 trial (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. Trial C202 was a 7-day trial of three daily doses of bedaquiline (25, 100 and 400mg) in treatment-naïve participants with MDR-TB. In this trial, the 400mg dose group demonstrated positive EBA and was numerically superior to the 25 and 100mg doses. In trial TMC207-CL001, doses of 100, 200, 300 and 400mg daily (following a 2-day loading dose) were studied in participants 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 participants with TB and that higher doses appear to have greater efficacy.

A 14-day EBA regimen trial (TB Alliance Trial 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 participants 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 participants given bedaquiline 400 mg/d after a 2-day loading dose. In the cohort of 15 participants 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 participants 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 trial (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 participants 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 participants in the bedaquiline group became MGIT culture negative compared to 8.7% of participants 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 participants in the bedaquiline group and 65.2% of participants 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 participants 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 participants. Culture conversion rates after 2 weeks of treatment with bedaquiline as part of an individualized anti-tuberculosis regimen were higher in participants with lower extent of resistance of the M. Tb strain and in participants with no lung cavitation compared to participants with cavitations (in one or both lungs).

2.5.1.3 Bedaquiline Clinical Safety

In the clinical trials conducted to date, a total of approximately 645 participants (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 participants received bedaquiline in a monotherapy EBA trial of 14 days (trial TMC207-CL001) 45 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001 and 45 more in trial NC- 003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). In these trials, bedaquiline has been shown to be an effective treatment for participants 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 trial 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 trials, 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 participants) 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

SOC ADR (Grouped term), n (%)	Investigational Treatment Phase Controlled Trials TMC207 24 Weeks N = 79	 Any N = 102	 Placebo 24 Weeks N = 81	 Any N = 105
At least grade 3 ADR	*5 (6.3)*	*5 (4.9)*	*0*	*0*
Nervous system disorders	**1 (1.3)**	**1 (1.0)**	**0**	**0**
Headache	1 (1.3)	1 (1.0)	0	0
Cardiac disorders	**0**	**0**	**0**	**0**
ECG QT Prolonged	0	0	0	0
Gastrointestinal disorders	**0**	**0**	**0**	**0**
Diarrhea	0	0	0	0
Vomiting	0	0	0	0
Hepatobiliary disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Transaminases increased [a]	2 (2.5)	2 (2.0)	0	0
Musculoskeletal and connective tissue disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Arthralgia	2 (2.5)	2 (2.0)	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 participants in the Any bedaquiline group and 5 participants 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 participants 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 participants (12.7%) compared to 3 placebo participants (3.7%). Based on the pooled results (Stage 1 and 2) while being followed in the placebo- controlled trial, 7 participants in the Any bedaquiline group and 1 Participant 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 haemoptysis. 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 participants 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 Participant in the bedaquiline group (pulmonary TB) and 2 participants in the Placebo group (TB-related illness and pulmonary TB) in Stage 1 died, and 4 participants in the bedaquiline group (3 participants with TB-related illness, 1 Participant motor vehicle accident) and 2 participants in the Placebo group (both TB-related illness) died after they discontinued Stage 2 of the trial. None of these participants 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, diarrhoea, blood uric acid increased, hypokalaemia, pruritus, injection site pain, insomnia, and tinnitus. From start of the trial up to the final analysis, 12 participants 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), haemoptysis, hypertension, and pyopneumothorax/respiratory failure. 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 participants 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 participants (6.9%) have died (12 participants during the trial and 4 participants 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 participants 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[7] notes that treatment initiation is not recommended in patients with:

- Heart failure;
- QTcF interval > 500 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).
- Hypokalaemia

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. If 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. participants should be monitored during treatment. Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in those participants with diminished hepatic reserve.[7]

Additional safety information from a recently completed trial

In a recently completed phase I trial not yet included in the bedaquiline Investigators Brochure that evaluated drug-drug interactions between bedaquiline and either rifampin or rifabutin, 7

participants experienced SAEs. Of those participants, 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 participant 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.

2.5.2 Pretomanid (P)

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]

2.5.2.1 Pharmacology

Key in Vitro Evaluation of Pretomanid Bactericidal Activity

Non-clinical in vitro trials demonstrated that pretomanid was active against actively growing drug- sensitive and drug-resistant MTB strains as well as against non-replicating MTB. The minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive MTB isolates *in vitro* was shown to be like the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of MTB with MIC values ranging from 0.03 to 0.53 µg/mL. The Investigator's Brochure contains further information on *in vitro* bactericidal activity.[16]

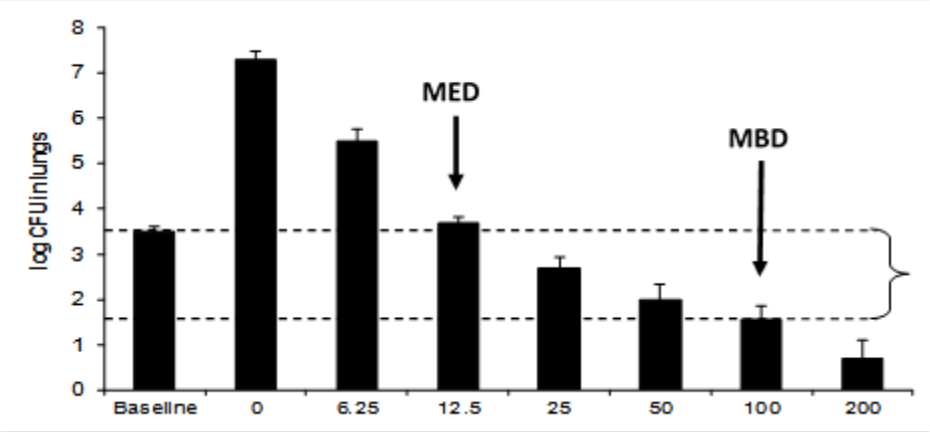
Although not thoroughly elucidated at this time, pretomanid has a novel mechanism of action that appears to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reduction of pretomanid by a deazaflavin (F420)-dependent nitroreductase has been shown to be associated with generation of reactive nitrogen species, including nitric oxide (NO),[29] although the exact target(s) of the reactive nitrogen species are not known. Transcriptional profiling trials also suggest that pretomanid affects both cell wall biosynthesis and the respiratory complex of MTB.[30, 31]

2.5.2.2 Key Non-Clinical Trials of Pretomanid

The activity of pretomanid as a single agent or as part of a multi-drug combination regimen has been examined in a number of mouse trials.[13, 14, 18, 32, 33] In a mouse model of established TB, the activity of various doses of pretomanid (given once daily, 5 days/week, for 1 month), initiated 22 days after inhalation infection with H37Rv MTB is shown in Figure 2. In this model, the minimum effective dose (MED) for pretomanid, defined as the lowest dose able to prevent the development of gross lung lesions and splenomegaly, was 12.5 mg/kg/day, while the minimum bactericidal dose (MBD), defined as the lowest dose able to reduce lung colony forming units (CFU) by 99%, was 100 mg/kg/day. Moreover, in these experiments, the activity of pretomanid at 100 mg/kg was comparable to the activity of isoniazid at 25 mg/kg.

Figure 2. Log10 CFU Counts in Lungs

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



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

2.5.2.3 Non-Clinical Toxicology and Safety

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

In the repeat-dose toxicity trials, the lowest no-observed adverse effect level (NOAELs) was 10 mg/kg/day in a 26-week trial in rats, 50 mg/kg/day in a 13-week trial in monkeys and <25 mg/kg/day (based on findings of thickening of the gastrointestinal tract at all doses) in a 9-month trial in monkeys. The major findings in safety and toxicity trials are listed below in Table 2 and are detailed in the Investigator's Brochure.[15]

Table 2. Key findings of Pretomanid in Safety and Toxicity Trials

Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behaviour at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
Testicular toxicity Although rat and rabbit embryonic development trials indicate no effects of pretomanid on foetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose toxicology trials and a Segment I fertility trial. In this fertility trial, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower dose not associated with testicular atrophy. A detailed trial in sexually mature male monkeys

demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing.
Cataracts Cataracts developed in rats with prolonged daily administration of pretomanid at doses ≥100 mg/kg/day. In one 13-week trial 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 trial in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.
hERG inhibition and QT prolongation Altered ventricular repolarisation due to inhibition of hERG-mediated potassium current and manifested on the ECG as a prolonged QT interval corrected for heart rate (QTc). Pretomanid inhibited hERG current with IC50 values of approximately 6.2 µg/mL. Following a single pretomanid dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Co-administration of pretomanid with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at pretomanid doses of ≥150 mg/kg/day.

2.5.2.4 Clinical Background Information

Pretomanid has been evaluated in 8 single- and multi-dose Phase 1 trials with healthy adult male and female participants, with 163 participants receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 7 days. These Phase 1 trials have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid. Two additional Phase 1 trials Sponsored by the NIH included a Thorough QT trial and a trial of drug interactions among pretomanid, efavirenz and ritonavir/lopinavir. Further details of the trials are in the Investigator's Brochure.[15]

2.5.2.5 Pharmacokinetics

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

Drug interaction with midazolam: Trial CL-006 was an open-label, fixed-sequence drug-drug interaction trial to evaluate the effects of multiple-dose administration of pretomanid on the PK of midazolam, a sensitive probe substrate and representative compound for drugs metabolised by CYP3A enzymes. Dosing with pretomanid at 400 mg/day for 14 days (to steady state) had minimal effect on the PK of midazolam and its 1-hydroxy metabolite as assessed by measurement of the Day 17: Day 1 ratios of maximum concentration (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$. The C_{max} and AUC values for midazolam after co-administration with pretomanid were approximately 85% of those observed after treatment with midazolam alone. Furthermore, midazolam and 1-hydroxy

midazolam time to maximum concentration (T_{max}) and half-life ($t_{1/2}$) values were not different in the presence or absence of pretomanid. Therefore, 14 days' dosing with 400 mg/day pretomanid does not appear to significantly inhibit CYP3A4 in humans.

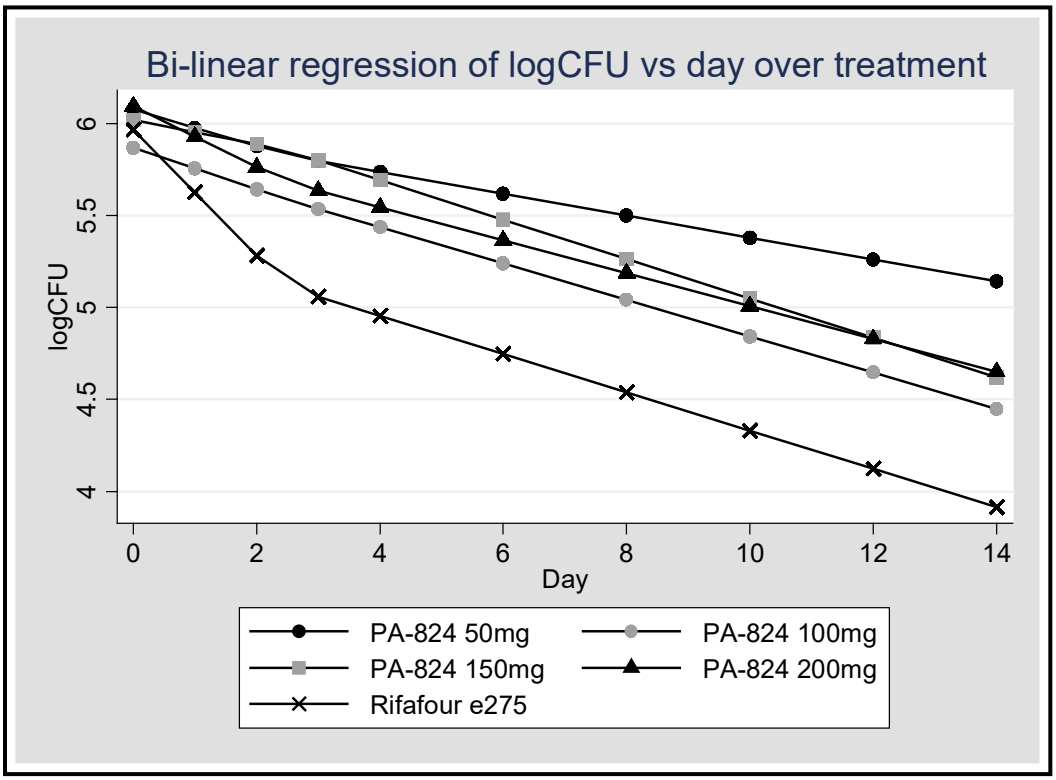
Drug interaction with efavirenz, ritonavir/lopinavir, and rifampicin: The US NIH Sponsored this drug interaction trial with rifampicin, a known hepatic enzyme inducer, and with the antiretroviral drugs efavirenz and ritonavir/lopinavir (LPV/r) in healthy participants. Participants in Arm 1 were randomised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

In conclusion, compared to pretomanid alone, plasma pretomanid values (based on geometric mean ratios) for C_{max}, $AUC_{0\text{-}24h}$, and C_{min} were reduced 28%, 35%, and 46% with efavirenz; 13%, 17%, and 21% with LPV/r; and 53%, 66%, and 85% with rifampicin, respectively.

2.5.2.6 Pretomanid Clinical Efficacy

The first two Phase 2 trials to evaluate the early bactericidal effect (EBA) of pretomanid oral monotherapy (50 to 1200 mg/day for 14 days) examined the dose-response for pretomanid in participants with newly diagnosed pulmonary TB infection. The first trial (CL-007) demonstrated good EBA, but all doses in this trial (200 to 1200 mg/day) had the same activity. The second trial (CL-010) evaluated a lower dose range (50 to 200 mg/day) and the maximum effect on EBA was seen at a dose of 100 mg/day over 14 days (Figure 3).[34]

Figure 3. Mean log Colony Forming Unit Values over Time Trial CL-010



CFU = colony-forming unit; PRETOMANID = pretomanid

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

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

2.5.2.7 Pretomanid Clinical Safety

The pretomanid Investigator's Brochure[15] provides detailed safety information.

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

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

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

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

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

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

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

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

- Central Nervous System Safety –While pretomanid alone or combined in various regimens has been well tolerated overall, one participant in Trial NC-002 of the Pa-M-Z regimen had a seizure without any prior seizure history, and some animals in toxicology trials have had

seizures at high drug exposures. Consequently, close surveillance will be made of participants in the Phase 3 trial for seizures or any central nervous system adverse events of potential concern.

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

2.5.3 Moxifloxacin (M)

Moxifloxacin (M)[19] is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by nor induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that “all patients [with MDR-TB] should receive a Group 3 medication if the strain of MTB is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]” It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

2.5.3.1 Moxifloxacin Clinical Trials

Moxifloxacin is commonly used as second line therapy for TB (e.g. MDR- TB) and has also been evaluated in several clinical studies of participants with TB, including four 8-week treatment period Phase 2b studies (see Table 3 below).

Table 3. Summary of Phase 2b trials in which moxifloxacin were administered as part of a four-drug regimen during the intensive phase of treatment (total treatment duration: 2 months)

Trial	Design	Objective	Participants (N)	Status
Trial 27	Randomized, double-blind, controlled	To compare the sputum culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using the standard 4-drug regimen HRZE with a standard regimen with M replacing E.	336	Completed
OFLOTUB Trial	Randomized, Open label, Controlled	To compare the bactericidal activities of regimens where gatifloxacin, M, and ofloxacin were substituted for E in the 2-month initial phase of standard TB treatment with HRZE.	217	Completed
Johns Hopkins (FDA orphan drug) Trial	Randomized, double-blind, Controlled	To compare the sputum culture conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE) with a regimen with M replacing E (HRZM).	170	Completed
Trial 28	Randomized, double-blind, Controlled	To compare the culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE 5 days per week) with a regimen with M replacing H (MRZE 5 days per week).	433	Completed

2.5.3.2 Moxifloxacin Clinical Safety

In Trial 27,[35] the moxifloxacin-containing TB regimens (HRZM) were shown to be safe and well tolerated. There was no difference in SAEs between the HRZM and HRZE treatment arms, and most SAEs were hospitalizations thought to be unrelated to the trial treatment. Participants treated with the moxifloxacin-containing regimen were more likely to report nausea (22% vs. 9%, p = 0.002), but this was generally mild and did not lead to treatment discontinuation as similar proportions of participants in both groups completed trial drug treatment (88% HRZM-treated vs. 89% HRZE-treated). The one death during the first 2 months of treatment was thought to be caused by a pulmonary embolism unrelated to tuberculosis therapy.

In the OFLOTUB trial,[36] AEs and SAEs occurred with equal frequency in the four treatment arms. The most frequent AEs were raised amylase (in 41% of participants due to HIV infection), raised transaminase (10%), arthralgia (9%), anaemia (7%), hypokalaemia (6%) and vomiting (5%). No Participant was withdrawn from the trial due to an adverse event. There were 4 deaths in the trial: 2 in the control group, 1 each in the moxifloxacin and ofloxacin arms. Importantly, participants in this trial who received moxifloxacin and pyrazinamide in addition to isoniazid and rifampin had more rapid sputum clearance than participants on the four standard first line drugs

(isoniazid, rifampin, pyrazinamide and ethambutol). This difference was evident 14 days after initiation of treatment.

In the JHU trial,[37] AEs did not differ by treatment group. There were 16 SAEs (8 in each group) in 12 participants. Only 1 event was judged related to trial drug (grade 3 cutaneous reaction in the ethambutol group). Eight participants died during the trial, including 1 in each group still receiving trial phase treatment. No death was attributed to trial treatment. Only 5 participants discontinued treatment because of toxic effects; 2 participants in the moxifloxacin group stopped because of grade 2 nausea and vomiting and 1 because of grade 2 paraesthesia's and ataxia. Two participants in the E group stopped because of grade 2 rash and pruritus and 1 because of grade 3 peripheral neuropathy. There was no change in the QTc interval on serial electrocardiograms taken during the trial.

In Trial 28,[38] the proportions of participants with SAEs during the intensive phase treatment were similar between arms (isoniazid 3.9% vs. moxifloxacin 4.2%; P = 0.88). Three SAEs attributed to trial treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group. Seven participants died during the trial including 3 participants receiving the moxifloxacin treatment regimen and 4 participants receiving the isoniazid treatment regimen. The 3 moxifloxacin participants died during the intensive phase of TB treatment. Two participants died from advanced pulmonary TB judged not related to trial treatment and 1 Participant (who developed diabetic ketoacidosis considered possibly related to trial treatment) died from possible acute pulmonary embolus unrelated to trial treatment. The 4 isoniazid deaths occurred during the continuation phase, and all 4 were considered unrelated to trial treatment. Nausea was more common among participants in the moxifloxacin arm than in the isoniazid arm (19.6% vs. 11.7%, respectively; P = 0.03) although similar proportions reported vomiting. However, the proportions of participants with hepatitis, defined as serum AST 3 times or greater than the upper limit of normal, were similar between treatment arms during intensive phase (isoniazid 3.4% vs. moxifloxacin 3.3%; P = 0.93). Moxifloxacin has also been evaluated in combination with pretomanid for two weeks in participants with TB (Trial NC-001) and for 8 weeks in NC-002 (as reviewed above).

For additional information on moxifloxacin, refer to the IB[39] and the manufacturer's package insert.[19]

2.5.4 Pyrazinamide (Z)

Pyrazinamide (Z) is a standard drug used as part of the four drug HRZE regimen used for the first two months of intensive therapy for drug-sensitive TB as recommended by the WHO and many National TB programs. Please see the Package Insert[20] for more detail. Z is active against TB *in vitro* and it potentiates the bactericidal and sterilizing activity of both bedaquiline and pretomanid in mouse models of TB infection.[8, 15] Pyrazinamide enhanced the bactericidal activity of both bedaquiline and pretomanid in Trial NC-001-(J-M-Pa-Z) as noted by decreases over 14 days in the CFU counts in sputum among participants.

The pyrazinamide product label notes that pyrazinamide is contraindicated in persons with severe hepatic damage, who have shown hypersensitivity to it, and with acute gout. The most serious side effect is hepatotoxicity. Its frequency appears to be dose-related and thus liver function should be assessed before and regularly during treatment with pyrazinamide. Hyperuricemia commonly occurs and is occasionally accompanied by arthralgia and may lead to attacks of gout.

Photosensitivity and skin rash have been reported less frequently. Other side effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria.

Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert. [20]

2.6 Overall Benefit/Risk Assessment

Some participants with pulmonary TB in this trial will be given a regimen of **BPaMZ**. These drugs individually and in combination are known to have anti-tuberculosis activity and is not expected to have an adverse impact on the ultimate cure of TB in these participants. Based on NC-005 and other regimens using each of the regimen drugs in different combinations there is good evidence that this may be a highly effective therapy for both DS-TB and DR-TB.

For DS-TB the potential for a shorter regimen than 6 months is expected to be successful based on preclinical and clinical information as listed before. Participants in this trial will have their TB infection carefully characterized, with drug sensitivity profiles established, and they will receive treatment with trial drugs that have demonstrated activity against MTB.

Participants will receive individualized medical attention; this will allow a continuous monitoring of the health conditions of each participant, any of whom can be withdrawn at any stage of the trial and removed from trial treatment should his/her condition suggest to the Investigator that this would be in his/her best interest. Multiple blood samples will be taken for safety laboratory studies, and ECGs will be taken at multiple time points.

One concern, the combination of two agents with known QT-prolonging effects (bedaquiline and moxifloxacin), has been addressed specifically by carefully identifying and excluding participants with risk factors that might predispose them to cardiac arrhythmias, screening all participants for evidence of existing cardiac disease and monitoring all participants with ECGs throughout the trial.

The trial drugs in the proposed regimens to be tested in this trial have all demonstrated safety and efficacy in the treatment of pulmonary tuberculosis in non-clinical and clinical studies. Specifically, the regimen B-Pa-Z was generally well-tolerated and demonstrated bactericidal activity in a 14-day EBA trial. The potential risks associated with the trial drugs and regimens has been identified as outlined below and will be monitored carefully throughout the conduct of the trial.

The BPaMZ regimen is a novel regimen treatment expected to be effective, safe and well-tolerated and might even shorten the current treatment duration for patients with TB. Based on data from previous trial evaluations of key monitoring and safety information as outlined before suggests a favourable benefit-to-risk ratio trials.

Key Monitoring and Safety Information Regarding Regimen Agents

2.6.1 Bedaquiline (B)

2.6.1.1 Adverse Drug Reactions for bedaquiline

Participants in the Any bedaquiline group compared to the Any Placebo group (difference > 5.0%) had headache (23.5% versus 11.4%, respectively), nausea (35.3% versus 25.7%, respectively),

arthralgia (29.4% versus 20.0%, respectively), and transaminases increased (6.9% versus 1.0%, respectively).and diarrhoea (11.4% versus 5.9%, respectively).

2.6.1.2 Cardiovascular safety

During clinical studies with bedaquiline a prolongation of QTc interval was observed. An ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.

Bedaquiline 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

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. If co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

In the DR-TB treatment arm of the present trial, moxifloxacin will be co-administered with bedaquiline. This is to prevent the development of resistance to the other drugs in the regimen in case the participant's strain of MTB is resistant to pyrazinamide. ECG assessments will be performed on all participants at screening, baseline, and at treatment visits specified in the flow chart.

2.6.1.3 Hepatic safety

Increases in transaminases were seen in clinical studies during administration of bedaquiline with the background regimen. Participants should be monitored during treatment.

Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in participants with diminished hepatic reserve.

2.6.2 Pretomanid (P)

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 diarrhoea)
- Skin and subcutaneous tissue disorders

2.6.2.1 Hepatic Safety

Hepatic enzyme increases have been seen in participants 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 NC-008 trial will include specific monitoring of hepatic enzymes.

For additional information refer to pretomanid IB.[15]

2.6.3 Moxifloxacin (M)

In the usual daily doses of 400 mg/day, moxifloxacin is well tolerated. As stated in the Package Insert[19] the most frequent individual drug related AEs observed in clinical trials with 400 mg oral moxifloxacin therapy were nausea (7.5%) and diarrhoea (5.8%). Fluoroquinolones, including moxifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages.

A known but rare side effect of fluoroquinolones, including moxifloxacin is exacerbation of myasthenia gravis. In addition, moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some participants. It should be used with caution in participants being treated concomitantly with other drugs where an additive effect on the QT interval cannot be excluded.

Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, as well as peripheral neuropathy may occur after the first or subsequent doses of moxifloxacin. For additional information, refer to the moxifloxacin package insert.[19]

2.6.4 Pyrazinamide (Z)

The dose of pyrazinamide that will be used in this trial is an approved dosage for the treatment of TB. The most serious side-effect of pyrazinamide is hepatotoxicity and its frequency appears to be dose-related. Hyperuricemia commonly occurs, occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side-effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria. Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert.[20]

2.6.5 HRZE/HR Control

The **HRZE** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets) combination will be given the first 8 weeks and the **HR** (isoniazid 75 mg plus rifampicin 150 mg combination tablets) combination will be given from Weeks 9 to 26.

Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE.

Please see the HRZE and HR Package Inserts[22, 40] for known and potential risks and benefits.

3.0 Trial Objectives

3.1 Primary Endpoint

To evaluate the time to culture negativity over 8 weeks from the start of the treatment regimens in participants with:

- Drug Sensitive TB (DS-TB)

- Drug Resistant TB (DR-TB)

DR-TB are defined as participants with:

1. *mono-resistance to rifampicin or isoniazid, OR*
2. *resistance to both rifampicin and isoniazid (DR-TB)*

3.2 Secondary Endpoints

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 52 weeks (12 months) and 104 weeks (or 24 months) weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
  - Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
  - Quantitative and qualitative ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones
- Changes in lens opacities.

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [C_{min}], maximum

plasma concentration [C_{max}], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of concomitant medications, including antiretroviral therapy (ART), where feasible.

Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

3.3 Exploratory Objectives

- Evaluate whether any of the secondary endpoints predicts relapse free cure.
- Subgroup analysis of populations by HIV status.

4.0 Trial Design

4.1 Summary of Trial Design

This is a Phase 2c, multi-centre, open-label, partially randomized clinical trial conducted in 3 treatment groups. Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment randomisation and allocation during the treatment phase of the trial.

The trial will be performed globally at multiple centres located throughout the world.

A total of 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation, with a target of 50% of the participants being HIV positive. Up to 150 DR-TB participants will be enrolled and assigned to the treatment arm described in Table 4 below.

Refer to Section 3.0 Trial Objectives above and Section 9.3 Interim Analysis for details of the planned interim analysis and potential updates to the trial objectives and sample size.

Participants with Drug Sensitive TB (DS-TB):

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 Weeks, or HRZE/HR combination tablets daily for 26 Weeks. Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation.

Participants with Drug Resistant TB (DR-TB):

Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).

Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive.

DR participants will be treated with 6 months of BPaMZ. DS participants will be randomised using an interactive web response system (IWRS) stratifying for cavitation and HIV status to allocate participants evenly across the arms after they have given written, informed consent during the Screening visit (Days -9 to -1).

4.2 Treatment Plan: Schedule of Assessments

- Screening Period (Day -9 to Day -1)
- Treatment Period (Day 1 to Week 17 / Week 26)
- Follow-Up Period (Week 39 to Week 104)

Refer to:

- Synopsis Flow Chart and Procedures (Section 1.2) for the timing of all procedures and laboratory samples to done at each visit.
- Trial Procedures (Section 7.0 Trial Variables and Procedures) for details regarding specific procedures or laboratory tests.

Each participant will receive up to 26 weeks of treatment. The trial IMP regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the

Sponsor's Medical Monitor prior to implementation unless an interruption/pause is required urgently for a safety concern.

All participants will enter post-treatment follow-up which continues until Week 104 after start of treatment / randomisation.

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

Table 4: Treatment Groups

	Treatment Group	Treatment Duration	No of Participants
1	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily	17 weeks (4 months)	150 DS-TB
2	**HRZE Tablets (Weeks 1-8):** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). Followed by, **HR Tablets (Weeks 9-26):** (isoniazid 75 mg plus rifampicin 150 mg combination tablets).	First 8 weeks (2 months) then 17 weeks (4 months) Total 6 months	150 DS-TB
3	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily.	26 weeks (6 months)	Up to 150 DR-TB

5.0 Trial Population

The participant must meet all inclusion and no exclusion criteria within the screening period. Retesting for any laboratory or ECG parameters is allowed within the screening period. Sponsor may consider replacement of late exclusions.

5.1 Inclusion Criteria

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

1. Signed written consent prior to undertaking any trial-related procedures.
2. Male or female, aged 18 years or over.
3. Body weight (in light clothing and no shoes) ≥ 30 kg.
4. Sputum positive for tubercule bacilli (at least 1+ on the International Union Against Tuberculosis and Lung Disease [IUATLD]/WHO scale (Appendix 1) on smear microscopy) at the trial laboratory.
5. Disease Characteristics - Participants with one of the following pulmonary TB conditions:

   DS-TB treatment arm participants should be:

   a. sensitive to rifampicin, isoniazid and fluoroquinolones by rapid sputum-based test **AND**

   b. either newly diagnosed for TB or have a history of being untreated for at least 3 years after cure from a previous episode of TB.

   DR-TB treatment arm participants should be:

   a. Resistant to rifampicin and/or isoniazid; but sensitive to fluoroquinolones by rapid sputum-based test **AND**

   b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 3 days at start of screening.

   c. Participants with resistance to injectables by rapid sputum-based test are allowed in the trial.

   When Phenotypic DST and/or whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.

6. A chest x-ray, within 6 months prior to or during the Screening visit, which in the opinion of the Investigator is compatible with pulmonary TB.

7. Contraception:

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

   Non-childbearing potential:

   a. Female participant or male participants female sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or

   b. Male participant

   Effective birth control methods:

   a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or

   b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device.

   c. Male participants' female sexual partner: Barrier method combined with hormone-based contraceptives or an intra-uterine device.

   Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 6 months after the last dose of trial IMP or discontinuation from trial IMP 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 participants to prevent pregnancy.

5.2 Exclusion Criteria

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

Medical History and Concurrent Conditions:

1. Any non-TB related condition where participation in the trial, as judged by the Investigator, could compromise the well-being of the participant or prevent, limit or confound protocol specified assessments.
2. Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
3. Historical and or current use of local traditional medications/herbs which in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
4. Being, or about to be, treated for malaria.
5. Is critically ill and, in the judgment of the Investigator, has a diagnosis likely to result in death during the trial or the follow-up period.

6. TB meningitis or other forms of extrapulmonary tuberculosis with high risk of a poor outcome, or likely to require a longer course of therapy (such as TB of the bone or joint), as judged by the Investigator.
7. History of allergy or hypersensitivity to any of the trial IMP or related substances, including known allergy to any fluoroquinolone antibiotic, history of tendinopathy associated with quinolones or suspected hypersensitivity to any rifampicin antibiotics.
8. For HIV infected participants any of the following:

    a. CD4+ count <100 cells/µL
    b. Karnofsky score <60% (Appendix 5)
    c. Received intravenous antifungal medication within the last 90 days
    d. WHO Clinical Stage 4 HIV disease (Appendix 3)

9. Participants who recently started or expected to need to start ART within 1 month after randomization. Participants who have been on ARTs for more than 30 days prior to start of the Screening visit or expected to start ART greater than 30 days after randomization may be included.
10. Having participated in other clinical trials with investigational agents within 8 weeks prior to start of trial IMP or currently enrolled in an investigational trial.
11. Participants with any of the following at the Screening visit (per measurements and reading done by ECG):

    a. QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with the Sponsor Medical Monitor before enrolment.
    b. Heart failure
    c. A personal or family history of congenital QT prolongation
    d. A history of or known, untreated, ongoing hypothyroidism
    e. A history of or ongoing bradyarrhythmia
    f. A history of Torsade de Pointe

12. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening.
13. Females who have a positive pregnancy test at the Screening visit or already known to be pregnant, breast-feeding, or planning to conceive a child during the trial or within 6 months of stopping treatment. Males planning to conceive a child during the trial or within 6 months of stopping treatment.

<u>Previous and Concomitant Therapy</u>

14. Previous treatment for TB:

    - <u>For DS-TB participants</u>: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days at the start of the Screening visit.
    - <u>For the DR-TB participants</u>: Previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 3 days at the start of the Screening visit.

15. Any diseases or conditions in which the use of the standard TB drugs or any of their components is contra-indicated, including but not limited to drug allergy.
16. Use of any drug within 30 days prior to randomisation known to prolong QTc interval (including, but not limited to, amiodarone, amitriptyline, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinacrine, quinidine, sotalol, sparfloxacin, thioridazine).
17. Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), as they can lead to visual opacities or cataracts.
18. For HIV infected participants:

    a. The following antiretroviral therapy (ART) should not be used with either (BPaMZ and HRZE/HR) trial regimen:

        1. Stavudine
        2. Didanosine
        3. Triple NRTI regimen is not considered optimal for HIV treatment (poor efficacy)

    b. In the case where participants are randomized to HRZE arm, <u>rilpivirine and etravirine cannot be given</u> with rifampicin due to drug-drug interactions. A standard NRTI backbone may be used in combination with one of the following:

        1. Efavirenz requires no dose adjustment
        2. Dolutegravir dose adjustment is required – double dose when co-prescribed with rifampicin.
        3. Raltegravir requires no dose adjustment
        4. Lopinavir/r dose adjustment is required – double dose when co-prescribed with rifampicin
        5. Nevirapine requires no dose adjustment, however, please note that nevirapine based regimens are associated with higher ART failure in participants having or known to have a previous viral load more than or equal to 100,000/ mL

    c. In the case where participants are randomized to the BPaMZ trial regimen, a standard NRTI backbone may be combined with the following:

        1. Rilpivirine
        2. Dolutegravir
        3. Raltegravir
        4. Nevirapine
        5. Lopinavir/r
        6. <u>Participants who are on efavirenz, atazanavir/r or darunavir/r at the time of screening and have an undetectable viral load</u>, should have their ART switched to one of the agents listed above (1-5). It would be preferable to switch to another permissible ARV within the same class accompanied by the same nucleoside backbone.

d. ART regimen choice should be discussed with the Sponsor Medical Monitors if there are any concerns.

Confirmed plans to use Isoniazid prophylaxis for HIV positive participants during the treatment and follow up period is not permitted.

Diagnostic and Laboratory Abnormalities

19. Participants with the following toxicities at screening as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (Draft November 2007) (Appendix 2) where applicable:

    a. platelets <75,000/mm^3
    b. creatinine >1.5 times upper limit of normal (ULN)
    c. eGFR ≤ 60 mL/min
    d. haemoglobin <8.0 g/dL
    e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once
    f. GGT: greater than 3 x ULN
    g. AST:
        - ≥3.0 x ULN to be excluded;
        - results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor
    h. ALT:
        - ≥3.0 x ULN to be excluded
        - greater than ULN must be discussed with and approved by the Sponsor Medical Monitor
    i. ALP:
        - ≥3.0 x ULN to be excluded
        - 2.0 – <3.0 x ULN must be discussed with and approved by the Sponsor Medical Monitor
    j. Total bilirubin:
        - >1.5 x ULN to be excluded;
        - greater than 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor
    k. Direct bilirubin:
        - greater than 1x ULN to be excluded

All the inclusion and none of the exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the Investigator has reason to suspect that there might be a health problem (other than TB), enrolment should only be considered after discussing the case with the Sponsor Medical Monitor.

No protocol waivers will be granted by the TB Alliance.

5.3 Restrictions

Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are necessary for the participant's welfare, 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 reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected to prevent any potentially serious and/or life-threatening drug interactions.

The following recommendations should be followed with regards to concomitant medication to avoid possible drug interaction with the IMP:

Participants on a **moxifloxacin** containing treatment arm: The IMP should be taken either 4 hours before or 8 hours after taking the following products:

- An antacid, multivitamin, or other product that has magnesium, aluminium, iron or zinc
- Sucralfate
- Didanosine

Participants on the **HRZE/HR** treatment arm:

- Any aluminium-containing antacids should be taken at least one hour after the IMP dose.

The following medicinal products are prohibited from the Screening visit and during the treatment period:

- Quinolone antimalarial (e.g., chloroquine and quinacrine). Participants who have malaria at screening are to be excluded. However, if a participant develops malaria during the trial, the Investigator is advised to consult the Malaria Treatment Guidance document regarding the interaction between moxifloxacin and bedaquiline with anti-malarial drugs. Investigators may also contact the Sponsor Medical Monitor for further guidance.

- Chronic systemic glucocorticoids (topical, inhaled or intranasal glucocorticoids are allowed) due to their potential to cause visual opacities. Short term systemic glucocorticoids are allowed for emergency situations (e.g. for treatment of pulmonary exacerbation when inhaled glucocorticoids is inadequate).

- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, other quinolones, thioamides, and metronidazole.

The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible (unless this is required for emergency management of the participant). Investigators may also contact the Sponsor Medical Monitor for further guidance.

- Any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl,

mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). The exception is moxifloxacin and bedaquiline administered as part of the trial IMP, with ECG monitoring, to help ensure participant safety.

- Any drug known to be hepatotoxic (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, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).

5.4 Treatment Discontinuation and/or Early Withdrawal

Any participant for whom the Investigator decides to temporarily discontinue their IMP is to be discussed with the Sponsor Medical Monitor and, if applicable, be restarted on IMP as soon as possible.

A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following:

- Withdrawal of informed consent
- Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment
- Pregnancy
- At the specific request of the Sponsor or termination of the trial by the Sponsor
- Lost to follow-up
- When Phenotypic DST and/or whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.

A participant may withdraw from the trial at any time at his/her request (withdrawal of consent) or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative issues.

When a participant withdraws consent from the trial, no additional follow-up visits will be performed.

Participants who withdraw from the trial after having received IMP will not be replaced.

All participants withdrawn from trial and who received at least one dose of IMP will be requested to return for an Early Withdrawal visit and the applicable safety Follow-Up visits, as per the Synopsis Flow Chart and Procedures (Section 1.2 footnote c), as well as Table 5.

5.4.1 Early Withdrawal

In case of early withdrawal during the treatment or follow-up period, 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:

- Sputum sample collection x 2 (one EMS brought from home and one spot at the research site under the coaching and observation of the trial staff). If no EMS was provided by the participant, 2 spot samples may be collected at the site, at least 30 minutes apart.
- Urine pregnancy test (women of child bearing potential, whether they are sexually active or not)
- Laboratory safety sampling (including male reproductive hormone tests);
- Single 12-lead ECG
- TB Symptoms Profile
- Patient Reported Health Status Questionnaire
- Vital signs
- Full physical examination, including weight
- Ophthalmology examination, if required as described in Table 5
- IMP compliance check (if participant on IMP)
- Concomitant medications
- Adverse events

Once a participant has been withdrawn early from the trial, they will be requested to attend follow-up visits as described in Table 5:

Table 5: Follow-up Visits Required for Early Withdrawal Participants

Treatment Duration at EWD visit	**Ophthalmology Examination at EWD[a]**	**Ophthalmology Examination** **Visit 3 months after EWD Visit[a]**	**Week 52** (Month12) **Follow-up Visit**	**Week 104** (Month 24) **Follow-up Visit**
≤ 14 days	Not required	Not required	Required	Required
15 days to ≤ 12 weeks	Not required	Required	Required	Required
> 12 weeks	Required	Required	Required, if not already performed	Required

a. If an additional visit is required for an ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 3 months after the EWD visit date.

The Weeks 52 and 104 visits will be performed to collect SAE information (including verification of survival) and participant reported TB outcome information. This visit may be telephonic, a home or a site visit at Weeks 52) and/or Week 104 after the participants' start of treatment date.

5.4.2 Unscheduled Visits

Any visit which is conducted in addition to those required by the Synopsis Flow Chart and Procedures (Section 1.2), should be considered unscheduled regardless of the reason for the visit. The assessments which are undertaken as part of an Unscheduled visit should be as clinically indicated.

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

- For any medical reason, as determined by the Investigator or participant.
- If both sputum samples (EMS and spot) at Week 8 or later are contaminated, the participant should return for an unscheduled visit/s to give additional sputum samples or to document that the participant is not able to produce sputum.
- If after having converted to culture negative, the participant has a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 or Week 26), the participant should return for unscheduled visit/s to provide additional sputum samples, at a minimum of 7 days apart, or to document that the participant is not able to produce a sputum sample.

Determination of the participant's primary outcome status requires sputum culture results at the following time-points during the trial:

- End of Follow-up Period (Week 52 and 104)
- Early Withdrawal, if applicable

At least one of the following criteria should be met at these time-points to confirm a participant's primary outcome status:

- 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 the participant is clinically asymptomatic

Should the participant's primary outcome not meet any of the above criteria, the Investigator should continue to recall the participant for an Unscheduled visit to collect sputum samples until the criteria is met and the primary outcome can be determined.

Additional sputum samples: Two samples at each visit – ideally, one EMS and one spot sputum sample at the research site under the coaching and observation of the trial staff). If no EMS was provided by the participant, 2 spot sputum samples may be collected on site, at least 30 minutes apart. Additional sputum samples should be collected at least 7 days after the previous sample.

Table 6: Summary of Scenarios Requiring Unscheduled Visits for Mycobacteriology Testing

Time-point	Scenario	Unscheduled Visit/s Required?	Comment
Week 8 or later	Both sputum cultures are contaminated	Yes	Provide additional samples until a positive or negative result is reported, or it is confirmed that the participant is unable to produce sputum
At or after the last treatment visit (Week 17 or Week 26)	Previously converted to culture negative but now has an MTB-positive culture	Yes	Provide additional samples at least 7 days after the previous sample until the result is confirmed, or it is confirmed that the participant is unable to produce sputum.
End of Follow-up Period (Week 52 and 104) Early Withdrawal, if applicable	Participant's primary outcome status cannot be confirmed by: 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	Yes	Provide additional samples at least 7 days after the previous sample until one of the criteria is met and the primary outcome status can be determined.

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

5.4.3 Lost-to-Follow-up

Every reasonable attempt must be made to minimise Lost-to-Follow-up (LTFU) participants. A minimum of three contact attempts (telephonic/home visit) will be made for participants who do

not arrive for their scheduled trial visits. If these attempts are unsuccessful the participant will be considered LTFU. All attempts to contact the participant must be clearly documented in the participant's source documents.

5.4.4 Early Withdrawal due to TB

Ultimately it is the Investigator's decision whether a participant requires early withdrawal from the trial due to a concern that the participant has symptomatic worsening of TB and/or bacteriological failure/relapse.

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

If the Investigator decides to withdraw a participant due to TB, additional sputum samples may need to be collected to ensure the participant's outcome status as determined in Section 5.5.

All early withdrawn participants who are confirmed sputum positive (two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These participants will be referred to their applicable DS/DR local community TB clinics for standard anti-tuberculosis chemotherapy according to National TB Treatment Guidelines.

The participant will be provided with a referral letter from the Investigator to take with them to their National Treatment Program (NTP) clinic and the referral letter, at a minimum, should include all treatment received by the participant and information about any suspected/confirmed adverse event/reaction related to any of the trial IMP's and or concomitant medications. A follow-up call should be made by the trial site staff to the clinic to ensure the participant attended the NTP clinic.

5.5 Participant Progress Definitions

Table 7: Participant Progress Definitions

Status	Treatment	Follow-Up
Screen Failure	Participants from whom informed consent is obtained and is documented in writing (i.e., participant signs an informed consent form) but who are not randomized	
Completed Treatment / Completed Follow-Up*	Participants who complete the full course of IMP	Participants who complete all follow-up visits
Completed Treatment / Discontinued Follow-Up	Participants who complete the full course of IMP	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)

Status	Treatment	Follow-Up
Completed Treatment / Lost to Follow-Up	Participants who complete the full course of IMP	Participants who are unable to be contacted on or before their final visit
Discontinued Treatment / Completed FU	Participants who discontinue IMP prior to completion of the protocol-defined treatment course	Participants who complete all applicable follow-up visits
Discontinued Treatment / Discontinued Follow-Up**	Participants who discontinue IMP prior to completion of the protocol-defined treatment course	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)
Lost to Follow-Up	Participants who are unable to be contacted on or before their final treatment visit and it cannot be confirmed whether treatment was completed	

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

** Early Withdrawal

5.6 Trial Stopping Rules

There are no trial specific stopping rules.

The trial or parts of the trial can be stopped by the Sponsor on advice from the Data Safety and Monitoring Committee (DSMC) after their review of applicable trial data. In addition, the Sponsor has the right to stop the trial or a specific trial site at any time, although this should only occur after consultation between the involved parties. Should this occur, the local and central Ethics Committee/Institutional Review Board (EC/IRB) and Regulatory Authorities will be informed.

Should a trial site be closed prematurely, all trial materials (except source documentation that must remain at the site) will be returned to the Sponsor or applicable vendor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Participants currently on trial IMP will receive an appropriate regimen and all participants will be referred to their applicable DS-TB/DR-TB NTP clinic.

6.0 Treatment

6.1 IMP Administration

6.1.1 Instructions for Dosing of Test Regimen (BPaMZ)

- Treatment will be orally administered once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months).

6.1.2 Instructions for Dosing Control Treatment Regimen (HRZE/HR)

- To be taken with a glass of water (approximately 240 ml).
- HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes.

HRZE/HR treatment will be administered orally once daily to DS-TB participants as follows:

Weight Band	Weight Range	Number of tablets per weight band
1	30-39 kg	2
2	40-54 kg	3
3	55-70 kg	4
4	≥ 71 kg	5

The participant's weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and dose to administer.

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

6.2 Participant Compliance

During site clinic visits, the IMP will be administered by the Investigator(s)/designated site personnel and when possible, the check for IMP compliance via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the participant has swallowed the IMP). During the trial, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how the IMP is to be taken, as well as to check the IMP cards for unused tablets in the containers at each visit during the treatment phase.

6.3 Treatment Modification(s)

The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the Investigator to identify and address the cause(s) (e.g. side effects).

Participants that do not take:

- Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required.
- If more than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been.

- If more than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial.
- If the participant misses a total (sum) of 56 cumulative missed doses, discontinue the IMP and withdraw the participant from the trial.
- If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose that was missed.

Any participant for whom the trial IMP is discontinued (including for non-adherence) will be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial IMP as soon as possible.

6.4 IMP Packaging and Labelling

The complete formulations of the IMP, bedaquiline and pretomanid, are found in the respective Investigator Brochures.[8, 15] The complete formulations of moxifloxacin, pyrazinamide, HRZE/HR are found in the Package Inserts.[19, 20, 22, 40]

The IMP will be packaged in weekly or bi-weekly cards as follows:

Week 1 to 8 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	14	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Week 9 to 17/26 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	7	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Control (HRZE/HR) Group: Dispensed *Bi-weekly*			
Weight Band	**Weight Range**	**Number of tablets per weight band**	**Number of tablets in each card**
1	30-39 kg	2	28
2	40-54 kg	3	42
3	55-70 kg	4	56
4	≥71 kg	5	70

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

The packaging of each weekly and biweekly cards will be labelled with, at a minimum, the following information:

- Name of Sponsor
- Name of medication

- Dosage, quantity and method of administration
- Reference/lot number
- The statement “For Clinical Trial Use Only”
- Space for completion of name of Investigator and site number
- MedID: medication identification number
- Storage conditions
- Period of use
- The statement “Keep out of reach of children”
- Expiry date
- Directions for use
- Space for completion of participant number and visit/date dispensed

6.5 Blinding and Procedures for Breaking the Blind

As this is an open label trial there is no need for blinding or procedures to break the blind. The trial participants, the site staff, Sponsor, and CROs will not be blinded to treatment assignment.

6.6 Handling, Storage and Accountability

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

Only participants randomised in the trial may receive trial IMP and only authorized site staff may supply or administer trial IMP. All trial IMP’s must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

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

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

Further guidance and information for the handling, storage, accountability and final disposition of unused trial IMPs are provided in the Pharmacy Manual.

7.0 Trial Variables and Procedures

The Synopsis Flowchart and Procedures (Section 1.2) should be referenced for timing, sequence of assessments, and specific procedures.

7.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected:

- Written Informed Consent
- Visit dates
- Participant disposition
- Demography (date of birth, race and gender)
- Inclusion and exclusion criteria
- Clinically significant medical and TB treatment history (including past and current TB diagnosis, smoking and alcohol use)
- Screening coached spot sputum samples:
  - Smear microscopy for acid-fast bacilli
  - Rapid molecular tests for isoniazid, rifampicin, fluoroquinolones resistance (Hain MTBDRplus and HainMTBRsl)
  - Liquid Culture (MGIT) for Mycobacterium tuberculosis (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive.
- Urine pregnancy test: women of childbearing potential only, whether they are sexually active or not (non-childbearing potential for a female participant is defined as having bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months).
- Serology: HIV and CD4 count. Where required by regulatory authorities or ethics committees, a separate (EC/IRB approved) HIV informed consent form will be obtained from participants:
  - Prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the participant, HIV counselling that is provided to the participant by the trial site should be clearly documented in the participant's medical records/source. Participants have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the participant's medical records/source.
- Karnofsky Score (Appendix 5). Only for HIV positive participants.
- Chest X-Ray: A chest X-ray digital image within 6 months prior to or during the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor; this process will be documented in the Chest X-Ray / Radiology Manual. The investigator is responsible for review and analysis of the chest X-ray for participant's inclusion.
- Method of birth control: male and female participants and their sexual partners
- IMP details: randomization
- IMP compliance and actual dosing
- Concomitant medications

7.2 Efficacy Variables and Procedures

Two spot sputum samples are collected, one EMS brought from home or collected in the hospital ward (only if the participant is hospitalised) and one spot sputum sample collected at the research site under the coaching and observation of the trial staff or, if no EMS sample was provided by the participant, 2 samples may be collected on site at least 30 minutes apart. The mycobacteriology sampling methodology and requirements will be described in a separate document, the Mycobacteriology Laboratory Manual, which will be provided prior to the trial start. Sputum samples may not be obtained by induction.

The following analyses will be performed:

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

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

- Bacteriologic failure/relapse
- Time to sputum culture conversion
- Number of participants with sputum culture conversion

Every effort must 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 participant who never achieves culture negative status due to the inability to produce sputum but has completed Week 17 or Week 26 and post treatment follow-up (Weeks 39 to 104) and is without clinical or biological evidence of relapse, will be considered to have a favourable outcome.

TB Symptoms Profile:

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

Patient Reported Health Status Variables and Procedures:

- The Patient Reported Health Status variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2). Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire. 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 trial Participant Questionnaires Guideline, which will be provided prior to the trial start.

7.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2) and assessed for evaluation of the safety endpoints:

- The safety laboratory sampling methodology and requirements will be described in a separate document, the Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
    - Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count)
    - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, ALP, AST, ALT, lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO_2, creatine phosphokinase (CPK). GGT is only routinely included at the Screening visit (Day -9 to -1).
    - When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator should request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].
    - Hepatitis A, B and C serology test to be performed at Day 1 (baseline) or where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Protocol V4.0.
    - 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 ECG:
    - Investigator assessment: normal or abnormal
    - Central cardiologist assessment: heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.
    - Methodology:
        - Timing (Synopsis Flow Chart and Procedures, Section 1.2) and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start
        - ECGs are to be recorded for 10 seconds
        - ECGs are to be performed during a single visit
        - ECGs should be done before any phlebotomy when both included in a visit
        - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch)
    - ECGs to be performed prior to pre- and post-dose PK sampling as described below:
        - Day 1: pre-dose (within 2 hours prior to dosing)
        - Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
        - Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
        - Week 12: pre-dose (within 2 hours prior to dosing)
        - Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose
- Vital signs:
    - Vital signs (should be done before any phlebotomy in light clothing and with no shoes)

  - Systolic and diastolic blood pressure (mmHg) to be measured in a supine position (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 (beats per minute)
  - Respiratory rate (breaths per minute)
  - Axillary body temperature (°C)
- Physical Examination:
  - Height (m) is measured at the screening visit only
  - Full (complete) and limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded
  - Weight (kg) (in light clothing and with no shoes)
  - Using the variables of weight and height, the body mass index (BMI) will be calculated
- Ophthalmology Slit Lamp Examination:
  - To be done by an Ophthalmologist trained on Age-Related Eye Disease Scale 2 (AREDS2) assessment. The ophthalmology slit lamp methodology and requirements will be described in a separate document, the Ophthalmology Guideline. The following analyses will be performed: AREDS2 opacity typing and grading.
- Adverse events
- Investigator assessment:
  - The Investigator will review the participant status at specified visits in the Synopsis Flow Chart and Procedures (Section 1.2), including any time the Investigator determines that the participant fulfils the criteria for the primary outcome of treatment failure. The Investigator will assess whether TB treatment is considered a “success” or “failure”. If it is considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration.

7.4 PK Variables and Procedures

Plasma concentrations from sparse sampling (Synopsis Flow Chart and Procedures, Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid to further evaluate the effects of covariates on model parameters in this trial population.

PK data from the current trial may be combined with prior data to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{min}, C_{max}, AUC_{τ}, C_{mean}, and time above minimum inhibitory concentration) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.

7.5 Mycobacteriology Characterization Variable and Procedures

- Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative);
- MTB confirmed positive cultures (after the participant has previously converted to negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.

- Refer to the Mycobacteriology Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for:

- Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);
- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin;
- Drug Susceptibility Testing for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing (WGS), and comparison of sequences from baseline and relapse isolates.

If the participant's culture converts to negative and has a MTB positive culture at or after the last visit of the treatment period (Week 17 and Week 26), the MTB cultures will be tested at the trial mycobacteriology laboratories using Hain MTBDR*plus* and HainMTBR*sl* to detect resistance to isoniazid, rifampicin, fluoroquinolones and injectables.

All MTB isolates must be stored at the local mycobacteriology laboratories, until trial closure. In addition, MTB isolates as well as extracted MTB DNA from the applicable baseline and follow-up cultures will be stored at the central mycobacteriology laboratory for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure.

8.0 Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

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

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

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

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse. A "suspected transmission of infectious agent by a medicinal product" is also considered a serious adverse event under the SAE criterion "Other medically important condition".

8.1.3 Attribution/Causality

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

Table 8: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An AE, which is not related to the use of the drug.
Unlikely	An AE 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 AE, 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 AE, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by de-challenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An AE, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

8.1.4 Severity

Table 9: Definitions for Adverse Event Severity Gradings

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

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

8.2 Reporting

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

All AEs will be collected by the Investigator from the time a participant signs the Informed Consent Form through to their Week 104 follow-up visit. The exception to this is early withdrawal participants who will only have SAEs collected from their time of early withdrawal to their Week 104 follow-up visit at the timepoints specified in the Synopsis Flow Chart and Procedures (Section 1.2) and recorded in the CRF.

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

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

The Sponsor/Investigator/designee will inform Regulatory Authorities and/or EC/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 EC/IRB.

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

8.2.1 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- The end of the follow-up period; and
- 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 Investigator. However, this will have to be agreed upon with the Sponsor Medical Monitor.

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

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

New or updated SAE information will be recorded in the originally completed CRF and submitted to the Sponsor within 24 hours of receipt, per the eCRF completion guideline.

8.2.2 Clinical Laboratory Adverse Events

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

8.2.3 Disease Symptoms During Trial

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

- worsened while the participant is in the trial; and

- the Investigator assesses it as clinically significant;

it will be recorded as an adverse event. If there is:

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

it will not be recorded as an AE and this will be noted in the participant's source documentation. All TB related symptoms that meet SAE criteria will be recorded and reported as a SAE.

8.2.4 Overdose

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

8.2.5 Drug Interaction

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

8.2.6 Pregnancy

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

If a pregnancy is suspected while the participant is receiving IMP, the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner, the participant withdrawn from the trial and referred to the NTP for further management.

Protocol-required procedures for trial discontinuation and follow-up will be performed unless contraindicated by the pregnancy.

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

8.3 Monitoring for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in the preclinical toxicity studies of the Investigator's Brochures[8, 15] and Package Inserts.[19, 20, 22, 40]

AEs still ongoing at the end of the treatment period in the trial will be followed until satisfactory clinical resolution or stabilization, or until the end of the follow-up period and until all queries on these AEs have been resolved.

Grade 3 and Grade 4 laboratory abnormalities, and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.

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

8.3.1 ALT, AST and Bilirubin Elevations

The Investigator should refer to the Hepatoxicity Management Guideline, to appropriately monitor significant elevations of AST, ALT or Bilirubin. A separate Hepatoxicity Management Guideline document has been developed to aid investigators in the management of participants.

When managing participants with elevated liver enzymes at an Unscheduled visit, the Investigator should request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

8.3.2 Lipase

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

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

8.3.3 Musculoskeletal System and Cardiac Muscle Myalgia

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

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

8.3.4 Cardiac Rhythm Disturbances

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

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

<u>QTc prolongation</u>

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

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

8.4 Safety Monitoring by Data Monitoring Committee

A Data Safety Monitoring Committee (DSMC) will be appointed for the trial. The primary responsibility of the DSMC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial participants by monitoring participant safety, assess participant risk versus benefit, and assess data quality and general evaluation of the trial progress. Its activities will be delineated in a DSMC Charter that will define the membership, responsibilities and the scope and frequency of data reviews.

The DSMC will operate on a conflict-free basis independently of the Sponsor and the trial team. It will comprise at least 3 voting members that include at least 2 clinicians and one statistician.

The DSMC may have an organizational meeting prior to commencement of the trial. The DSMC will have meetings where it will review unblinded data during a closed session. These meetings will be planned at regular intervals.

The Sponsor or the DSMC may convene ad hoc meetings based on rates of SAEs and/or to review results of the futility analysis, or if safety concerns arise during the trial. After its assessment, the DSMC will recommend to the Sponsor continuation, modification or termination of the clinical trial.

9.0 Statistical Analysis

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

There will be 3 data analyses and trial reports generated for this trial:

1. When all participants have completed 8 weeks (2 months) of treatment from baseline.
2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy.
3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.

9.1 Analysis Populations

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

- The ITT population is defined as all randomized participants excluding late screening failures. Late screening failures are participants withdrawn from treatment because they were found to be ineligible (late exclusions from the trial), based on data collected *prior to randomization*.
- The mITT population is defined as the ITT population with extra exclusions (described in the SAP).
- The PP population is defined as the mITT population with extra exclusions (described in the SAP).
- The mITT analysis will be considered primary, with consistent findings required from the other main analysis populations to support the primary conclusion.

9.2 Sample Size

For the primary endpoint, time-to-culture conversion at 8 weeks,150 participants per arm (DS-TB participants) will provide at more than 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 90% power to detect a HR of least 2. This sample size also allows for one planned interim analysis of the primary endpoint (See Section 9.4.1)

For the key secondary endpoint of clinical outcome at 12 months from randomization, 150 patients per arm will provide 74% power based on assumptions using data from the largest most recent and completed phase 3 TB treatment trial which used the same control arm.[41] That is, assuming 16% unfavourable (see Section 9.4.2) in the control arm and 13% unassessable (see Section 9.6) at 52 weeks post randomization. A 12% margin of non-inferiority was chosen to preserve at least 75% of the estimated control arm effect against placebo (estimated to be 54%)[41, 42] which is considered an acceptable proportion on which to declare non-inferiority of the test regimen.

9.3 Interim Analyses

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard

ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

  *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objectives**

  *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46, 47, 48] and full details are provided in the Statistical Analysis Plan.

9.4 Primary and Secondary Efficacy Endpoint Analysis

9.4.1 Primary Efficacy Endpoint, Time to Culture Conversion at 8 Weeks

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

Participants will be classified as being culture positive, culture negative, dead or unassessable at 8 weeks. The proportion culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis and groups compared using a hazard ratio and 95% confidence interval.

Non-inferiority of the key secondary endpoint of clinical outcome will be assessed using the upper bound of the one-sided 97.5% confidence interval for the difference between the proportion of participants who are classified as having an unfavourable status on the intervention less the control regimen. If the upper bound of the one-sided 97.5% confidence limit for this difference in proportions is less than 12% (the margin of inferiority) the intervention will be non-inferior to the control arm.

9.4.2 Key Secondary Efficacy Endpoint, Clinical Outcome at 52 Weeks from Randomization

For the key secondary endpoint of clinical outcome (bacteriologic failure or relapse or clinical failure), participants will be classified as having a favourable, unfavourable or unassessable outcome status which will be defined in detail in the SAP. In general, participants achieving and maintaining culture negative status without any additional treatment will be considered favourable;

participants who fail on treatment or relapse in follow-up will be considered unfavourable and participants who are not assessable (and who have not already been declared as unfavourable) will be considered unassessable and excluded from the analysis.

9.4.3 Other Secondary Efficacy Endpoints

The secondary efficacy endpoints and analyses are as follows are:

- Clinical outcome (bacteriologic failure or relapse or clinical failure) at 104 weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight will be summarised and presented.
- Proportion of participants experiencing a change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status will be summarised and presented.

9.5 Safety and Tolerability Assessments

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 any AE occurring or worsening with an onset date on or after the date of the first dose of the study medication and within 14 days after the date of the last dose. Any adverse event that started beyond this timeframe and assessed as possibly related to study drug is considered 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.

9.6 Pharmacokinetics

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., C_{min}, C_{max}, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be

assessed; so, too, will the effects of concomitant medications including ART, as feasible. Data from other trials may be included to enhance the model-based analysis.

Detailed plans for the PopPK analysis will be outlined in a separate modelling plan, and results will be reported in separate modelling report.

9.7 Pharmacokinetics/Pharmacodynamics

Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate. Planning details and results will be included in the separate modelling plan and report.

10.0 Records Management

10.1 Data Collection

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

10.2 Source Documents

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

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

10.3 File Management at the Trial Centre

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

10.4 Records Retention at the Trial Centre

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

11.0 Quality Control and Assurance

11.1 Site Procedures

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

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

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

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

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

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

11.2 Monitoring

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

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

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

11.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol and GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the trial site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly.

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

11.4 Auditing

For 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 about accuracy, adequacy and consistency, and to assure that trials are in accordance with the guidelines. Having the highest quality data from trials is an essential aspect of drug development.

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The auditors or inspectors may also review site SOPs, training records, site facilities and other trial related systems/processes.

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

12.0 Ethics and Regulatory

12.1 Basic Principles

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

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

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

12.3 Regulatory Authorities

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

12.4 Informed Consent

Written informed consent will be obtained from all participants (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment procedures) are performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for 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 part of the research.

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

The trial will be included and updated in the appropriate Country registry and referenced in the informed consent forms (ICF).

Once the appropriate essential information has been provided to the participant and fully explained by the Investigators (or qualified designees) and it is felt that the participant understands the implications of participating, the EC/IRB approved written ICF will be signed and dated by both the participant and the person obtaining consent (Investigators or designees), and

by any other parties required by the EC/IRB. Ongoing participants must be re-consented to the most current version of the ICF(s) during their participation in the trial.

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

The monitor will inspect the original completed ICFs for all participants.

12.5 Confidentiality

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

13.0 Publication Policy

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

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

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory Investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors.[43]

Because the trial is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the Trial must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy. Specifically, (a) all peer-reviewed published research relating to the trial must be submitted for publication by TB Alliance through the Chronos Open Access Publishing Service established by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy.

14.0 Protocol Amendment Policy

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

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

15.0 Sponsor, Financial Aspects, Insurance and Indemnity

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

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

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

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

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

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Appendices

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	scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

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

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

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of Acquired Immune Deficiency Syndrome (AIDS), NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the DMID and modified to better meet the needs of participants 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
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
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or
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
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures

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

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

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

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

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

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient - no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of	no normalization with bronchodilator;FEV_1 25% - 50% of peak flow; or	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: Who Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection
Asymptomatic Acute retroviral syndrome
Clinical Stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical Stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections
Clinical Stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for >1 month Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) Persistent oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anemia (hemoglobin <8 g/dL) Neutropenia (neutrophils <500 cells/µL) Chronic thrombocytopenia (platelets <50,000 cells/µL)
Clinical Stage 4
HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Cryptococcosis, extrapulmonary (including meningitis) Disseminated nontuberculosis mycobacteria infection Progressive multifocal leukoencephalopathy Candida of the trachea, bronchi, or lungs Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)

Recurrent nontyphoidal Salmonella bacteremia
Lymphoma (cerebral or B-cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy
Symptomatic HIV-associated cardiomyopathy
Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

REF: World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children; 2007*

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: Cardiovascular Safety

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

All-important abnormalities from the ECG readings will be reported.

The percentage of participants with increases in QTc of <30, 30-60, or > 60 ms from baseline will also be tabulated at each time point.

Abnormality Code	ECG parameter			
	HR	PR	QRS	QTcorrected
Abnormalities on actual values				
“Abnormally low”	≤ 50 bpm	NAP	≤ 50 ms	-
“Abnormally high”	≥ 120 bpm	≥ 210 ms	≥ 120 ms	-
“]450 ms, 480 ms]	-	-	-	450 ms < QTc ≤ 480 ms
“]480 ms, 500 ms]	-	-	-	480 ms < QTc ≤ 500 ms
“More than 500 ms	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline				
“[30; 60] ms”	-	-	-	[30; 60] ms
“> 60 ms”	-	-	-	> 60 ms

Appendix 5: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

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

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

Protocol Amendment or Administrative Change

TB ALLIANCE

Trial Number	Trial Name
NC-008	SimpliciTB

X Protocol Amendment Number 3, Dated 30/SEP/2019
☐ Protocol Administrative Change Number _ _, Dated _ _/_ _ _/_ _ _ _

Summary - Protocol section changed		Does amendment / administrative change affect any of the elements listed?	
		YES	**NO**
A	Purpose of trial	☐	X
B	Design of trial	☐	X
C	Informed consent	☐	X
D	Recruitment procedure	☐	X
E	Measures of efficacy	☐	X
F	Schedule of samples	☐	X
G	Addition or deletion of tests or measures	X	☐
H	Number of participants	☐	X
I	Age range of participants	☐	X
J	Inclusion criteria	☐	X
K	Exclusion criteria	☐	X
L	Safety monitoring	X	☐
M	Duration of exposure to the investigational medicinal product(s)	☐	☐
N	Change of posology of the investigational medicinal product(s)	☐	X
O	Change of comparator	☐	X
P	Statistical analysis	☐	X

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Reasons for Protocol Amendment or Administrative Change:

1	Change:	TB Alliance logo has been changed on page 1, due to updated company logo that was implemented in Jul 2019.
2	Clarify:	Per Memo #3, Slit lamp ophthalmic examination to be performed at Week 17 and 26 for the 4-month treatment arm, and only at Week 26 for the 6-month treatment arms (Section 1.2, Synopsis Flow Chart and Procedures update, only) to ensure consistency with protocol Section 1.2 Flow Chart and Procedures footnote p.
3	Clarify:	Per Memo #5, ECG to be performed at Week 12 (Section 1.2, Synopsis Flow Chart and Procedures update, only) to ensure consistency with the protocol Section 1.2 Flow Chart and Procedures footnote n, and Section 7.3 Safety and Tolerability Assessments.
4	Clarify:	Per Memo #6, Male Reproductive Hormone testing to be performed at the end of each 4 and 6-month treatment period (Section 1.2, Synopsis Flow Chart and Procedures update, only) in alignment with the protocol intention to perform this assessment at the end of each treatment period.
5	Clarify:	Per Memo #7, Male Reproductive Hormone testing to be performed at the early withdrawal visit (Section 1.2, Synopsis Flow Chart and Procedures update, only), to ensure consistency with the Section 5.4.1 Early Withdrawal.
6	Clarify:	Per Memo #8, pregnancy testing is to be performed on all female participants of childbearing potential. Females of non-childbearing potential are: Female participant or male participants' female sexual partner – bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months (Inclusion criteria #5.1.7 updated, only), to ensure consistency with the Section 1.2 Synopsis and Flow Chart and Procedures footnote k, Section 5.4.1 Early Withdrawal (urine pregnancy test) and Section 7.1 Demographic and Background Variables and Procedures (urine pregnancy test).
7	Change:	'When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator **should** (changed from 'can') request additional tests…' (Section 1.2, Synopsis Flow Chart and Procedures footnote l; Section 7.3 Safety and Tolerability Assessments; Section 8.3.1 ALT, AST and Bilirubin Elevations) to improve safety monitoring and management of participants.
8	Add:	Hepatitis A, B and C serology test to be performed at Day 1 (baseline) or where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Protocol V4.0, to improve safety monitoring and management of participants (Section 1.2, Synopsis Flow Chart and Procedures footnote l; Section 7.3 Safety and Tolerability Assessments).
9	Add:	'Where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C result for all participants already enrolled prior to Protocol V4.0', to improve safety monitoring and management of participants (Section 1.2, Synopsis Flow Chart and Procedures footnote s).
10	Add:	'When Phenotypic DST and **/ or** whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results'… wording updated, as Phenotypic DST results are

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		more readily available when this review and decision needs to be made, on an ongoing basis (Section 5.1.5 Inclusion Criteria and 5.4 Treatment Discontinuation and/or Early Withdrawal).
11	Change:	Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening with an onset date on or after the date of the first dose of the study medication and **within 14 days after the date of the last dose,** changed from …'until the last scheduled visit / assessment / measurement'… in Section 9.5 Safety and Tolerability Assessments, to be consistent with the Statistical Analysis Plan (SAP) definition of TEAEs.

#	Section	Previous Text Version 3.0, dated 14-Jan-19	Amended Text Version 4.0, dated 30-Sep-19 **Additional text - bold font.** Deleted text – ~~strike-through.~~	Reason for Change Insert reason # from table above
1	Page 1, title page	TB ALLIANCE	TB Alliance	1
2	Section 1.2 Synopsis Flow Chart and Procedures	X-mark present at Week 17 for the 6-month treatment arms	**X-mark has been removed from Week 17 for the 6-month treatment arms**, for the Ophthalmic examination assessment	2
3	Section 1.2 Synopsis Flow Chart and Procedures	X-mark not present	**X-mark has been included at Week 12**, for the assessment of the 12-lead ECG	3
4	Section 1.2 Synopsis Flow Chart and Procedures	X-marks present at Week 17 for the 6-month treatment arms, and at Week 26 for the 4-month treatment arm	**X-mark has been included at Week 17 for the 4-month and at Week 26 for the 6-month treatment arms**, for the assessment of the Male Reproductive Hormone Tests	4
5	Section 1.2 Synopsis Flow Chart and Procedures	X-mark not present	**X-mark has been included at Early Withdrawal**, for the assessment of the Male Reproductive Hormone Tests	5

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#	Section	Previous Text Version 3.0, dated 14-Jan-19	Amended Text Version 4.0, dated 30-Sep-19 **Additional text - bold font.** Deleted text – ~~strike-through.~~	Reason for Change Insert reason # from table above
6	Inclusion Criteria #5.1.7	a. Participant - not heterosexually active or practice sexual abstinence; or b. Female participant or male participants female sexual partner – bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or c. Male participant or female participants male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening;	~~a. Participant - not heterosexually active or practice sexual abstinence; or~~ b. Female participant or male participants female sexual partner – bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or ~~c.~~ Male participant ~~or female participants male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening;~~	6
7	Section 1.2, Synopsis Flow Chart and Procedures footnote l; Section 7.3 Safety and Tolerability Assessments; Section 8.3.1 ALT, AST and Bilirubin Elevations	When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator should request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].	When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator ~~can~~ **should** request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].	7

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#	Section	Previous Text Version 3.0, dated 14-Jan-19	Amended Text Version 4.0, dated 30-Sep-19 **Additional text - bold font.** Deleted text – ~~strike-through.~~	Reason for Change Insert reason # from table above
8	Section 1.2, Synopsis Flow Chart and Procedures footnote l; Section 7.3 Safety and Tolerability Assessments	No previous text	**Hepatitis A, B and C serology test to be performed at Day 1 (baseline) or where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Protocol V4.0**	8
9	Section 1.2, Synopsis Flow Chart and Procedures footnote s	No previous text	**Where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis serology result for all participants already enrolled prior to Protocol V4.0**	9
10	Section 5.1.5 Inclusion Criteria and 5.4 Treatment Discontinuation and/or Early Withdrawal	When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.	When Phenotypic DST and **/ or** whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.	10

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#	Section	Previous Text Version 3.0, dated 14-Jan-19	Amended Text Version 4.0, dated 30-Sep-19 **Additional text - bold font.** Deleted text – ~~strike-through.~~	Reason for Change Insert reason # from table above
11	Section 9.5 Safety and Tolerability Assessments	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.	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.~~ **any AE occurring or worsening with an onset date on or after the date of the first dose of the study medication and within 14 days after the date of the last dose**. **Any adverse event that started beyond this timeframe and assessed as possibly related to study drug is considered treatment-emergent**	11

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Sponsor

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

DocuSigned by:
Morounfolu Olugbosi
Signer Name: Morounfolu Olugbosi
Signing Reason: I approve this document
Signing Time: October 1, 2019 | 3:29 AM PDT
3DABF6C3410E4B8F85E1D6E511FA5A5F

Signature of Study Physician	Morounfolu Olugbosi Printed name	October 1, 2019 | 3:29 AM PDT Date

Principal Investigator

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

Signature of Principal Investigator	Printed name	Date

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17 April 2020

Memo to: Investigators and Site Staff, TB Alliance Project Team, Ethics Committees and Regulatory Authorities

RE: **SimpliciTB NC-008 (BPaMZ), Protocol Memo #9**

Global Protocol Version 4.0 dated 30 September 2019 and RUS Protocol V3.0 dated 1 October 2019, Section 9.0 Statistical Analysis:

To Whom It May Concern:

This memo serves to clarify that the Week 8 data analysis and trial report referenced in Section 9.0 of the protocol Statistical Analysis, will be performed when all participants have completed 52 Weeks (12 Months) of follow-up, from the start of therapy.

Protocol Section 9.0 Statistical Analysis will be revised at the next protocol update, to reflect this information.

As this data analysis and trial report will be performed when all participants have completed 52 Weeks (12 Months) follow-up from start of therapy, it is determined that there is no impact on participant safety or integrity of the study data.

Regards

DocuSigned by:
Morounfolu Olugbosi
Signer Name: Morounfolu Olugbosi
Signing Reason: I approve this document
Signing Time: April 17, 2020 | 8:12 AM EDT
3DABF6C3410E4B8F85E1D6E511FA5A5F

Dr Morounfolu Olugbosi, MD MSc

SimpliciTB Study Physician

Senior Director, Clinical Development/Head of South Africa Office, TB Alliance

Cc: Trial Master File, Investigator Site Files

Ethics Committees and Regulatory Authorities (as required)

Investigator Acknowledgement of Receipt:

I confirm receipt of this Memo #9 dated 16 April 2020, my understanding thereof and agree to implement it accordingly.

Principal Investigator Name Signature

Date

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

SIMPLICITB

Protocol Number:	NC-008 (B-Pa-M-Z)
Title:	An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).
Drug(s)/Combination(s):	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Version/Date:	Russia V1.0 / 10 July 2018, Incorporating Protocol V2.0 / 21 February 2018
Protocol Name:	**SimpliciTB**

PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (B-Pa-M-Z)**

Protocol Date: **Russia V1.0 / 10 July 2018, Incorporating Protocol V2.0 / 21 February 2018**

Protocol Name: **SimpliciTB**

SPONSOR: **Global Alliance for TB Drug Development**

I agree to the terms of this trial protocol.

DocuSigned by:
Morounfolu Olugbosi
Signer Name: Morounfolu Olugbosi
Signing Reason: I approve this document
Signing Time: 15 July 2018 | 23:46 PDT
3DABF6C3410E4B8F85E1D6E511FA5A5F

Signature of Study Physician

Morounfolu Olugbosi, MD MSc
Printed Name

July 16, 2018 | 2:46 AM EDT
Date

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New York, NY 10005
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E-mail: morounfolu.olugbosi@tballiance.org

LEAD INVESTIGATOR

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

Signature

Printed Name

Date

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (B-Pa-M-Z)**

Protocol Date: **Russia V1.0 / 10 July 2018, Incorporating Protocol V2.0 / 21 February 2018**

Protocol Name: **SimpliciTB**

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

_____ _____
Signature Printed Name

_____
Date

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Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AFB	Acid-fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AREDS2	Age Related Eye Disease Scale 2
ART	Anti-Retroviral Therapy
AST	Aspartate aminotransferase
AUC_{τ}	Area Under Curve over a dosing interval
B	Bedaquiline
BA	Bacterial activity
BMI	Body Mass Index
BPaMZ	Combination of bedaquiline plus pretomanid plus moxifloxacin plus pyrazinamide
C	Clofazimine
CFU	Colony Forming Units
$C_{(max), (min)}$	plasma Concentration (maximum), (minimum)
CO_2	Carbon dioxide
CPK	Creatine Phosphokinase
CYP3A4	Cytochrome P450 3A4
DMID	Division of Microbiology and Infection Disease
DNA	Deoxyribonucleic Acid
DR-TB	Drug-resistant tuberculosis For this particular protocol defined as TB participants with 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB) (participants with fluoroquinolone resistance are excluded)
DS-TB	Drug-sensitive tuberculosis
DSMC	Data Safety and Monitoring Committee
E	Ethambutol
EBA	Early Bactericidal Activity
EC	Ethics Committee
ECG	Electrocardiogram
EFV	Efavirenz
(e)CRF	(electronic) Case Report Form
EMS	Early Morning Sputum
EWD	Early Withdrawal
FTC	Emtricitabine
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
H	Isoniazid
hERG	Human *Ether-à-go-go* Related Gene
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
HR	Isoniazid plus rifampicin combination tablet
ICF	Informed Consent Form
ICH	International Council for Harmonisation

IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent to Treat
IUATLD	International Union Against Tuberculosis and Lung Disease
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Linezolid
LH	Luteinizing hormone
LLN	Lower Limit of Normal
LPV	Lopinavir
LTFU	Long term follow-up
M	Moxifloxacin
MBD	Minimum Bactericidal Dose
MIC	Minimum Inhibitory Concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi Drug Resistant Tuberculosis
MGIT	Mycobacterial Growth Inhibiting Tube
mITT	Modified Intent to Treat
ms	millisecond
NVP	Nevirapine
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NRTI	(Triple) Nucleosidase Reverse Transcriptase Inhibitor
Pa	Pretomanid
PD	Pharmacodynamic
PP	Per Protocol
PK	Pharmacokinetic
PR	PR interval
R	Rifampicin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSCC	Serial sputum colony counting
TB	Tuberculosis
TDF	Tenofovir
TEAE	Treatment Emergent Adverse Events
TTP	Time to Positivity
ULN	Upper Limit of Normal
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis
µg(/ml)	micrograms (per millilitre)
Z	Pyrazinamide (tablets)

1.0 Synopsis

1.1 Synopsis Summary

Synopsis	Description
Name of Sponsor/Company	Global Alliance for TB Drug Development
Name of Finished Products	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Number/Title	NC-008 / (B-Pa-M-Z)/ An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB)
Treatment Indication	Pulmonary Tuberculosis (TB)
Trial Objective(s)	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with: **Drug Sensitive TB (DS-TB)** – BPaMZ given for 17 Weeks (4 months), or – Standard HRZE/HR treatment given for 26 weeks (6 months) **Drug Resistant TB (DR-TB)** – BPaMZ given for 26 Weeks (6 months) **DR-TB Defined as participants with** 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)
Trial Design	Phase 2c multi-centre, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. All participants will enter post-treatment follow-up which continues until Week 104 (24 months) after start of treatment / randomisation. **Participants with Drug Sensitive TB (DS-TB):** Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation. **Participants with Drug Resistant TB (DR-TB):**

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td></td><td>Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).</td></tr>
<tr><td>Patient Population</td><td>A total of up to 450 male and female participants, diagnosed with DS-TB or DR-TB, aged 18 years and over with a target of up to 50% being HIV positive.

300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation.

Up to 150 DR-TB participants will be enrolled.</td></tr>
<tr><td>Test product, Dose and Mode of Administration</td><td>The Test Treatment Regimen (BPaMZ) consists of a combination of the following products and will be supplied as:
<table>
<tr><th>Product</th><th>Tablet Strength</th><th>Abbreviation</th></tr>
<tr><td>Bedaquiline</td><td>100 mg</td><td>(B)</td></tr>
<tr><td>Pretomanid</td><td>200 mg</td><td>(Pa)</td></tr>
<tr><td>Moxifloxacin</td><td>400 mg</td><td>(M)</td></tr>
<tr><td>Pyrazinamide</td><td>500 mg</td><td>(Z)</td></tr>
</table>
Instructions for Dosing of Test Regimen (BPaMZ):
Treatment will be administered orally once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months) in the following dosing schemes:

Participants with Drug Sensitive TB: (DS-TB)
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 17 weeks (Total treatment duration 4 months)

OR

Participants with Drug Resistant TB: (DR-TB)
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 26 weeks (Total treatment duration 6 months)</td></tr>
<tr><td>Positive Control Product, Dose and Mode of Administration</td><td>The Control Treatment Regimen (HRZE/HR) will be supplied as:

HRZE Tablets: (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). This combination will be given for the first 8 weeks.

AND

HR Tablets: (isoniazid 75 mg plus rifampicin 150 mg combination tablets). This combination will be given from Weeks 9 to 26.</td></tr>
</table>

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td></td><td>

Instructions for Dosing Control Treatment Regimen (HRZE/HR):

To be taken with a glass of water (approximately 240 ml). HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes:

Treatment will be administered orally once daily to the HRZE/HR randomized DS-TB participants as follows:

Weeks 1-26: HRZE/HR tablets daily dose per the participant's weight as follows:

<table>
<tr><th>Weight Band</th><th>Weight Range</th><th>Number of tablets</th></tr>
<tr><td>1</td><td>30-39 kg</td><td>2</td></tr>
<tr><td>2</td><td>40-54 kg</td><td>3</td></tr>
<tr><td>3</td><td>55-70 kg</td><td>4</td></tr>
<tr><td>4</td><td>≥ 71 kg</td><td>5</td></tr>
</table>

Vitamin B6 daily supplement to be taken with the HRZE/HR treatment, per each country's TB Treatment Guidelines.

</td></tr>
<tr><td>

Treatment Interruptions/Pauses

</td><td>

For All Trial Regimens:

The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical monitor prior to implementation, unless an interruption/pause is required urgently for a safety concern.

Action required for participants missing the following number of doses within the trial treatment regimens:

- Up to 7 consecutive doses: restart treatment, no extension of treatment required
- Greater than 7 and to ≤ 35 consecutive doses: restart treatment, extend the treatment by the number of consecutive doses missed, before the end of the treatment period (week 17/26). In this case, the last visit of the treatment period should also be pushed out to the date of the last dose
- Greater than 35 consecutive doses: discontinue treatment and withdraw participant from the trial
- If the participant misses a total (sum of) of 56 cumulative missed doses, discontinue IMP and withdraw participant from the trial.

Any participant for whom the trial medication is discontinued (including for non-adherence) will be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial medication as soon as possible.

</td></tr>
</table>

Synopsis	Description

Statistical Methods:

A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the statistical analysis plan (SAP,) which will be written and signed off prior to the first participant enrolled in the trial.

The primary analysis will be conducted using culture results from liquid culture (in the Mycobacterial Growth Indicator Tube (MGIT) system).

Criteria for Evaluation:

The primary efficacy endpoint will be time to culture negativity over 8 weeks. The primary hypothesis to be evaluated is:

> In the participants with DS-TB in the experimental BPaMZ treatment regimen, the time to culture negativity by 8 weeks will be superior, compared to the participants who are treated with the standard HRZE regimen.

There will be three main analyses. A modified Intent to Treat (mITT) analysis will be primary. A per-protocol (PP) analysis and an ITT analysis will also be performed for the secondary endpoint. These will be examined for consistency with the mITT analysis.

Note: Culture conversion requires at least 2 consecutive culture negative samples, at least 7 days apart (after positive baseline confirmation). Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered culture negative at that visit.

Secondary Endpoints

A key secondary endpoint will be the proportion of participants experiencing bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks (12 months). The hypothesis to be evaluated for this endpoint is:

> In the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen.

Other Secondary Endpoints

<u>Efficacy</u>:

- Incidence of bacteriologic failure or relapse or clinical failure at 104 weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

<u>Safety and Tolerability:</u>

Synopsis	Description

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
    - Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
    - Quantitative and qualitative electrocardiogram (ECG) results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones and lens opacities.

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

Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD):
Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [Cmin], maximum plasma concentration [Cmax], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of con-medications, including antiretroviral therapy (ART), where feasible. Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

Exploratory:
Evaluate whether any of the secondary endpoints predict relapse free cure. Subgroup analysis of populations by HIV status will be performed.

No formal statistical comparisons will be made for the participants enrolled with DR-TB. The responses of participants with DR-TB receiving BPaMZ will be compared for consistency with those responses of the DS-TB participants on the same regimen.

Sample Size
Primary endpoint: 150 participants per arm (DS-TB patients) will provide at least 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks.

Additional efficacy parameters will be evaluated including the incidence of bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks and 104 weeks from the start of treatment. Time to unfavourable outcome from assignment of trial treatment through follow-up as a function of time will be analysed using Kaplan-Meier analysis.

Trial Duration:
Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until week 104 from start of treatment. Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms is complete.

Synopsis	Description
There will be 3 database locks, data analyses and trial reports generated for this trial: 1. When all participants have completed 8 weeks (2 months) of treatment from baseline. 2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy. 3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.	

1.2 Synopsis Flow Chart and Procedures

Period	Screen-ing[a]	Treatment															Follow-Up[c]					
Visit[b]	Day -9 to -1	Day 1 (Baseline)[d]	Day 7 (Week 1)	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 17 *4-mth treatment*[e]	Week 17 *6-mth treatment*[e]	Week 22	Week 26 *4-mth treatment*[e]	Week 26 *6-mth treatment*[e]	Week 39	Week 52	Week 65	Week 78	Week 104	Early Withdrawal[c]
Visit Window[v]	N/A	+/- 3 Days									+/- 5 Days						+/- 14 Days					
Written Informed Consent	X																					
Demography	X																					
Medical/Treatment/ Smoking History	X																					
Inclusion/Exclusion	X	X																				
Sputum Sampling[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Status[h] and CD4 Count[i]	X																					
Karnofsky Score	X																					
Urine Drug Screen[j]	X																					
Urine Pregnancy Test[k]	X	X								X		X	X		X	X						X
Laboratory Safety Test[l]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X						X
Male Reproductive Hormone Tests[m]	X	X											X		X		X					
12-lead ECG[n]	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X					X
Chest X-Ray[o]	X																					
TB Symptoms Profile	X	X		X		X				X		X	X		X	X		X			X	X
Patient Reported Health Status	X	X		X		X				X		X	X		X	X		X			X	X
Vital Signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination[p]	X											X	X		X	X	X					X
Physical Examination – full[q]	X	X										X				X						X
Physical Examination – limited[r]			X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Pharmacokinetic Sampling[s]		X		X						X	X	X	X				X		X	X	X	
IMP Randomization/ Assignment[t]		X																				
IMP Compliance Check[u]			X	X	X	X	X	X	X	X	X	X	X	X[e]		X						X[t]
Concomitant Medications	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
Investigator Assessment[v]																		X			X	

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

a. **Screening:** Screening assessments can occur on different days within nine days prior to Day 1 dosing (randomisation).

b. **Visit Schedule (due to unforeseen circumstances):** If the duration of treatment is extended due to dose interruptions / pauses, the last visit of the treatment period should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time that the last visit of the treatment period would have been.

c. **Follow-up Visits for Early Withdrawal Participants:** Once a participant has been permanently withdrawn from the trial, they will be required to attend Early Withdrawal, Week 52 (if not already performed) and Week 104 follow-up visits. The Week 52 and Week 104 visits will be to collect Serious Adverse Event (SAE) information (including verification of survival) and participant reported TB outcome information only and may be telephonic, a home or a site visit. Visits will occur at Week 52 and/or Week 104 after the participant's start of treatment date. Refer to Table 5 for additional guidance.

d. **Day 1 (Baseline):** All procedures are to be completed prior to dosing.

e. **Last Visit of the Treatment Period:** Investigational Medicinal Product (IMP) Compliance Check is not performed at the Week 22 visit for participants who have completed treatment at Week 17.

f. **Sputum Sampling:** The sputum sampling methodology/requirements and tests will be described in a separate document, the Mycobacteria Laboratory Manual.
   - Days -9 to -1 (Screening). Two spot sputum samples taken 30 minutes apart will be collected at the research site under the coaching and observation of the trial staff. The following analyses will be performed on the first of these samples:
     - Smear microscopy for acid-fast bacilli (AFB);
     - Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance;
     - Liquid Culture (MGIT) for *Mycobacterium tuberculosis* (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive.
     - The second sample is collected as a back-up sample to the first sample in case it is technically not possible to obtain a result/s from the first sample. If the Day -9 to -1 (Screening) spot sputum smear shows an indeterminate result or is AFB negative, the test may be repeated on the back-up sample or on a freshly collected spot sputum/s and that result will be used.
   - Baseline to Week 104, including any unscheduled visits:
     - Two sputum samples (ideally one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff. If the participant forgets to bring in the Early Morning Sputum (EMS), then two spots are to be collected at the site, at least 30 min apart, and this altered sample collection is captured within case report form [CRF]).
     - If both sputum samples at Weeks 8, 17 (4-month treatment arm), 26 (6-month treatment arm), 52 or 104 are contaminated, the participant should return for an unscheduled visit(s) to give additional samples or to document that the participant is not able to produce sputum. If there is a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 for the 4-month treatment arms and Week 26 for the 6-month

treatment arms), the participant should return for an unscheduled visit(s) to give additional sputum samples a minimum of 7 days after the previous sample, or to document that the participant is not able to produce sputum.

- Additional samples may be required to define a participants' primary outcome status as described in Section 7.2.
- Liquid Culture (MGIT) for MTB, followed by a speciation test to detect presence or absence of MTB and obtain TTP when positive, will be performed on all samples.

g. **Mycobacteriology Characterisation Tests performed:**

- Day 1 (baseline) sputum sample (or any positive sample from screening out to Week 4 if the baseline cultures are contaminated or negative);
- MTB confirmed positive cultures at or after Week 17 (4-month treatment arms) or Week 26 (6-month treatment arms).

Refer to Mycobacteria Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates will be processed for:

- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin;
- Drug Susceptibility Testing for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, pyrazinamide and second line TB drugs including, but not limited to fluoroquinolones, and injectables using an indirect susceptibility test in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing, and comparison of sequences from baseline and relapse isolates.

h. **HIV Testing:** If HIV status is a confirmed known positive, a repeated HIV test is not needed provided that a documented HIV test result is available. If HIV status is unknown or suspected negative, a HIV test will be requested. If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated if documentation of testing method and negative HIV results can be provided. Repeated HIV testing, during the Screening period is permitted for indeterminate HIV results.

i. **CD4 Count:** Required for all HIV-positive participants.

j. **Urine Drug Screen:** Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at Screening only. Investigator to utilize this result to determine whether participant meets Exclusion criteria 2. Positive results will not automatically exclude a participant from the trial.

k. **Urine Pregnancy Test:** Women of childbearing potential only, whether they are sexually active or not.

l. **Safety Laboratory Assessments**: The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:

- Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count).
- Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium,

glucose, bicarbonate/carbon dioxide [CO_2], creatine phosphokinase [CPK]). GGT is only routinely included at the Screening visit (Day -9 to -1).

- 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.
- When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

m. **Male Reproductive Hormone Tests:** Testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin B to be done on male participants in ALL treatment groups.

n. **Single 12-Lead ECG:** To every extent possible, this should be performed at approximately the same time of day as the trial procedures (+/-1 hour). Central ECG analysis will be performed. Results from central reading of Day -9 to -1 (Screening) ECG must be used to determine eligibility.

o. **Chest X-Ray:** A chest x-ray (digital image only) within 6 months prior to or at the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor and this process will be described in a separate document, the Radiology Manual.

p. **Slit Lamp Ophthalmic Examination**: Slit lamp examination will be done at the Screening visit, the last visit of the treatment period, Week 17 or 26, and at Week 39 (9 months) for both treatment groups. An additional slit lamp at 6 months will be done for the 4-month treatment group. Slit lamp ophthalmology examination will be performed by an Ophthalmologist with AREDS2 training. Ophthalmology examinations may occur at any time within the window period for the applicable visit i.e. they do not have to be performed on the same day as the trial procedures.

q. **Physical Examination – Full:** Height (m) will only be collected at Day -9 to -1 (Screening).

r. **Physical Exam – Limited:** Limited physical exams will include weight and gross neurological, pulmonary, cardiovascular and abdominal exam(s).

s. **Pharmacokinetic (PK) Sampling:** This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE-HR treatment arm. Blood draws for PK samples collected pre-dose must be done after the ECG is performed. The dates and times of the two doses of IMP taken prior to all pre-dose PK samples will be collected. Specific PK blood draws will be obtained as follows:
   - Day 1: pre-dose (within 2 hours prior to dosing)
   - Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
   - Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
   - Week 12: pre-dose (within 2 hours prior to dosing)
   - Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose
   - Weeks 39, 65, 78 and 104 (for bedaquiline, bedaquiline metabolite M2): PK samples are to be obtained at any time on the day of the scheduled visit

t. **Investigational Medicinal Product (IMP) Randomization/Assignment:** Randomization may occur once all the Screening results are available and the Investigator has determined that the participant is eligible for the trial.

u. **IMP/Compliance Check:** IMP administration will be supervised per local site practice to assure compliance to regimen. Performed at all visits and Early Withdrawal (EWD), if during the treatment period.

v. **Investigator Assessment:** Investigator to review participant status and assess whether IMP or TB treatment at current visit is considered a “success” or “failure”. If considered a failure, the Investigator should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed, as shown on the flowchart, and at any time Investigator determines that participant fulfils criteria for outcome of treatment failure.

w. **Visit Windows**: The windows noted on the flowchart for timing of visit also apply to timing *within a visit.* Procedures should be performed within +/- 3 days of scheduled visit from Day 1 to Week 8 or +/- 5 Days of scheduled visit from Week 12 to Week 26 or +/- 14 days of scheduled visit at or after Week 39. Sites should make every effort to ensure all procedures are done on the same day, when possible.

2.0 Introduction and Rationale

2.1 Tuberculosis Disease

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in the developing countries of Africa, Asia and South America. TB is currently one of the top three killer infectious diseases, 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 40 years and are relatively ineffective in controlling TB as a public health problem. 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 participants, treatment takes 6 months or more to complete. This, long duration treatment **plus side effects**, result in poor adherence which particularly occurs after the second month of treatment.

The current TB treatment regimens and treatments for drug-sensitive TB are decades old. The available treatments have a lengthy duration of treatment, involve multi-drug therapy, and require large commitments of resources and infrastructure. High rates of noncompliance are common, which often results in increased mortality and chronic, infectious, drug-resistant cases. The present TB epidemic and the challenge of current treatment options demonstrate the clear need for effective novel TB drugs and **drug regimens** that are safe for drug sensitive and drug resistant TB disease and that are well-tolerated and will shorten the current treatment duration for patients.

The full application of the Directly Observed Treatment, Short-Course strategy is becoming more and more difficult in the developing countries of the world that are also battling to control the HIV-epidemic. Because of poor treatment adherence, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB are growing. Since the discovery of the rifamycins,[1] and their introduction into standard antituberculosis regimens, very few new classes of drugs have been evaluated with a view to their registration as antituberculosis agents. On December 28, 2012 the U.*S.* Food and Drug Administration approved bedaquiline (B) as part of combination therapy to treat adults with multi-drug resistant (MDR) pulmonary tuberculosis (TB) when other alternatives are not available. 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.

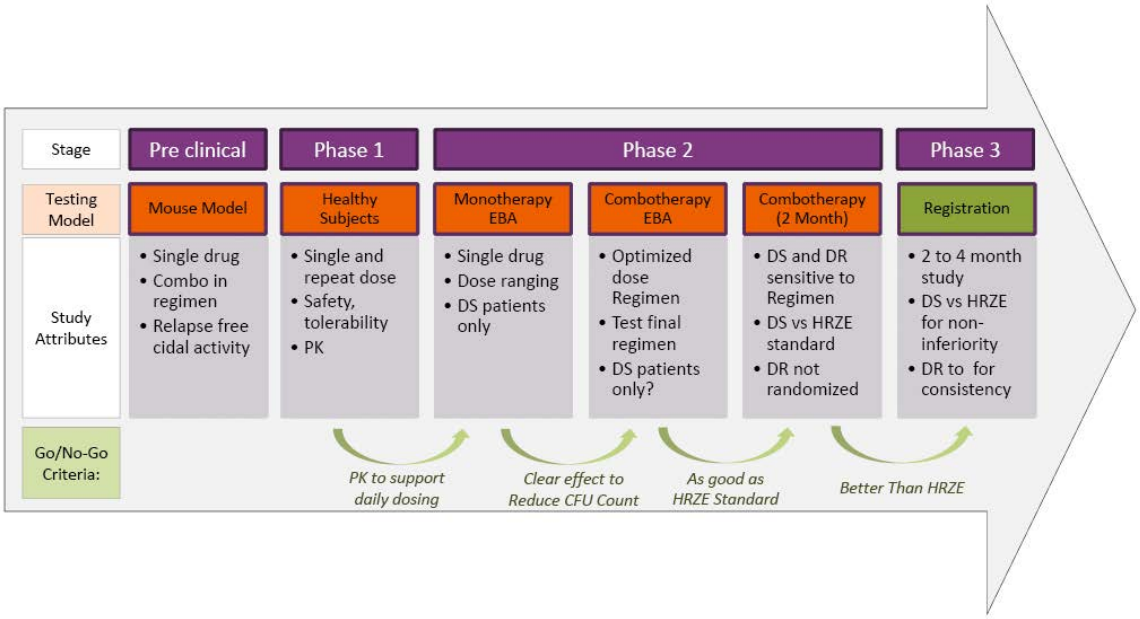
New combination regimens are desperately needed for two reasons: to shorten treatment to a duration more easily manageable by patients and public health services, and to provide more efficacious, safer and better tolerated, affordable treatments for the growing number of patients suffering from multidrug-resistant and extensively drug-resistant tuberculosis.

2.2 Tuberculosis Clinical Research

TB currently must be treated with multiple drugs to achieve maximal efficacy and prevent resistance. To transform treatment, novel TB regimens are needed. To telescope the time, it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm. This approach tests promising combinations of drugs together to find the most impactful treatment once the individual drug candidates have been tested in a robust pre-clinical program and the establishment of the individual drug candidates' safety and efficacy have been evaluated. It evaluates novel combinations of TB drugs — instead of single drugs — as part of a single development program, enabling the development of novel TB drug

regimens that have potential to transform treatment for drug-sensitive and drug-resistant tuberculosis. This approach offers the potential to reduce the time previously needed to develop a novel treatment regimen by up to 75%, shortening the clinical development from decades to years. The steps followed in this development model are shown in Figure 1 Between each step on the unified development pathway a decision is made as to whether to proceed.

Figure 1. Unified Drug Sensitive/Drug Resistant Regimen Development Path



Early Bactericidal Activity (EBA) Trials

EBA trials are the backbone clinical trials to quantify the bactericidal action of anti-tuberculosis agents alone or in combination by either trialling the fall in the number of colony forming units (CFU) or measuring the TTP in liquid culture of *M. tuberculosis* (*MTB*) present in the sputum of participants with microscopy smear-positive pulmonary TB. EBA trials have been conducted over 2, 5, 7 and 14 days.[2]. A review of EBA trials conducted on the key anti-TB drugs has shown the value these trials offer to demonstrate the early anti-TB effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in participants.[3]

8-week Bactericidal Activity (BA) Trials

EBA methodology of quantitative colony counting on solid medium has been adapted to Phase 2, 8-week TB treatment trials based on serial sputum colony counting (SSCC) or measurement of TTP liquid culture to provide a more sensitive efficacy endpoint than the previously used binary endpoint of rate of sputum conversion measured after 8 weeks of treatment.[4-6] Such trials are conducted to provide data on which to base the selection of treatment-shortening regimens.

2.3 Trial Rationale

This trial (SimpliciTB) will evaluate and support that, in additional to previous studies evaluated with BPaMZ, this drug regimen (BPaMZ) will be safe and effective, is well-tolerated and could potentially shorten the current treatment duration compared to Standard HRZE/HR treatment for patients with drug sensitive TB disease. This trial will also evaluate if this drug regimen (BPaMZ) given for 6 months will be safe and effective in drug resistant TB disease.

Therefore, the trial design addresses the need to find and evaluate a potentially effective and shorter regimen compared to regimens (Standard HRZE/HR) that are currently being used.

2.3.1 Trial Design Rationale

NC-008 (B-Pa-M-Z) trial - [**SimpliciTB**] - is a Phase 2c multi-centre, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. This trial is to evaluate the combination regimen of **Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) plus Pyrazinamide (Z)**, (BPaMZ) in participants with pulmonary TB.

All participants will enter post-treatment follow-up which continues until Week 104 (24 months) after start of treatment / randomisation.

Participants with Drug Sensitive TB (DS-TB):

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months),

or

HRZE/HR combination tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with HIV and cavitation.

Participants with Drug Resistant TB (DR-TB) are defined as:

1. mono-resistance to rifampicin or isoniazid, OR

2. resistance to both rifampicin and isoniazid (multi-drug resistant tuberculosis [MDR-TB])

Up to 150 participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months). Approximately 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation to either BPaMZ for 4 months or HRZE/HR for 6 months.

The trial is sufficiently statistically powered to not only show superiority of 2 months' culture conversion, but should also demonstrate non-inferiority for cure at 12 months. (This is in the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen).

As previously described in the background information, in order to telescope the time it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm and utilize data generated in non-clinical and clinical studies regarding combining of anti-tuberculosis agents which could contribute significantly to the sterilization of lesions and thus treatment shortening. Therefore, the trial design and proposed trial regimen

(**BPaMZ)** which is supported with previous non-clinical and clinical studies outlined below should address the need and manner of evaluating an effective shorter regimen compared to regimes that are currently being used.

2.3.2 Trial Drug Regimen Rationale

The **BPaMZ** regimen has been studied singularly and in different combinations as outlined above. Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. It essentially provides protection against the development of new resistance to the B-Pa-Z drugs. Based on the exciting and promising results seen in NC-005, this regimen can be initiated in drug sensitive and drug resistant TB participants whom are sensitive to the individual drugs in the regimen (excluding extensively drug-resistant tuberculosis [XDR-TB]) and has the potential to shorten TB treatment to less than 4 months in drug sensitive TB. These are also oral regimens, removing the need for injectables as part of MDR-TB treatment and also project to be markedly less expensive than current MDR-TB therapy. Additionally, these regimens can be administered in a fixed dose for all patients, and will therefore be simpler for health systems to deliver and patients to use.

2.4 Agents used within SimpliciTB

Bedaquiline (TMC207; Sirturo™ package insert)[7] is a novel agent approved for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[9, 10]) *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. Tb* isolates,[10, 11], and is also bactericidal against non-replicating *M. Tb.*[12] In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. Tb*.[3, 4] 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.[13] 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 DS- and MDR-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[13] and in a subsequent trial it was more active in the mouse model than HRZ.[14] Thus, a novel regimen with a 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.

Pretomanid, (Pa)[15] is a new chemical entity being developed by TB Alliance for the treatment of TB. It is 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 has been under development for several years, and entered clinical trials in 2005. Several trials of pretomanid have also been conducted previously in healthy volunteers. Collectively, these trials in participants with active TB and healthy participants have defined the efficacy, safety and pharmacokinetic features of the drug. Overall, pretomanid has mycobactericidal activity in participants and is well tolerated and bioavailable after oral dosing. Pretomanid demonstrated in vitro activity against both drug-sensitive (DS) and MDR-TB,[17] and in vivo activity in a mouse model of TB[17, 18] with a significant promise for shortening treatment of active TB.

Moxifloxacin (M)[19] is a microbial compound, approved in most countries around the world for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and soft tissue infections. Clinical studies have been carried out for many additional indications (urinary tract infections, pelvic infections, pharyngitis/tonsillitis, and tuberculosis). Moxifloxacin is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by or induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the MTB strain is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]" It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

Pyrazinamide (Z)[20] is a pyrazine analogue of nicotinamide and an approved anti-tuberculosis agent which is indicated for the initial treatment of active tuberculosis in adults and children when combined with other anti-tuberculosis agents and contributes significantly to the sterilization of lesions and thus treatment shortening.[21]

Control Group: HRZE/HR

The **HRZE/HR** combination [HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets] is approved indicated and commonly used as a 6-month treatment for drug-sensitive TB patients. Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE. Please see the HRZE package insert for more information.[22]

Additional background data supporting the combined use of new novel agents in this BPaMZ regimen for the treatment of TB:

Data from preclinical studies suggest that a regimen consisting of moxifloxacin plus pretomanid plus pyrazinamide may not only be appropriate for treating both DS and MDR-TB but may also **shorten duration of therapy**. Results from an 8-week Phase 2b SSCC trial, NC-002-(M-Pa-Z), showed that this **combination regimen** was effective as measured by time dependent decline of viable bacteria in participants with DS pulmonary TB. The combination was also shown to be safe and well tolerated supporting the evaluation of this combination in a Phase 3 trial. In this NC-002 trial 71.4% of participants with DS-TB treated with PaMZ at the 100-mg daily dose of pretomanid converted sputum to negative for *MTB* growth in liquid culture in comparison with only 37.8 % of participants treated with the HRZE control ($p<0.05$).

Studies in mice infected with *MTB* demonstrated reductions in cultured colony counts from lungs over an 8-week period when treated with the PaMZ regimen that were substantially, and statistically significantly greater, than the reductions in mice treated with an HRZ control. Experiments in mice found that mice did not relapse with MTB infection when treated with PaMZ for 4 months and followed for 3 months off treatment, in comparison to mice that required 6 months of treatment with HRZ to prevent relapse.[14]

Drug Resistant TB Background:

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in many countries. TB is the world's leading cause for mortality from infectious disease and is responsible for more deaths than HIV.[23] 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. Because of poor treatment adherence, in addition to primary transmission, **drug resistance** is becoming more common and fears of an epidemic with strains of extensively drug-resistant TB (XDR-TB) that is very difficult to treat are growing. Novel drugs and regimens for TB are needed for the growing number of patients with drug resistant-TB.

The regulatory approvals of bedaquiline and delamanid have given hope that outcomes for patients with drug resistant TB might be improved when added to background regimens. Experience recently published from the C209 uncontrolled trial of bedaquiline given on a background of multiple drugs notes that the subset of 38 participants with XDR-TB had rates of sputum culture conversion to negative of 62.2%.[24] However, in this trial only one participant with XDR-TB was co-infected with HIV. All participants were required to have Mycobacterium tuberculosis (MTB) isolates susceptible to at least 3 drugs at enrolment and participants had a median of only 5.4 months of treatment-free follow-up. This trial added bedaquiline for 6 months to a background regimen of many drugs given for 18 months or longer. While treatment success for MDR-TB is better than for XDR-TB, **overall success in treating MDR-TB is still approximately 50%** according to the World Health Organization 2015 Global TB Report.[23] This report presented that overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, 10% failed treatment, and for 8% there was no outcome information.

With such poor historical outcomes for patients with drug resistant-TB and with the complexity, expense and toxicity of treatments for all forms of drug resistant TB, **novel drug combinations are desperately needed to improve treatment outcomes**. Linezolid was identified in a small trial as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen[25] and this drug has increasingly been added to complex regimens to treat patients with MDR-TB.

With the current availability of the following three drugs for which there is little, if any, pre-existing resistance among strains of MTB (pretomanid [Pa], bedaquiline [B], and linezolid [L]). Mice infected with MTB had relapse-free cures with 3 months of treatment with a B-Pa-L regimen. While it is not known whether that treatment duration will translate to humans, the ongoing Nix-TB clinical trial hypothesizes patients with pulmonary XDR-TB or MDR-TB not responsive to or intolerant to therapy may have relapse-free cure after as little as 6 months' treatment with the B-Pa-L regimen.[26] Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. The proposed trial [SimpliciTB] allows the opportunity to assess the efficacy, safety and tolerability of BPaMZ, a new 6 months regimen that may be administered orally once daily to treat patients with drug resistant -TB (excluding participants with XDR-TB).

Therefore, the **overall purpose** of the present proposed trial **[SimpliciTB]** is to assess the efficacy, safety and tolerability of the **BPaMZ** regime after 4 months of treatment in adult participants with drug sensitive TB and after 6 months of treatment in participants with multi drug-resistant TB. The trial will also generate data of the potential for a shorted treatment

duration with the **BPaMZ** regime after 4 months compared to a 6-month **HRZE/HR** (control) treatment regime in adult participants with drug sensitive TB.

This trial will be conducted in accordance with the Protocol, ICH Guidelines for Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirement(s).

2.5 Background of Agents to be Studied in SimpliciTB

2.5.1 Bedaquiline (B)

Bedaquiline (formerly known as TMC-207; Sirturo™ package insert[7]) is approved agent for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[11] In vitro, bedaquiline potently inhibits both drug-sensitive and drug-resistant MTB isolates,[11, 12] and is also bactericidal against non-replicating MTB[12] 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 MTB.[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.[27].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[27] and in a subsequent trial it was more active in the mouse model than HRZ.[28]. 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.

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as 200 mg daily for 8 weeks then 100 mg daily for 9 weeks in participants with DS-TB and 200 mg daily for 8 weeks then 100 mg daily for 18 weeks in participants with DR-TB. This daily dosing scheme will allow more convenient dosing that should ultimately enhance patient adherence and may allow the formulation of fixed dose combinations with other drugs. This daily dosing regimen is supported by safety and efficacy demonstrated in the NC-005 trial that administered bedaquiline 200 mg daily over 8 weeks, and by pharmacokinetic modelling and simulation of the daily dosing scheme. This supportive information is detailed below.

2.5.1.1 Bedaquiline Non-Clinical Studies

Full details of the preclinical studies are provided in the current bedaquiline Investigator's Brochure,[8] and Sirturo ™ label.[7] *In vitro* studies have demonstrated that the range of minimum inhibitory concentrations (MICs) for MTB 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 MTB. 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 MTB but 3-6 times less active than the parent compound bedaquiline. Bedaquiline demonstrated similar *in vitro* efficacy against MTB 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 International Council for Harmonisation (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.[8]

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 and ECG parameters.

Prior to the use of pretomanid in combination with bedaquiline in clinical trial NC-001, a preclinical cardiovascular safety pharmacology trial 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.[28] 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) Investigators Brochure for more detail.

2.5.1.2 Bedaquiline Clinical Studies

In the clinical studies conducted to date, a total of approximately 645 participants (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 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001, and 45 more in trial NC-003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). Four short-term Phase 2a trials enrolled treatment-naïve participants (C202, TMC207-CL001, NC-001 and NC-003). One long-term, open-label, Phase 2 trial, in MDR-TB participants (bedaquiline- TiDP13-C209) and one long-term, Phase 2b trial, consisting of 2 different stages in participants 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,[8] and Sirturo™ label.[7].

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 participants. 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 trial, 800 mg single dose in trial 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 participants and participants 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 α 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 participants 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 trial (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 trial (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. Trial C202 was a 7-day trial of three daily doses of bedaquiline (25, 100 and 400mg) in treatment-naïve participants with MDR-TB. In this trial, the 400mg dose group demonstrated positive EBA and was numerically superior to the 25 and 100mg doses. In trial TMC207-CL001, doses of 100, 200, 300 and 400mg daily (following a 2-day loading dose) were studied in participants 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 participants with TB and that higher doses appear to have greater efficacy.

A 14-day EBA regimen trial (TB Alliance Trial 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 participants 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 participants given bedaquiline 400 mg/d after a 2-day loading dose. In the cohort of 15 participants 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 participants 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 trial (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 participants 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 participants in the bedaquiline group became MGIT culture negative compared to 8.7% of participants 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 participants in the bedaquiline group and 65.2% of participants 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 participants 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 participants. Culture conversion rates after 2 weeks of treatment with bedaquiline as part of an individualized anti-tuberculosis regimen were higher in participants with lower extent of resistance of the M. Tb strain and in participants with no lung cavitation compared to participants with cavitations (in one or both lungs).

2.5.1.3 Bedaquiline Clinical Safety

In the clinical trials conducted to date, a total of approximately 645 participants (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 participants received bedaquiline in a monotherapy EBA trial of 14 days (trial TMC207-

CL001) 45 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001 and 45 more in trial NC- 003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). In these trials, bedaquiline has been shown to be an effective treatment for participants 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 trial 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 trials, 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 participants) 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	**1 (1.3)**	**1 (1.0)**	**0**	**0**
Headache	1 (1.3)	1 (1.0)	0	0
Cardiac disorders	**0**	**0**	**0**	**0**
ECG QT Prolonged	0	0	0	0
Gastrointestinal disorders	**0**	**0**	**0**	**0**
Diarrhea	0	0	0	0
Vomiting	0	0	0	0
Hepatobiliary disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Transaminases increased [a]	2 (2.5)	2 (2.0)	0	0
Musculoskeletal and connective tissue disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Arthralgia	2 (2.5)	2 (2.0)	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 participants in the Any bedaquiline group and 5 participants 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 participants 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 participants (12.7%) compared to 3 placebo participants (3.7%). Based on the pooled results (Stage 1 and 2) while being followed in the placebo- controlled trial, 7 participants in the Any bedaquiline group and 1 Participant 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 haemoptysis. 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 participants 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 Participant in the bedaquiline group (pulmonary TB) and 2 participants in the Placebo group (TB-related illness and pulmonary TB) in Stage 1 died, and 4 participants in the bedaquiline group (3 participants with TB-related illness, 1 Participant motor vehicle accident) and 2 participants in the Placebo group (both TB-related illness) died after they discontinued Stage 2 of the trial. None of these participants 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, diarrhoea, blood uric acid increased, hypokalaemia, pruritus, injection site pain, insomnia, and tinnitus. From start of the trial up to the final analysis, 12 participants 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), haemoptysis, hypertension, and pyopneumothorax/respiratory failure. 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 participants 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 participants (6.9%) have died (12 participants during the trial and 4 participants 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 participants 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[7] notes that treatment initiation is not recommended in patients with:

- Heart failure;
- QTcF interval > 500 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).
- Hypokalaemia

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. If 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. participants should be monitored during treatment. Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in those participants with diminished hepatic reserve.[7]

Additional safety information from a recently completed trial

In a recently completed phase I trial not yet included in the bedaquiline Investigators Brochure that evaluated drug-drug interactions between bedaquiline and either rifampin or rifabutin, 7 participants experienced SAEs. Of those participants, 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 participant 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.

2.5.2 Pretomanid (P)

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]

2.5.2.1 Pharmacology

Key in Vitro Evaluation of Pretomanid Bactericidal Activity

Non-clinical in vitro trials demonstrated that pretomanid was active against actively growing drug- sensitive and drug-resistant MTB strains as well as against non-replicating MTB. The minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive MTB isolates *in vitro* was shown to be like the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of MTB with MIC values ranging from 0.03 to 0.53 µg/mL. The Investigator's Brochure contains further information on *in vitro* bactericidal activity.[16]

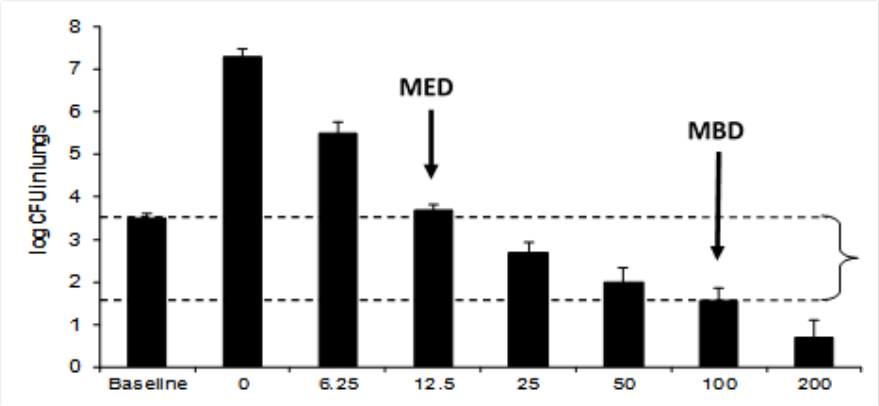
Although not thoroughly elucidated at this time, pretomanid has a novel mechanism of action that appears to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reduction of pretomanid by a deazaflavin (F420)-dependent nitroreductase has been shown to be associated with generation of reactive nitrogen species, including nitric oxide (NO),[29] although the exact target(s) of the reactive nitrogen species are not known. Transcriptional profiling trials also suggest that pretomanid affects both cell wall biosynthesis and the respiratory complex of MTB.[30, 31]

2.5.2.2 Key Non-Clinical Trials of Pretomanid

The activity of pretomanid as a single agent or as part of a multi-drug combination regimen has been examined in a number of mouse trials.[13, 14, 18, 32, 33] In a mouse model of established TB, the activity of various doses of pretomanid (given once daily, 5 days/week, for 1 month), initiated 22 days after inhalation infection with H37Rv MTB is shown in Figure 2. In this model, the minimum effective dose (MED) for pretomanid, defined as the lowest dose able to prevent the development of gross lung lesions and splenomegaly, was 12.5 mg/kg/day, while the minimum bactericidal dose (MBD), defined as the lowest dose able to reduce lung colony forming units (CFU) by 99%, was 100 mg/kg/day. Moreover, in these experiments, the activity of pretomanid at 100 mg/kg was comparable to the activity of isoniazid at 25 mg/kg.

Figure 2. Log10 CFU Counts in Lungs

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



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

2.5.2.3 Non-Clinical Toxicology and Safety

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

In the repeat-dose toxicity trials, the lowest no-observed adverse effect level (NOAELs) was 10 mg/kg/day in a 26-week trial in rats, 50 mg/kg/day in a 13-week trial in monkeys and <25 mg/kg/day (based on findings of thickening of the gastrointestinal tract at all doses) in a 9-month trial in monkeys. The major findings in safety and toxicity trials are listed below in Table 2 and are detailed in the Investigator's Brochure.[15]

Table 2. Key findings of Pretomanid in Safety and Toxicity Trials

Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behaviour at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
Testicular toxicity Although rat and rabbit embryonic development trials indicate no effects of pretomanid on foetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose toxicology trials and a Segment I fertility trial. In this fertility trial, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower dose not associated with testicular atrophy. A detailed trial in sexually mature male monkeys demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing.
Cataracts Cataracts developed in rats with prolonged daily administration of pretomanid at doses ≥100 mg/kg/day. In one 13-week trial 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 trial in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.
hERG inhibition and QT prolongation Altered ventricular repolarisation due to inhibition of hERG-mediated potassium current and manifested on the ECG as a prolonged QT interval corrected for heart rate (QTc). Pretomanid inhibited hERG current with IC50 values of approximately 6.2 µg/mL. Following a single pretomanid dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Co-administration of pretomanid with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at pretomanid doses of ≥150 mg/kg/day.

2.5.2.4 Clinical Background Information

Pretomanid has been evaluated in 8 single- and multi-dose Phase 1 trials with healthy adult male and female participants, with 163 participants receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 7 days. These Phase 1 trials have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid. Two additional Phase 1 trials Sponsored by the NIH included a Thorough QT trial and a trial of drug interactions among pretomanid, efavirenz and ritonavir/lopinavir. Further details of the trials are in the Investigator's Brochure.[15]

2.5.2.5 Pharmacokinetics

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

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

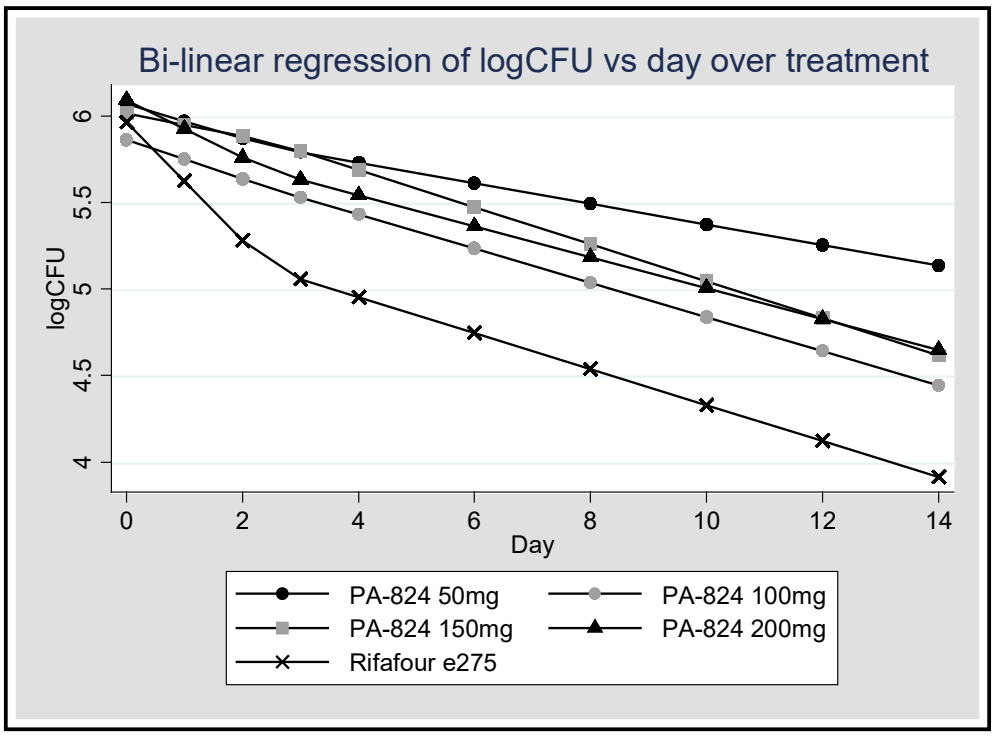
Drug interaction with efavirenz, ritonavir/lopinavir, and rifampicin: The US NIH Sponsored this drug interaction trial with rifampicin, a known hepatic enzyme inducer, and with the antiretroviral drugs efavirenz and ritonavir/lopinavir (LPV/r) in healthy participants. Participants in Arm 1 were randomised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

In conclusion, compared to pretomanid alone, plasma pretomanid values (based on geometric mean ratios) for C_{max}, $AUC_{0\text{-}24h}$, and C_{min} were reduced 28%, 35%, and 46% with efavirenz; 13%, 17%, and 21% with LPV/r; and 53%, 66%, and 85% with rifampicin, respectively.

2.5.2.6 Pretomanid Clinical Efficacy

The first two Phase 2 trials to evaluate the early bactericidal effect (EBA) of pretomanid oral monotherapy (50 to 1200 mg/day for 14 days) examined the dose-response for pretomanid in participants with newly diagnosed pulmonary TB infection. The first trial (CL-007) demonstrated good EBA, but all doses in this trial (200 to 1200 mg/day) had the same activity. The second trial (CL-010) evaluated a lower dose range (50 to 200 mg/day) and the maximum effect on EBA was seen at a dose of 100 mg/day over 14 days (Figure 3).[34]

Figure 3. Mean log Colony Forming Unit Values over Time Trial CL-010



CFU = colony-forming unit; PRETOMANID = pretomanid

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

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

2.5.2.7 Pretomanid Clinical Safety

The pretomanid Investigator's Brochure[15] provides detailed safety information.

Across the 16 clinical trials with pretomanid completed to date, a total of 649 participants have been exposed to pretomanid, including 289 healthy participants across the 10 Phase 1 trials

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

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

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

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

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

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

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

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

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

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

2.5.3 Moxifloxacin (M)

Moxifloxacin (M)[19] is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by nor induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that “all patients [with MDR-TB] should receive a Group 3 medication if the strain of MTB is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]” It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

2.2.3.1. Moxifloxacin Clinical Trials

Moxifloxacin is commonly used as second line therapy for TB (e.g. MDR- TB), and has also been evaluated in several clinical studies of participants with TB, including four 8-week treatment period Phase 2b studies (see Table 3 below).

Table 3. Summary of Phase 2b trials in which moxifloxacin were administered as part of a four-drug regimen during the intensive phase of treatment (total treatment duration: 2 months)

Trial	Design	Objective	Participants (N)	Status
Trial 27	Randomized, double-blind, controlled	To compare the sputum culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using the standard 4-drug regimen HRZE with a standard regimen with M replacing E.	336	Completed
OFLOTUB Trial	Randomized, Open label, Controlled	To compare the bactericidal activities of regimens where gatifloxacin, M, and ofloxacin were substituted for E in the 2-month initial phase of standard TB treatment with HRZE.	217	Completed
Johns Hopkins (FDA orphan drug) Trial	Randomized, double-blind, Controlled	To compare the sputum culture conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE) with a regimen with M replacing E (HRZM).	170	Completed
Trial 28	Randomized, double-blind, Controlled	To compare the culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE 5 days per week) with a regimen with M replacing H (MRZE 5 days per week).	433	Completed

2.5.3.1 Moxifloxacin Clinical Safety

In Trial 27,[35] the moxifloxacin-containing TB regimens (HRZM) were shown to be safe and well tolerated. There was no difference in SAEs between the HRZM and HRZE treatment arms, and most SAEs were hospitalizations thought to be unrelated to the trial treatment. Participants treated with the moxifloxacin-containing regimen were more likely to report nausea (22% vs. 9%, p = 0.002), but this was generally mild and did not lead to treatment discontinuation as similar proportions of participants in both groups completed trial drug treatment (88% HRZM-treated vs. 89% HRZE-treated). The one death during the first 2 months of treatment was thought to be caused by a pulmonary embolism unrelated to tuberculosis therapy.

In the OFLOTUB trial,[36] AEs and SAEs occurred with equal frequency in the four treatment arms. The most frequent AEs were raised amylase (in 41% of participants due to HIV infection), raised transaminase (10%), arthralgia (9%), anaemia (7%), hypokalaemia (6%) and vomiting (5%). No Participant was withdrawn from the trial due to an adverse event. There were 4 deaths in the trial: 2 in the control group, 1 each in the moxifloxacin and ofloxacin arms. Importantly, participants in this trial who received moxifloxacin and pyrazinamide in addition to isoniazid and rifampin had more rapid sputum clearance than participants on the four

standard first line drugs (isoniazid, rifampin, pyrazinamide and ethambutol). This difference was evident 14 days after initiation of treatment.

In the JHU trial,[37] AEs did not differ by treatment group. There were 16 SAEs (8 in each group) in 12 participants. Only 1 event was judged related to trial drug (grade 3 cutaneous reaction in the ethambutol group). Eight participants died during the trial, including 1 in each group still receiving trial phase treatment. No death was attributed to trial treatment. Only 5 participants discontinued treatment because of toxic effects; 2 participants in the moxifloxacin group stopped because of grade 2 nausea and vomiting and 1 because of grade 2 paraesthesia's and ataxia. Two participants in the E group stopped because of grade 2 rash and pruritus and 1 because of grade 3 peripheral neuropathy. There was no change in the QTc interval on serial electrocardiograms taken during the trial.

In Trial 28,[38] the proportions of participants with SAEs during the intensive phase treatment were similar between arms (isoniazid 3.9% vs. moxifloxacin 4.2%; P = 0.88). Three SAEs attributed to trial treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group. Seven participants died during the trial including 3 participants receiving the moxifloxacin treatment regimen and 4 participants receiving the isoniazid treatment regimen. The 3 moxifloxacin participants died during the intensive phase of TB treatment. Two participants died from advanced pulmonary TB judged not related to trial treatment and 1 Participant (who developed diabetic ketoacidosis considered possibly related to trial treatment) died from possible acute pulmonary embolus unrelated to trial treatment. The 4 isoniazid deaths occurred during the continuation phase, and all 4 were considered unrelated to trial treatment. Nausea was more common among participants in the moxifloxacin arm than in the isoniazid arm (19.6% vs. 11.7%, respectively; P = 0.03) although similar proportions reported vomiting. However, the proportions of participants with hepatitis, defined as serum AST 3 times or greater than the upper limit of normal, were similar between treatment arms during intensive phase (isoniazid 3.4% vs. moxifloxacin 3.3%; P = 0.93). Moxifloxacin has also been evaluated in combination with pretomanid for two weeks in participants with TB (Trial NC-001) and for 8 weeks in NC002 as reviewed above in Section 2.2.3 (Trial NC-001).

For additional information on moxifloxacin, refer to the IB[39] and the manufacturer's package insert.[19]

2.5.4 Pyrazinamide (Z)

Pyrazinamide (Z) is a standard drug used as part of the four drug HRZE regimen used for the first two months of intensive therapy for drug-sensitive TB as recommended by the WHO and many National TB programs. Please see the Package Insert[20] for more detail. Z is active against TB *in vitro* and it potentiates the bactericidal and sterilizing activity of both bedaquiline and pretomanid in mouse models of TB infection.[8, 15] Pyrazinamide enhanced the bactericidal activity of both bedaquiline and pretomanid in Trial NC-001-(J-M-Pa-Z) as noted by decreases over 14 days in the CFU counts in sputum among participants.

The pyrazinamide product label notes that pyrazinamide is contraindicated in persons with severe hepatic damage, who have shown hypersensitivity to it, and with acute gout. The most serious side effect is hepatotoxicity. Its frequency appears to be dose-related and thus liver function should be assessed before and regularly during treatment with pyrazinamide. Hyperuricemia commonly occurs and is occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other

side effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria.

Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert. [20]

2.6 Overall Benefit/Risk Assessment

Some participants with pulmonary TB in this trial will be given a regimen of **BPaMZ**. These drugs individually and in combination are known to have anti-tuberculosis activity and is not expected to have an adverse impact on the ultimate cure of TB in these participants. Based on NC-005 and other regimens using each of the regimen drugs in different combinations there is good evidence that this may be a highly effective therapy for both DS-TB and DR-TB.

For DS-TB the potential for a shorter regimen than 6 months is expected to be successful based on preclinical and clinical information as listed before. Participants in this trial will have their TB infection carefully characterized, with drug sensitivity profiles established, and they will receive treatment with trial drugs that have demonstrated activity against MTB.

Participants will receive individualized medical attention; this will allow a continuous monitoring of the health conditions of each participant, any of whom can be withdrawn at any stage of the trial and removed from trial treatment should his/her condition suggest to the Investigator that this would be in his/her best interest. Multiple blood samples will be taken for safety laboratory studies, and ECGs will be taken at multiple time points.

One concern in particular, the combination of two agents with known QT-prolonging effects (bedaquiline and moxifloxacin), has been addressed specifically by carefully identifying and excluding participants with risk factors that might predispose them to cardiac arrhythmias, screening all participants for evidence of existing cardiac disease and monitoring all participants with ECGs throughout the trial.

The trial drugs in the proposed regimens to be tested in this trial have all demonstrated safety and efficacy in the treatment of pulmonary tuberculosis in non-clinical and clinical studies. Specifically, the regimen B-Pa-Z was generally well-tolerated and demonstrated bactericidal activity in a 14-day EBA trial. The potential risks associated with the trial drugs and regimens has been identified as outlined below and will be monitored carefully throughout the conduct of the trial.

The BPaMZ regimen is a novel regimen treatment expected to be effective, safe and well-tolerated and might even shorten the current treatment duration for patients with TB. Based on data from previous trial evaluations of key monitoring and safety information as outlined before suggests a favourable benefit-to-risk ratio trials.

Key Monitoring and Safety Information Regarding Regimen Agents

2.6.1 Bedaquiline (B)

2.6.1.1 Adverse Drug Reactions for bedaquiline

Participants in the Any bedaquiline group compared to the Any Placebo group (difference > 5.0%) had headache (23.5% versus 11.4%, respectively), nausea (35.3% versus 25.7%, respectively), arthralgia (29.4% versus 20.0%, respectively), and transaminases increased (6.9% versus 1.0%, respectively).and diarrhoea (11.4% versus 5.9%, respectively).

2.6.1.2 Cardiovascular safety

During clinical studies with bedaquiline a prolongation of QTc interval was observed. An ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.

Bedaquiline 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

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. If co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

In the DR-TB treatment arm of the present trial, moxifloxacin will be co-administered with bedaquiline. This is to prevent the development of resistance to the other drugs in the regimen in case the participant's strain of MTB is resistant to pyrazinamide. ECG assessments will be performed on all participants at screening, baseline, and at treatment visits specified in the flow chart.

2.6.1.3 Hepatic safety

Increases in transaminases were seen in clinical studies during administration of bedaquiline with the background regimen. Participants should be monitored during treatment.

Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in participants with diminished hepatic reserve.

2.6.2 Pretomanid (P)

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 diarrhoea)
- Skin and subcutaneous tissue disorders

2.6.2.1 Hepatic Safety

Hepatic enzyme increases have been seen in participants 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 NC-008 trial will include specific monitoring of hepatic enzymes.

For additional information refer to pretomanid IB.[15]

2.6.3 Moxifloxacin (M)

In the usual daily doses of 400 mg/day, moxifloxacin is well tolerated. As stated in the Package Insert[19] the most frequent individual drug related AEs observed in clinical trials with 400 mg oral moxifloxacin therapy were nausea (7.5%) and diarrhoea (5.8%). Fluoroquinolones, including moxifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages.

A known but rare side effect of fluoroquinolones, including moxifloxacin is exacerbation of myasthenia gravis. In addition, moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some participants. It should be used with caution in participants being treated concomitantly with other drugs where an additive effect on the QT interval cannot be excluded.

Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, as well as peripheral neuropathy may occur after the first or subsequent doses of moxifloxacin. For additional information, refer to the moxifloxacin package insert.[19]

2.6.4 Pyrazinamide (Z)

The dose of pyrazinamide that will be used in this trial is an approved dosage for the treatment of TB. The most serious side-effect of pyrazinamide is hepatotoxicity and its frequency appears to be dose-related. Hyperuricemia commonly occurs, occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side-effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria. Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert.[20]

2.6.5 HRZE/HR Control

The **HRZE** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets) combination will be given the first 8 weeks and the **HR** (isoniazid 75 mg plus rifampicin 150 mg combination tablets) combination will be given from Weeks 9 to 26.

Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE.

Please see the HRZE and HR Package Inserts[22, 40] for known and potential risks and benefits.

3.0 Trial Objectives

3.1 Primary Objectives

To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with:

Drug Sensitive TB (DS-TB)

- BPaMZ given for 17 Weeks (4 months)
- Standard HRZE/HR treatment given for 26 weeks (6 months)

Drug Resistant TB (DR-TB)

– BPaMZ given for 26 Weeks (6 months)

DR-TB are defined as participants with:

1. *mono-resistance to rifampicin or isoniazid, OR*
2. *resistance to both rifampicin and isoniazid (DR-TB)*

3.2 Secondary Objectives

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 52 weeks (or 12 months) and 104 weeks (or 24 months) weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
  - Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
  - Quantitative and qualitative ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones and lens opacities.

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., Cmin, Cmax, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of con-medications including antiretroviral therapy (ART), as feasible.

Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

3.3 Exploratory Objectives

- Evaluate whether any of the secondary endpoints predicts relapse free cure.

- Subgroup analysis of populations by HIV status.

No formal statistical comparisons will be made for the participants enrolled with DR-TB.

4.0 Trial Design

4.1 Summary of Trial Design

This is a Phase 2c, multi-centre, open-label, partially randomized clinical trial conducted in 3 treatment groups. Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment allocation during the treatment phase of the trial.

The trial will be performed globally at multiple centres located throughout all regions of the world.

A total of 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation. Up to 150 DR-TB participants will be enrolled and assigned to the treatment arm described in Table 4 below.

Participants with Drug Sensitive TB (DS-TB):

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR combination tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation.

Participants with Drug Resistant TB (DR-TB):

Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).

Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive. An interactive web response system (IWRS) will be used which will utilize a dynamic randomization system using cavitation with a random element to allocate participants evenly across the arms by HIV status and type of TB (DS versus DR) after they have given written, informed consent during the Screening Visit (Days -9 to -1) and met all eligibility criteria.

4.2 Treatment Plan: Schedule of Assessments

- Screening Period (Day -9 to Day -1)
- Treatment Period (Day 1 to Week 17 (4-month treatment); or Week 26 (6-month treatment))
- Follow-Up Period (Week 39 to Week 104)

Refer to:

- Synopsis Flow Chart and Procedures (Section 1.2; flow chart) for the timing of all procedures and laboratory samples to done at each visit.
- Trial Procedures (Section 7.0, Trial Variables and Procedures) for details regarding specific procedures or laboratory tests.

Each participant will receive up to 26 weeks of treatment. The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation unless an interruption/pause is required urgently for a safety concern.

All participants will enter post-treatment follow-up which continues until Week 104 (24 months) after start of treatment / randomisation.

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

Table 4: Treatment Groups

	Treatment Group	Treatment Duration	No of Participants
1	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily	17 weeks (4 months)	150 DS-TB
2	**HRZE Tablets (Weeks 1-8):** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). Followed by **HR Tablets (Weeks 9-26):** (isoniazid 75 mg plus rifampicin 150 mg combination tablets).	First 8 weeks (2 months) then 17 weeks (4 months) Total 6 months	150 DS-TB
3	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily.	26 weeks (6 months)	Up to 150 DR-TB

5.0 Trial Population

The participant must meet all inclusion and no exclusion criteria within the screening period. Retesting for any laboratory or ECG parameters is allowed within the screening period. Sponsor may consider replacement of late exclusions. It is the intent of the protocol that the participants are hospitalized according to local practices and at the judgment of the treating physician / investigator.

5.1 Inclusion Criteria

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

1. Signed written consent prior to undertaking any trial-related procedures.
2. Male or female, aged 18 years or over.
3. Body weight (in light clothing and no shoes) ≥ 30 kg.

4. Sputum positive for tubercule bacilli (at least 1+ on the International Union Against Tuberculosis and Lung Disease [IUATLD]/WHO scale (Appendix 1) on smear microscopy) at the trial laboratory.
5. Disease Characteristics:
   - Participants with one of the following pulmonary TB conditions:

     DS-TB treatment arm participants should be:

     a. sensitive to rifampicin and isoniazid by rapid sputum based test **AND**

     b. either newly diagnosed for TB or have a history of being untreated for at least 3 years after cure from a previous episode of TB.

     If they are randomised into the trial due to being sensitive to rifampicin and isoniazid by rapid molecular sputum based test, however on receipt of the rifampicin and/or isoniazid phenotypic resistance testing in liquid culture this shows they are rifampicin or isoniazid resistant, they will be:

     a. Excluded as late exclusions;

     b. Possibly replaced as determined by the Sponsor.

     DR-TB treatment arm participants should be:

     a. Resistant to rifampicin and/or isoniazid.

     b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 7 days at start of screening.

6. A chest x-ray, within 6 months prior to or during the Screening visit, which in the opinion of the Investigator is compatible with pulmonary TB.
7. Contraception:

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

   Non-childbearing potential:

   a. Participant - not heterosexually active or practice sexual abstinence; or

   b. Female participant or male participants female sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or

   c. Male participant or female participants male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening;

   Effective birth control methods:

   a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or

b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female participant.

c. Male participants' female sexual partner: Double barrier method or hormone-based contraceptives or an intra-uterine device for the female partner.

Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 12 weeks after the last dose of trial medication or discontinuation from trial 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 participants to prevent pregnancy.

5.2 Exclusion Criteria

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

Medical History and Concurrent Conditions:

1. Any non-TB related condition where participation in the trial, as judged by the Investigator, could compromise the well-being of the participant or prevent, limit or confound protocol specified assessments.
2. Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
3. Being, or about to be, treated for malaria.
4. Is critically ill and, in the judgment of the Investigator, has a diagnosis likely to result in death during the trial or the follow-up period.
5. TB meningitis or other forms of extrapulmonary tuberculosis with high risk of a poor outcome, or likely to require a longer course of therapy (such as TB of the bone or joint), as judged by the Investigator.
6. History of allergy or hypersensitivity to any of the trial IMP or related substances, including known allergy to any fluoroquinolone antibiotic, history of tendinopathy associated with quinolones or suspected hypersensitivity to any rifampicin antibiotics.
7. For HIV infected participants any of the following:

    a. CD4+ count <100 cells/µL
    b. Karnofsky score <60% (Appendix 5)
    c. Received intravenous antifungal medication within the last 90 days
    d. WHO Clinical Stage 4 HIV disease (Appendix 3)

8. Participants who recently started or expected to need to start ART within 1 month after randomization. Participants who have been on ARTs for more than 30 days prior to start of the Screening visit, or expected to start ART greater than 30 days after randomization may be included.
9. Resistant to fluoroquinolones (rapid, sputum-based molecular screening tests)

    a. If they are randomised into the trial due to being sensitive to fluoroquinolones by rapid sputum based test, however on receipt of the moxifloxacin phenotypic resistance testing in liquid culture they are found to be fluoroquinolones resistant, they will be excluded as late exclusions.

10. Having participated in other clinical trials with investigational agents within 8 weeks prior to start of trial medication or currently enrolled in an investigational trial.
11. Participants with any of the following at the Screening visit (per measurements and reading done by ECG):

    a. QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with the Sponsor Medical Monitor before enrolment.
    b. Heart failure
    c. A personal or family history of congenital QT prolongation
    d. A history of or known, untreated, ongoing hypothyroidism
    e. A history of or ongoing bradyarrhythmia
    f. A history of Torsade de Pointe

12. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening.
13. Females who have a positive pregnancy test at the Screening visit or already known to be pregnant, breast-feeding, or planning to conceive a child during the trial or within 6 months of stopping treatment. Males planning to conceive a child during the trial or within 6 months of stopping treatment.
14. Participants with lactose intolerance, lactase deficiency and/or glucose-galactose malabsorption.

<u>Previous and Concomitant Therapy</u>

15. Previous treatment with pretomanid or bedaquiline.
16. Previous treatment for TB which includes, but is not limited to, gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.
17. For DS-TB participants: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days prior to randomization.
18. For the DR-TB participants: Previous treatment for DR-TB/MDR-TB, although may have been on a DR/MDR-TB treatment regimen for no longer than 7 days at start of screening.
19. Any diseases or conditions in which the use of the standard TB drugs or any of their components is contra-indicated, including but not limited to drug allergy.
20. Use of any drug within 30 days prior to randomisation known to prolong QTc interval (including, but not limited to, amiodarone, amitriptyline, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinacrine, quinidine, sotalol, sparfloxacin, thioridazine).
21. Use of systemic glucocorticoids within one year of start of screening (topical, inhaled or intranasal glucocorticoids are allowed) due to visual opacities or cataracts.
22. For HIV infected participants, only the following types of ART are permissible:

    a. Lopinavir/ritonavir based regimen consisting of lopinavir/ritonavir in combination with any two NRTI. TDF/ABC and FTC/3TC.

b. Integrase inhibitor (e.g., dolutegravir) in combination with TDF/ABC and FTC/3TC.
c. In participants who have viral load suppressed on efavirenz at the time of screening, their ART can be changed to rilpivirine in combination with TDF/ABC and FTC/3TC. If possible, the same nucleoside backbone should be used.
d. Nevirapine (NVP) based regimen consisting of NVP in combination with any two nucleosidase reverse transcriptase inhibitors (NRTIs) tenofovir (TDF)/abacavir (ABC) and emtricitabine (FTC)/lamivudine (3TC).

23. In the case where participants are randomized to a rifampicin containing regime:

a. EFV can be used with rifampicin.
b. LPV needs to be double dosed.
c. Rilpivirine cannot be given with rifampicin

Diagnostic and Laboratory Abnormalities

24. Participants with the following toxicities at screening as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (Draft November 2007) (Appendix 2) where applicable:

a. platelets grade 2 or greater (<100,000/mm^3)
b. creatinine grade 2 or greater (>1.5 times upper limit of normal [ULN])
c. eGFR ≤ 60 mL/min/m^2
d. haemoglobin grade 2 or greater (≤8.0 g/dL)
e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once
f. GGT: greater than 3 x ULN
g. AST:
   - grade 3 or greater (≥3.0 x ULN) to be excluded;
   - results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor
h. ALT:
   - grade 3 or greater (≥3.0 x ULN) to be excluded
   - greater than ULN must be discussed with and approved by the Sponsor Medical Monitor
i. ALP:
   - grade 3 or greater (≥3.0 x ULN) to be excluded
   - grade 2 (2.0 – <3.0 x ULN) must be discussed with and approved by the Sponsor Medical Monitor
j. Total bilirubin:
   - >1.5 x ULN to be excluded;
   - 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor
k. Direct bilirubin:
   - greater than 1x ULN to be excluded

All the inclusion and none of the exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the Investigator has reason to suspect that there might be a health problem (other

than TB), enrolment should only be considered after discussing the case with the Sponsor Medical monitor.

No protocol waivers will be granted by the TB Alliance.

5.3 Restrictions

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

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

The following recommendations should be followed with regards to concomitant medication to avoid possible drug interaction with the IMP:

Participants on a **moxifloxacin** containing treatment arm: The IMP should be taken either 4 hours before or 8 hours after taking the following products:

- An antacid, multivitamin, or other product that has magnesium, aluminium, iron or zinc
- Sucralfate
- Didanosine

Participants on the **HRZE/HR** treatment arm:

- Any aluminium-containing antacids should be taken at least one hour after the IMP dose.

The following medicinal products are prohibited from Day -9 to Day -1 (Screening) and during the treatment period:

- Quinolone antimalarial (e.g., chloroquine and quinacrine). Participants who have malaria at screening are to be excluded. However, if a participant develops malaria during the trial, the Investigator is advised to consult the Malaria Treatment Guidance document regarding the interaction between moxifloxacin and bedaquiline with anti-malarial drugs. Investigators may also contact the Sponsor Medical Monitor for further guidance.
- Chronic systemic glucocorticoids (topical, inhaled or intranasal glucocorticoids are allowed) due to their potential to cause visual opacities. Short term systemic glucocorticoids are allowed for emergency situations (e.g. for treatment of pulmonary exacerbation when Inhaled glucocorticoids is inadequate).
- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid,

rifapentine, thioacetazone, capreomycin, other quinolones, thioamides, and metronidazole.

The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible unless discussed with the Sponsor Medical Monitor:

- Any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). The exception is moxifloxacin and bedaquiline administered as part of the trial IMP, with ECG monitoring, to help ensure participant safety.
- Any drug known to be hepatotoxic (including but not limited to acetaminophen/paracetamol, acetazolamide, allopurinol, amiodarone, amitriptyline, amoxicillin, amprenavir, atorvastatin, augmentin/co-amoxiclav, azathioprine, baclofen, bumetanide, captopril, carbamazepine, celecoxib, chlorpromazine, chlorpromazine, clindamycin, clopidogrel, contraceptive pill, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).

5.4 Treatment Discontinuation and/or Early Withdrawal

Any participant for whom the Investigator decides to temporarily discontinue their IMP is to be discussed with the Sponsor Medical Monitor and, if applicable, be restarted on IMP as soon as possible.

A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following:

- Withdrawal of informed consent
- Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment.
- Pregnancy
- At the specific request of the Sponsor or termination of the trial by the Sponsor.
- Lost to follow-up
- Drug-Sensitive TB treatment arms: participants, who have been randomised onto the trial as a rifampicin sensitive participant on the rapid sputum based test result, who on receipt of the rifampicin resistance testing using an indirect susceptibility test in liquid culture, shows a rifampicin resistant result.
- Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum based test result, who on receipt of the fluoroquinolone resistance testing

using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result.
- Early withdrawal due to TB (see Section 5.4.4)

A participant may withdraw from the trial at any time at his/her request (withdrawal of consent), or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative issues. When a participant withdraws consent from the trial, no additional follow-up visits will be performed.

Participants who withdraw from the trial after having received IMP will not be replaced.

All participants withdrawn from trial and who received at least one dose of IMP will be requested to return for an Early Withdrawal visit and the applicable safety Follow-Up visits, as per the Synopsis Flow Chart and Procedures (Section 1.2 footnote c), as well as Table 5.

5.4.1 Early Withdrawal

In case of early withdrawal during the treatment or follow-up period, 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:

- Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff). If no early morning sputum sample was provided by the participant, 2 samples may be collected at the site, at least 30 minutes apart.
- Urine pregnancy test (women of child bearing potential, whether they are sexually active or not)
- Laboratory safety sampling (including male reproductive hormone tests);
- Single 12-lead ECG
- TB Symptoms Profile
- Patient Reported Health Status Questionnaire
- Vital signs
- Full physical examination, including weight
- Ophthalmology examination, if required as described in Table 5
- IMP compliance check (if participant on IMP)
- Concomitant medications
- Adverse events

Once a participant has been withdrawn early from the trial, they will be requested to attend follow-up visits as described in Table 5:

Table 5: Follow-up Visits Required for Early Withdrawal Participants

Treatment Duration at EWD visit	**Ophthalmology Examination at EWD[a]**	**Ophthalmology Examination** **Visit 3 months after EWD Visit[a]**	**Week 52** (Month12) **Follow-up Visit**	**Week 104** (Month 24) **Follow-up Visit**
≤ 14 days	Not required	Not required	Required	Required
15 days to ≤ 12 weeks	Not required	Required	Required	Required

> 12 weeks	Required	Required	Required, if not already performed	Required

a. If an additional visit is required for an ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 3 months after the EWD visit date.

The Weeks 52 and 104 (Month 12 and 24) visits will be performed to collect SAE information (including verification of survival) and participant reported TB outcome information. This visit may be telephonic, a home or a site visit at Weeks 52 (Month 12) and/or Week 104 (Month 24) after the participants' start of treatment date.

5.4.2 Unscheduled Visits

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

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

- If both sputum samples (Early Morning and Spot) at Week 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum.
- If there is a MTB confirmed positive culture at or after the end of treatment at Week 17 (4-month treatment) or Week 26 (6-month treatment), the participant should return for an Unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum. If no early morning sputum sample was provided by the participant, 2 samples may be collected at the site, at least 30 minutes apart.

To be able to define a participant's primary outcome status it may be necessary in certain situations to contact a participant and request they visit the site to collect additional sputum samples at unscheduled visits, as follows:

- To be assessed on sputum culture results from:
  - End of Treatment Period (Week 17 or 26)
  - End of Follow-up Period (Month 12 and 24)
  - Early Withdrawal, if applicable
- To confirm whether the participant 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, two sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) should be taken at least 7 days apart until they fall into one of the above categories. If no early morning sputum sample was provided by the participant, 2 samples may be collected on site at least 30 minutes apart.

If the Investigator is unsure of the outcome in any of the above scenarios the Investigator is to contact the Sponsor Medical Monitor and discuss and agree on how the participant is to be managed.

5.4.3 Lost-to-Follow-up

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

5.4.4 Early Withdrawal due to TB

Ultimately it is the Investigator's decision whether a participant requires early withdrawal from the trial due to a concern that the participant has symptomatic worsening of TB and/or bacteriological failure/relapse.

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

If the Investigator decides to withdraw a participant due to TB, additional sputum samples may need to be collected to ensure the participant's outcome status as determined in Section 5.5.

All early withdrawn participants who are confirmed sputum positive (two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These participants will be referred to their applicable DS/DR local community TB clinics for standard anti-tuberculosis chemotherapy according to National TB Treatment Guidelines. The participants will be provided with a referral letter from the Investigator to take with them to the TB clinic. A follow-up call will be made by the trial site staff to the clinic to ensure the participant attended the clinic.

5.5 Participant Progress Definitions

Status	Treatment	Follow-Up
Screen Failure	Participants from whom informed consent is obtained and is documented in writing (i.e., participant signs an informed consent form) but who are not randomized	
Completed Treatment / Completed Follow-Up*	Participants who complete the full course of IMP	Participants who complete all follow-up visits
Completed Treatment / Discontinued Follow-Up	Participants who complete the full course of IMP	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)

Completed Treatment / Lost to Follow-Up	Participants who complete the full course of IMP	Participants who are unable to be contacted on or before their final visit
Discontinued Treatment / Completed FU	Participants who discontinue treatment prior to completion of the protocol-defined treatment course	Participants who complete all applicable follow-up visits
Discontinued Treatment / Discontinued Follow-Up**	Participants who discontinue treatment prior to completion of the protocol-defined treatment course	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)
Lost to Follow-Up	Participants who are unable to be contacted on or before their final treatment visit and it cannot be confirmed whether treatment was completed	

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

** Early Withdrawal

5.6 Trial Stopping Rules

There are no trial specific stopping rules.

The trial or parts of the trial can be stopped by the Sponsor on advice from the Data Safety and Monitoring Committee (DSMC) after their review of applicable trial data. In addition, the Sponsor has the right to stop the trial or a specific trial site at any time, although this should only occur after consultation between the involved parties. Should this occur, the local and central Ethics Committee/Institutional Review Board (EC/IRB) and Regulatory Authorities will be informed.

Should a trial site be closed prematurely, all trial materials (except documentation that must remain at the site) will be returned to the Sponsor or vendor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Participants currently on treatment will receive an appropriate regimen and all participants will be referred to their applicable DS-TB/DR-TB National Treatment Program.

6.0 Treatment

6.1 IMP Administration

6.1.1 Instructions for Dosing of Test Regimen (BPaMZ):

- Treatment will be orally administered once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months).

6.1.2 Instructions for Dosing Control Treatment Regimen (HRZE/HR):

- To be taken with a glass of water (approximately 240 ml).
- HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes.

HRZE/HR treatment will be administered orally once daily to DS-TB participants as follows:

Weight Band	Weight Range	Number of tablets per weight band
1	30-39 kg	2
2	40-54 kg	3
3	55-70 kg	4
4	≥ 71 kg	5

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

6.2 Participant Compliance

During site clinic visits, the IMP will be administered by the Investigator(s)/designated site personnel and when possible, the check for IMP compliance via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the participant has swallowed the IMP). During the trial, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how the IMP is to be taken as well as check cards for unused tablets in the containers at each visit during the treatment phase.

6.3 Treatment Modification(s)

The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the Investigator to identify and address the cause(s) (e.g. side effects).

Participants that do not take:

- Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required.
- Greater than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been.
- Greater than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial.
- If the participant misses a total (sum) of 56 cumulative missed doses, discontinue IMP and withdraw participant from the trial.

Any participant for whom the trial medication is discontinued (including for non-adherence) will be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial medication as soon as possible.

6.4 IMP Packaging and Labelling

The complete formulations of the IMP, bedaquiline and pretomanid, are found in the respective Investigator Brochures.[8, 15] The complete formulations of moxifloxacin, pyrazinamide, HRZE/HR are found in the Package Inserts.[19, 20, 22, 40]

The IMP will be packaged in weekly or bi-weekly cards as follows:

Week 1 to 8 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	14	B

Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Week 9 to 17/26 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	7	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Control (HRZE/HR) Group: Dispensed *Bi-weekly*			
Weight Band	**Weight Range**	**Number of tablets per weight band**	**Number of tablets in each card**
1	30-39 kg	2	28
2	40-54 kg	3	42
3	55-70 kg	4	56
4	≥71 kg	5	70

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

The packaging of each weekly and biweekly cards will be labelled with, at a minimum, the following information:

- Name of Sponsor
- Name of medication
- Dosage, quantity and method of administration
- Reference/lot number
- The statement "For Clinical Trial Use Only"
- Space for completion of name of Investigator and site number
- MedID: medication identification number
- Storage conditions
- Period of use
- The statement "Keep out of reach of children"
- Expiry date
- Directions for use
- Space for completion of participant number and visit/date dispensed

6.5 Blinding and Procedures for Breaking the Blind

As this is an open label trial there is no need for blinding or procedures to break the blind. The trial participants, the site staff, Sponsor, and CROs will not be blinded to treatment assignment.

6.6 Handling, Storage and Accountability

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

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

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

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

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

7.0 Trial Variables and Procedures

The Synopsis Flowchart and Procedures in Section 1.2 should be referenced for timing, sequence of assessments, and specific procedures.

7.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected:

- Written Informed Consent
- Visit dates
- Participant disposition
- Demography (date of birth, race and gender)
- Inclusion and exclusion criteria
- Clinically significant medical and TB treatment history (including past and current TB diagnosis, smoking and alcohol use)
- Screening coached spot sputum samples:
  - Smear microscopy for acid-fast bacilli
  - Gene Xpert, Hain Assay MTBDRplus or equivalent to determine MTB complex and rifamycin resistance
- Urine pregnancy test: women of childbearing potential only, whether they are sexually active or not (Non-childbearing potential for a female participant is defined as having bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months).
- Serology: HIV and CD4 count. Where required by regulatory authorities or ethics committees, a separate (EC/IRB approved) HIV informed consent form will be obtained from participants:
  - Prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the participant, HIV counselling that is provided to the participant by the trial site should be clearly documented in the participant's medical records/source. Participants have the right to decline to know or receive their HIV

test results. This decision should be clearly documented in the participant's medical records/source.

- Karnofsky Score (Appendix 4)
- Chest X-Ray: A chest X-ray digital image within 6 months prior to or during the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor; this process will be documented in the Radiology Manual. The investigator is responsible for review and analysis of the chest X-ray for participant's inclusion.
- Method of birth control: male and female participants and their partners
- IMP details: randomization
- IMP compliance and actual dosing
- Concomitant medications

7.2 Efficacy Variables and Procedures

Two spot sputum samples are collected, one early morning brought from home or collected in the hospital ward (only if the participant is hospitalised) and one spot sputum sample collected at the research site under the coaching and observation of the trial staff or, if no early morning sputum sample was provided by the participant, 2 samples may be collected on site at least 30 minutes apart. The mycobacteriology sampling methodology and requirements will be described in a separate document, the Mycobacteriology Laboratory Manual, which will be provided prior to the trial start. Sputum samples may not be obtained by induction.

The following analyses will be performed:

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

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

- Bacteriologic failure/relapse
- Time to sputum culture conversion
- Number of participants with sputum culture conversion

Every effort must 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 participant who never achieves culture negative status due to the inability to produce sputum, but has completed Week 26 (6 months) post treatment completion follow-up and is without clinical or biological evidence of relapse, will be considered to have a favourable outcome.

TB Symptoms Profile:

- The TB Symptoms Profile (Appendix 6) will record participants' ratings of the severity of common TB symptoms.

Patient Reported Health Status Variables and Procedures:

- The Patient Reported Health Status variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2). Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire (Appendix 7).

This descriptive system consists of five health-related quality of life dimensions, each of which will be recorded using five levels of severity.

Methodology: The Patient Reported Health Status methodology and requirements will be described in a separate document/guideline which will be provided prior to the trial start.

7.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the Synopsis Flow Chart and Procedures 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 Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
    - Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count)
    - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, ALP, AST, ALT, lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO_2, creatine phosphokinase (CPK). GGT is only routinely included at the Screening visit (Day -9 to -1).
    - When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].
    - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator
- 12-lead ECG:
    - Investigator assessment: normal or abnormal
    - Central cardiologist assessment: heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.
    - Methodology:
        - Timing and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start
        - ECGs are to be recorded for 10 seconds
        - ECGs are to be performed during a single visit
        - ECGs should be done before any phlebotomy when both included in a visit
        - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch)
- Vital signs:
    - Vital signs (should be done before any phlebotomy in light clothing and with no shoes)
    - Systolic and diastolic blood pressure (mmHg) to be measured in a supine position (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 (beats per minute)

  - Respiratory rate (breaths per minute)
  - Axillary body temperature (°C)
- Physical Examination:
  - Height (m) is measured at the screening visit only
  - Full (complete) and limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded
  - Weight (kg) (in light clothing and with no shoes)
  - Using the variables of weight and height, the body mass index (BMI) will be calculated
- Ophthalmology Slit Lamp Examination:
  - To be done by an Ophthalmologist trained on Age-Related Eye Disease Scale 2 (AREDS2) assessment. The ophthalmology slit lamp methodology and requirements will be described in a separate document, the Ophthalmology Guideline. The following analyses will be performed: AREDS2 opacity typing and grading.
- Adverse events
- Investigator assessment:
  - The Investigator will review the participant status at specified visits in the Synopsis Flow Chart and Procedures, including any time the Investigator determines that the participant fulfils the criteria for the primary outcome of treatment failure. The Investigator will assess whether TB treatment is considered a “success” or “failure”. If it is considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration.

7.4 PK Variables and Procedures

Plasma concentrations from sparse sampling (see Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin and pyrazinamide to further evaluate the effects of covariates on model parameters in this trial population.

PK data from the current trial may be combined with prior data (e.g., from the NC-005 trial) to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{min}, C_{max}, AUC_{τ}, C_{mean}, and time above minimum inhibitory concentration) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

7.5 Mycobacteriology Characterization Variable and Procedures

The following Mycobacterial Characterization variables will be collected:

Positive Culture (for MTB) from:

- Day 1 or if Day 1 is not available, first positive result between screening through Week 4
- Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be sub-cultured and sent to the central microbiology laboratory from the applicable local microbiology laboratory, for relevant participants / no positive cultures from screening through week 4
- When applicable, at last visit of the treatment period (Week 17 for the 4-month treatment arm and Week 26 for the 6-month treatment arm) or visits with positive cultures, during the post-treatment follow-up period

The MTB isolates will be processed at the central microbiology laboratory for:

- MIC against bedaquiline, pretomanid and moxifloxacin
- Drug Susceptibility Testing in liquid culture for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide, and second line TB drugs including but not limited to fluoroquinolones, and injectables
- Extraction of organismal (MTB) DNA for whole genome sequencing, and the comparison of sequences from baseline and relapse isolates.

All Day 1 (Baseline) MTB isolates and isolates from positive cultures to be stored at the local and central microbiology laboratories, until trial closure. Extracted MTB DNA to be stored at the central microbiology laboratory until trial closure. The extracted MTB DNA and isolates will then be stored for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure.

The MTB isolates will be processed at the trial microbiology laboratories for positive MTB complex at/after the last visit of the treatment period (Week 17 for the 4-month treatment arm and Week 26 for the 6-month treatment arm) via Hain MTBDR*plus* and HainMTBR*sl.*

8.0 Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

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

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

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

accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect; or
- Is a medically important event

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse. A “suspected transmission of infectious agent by a medicinal product” is also considered a serious adverse event under the SAE criterion “Other medically important condition”.

8.1.3 Attribution/Causality

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

Table 6: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An AE, which is not related to the use of the drug.
Unlikely	An AE 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 AE, 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 AE, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by de-challenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An AE, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

8.1.4 Severity

Table 7: Definitions for Adverse Event Severity Gradings

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

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

8.2 Reporting

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

All AEs will be collected by the Investigator from the time a participant signs the Informed Consent Form through to their Week 104 (Month 24) follow-up visit. The exception to this is early withdrawal participants who will only have SAEs collected from their time of early withdrawal to their Week 104 (Month 24) follow-up visit at the timepoints specified in the Synopsis Flow Chart and Procedures (Section 1.2) and recorded in the CRF.

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

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

The Sponsor/Investigator/designee will inform Regulatory Authorities and/or EC/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 EC/IRB.

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

8.2.1 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- The end of the follow-up period; and
- 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 Investigator. However, this will have to be agreed upon with the Sponsor Medical Monitor.

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

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

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

8.2.2 Clinical Laboratory Adverse Events

Changes in the results of the clinical laboratory assessment results and which the Investigator determines are clinically significant will be reported as AEs. It is the Investigators' responsibility to review the results of all laboratory tests as they become available. This review

must be documented by the Investigators' dated signature on the laboratory report. For each abnormal laboratory test result, the Investigator needs to ascertain and document if this is a clinically significant change from baseline for that individual participant. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is determined by the Investigator to be a clinically significant change from baseline for that participant, it is considered to be an AE.

8.2.3 Disease Symptoms During Trial

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

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

it will be recorded as an adverse event. If there is:

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

it will not be recorded as an AE and this will be noted in the participant's source documentation. All TB related symptoms that meet SAE criteria will be recorded and reported as a SAE.

8.2.4 Overdose

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

8.2.5 Drug Interaction

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

8.2.6 Pregnancy

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

- Any time during the trial
- Within 6 months after the last dose of IMP

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

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

8.3 Monitoring for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in the preclinical toxicity studies of the Investigator's Brochures[8, 15] and Package Inserts.[19, 20, 22, 40]

AEs still ongoing at the end of the treatment period in the trial will be followed until satisfactory clinical resolution or stabilization, or until the end of the follow-up period and until all queries on these AEs have been resolved.

Grade 3 and Grade 4 laboratory abnormalities, and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.

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

8.3.1 ALT, AST and Bilirubin Elevations

The Investigator should refer to Appendix 8 Liver Toxicity Management, to appropriately monitor significant elevations of AST, ALT or Bilirubin. A separate Hepatoxicity Management Guideline document has been developed to aid investigators in the management of participants.

When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

8.3.2 Lipase

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

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

8.3.3 Neurological

Participants co-administration with a serotonergic agent, including anti-depressants, should be monitored closely for signs of serotonin syndrome. The Investigator should determine

whether the full regimen or the concomitant agent should be discontinued for those who experience signs or symptoms of serotonin syndrome such as cognitive dysfunction, hyperrexia, hyperreflexia and incoordination.

8.3.4 Musculoskeletal System and Cardiac Muscle Myalgia

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

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

8.3.5 Cardiac Rhythm Disturbances

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

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

<u>QTc prolongation</u>

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

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

8.4 Safety Monitoring by Data Monitoring Committee

A Data Safety Monitoring Committee (DSMC) will be appointed for the trial. The primary responsibility of the DSMC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial participants by monitoring participant safety, assess participant risk versus benefit, and assess data quality and general evaluation of the trial progress. Its activities will be delineated in a DSMC charter that will define the membership, responsibilities and the scope and frequency of data reviews.

The DSMC will operate on a conflict-free basis independently of the Sponsor and the trial team. It will comprise at least 3 voting members that include at least 2 clinicians and one statistician.

The DSMC may have an organizational meeting prior to commencement of the trial. The DSMC will have meetings where it will review unblinded data during a closed session. These meetings will be planned at regular intervals.

The Sponsor or the DSMC may convene ad hoc meetings based on rates of SAEs and/or to review results of the futility analysis, or if safety concerns arise during the trial. After its assessment, the DSMC will recommend to the Sponsor continuation, modification or termination of the clinical trial.

9.0 Statistical Analysis

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

9.1 Analysis Populations

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

- The ITT population is defined as all randomized participants excluding late screening failures. Late screening failures are participants withdrawn from treatment because they were found to be ineligible (late exclusions from the trial), based on data collected *prior to randomization*.
- The mITT population is defined as the ITT population with extra exclusions (described in the SAP).
- The PP population is defined as the mITT population with extra exclusions (described in the SAP).
- The mITT analysis will be considered primary, with consistent findings required from the other main analysis populations to support the primary conclusion.

9.2 Sample Size

For the primary endpoint, time-to-culture conversion at 8 weeks,150 participants per arm (DS-TB participants) will provide at more than 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 90% power to detect a HR of least 2. Currently no formal interim analysis is planned. (See Section 9.4.1)

For the key secondary endpoint of clinical outcome at 12 months from randomization, 150 patients per arm will provide 74% power based on assumptions using data from the largest most recent and completed phase 3 TB treatment trial which used the same control arm.[41] That is, assuming 16% unfavourable (see Section 9.4.2) in the control arm and 13% unassessable (see Section 9.6) at 52 weeks post randomization. A 12% margin of non-inferiority was chosen to preserve at least 75% of the estimated control arm effect against placebo (estimated to be 54%)[41, 42] which is considered an acceptable proportion on which to declare non-inferiority of the test regimen.

9.3 Interim Analyses

There is no planned interim analysis in this trial.

9.4 Primary and Secondary Efficacy Endpoint Analysis

9.4.1 Primary Efficacy Endpoint, Time to Culture Conversion at 8 Weeks

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

Participants will be classified as being culture positive, culture negative, dead or unassessable at 8 weeks. The proportion culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis and groups compared using a hazard ratio and 95% confidence interval.

Non-inferiority of the key secondary endpoint of clinical outcome will be assessed using the upper bound of the one-sided 97.5% confidence interval for the difference between the proportion of participants who are classified as having an unfavourable status on the intervention less the control regimen. If the upper bound of the one-sided 97.5% confidence limit for this difference in proportions is less than 12% (the margin of inferiority) the intervention will be non-inferior to the control arm.

9.4.2 Key Secondary Efficacy Endpoint, Clinical Outcome at 52 Weeks from Randomization

For the key secondary endpoint of clinical outcome (bacteriologic failure or relapse or clinical failure), participants will be classified as having a favourable, unfavourable or unassessable outcome status which will be defined in detail in the SAP. In general, participants achieving and maintaining culture negative status without any additional treatment will be considered favourable; participants who fail on treatment or relapse in follow-up will be considered unfavourable and participants who are not assessable (and who have not already been declared as unfavourable) will be considered unassessable and excluded from the analysis.

9.4.3 Other Secondary Efficacy Endpoints

The secondary efficacy endpoints and analyses are as follows are:

- Clinical outcome (bacteriologic failure or relapse or clinical failure) at 104 weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight will be summarised and presented.
- Proportion of participants experiencing a change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status will be summarised and presented.

9.5 Safety and Tolerability Assessments

- 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.

9.6 Pharmacokinetics

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., C_{min}, C_{max}, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so, too, will the effects of concomitant medications including ART, as feasible. Data from other trials may be included to enhance the model-based analysis.

Detailed plans for the PopPK analysis will be outlined in a separate modelling plan, and results will be reported in separate modelling report.

9.7 Pharmacokinetics/Pharmacodynamics

Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate. Planning details and results will be included in the separate modelling plan and report.

10.0 Records Management

10.1 Data Collection

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

10.2 Source Documents

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

All source documents pertaining to this trial will be maintained by the Investigators. The Investigator must permit trial related monitoring, audits, Independent Ethics

Committee/Institutional Review Board (EC/IRB) review and regulatory inspections providing authorized personnel direct access to source documents, including documents required to confirm inclusion/exclusion and relevant in-patient records while participants are on trial treatment.

10.3 File Management at the Trial Centre

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

10.4 Records Retention at the Trial Centre

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

11.0 Quality Control and Assurance

11.1 Site Procedures

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

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

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

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

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

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

11.2 Monitoring

The Investigator is responsible for the validity of all data collected at the clinical site and must accept the various monitoring procedures employed by the Sponsor. The purpose of monitoring is to verify that the rights and well-being of human participants are protected; that trial data are accurate, complete and verifiable with source data; and that the trial is conducted

in compliance with the protocol, International GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

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

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

11.3 Protocol Deviations

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

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

11.4 Auditing

For 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 about accuracy, adequacy and consistency, and to assure that trials are in accordance with the guidelines. Having the highest quality data from trials is an essential aspect of drug development.

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The auditors or inspectors may also review site SOPs, training records, site facilities and other trial related systems/processes.

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

12.0 Ethics and Regulatory

12.1 Basic Principles

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

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

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

12.3 Regulatory Authorities

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

12.4 Informed Consent

Written informed consent will be obtained from all participants (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment procedures) are performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for 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 part of the research.

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

The trial will be included and updated in the appropriate Country registry and referenced in the informed consent forms (ICF).

Once the appropriate essential information has been provided to the participant and fully explained by the Investigators (or qualified designees) and it is felt that the participant understands the implications of participating, the EC/IRB approved written informed consent

form will be signed and dated by both the participant and the person obtaining consent (Investigators or designees), and by any other parties required by the EC/IRB. Ongoing participants must be re-consented to the most current version of the ICF(s) during their participation in the trial.

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

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

12.5 Confidentiality

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

13.0 Publication Policy

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

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

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory Investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors.[43]

Because the Trial is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the Trial must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy. Specifically, (a) all peer-reviewed published research relating to the Trial must be submitted for publication by TB Alliance through the Chronos Open Access Publishing Service established by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy.

14.0 Protocol Amendment Policy

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

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

15.0 Sponsor, Financial Aspects, Insurance and Indemnity

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

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

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

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

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

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Appendices

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	scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

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

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

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

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

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

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

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

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

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

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

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

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

GASTROINTESTINAL

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	Subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia

Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint 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: Who Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection
Asymptomatic Acute retroviral syndrome
Clinical Stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical Stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections
Clinical Stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for >1 month Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) Persistent oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anemia (hemoglobin <8 g/dL) Neutropenia (neutrophils <500 cells/µL) Chronic thrombocytopenia (platelets <50,000 cells/µL)
Clinical Stage 4
HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Cryptococcosis, extrapulmonary (including meningitis) Disseminated nontuberculosis mycobacteria infection Progressive multifocal leukoencephalopathy Candida of the trachea, bronchi, or lungs Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis) Recurrent nontyphoidal Salmonella bacteremia Lymphoma (cerebral or B-cell non-Hodgkin) Invasive cervical carcinoma

Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy
Symptomatic HIV-associated cardiomyopathy
Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

REF: World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children; 2007*

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: Cardiovascular Safety

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

All-important abnormalities from the ECG readings will be reported.

The percentage of participants with increases in QTc of <30, 30-60, or > 60 ms from baseline will also be tabulated at each time point.

Abnormality Code	ECG parameter			
	HR	PR	QRS	QTcorrected
Abnormalities on actual values				
“Abnormally low”	≤ 50 bpm	NAP	≤ 50 ms	-
“Abnormally high”	≥ 120 bpm	≥ 210 ms	≥ 120 ms	-
“]450 ms, 480 ms]	-	-	-	450 ms < QTc ≤ 480 ms
“]480 ms, 500 ms]	-	-	-	480 ms < QTc ≤ 500 ms
“More than 500 ms	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline				
“[30; 60] ms”	-	-	-	[30; 60] ms
“> 60 ms”	-	-	-	> 60 ms

Appendix 5: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

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

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

Appendix 6: Tuberculosis Symptoms Profile

TUBERCULOSIS SYMPTOM PROFILE (V3)

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

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

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

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

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

During the past 7 days, how would you rate your appetite?

☐ Good ☐ Fair ☐ Poor

Approved, Issued Date 09-Apr-2012

Appendix 7: Patient Reported Health Status 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 ❑

2

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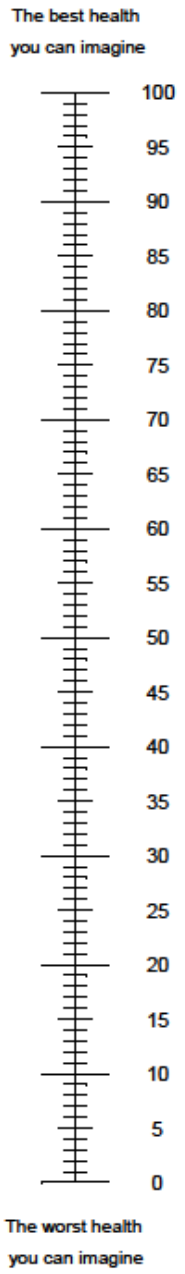
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the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

YOUR HEALTH TODAY = ☐



3

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Appendix 8: Liver Toxicity Management

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

In pre-marketing clinical trials of new drugs and regimens it is especially important to identify and carefully manage any trial participants who are at risk of progression to serious liver injury. The observation of altered liver function to a degree that has a high risk of progressing to liver failure as been referred to informally as Hy's Law;[44, 45]; this reflects that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components:

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

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

Procedure

Blood tests for liver function will be taken routinely at screening (Day -9 to -1) and at the specific time points designated in the protocol, and at Early Withdrawal. If at any other visit the clinician suspects derangement of liver function, e.g. the participant describes nausea and vomiting, right upper abdominal pain or is jaundiced, blood should be taken for liver function tests and the participant comprehensively assessed for evidence of hepatitis or hepatic impairment and any potentially contributing causes.

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

The laboratory source (print-out of any results) should be stored alongside or transcribed into the clinical source document. Each abnormal value should be marked as clinically significant

(CS) or non-clinically significant (NCS); the assessment of significance is at the discretion of the Investigator. All clinically significant abnormal results must be recorded as Adverse Events in the eCRF and graded clinically as per the DMID adult toxicity table grading, (Appendix 2). Assessments and decision making for elevations in aminotransferase values or bilirubin of various levels of concern are detailed below:

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

Temporarily Stopping and Restarting Trial Medication

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

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

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

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

Protocol Amendment

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GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

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

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

Reasons for Protocol Amendment:	
1	**Additional** text, Synopsis Section Statistical Methods: Exploratory, 'The responses of participants with DR-TB receiving BPaMZ will be compared for consistency with those responses of the DS-TB participants on the same regimen.'
2	**Additional** text, Section 1.2 Synopsis Flow Chart and Procedures, Item s. 'Weeks 39, 65, 78 and 104 ***(for bedaquiline, bedaquiline metabolite M2)***: PK samples are to be obtained at any time on the day of the scheduled visit.
3	**Amended** text, Section 2.5.1 Bedaquiline (B) 2nd paragraph… 'Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as 200 mg daily for 8 weeks then 100 mg daily for 9 weeks in participants with DS-TB and 200 mg daily for 8 weeks then 100 mg daily for 18 weeks in participants with DR-TB.'
4	**Additional** text, Section 5.2 Trial Population, 'It is the intent of the protocol that the participants are hospitalized according to local practices and at the judgment of the treating physician / investigator.'
5	**Additional** 14th Exclusion Criteria, Section 5.2, 'Participants with lactose intolerance, lactase deficiency and/or glucose-galactose malabsorption'.
6	**Change** in number sequence of Section 5.2 Exclusion Criteria, Previous and Concomitant Therapy numbers 13-22, changed to 14-23, due to the addition of the Exclusion Criteria #14, as described above
7	**Change and addition** of text in Section 7.4 PK Variables and Procedures, to updated population PK models for pyrazinamide and moxifloxacin, remove the reference to linezolid, and to reference the NC-005 study and at the same time removing the reference to the Nix study.
8	**Change** the text in Section 9.2 Sample Size (end 1st paragraph) to make it consistent with the text in Section 9.3 Interim Analysis, to read 'Currently no formal interim analysis is planned'.

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Protocol Amendment

#	Section	Previous Text Version 2.0 dated 21 Feb 2018	Amended Text Russia V1.0 dated 10 Jul 2018 Additional text - bold font. Deleted text – strike-through.	Reason for Change Insert reason # from table above
1	Synopsis	Statistical Methods, Exploratory No formal statistical comparisons will be made for the participants enrolled with DR-TB.	Statistical Methods, Exploratory No formal statistical comparisons will be made for the participants enrolled with DR-TB. **The responses of participants with DR-TB receiving BPaMZ will be compared for consistency with those responses of the DS-TB participants on the same regimen.**	1
2	Section 1.2	Synopsis Flow Chart and Procedures, Item s. Weeks 39, 65, 78 and 104: PK samples are to be obtained at any time on the day of the scheduled visit	Synopsis Flow Chart and Procedures, Item s. Weeks 39, 65, 78 and 104 **(for bedaquiline, bedaquiline metabolite M2)**: PK samples are to be obtained at any time on the day of the scheduled visit	2
3	Section 2.5.1	Bedaquiline (B), 2nd paragraph Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as 200 mg daily for 8 weeks followed by 100 mg daily for the remaining 17 weeks or 30 weeks if treatment is extended.	Bedaquiline (B), 2nd paragraph Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as **200 mg daily for 8 weeks then 100 mg daily for 9 weeks in participants with DS-TB and 200 mg daily for 8 weeks then 100 mg daily for 18 weeks in participants with DR-TB**.	3

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Protocol Amendment

#	Section	Previous Text Version 2.0 dated 21 Feb 2018	Amended Text Russia V1.0 dated 10 Jul 2018 Additional text - bold font. Deleted text – strike-through.	Reason for Change Insert reason # from table above
4	Section 5.2	Trial Population NA	Trial Population **It is the intent of the protocol that the participants are hospitalized according to local practices and at the judgment of the treating physician / investigator**	4
5	Section 5.2	Exclusion Criteria #14, Medical History and Concurrent Conditions NA	Exclusion Criteria #14, Medical History and Concurrent Conditions **Participants with lactose intolerance, lactase deficiency and/or glucose-galactose malabsorption.**	5
6	Section 5.2	Exclusion Criteria # 14 to 23, Previous Concomitant Therapy NA	Exclusion Criteria # 14 to 23, Previous Concomitant Therapy Previously numbered items 14 to 23, have been re-numbered as 15 to 24 due to the additional exclusion criteria described above.	6

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Protocol Amendment

#	Section	Previous Text Version 2.0 dated 21 Feb 2018	Amended Text Russia V1.0 dated 10 Jul 2018 Additional text - bold font. Deleted text – strike-through.	Reason for Change Insert reason # from table above
7	Section 7.4	PK Variables and Procedures Plasma concentrations from sparse sampling (see Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid and linezolid to further evaluate the effects of covariates on model parameters in this trial population. PK data from the current trial may be combined with prior data (e.g., from the Nix trial) to enhance this population PK analysis.	PK Variables and Procedures Plasma concentrations from sparse sampling (see Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, ~~and linezolid~~ **moxifloxacin and pyrazinamide** to further evaluate the effects of covariates on model parameters in this trial population. PK data from the current trial may be combined with prior data (e.g., from the ~~Nix~~ **NC-005** trial) to enhance this population PK analysis.	7
8	Section 9.2	Sample Size <u>For the primary endpoint</u>, time-to-culture conversion at 8 weeks,150 participants per arm (DS-TB participants) will provide at more than 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 90% power to detect a HR of least 2. This sample size also allows for one planned interim analysis of the primary endpoint.-(See Section 9.4.1)	Sample Size <u>For the primary endpoint</u>, time-to-culture conversion at 8 weeks,150 participants per arm (DS-TB participants) will provide at more than 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 90% power to detect a HR of least 2. ~~This sample size also allows for one planned interim analysis of the primary endpoint.~~ **Currently no formal interim analysis is planned.** (See Section 9.4.1)	8

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Sponsor

I agree to the terms of this protocol amendment

DocuSigned by:
Morounfolu Olugbosi
Signer Name: Morounfolu Olugbosi
Signing Reason: I approve this document
Signing Time: 13 July 2018 | 10:43 PDT
3DABF6C3410E4B8F85E1D6E511FA5A5F

Signature of Study Physician	Printed name	Date
	Morounfolu Olugbosi	July 13, 2018 | 1:43 PM EDT

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Principal Investigator

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

_____	_____	_____
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Title:	An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).
Drug(s)/Combination(s):	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Version/Date:	Russia V2.0 / 25 Jan 2019, Incorporating Protocol V3.0 / 14 January 2019
Protocol Name:	SimpliciTB

PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (BPaMZ)**

Protocol Date: **Russia V2.0 / 25 January 2019, Incorporating Protocol V3.0 / 14 January 2019**

Protocol Name: **SimpliciTB**

SPONSOR: **TB Alliance**

I agree to the terms of this trial protocol.

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Signature of Study Physician

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PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

Protocol Number: **NC-008 (BPaMZ)**

Protocol Date: **Russia V2.0 / 25 January 2018, Incorporating Protocol V3.0 / 14 January 2018**

Protocol Name: **SimpliciTB**

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Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AFB	Acid-fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AREDS2	Age Related Eye Disease Scale 2
ART	Anti-Retroviral Therapy
AST	Aspartate aminotransferase
AUC_{τ}	Area Under Curve over a dosing interval
B	Bedaquiline
BA	Bacterial activity
BMI	Body Mass Index
BPaMZ	Combination of bedaquiline plus pretomanid plus moxifloxacin plus pyrazinamide
C	Clofazimine
CFU	Colony Forming Units
$C_{(max), (min)}$	plasma Concentration (maximum), (minimum)
CO_2	Carbon dioxide
CPK	Creatine Phosphokinase
CYP3A4	Cytochrome P450 3A4
DMID	Division of Microbiology and Infection Disease
DNA	Deoxyribonucleic Acid
DR-TB	Drug-resistant tuberculosis For this particular protocol defined as TB participants with 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB) (participants with fluoroquinolone resistance are excluded)
DS-TB	Drug-sensitive tuberculosis
DSMC	Data Safety and Monitoring Committee
DST	Drug Susceptibility Testing
E	Ethambutol
EBA	Early Bactericidal Activity
EC	Ethics Committee
ECG	Electrocardiogram
EFV	Efavirenz
(e)CRF	(electronic) Case Report Form
EMS	Early Morning Sputum
EWD	Early Withdrawal
FTC	Emtricitabine
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
H	Isoniazid
HR	Hazard Ratio
hERG	Human *Ether-à-go-go* Related Gene
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
HR	Isoniazid plus rifampicin combination tablet

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent to Treat
IUATLD	International Union Against Tuberculosis and Lung Disease
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Linezolid
LH	Luteinizing hormone
LLN	Lower Limit of Normal
LPV	Lopinavir
LTFU	Lost to follow-up
M	Moxifloxacin
MBD	Minimum Bactericidal Dose
MIC	Minimum Inhibitory Concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi Drug Resistant Tuberculosis
MGIT	Mycobacterial Growth Inhibiting Tube
mITT	Modified Intent to Treat
ms	millisecond
NVP	Nevirapine
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NRTI	(Triple) Nucleosidase Reverse Transcriptase Inhibitor
Pa	Pretomanid
PD	Pharmacodynamic
PP	Per Protocol
PK	Pharmacokinetic
PR	PR interval
R	Rifampicin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSCC	Serial sputum colony counting
TB	Tuberculosis
TDF	Tenofovir
TEAE	Treatment Emergent Adverse Events
TTP	Time to Positivity
ULN	Upper Limit of Normal
WGS	Whole Genome Sequencing
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis
µg(/ml)	micrograms (per millilitre)
Z	Pyrazinamide (tablets)

1.0 Synopsis

1.1 Synopsis Summary

Synopsis	Description
Name of Sponsor/Company	TB Alliance
Name of Finished Products	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Number/Title	NC-008 (BPaMZ) An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB)
Treatment Indication	Pulmonary Tuberculosis (TB)
Trial Objective(s)	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the treatment regimens in participants with Drug Sensitive TB (DS-TB) and Drug Resistant TB (DR-TB). DR-TB is defined as participants with: 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)
Trial Design	Phase 2c multi-centre, open-label, partially randomized clinical trial in Drug Sensitive-TB (DS-TB) and Drug Resistant-TB (DR-TB) participants. All participants will enter post-treatment follow-up which continues until Week 104 from start of treatment / randomisation. **Participants with DS-TB:** Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation. **Participants with DR-TB:** Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).
Participant Population	Up to 450 male and female participants, diagnosed with DS-TB or DR-TB, aged 18 years and over with a target of up to 50% being HIV positive.

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td></td><td>300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation.

Up to 150 DR-TB participants will be enrolled.</td></tr>
<tr><td>Test Product, Dose and Mode of Administration</td><td>The Test Product (BPaMZ) consists of a combination of the following products and will be supplied as:
<table>
<tr><th>Product</th><th>Tablet Strength</th><th>Abbreviation</th></tr>
<tr><td>Bedaquiline</td><td>100 mg</td><td>(B)</td></tr>
<tr><td>Pretomanid</td><td>200 mg</td><td>(Pa)</td></tr>
<tr><td>Moxifloxacin</td><td>400 mg</td><td>(M)</td></tr>
<tr><td>Pyrazinamide</td><td>500 mg</td><td>(Z)</td></tr>
</table>
Instructions for Dosing BPaMZ:

Investigational Medicinal Product (IMP) will be administered orally once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months) in the following dosing schemes:

Participants with DS TB:
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 17 weeks (total treatment duration 4 months)

OR

Participants with DR-TB:
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 26 weeks (Total treatment duration 6 months).</td></tr>
<tr><td>Positive Control Product, Dose and Mode of Administration</td><td>The Control Treatment Regimen (HRZE/HR) will be supplied as:

HRZE Tablets: isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets. This combination will be given for the first 8 weeks.

AND

HR Tablets: isoniazid 75 mg plus rifampicin 150 mg combination tablets. This combination will be given from Weeks 9 to 26.

Instructions for Dosing Control Treatment Regimen

To be taken with a glass of water (approximately 240 ml). HRZE or HR should not be taken with a meal (generally, no closer to</td></tr>
</table>

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td></td><td>meals than 1 hour before or 2 hours after a meal) in the following dosing schemes:

Treatment will be administered orally once daily to the HRZE/HR randomized DS-TB participants as follows:

Weeks 1-26: HRZE/HR tablets daily dose per the participant's weight as follows:

<table>
<tr><th>Weight Band</th><th>Weight Range</th><th>Number of tablets</th></tr>
<tr><td>1</td><td>30-39 kg</td><td>2</td></tr>
<tr><td>2</td><td>40-54 kg</td><td>3</td></tr>
<tr><td>3</td><td>55-70 kg</td><td>4</td></tr>
<tr><td>4</td><td>≥ 71 kg</td><td>5</td></tr>
</table>

The participant's weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and HRZE and HR dose to administer.

Vitamin B6 daily supplement to be taken with the HRZE/HR treatment, as per each country's TB Treatment Guidelines.</td></tr>
<tr><td>Treatment Interruptions/Pauses</td><td>For All Trial Regimens

The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation, unless an interruption/pause is required urgently for a safety concern.

Action required for participants missing the following number of doses within the trial treatment regimens:

• Up to 7 consecutive doses: restart treatment, no extension of treatment required.
• If more than 7 and to ≤ 35 consecutive doses missed, before the end of the treatment period (Week 17/26): restart treatment, extend the treatment by the number of consecutive doses missed. In this case, the last visit of the treatment period should also be pushed out to the date of the last dose
• If more than 35 consecutive doses: discontinue treatment and withdraw participant from the trial
• If the participant misses a total of 56 cumulative missed doses, discontinue the IMP and withdraw the participant from the trial.
• If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose, that was missed.</td></tr>
</table>

Synopsis	Description
	Any participant for whom the trial IMP is discontinued (including for non-adherence) should be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial IMP as soon as possible.

Statistical Methods:
A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the statistical analysis plan (SAP,) which will be written and signed off prior to the interim analysis.

Criteria for Evaluation

Primary Endpoint

The primary efficacy endpoint will be time to culture negativity over 8 weeks. The primary hypothesis to be evaluated is:

- In the participants with DS-TB in the experimental BPaMZ treatment regimen, the time to culture negativity by 8 weeks will be superior, compared to the participants who are treated with the standard HRZE/HR regimen.

Secondary Endpoints

- A key secondary efficacy endpoint will be the proportion of participants experiencing bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks.

The hypothesis to be evaluated for this endpoint is:

- In the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE/HR regimen.

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

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

  Note:

  - Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.

Synopsis	Description

- Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit.

Other Secondary Endpoints

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 104 weeks from the start of treatment.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of treatment.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
- Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
- Quantitative and qualitative electrocardiogram (ECG) results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones.
- Changes in lens opacities.

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [Cmin], maximum plasma concentration [Cmax], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide.

Effects of baseline covariates on exposure will be assessed; so too, will the effects of concomitant medications, including antiretroviral therapy (ART), where feasible. Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

Exploratory Objectives:

Evaluate whether any of the secondary endpoints predict relapse free cure. Subgroup analysis of populations by HIV status will be performed.

Synopsis	Description

No formal statistical comparisons will be made for the participants enrolled with DR-TB. The responses of participants with DR-TB receiving BPaMZ will be compared for consistency with those responses of the DS-TB participants on the same regimen.

Sample Size

Primary endpoint: 150 participants per arm (DS-TB patients) will provide at least 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks.

Additional efficacy parameters will be evaluated including the incidence of bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks and 104 weeks from the start of treatment. Time to unfavourable outcome from assignment of trial treatment through follow-up as a function of time will be analysed using Kaplan-Meier analysis.

Interim Analysis

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

*To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objective**

*To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46,47,48] and full details are provided in the Statistical Analysis Plan.

Synopsis	Description
Trial Duration: Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until 104 weeks from start of treatment). Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms are complete.	

1.2 Synopsis Flow Chart and Procedures

Period	Screen-ing[a]	Treatment															Follow-Up[c]					
Visit[b]	Day -9 to -1	Day 1 (Baseline)[d]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 17 *4-mth treatment*[e]	Week 17 *6-mth treatment*[e]	Week 22	Week 26 *4-mth treatment*[e]	Week 26 *6-mth treatment*[e]	Week 39	Week 52	Week 65	Week 78	Week 104	Early Withdrawal[c]
Visit Window[v]	N/A	+/- 3 Days									+/- 5 Days						+/- 14 Days					
Written Informed Consent	X																					
Demography	X																					
Medical/Treatment/ Smoking History	X																					
Inclusion/Exclusion	X	X																				
Sputum Sampling[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Status[h] and CD4 Count[i]	X																					
Karnofsky Score[x]	X																					
Urine Drug Screen[j]	X																					
Urine Pregnancy Test[k]	X	X								X		X	X		X	X						X
Laboratory Safety Test[l]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X						X
Male Reproductive Hormone Tests[m]	X	X											X		X		X					
12-lead ECG[n]	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X					X
Chest X-Ray[o]	X																					
TB Symptoms Profile	X	X		X		X				X		X	X		X	X		X			X	X
Patient Reported Health Status	X	X		X		X				X		X	X		X	X		X			X	X
Vital Signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination[p]	X											X	X		X	X	X					X
Physical Examination – full[q]	X	X										X				X						X
Physical Examination – limited[r]			X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Pharmacokinetic Sampling[s]		X		X						X	X	X	X				X		X	X	X	
IMP Randomization/ Assignment[t]		X																				
IMP Compliance Check[u]			X	X	X	X	X	X	X	X	X	X	X	X[e]		X						X[t]
Concomitant Medications	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
Investigator Assessment[v]																		X			X	

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

a. **Screening:** Screening assessments can occur on different days within nine days before to Day 1 (Baseline).

b. **Visit Schedule (due to unforeseen circumstances):** If the duration of treatment is extended due to dose interruptions / pauses (7 to ≤ 35 consecutive doses), the last visit of the corresponding treatment period should also be pushed out to the date of the last dose. It is not necessary to have an unscheduled visit at the time that the last visit of the treatment period would have been scheduled on.

c. **Follow-up Visits for Early Withdrawal Participants:** Once a participant has been permanently withdrawn from the trial, they will be required to attend an Early Withdrawal visit (Week 52, if not already performed) and Week 104 follow-up visits. The Week 52 and Week 104 visits will be performed to collect Serious Adverse Event (SAE) information (including verification of survival) and the participant reported TB outcome information only, and may be performed telephonically, at home or a site visit. Visits will occur at Week 52 and/or Week 104 after the participant's start of treatment date. Refer to Table 5 for additional guidance.

d. **Day 1 (Baseline):** All procedures are to be completed before dosing.

e. **Last Visit of the Treatment Period:** Investigational Medicinal Product (IMP) Compliance Check is not performed at the Week 22 visit for participants who have completed treatment at Week 17.

f. **Sputum Sampling:** The sputum sampling methodology/requirements and tests will be described in a separate document, the Mycobacteriology Laboratory Manual.

- Screening (Days -9 to -1). Two spot sputum samples taken 30 minutes apart will be collected at the research site under the coaching and observation of the trial staff. The following analyses will be performed on the first of these samples:
  - Smear microscopy for acid-fast bacilli (AFB);
  - Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance (Hain MTBDplus and Hain MTBRsl);
  - Liquid Culture (MGIT) for *Mycobacterium tuberculosis* (MTB), followed by a speciation test to detect the presence or absence of MTB and obtain the time to positivity (TTP) when positive.
  - The second sample is collected as a back-up sample to the first sample in case it is technically not possible to obtain a result/s from the first sample. If the Screening spot sputum smear shows an indeterminate result or is AFB negative, the test may be repeated on the back-up sample or on a freshly collected spot sputum, and then that result will be used.
- Day 1 (Baseline) to Week 104 and Unscheduled visits for additional sputum samples:
  - Two sputum samples are collected, ideally one Early Morning Sputum (EMS) brought from home and one spot sputum sample at the research site, under the coaching and observation of the trial staff. If the participant forgets to bring in the EMS, then two spot sputum samples are to be collected at the site, at least 30 min apart, and this altered sample collection is captured within case report form (CRF).

- If both sputum cultures at Weeks 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional sputum samples or to document that the participant is not able to produce a sputum sample.

- If after having converted to culture negative, and the participant has a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 or Week 26), the participant should return for an unscheduled visit/s to provide additional sputum samples, at a minimum of 7 days apart, or to document that the participant is not able to produce a sputum sample.
- Additional samples may be required to define a participants' primary outcome status as described in Sections 5.4.2 and 7.2.
- Liquid Culture (MGIT) for MTB, followed by a speciation test to detect the presence or absence of MTB and obtain TTP when positive, will be performed on all samples.

g. **Mycobacteriology Characterisation Tests performed:**

- Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative);
- MTB confirmed positive cultures (after the participant has previously converted to culture negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.
- Refer to Mycobacteriology Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for:

- Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);
- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin;
- Drug Susceptibility Testing (DST) for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing (WGS), and comparison of sequences from baseline and relapse isolates.

h. **HIV Testing:** If HIV status is a confirmed known positive, a repeated HIV test is not needed provided that a documented HIV test result (ELISA, Western Blot or Electro-Chemiluminescence) is available. If the HIV status is unknown or suspected negative, a HIV test will be requested. If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated if documentation of testing method and negative HIV results can be provided. Repeated HIV testing, during the Screening period is permitted for indeterminate HIV results.

i. **CD4 Count:** Required for all HIV-positive participants.

j. **Urine Drug Screen:** Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at Screening only. Investigator to utilize this result to determine whether participant meets Exclusion Criteria 2. Positive results will not automatically exclude a participant from the trial.

k. **Urine Pregnancy Test:** Women of childbearing potential only, whether they are sexually active or not.

l. **Safety Laboratory Assessments**: The safety laboratory sampling methodology and requirements will be described in a separate document, the Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:

- Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count).
- Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/carbon dioxide [CO_2], creatine phosphokinase [CPK]). GGT is only routinely included at the Screening visit (Day -9 to -1).
- 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.
- When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

m. **Male Reproductive Hormone Tests:** Testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin B to be done on male participants in ALL treatment groups.

n. **Single 12-Lead ECG:** ECGs to be performed prior to pre- and post-dose PK sampling as described below:

- Day 1: pre-dose (within 2 hours prior to dosing)
- Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 12: pre-dose (within 2 hours prior to dosing)
- Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose

Central ECG analysis will be performed. Results from central reading of Screening ECG must be used to determine eligibility.

o. **Chest X-Ray:** A chest x-ray (digital image only) within 6 months prior to or at the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor and this process will be described in a separate document, the Radiology Manual.

p. **Slit Lamp Ophthalmic Examination**: Slit lamp examination will be done at the Screening visit, the last visit of the treatment period (Week 17 or 26) and at Week 39 for both treatment groups. An additional slit lamp at Week 26 will be done for the 4-month treatment group. Slit lamp ophthalmology examination will be performed by an Ophthalmologist with AREDS2 training. Ophthalmology examinations may occur at any time within the window period for the applicable visit i.e. they do not have to be performed on the same day as the trial procedures.

q. **Physical Examination, Full:** Height (m) will only be collected at Screening.

r. **Physical Exam, Limited:** Limited physical exams will include weight and gross neurological, pulmonary, cardiovascular and abdominal exam(s).

s. **Pharmacokinetic (PK) Sampling:** This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE/HR treatment arm. Blood draws for PK samples collected pre-and post-dose must be done after the ECG is performed. The dates and times of IMP taken prior to all pre-dose PK samples will be collected. Specific PK blood draws will be obtained as follows:

- Day 1: pre-dose (within 2 hours prior to dosing)
- Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 12: pre-dose (within 2 hours prior to dosing)
- Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose
- Weeks 39, 65, 78 and 104 (for bedaquiline, bedaquiline metabolite M2): PK samples are to be obtained at any time on the day of the scheduled visit.

Only bedaquiline and M2 will be measured.

If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.

t. **Investigational Medicinal Product (IMP) Randomization/Assignment:** Randomization/Assignment may occur once all the Screening results are available and the Investigator has determined that the participant is eligible for the trial.

u. **IMP/Compliance Check:** IMP administration will be supervised per local site practice to assure compliance to the regimen. Performed at all visits and Early Withdrawal (EWD), if during the treatment period.

v. **Investigator Assessment:** Investigator to review the participant status and assess whether IMP or TB treatment at Week 52 and 104 is considered a “success” or “failure”. If considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed, at Week 52 and 104, and at any time the Investigator determines that the participant fulfils the criteria for outcome of treatment failure.

w. **Visit Windows**: The windows noted on the flowchart for timing of visit also apply to the timing *within a visit.* Procedures should be performed within +/- 3 days of scheduled visit from Day 1 to Week 8 or +/- 5 Days of scheduled visit from Week 12 to Week 26 or +/- 14 days of scheduled visit at or after Week 39. Sites should make every effort to ensure all procedures are done on the same day, when possible.

x. **Karnofsky Score**: Only to be performed on HIV+ participants.

2.0 Introduction and Rationale

2.1 Tuberculosis Disease

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in the developing countries of Africa, Asia and South America. TB is currently one of the top three killer infectious diseases, 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 40 years and are relatively ineffective in controlling TB as a public health problem. 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 participants, treatment takes 6 months or more to complete. This, long duration treatment **plus side effects**, result in poor adherence which particularly occurs after the second month of treatment.

The current TB treatment regimens and treatments for drug-sensitive TB are decades old. The available treatments have a lengthy duration of treatment, involve multi-drug therapy, and require large commitments of resources and infrastructure. High rates of noncompliance are common, which often results in increased mortality and chronic, infectious, drug-resistant cases. The present TB epidemic and the challenge of current treatment options demonstrate the clear need for effective novel TB drugs and **drug regimens** that are safe for drug sensitive and drug resistant TB disease and that are well-tolerated and will shorten the current treatment duration for patients.

The full application of the Directly Observed Treatment, Short-Course strategy is becoming more and more difficult in the developing countries of the world that are also battling to control the HIV-epidemic. Because of poor treatment adherence, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB are growing. Since the discovery of the rifamycins,[1] and their introduction into standard antituberculosis regimens, very few new classes of drugs have been evaluated with a view to their registration as antituberculosis agents. On December 28, 2012 the U.*S.* Food and Drug Administration approved bedaquiline (B) as part of combination therapy to treat adults with multi-drug resistant (MDR) pulmonary tuberculosis (TB) when other alternatives are not available. 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.

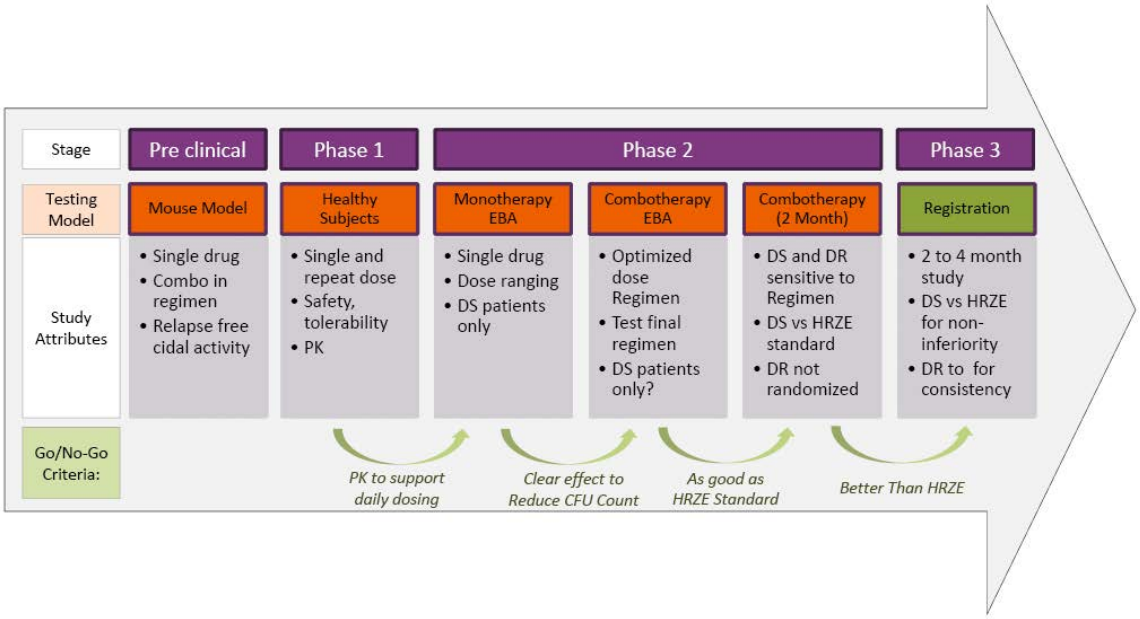
New combination regimens are desperately needed for two reasons: to shorten treatment to a duration more easily manageable by patients and public health services, and to provide more efficacious, safer and better tolerated, affordable treatments for the growing number of patients suffering from multidrug-resistant and extensively drug-resistant tuberculosis.

2.2 Tuberculosis Clinical Research

TB currently must be treated with multiple drugs to achieve maximal efficacy and prevent resistance. To transform treatment, novel TB regimens are needed. To telescope the time, it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm. This approach tests promising combinations of drugs together to find the most impactful treatment once the individual drug candidates have been tested in a robust pre-clinical program and the establishment of the individual drug candidates' safety and efficacy have been evaluated. It evaluates novel combinations of TB drugs — instead of single drugs — as part of a single development program, enabling the development of novel TB drug

regimens that have potential to transform treatment for drug-sensitive and drug-resistant tuberculosis. This approach offers the potential to reduce the time previously needed to develop a novel treatment regimen by up to 75%, shortening the clinical development from decades to years. The steps followed in this development model are shown in Figure 1 Between each step on the unified development pathway a decision is made as to whether to proceed.

Figure 1. Unified Drug Sensitive/Drug Resistant Regimen Development Path



Early Bactericidal Activity (EBA) Trials

EBA trials are the backbone clinical trials to quantify the bactericidal action of anti-tuberculosis agents alone or in combination by either trialling the fall in the number of colony forming units (CFU) or measuring the TTP in liquid culture of *M. tuberculosis* (*MTB*) present in the sputum of participants with microscopy smear-positive pulmonary TB. EBA trials have been conducted over 2, 5, 7 and 14 days.[2]. A review of EBA trials conducted on the key anti-TB drugs has shown the value these trials offer to demonstrate the early anti-TB effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in participants.[3]

8-week Bactericidal Activity (BA) Trials

EBA methodology of quantitative colony counting on solid medium has been adapted to Phase 2, 8-week TB treatment trials based on serial sputum colony counting (SSCC) or measurement of TTP liquid culture to provide a more sensitive efficacy endpoint than the previously used binary endpoint of rate of sputum conversion measured after 8 weeks of treatment.[4-6] Such trials are conducted to provide data on which to base the selection of treatment-shortening regimens.

2.3 Trial Rationale

The SimpliciTB NC-008 (BPaMZ) trial will evaluate and support that, in additional to previous studies evaluated with BPaMZ, this drug regimen (BPaMZ) will be safe and effective, is well-tolerated and could potentially shorten the current treatment duration compared to the standard HRZE/HR treatment for patients with drug sensitive TB disease. This trial will also evaluate if the BPaMZ drug regimen given for 6 months will be safe and effective in drug resistant TB disease.

Therefore, the trial design addresses the need to find and evaluate a potentially effective and shorter regimen compared to regimens (standard HRZE/HR) that are currently being used.

2.3.1 Trial Design Rationale

The SimpliciTB NC-008 (BPaMZ) trial is a Phase 2c multi-centre, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. This trial is to evaluate the combination regimen of **Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) plus Pyrazinamide (Z)**, (BPaMZ), in participants with pulmonary TB.

All participants will enter post-treatment follow-up which continues until Week 104 after start of treatment / randomisation.

Participants with DS-TB:

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either:

- BPaMZ daily for 17 weeks (4 months),

OR

- HRZE/HR combination tablets daily for 26 weeks (6 months).

Participants will be stratified for co-infection with HIV and cavitation.

Participants with DR-TB are defined as:

1. mono-resistance to rifampicin or isoniazid, OR

2. resistance to both rifampicin and isoniazid (multi-drug resistant tuberculosis [MDR-TB])

Up to 150 participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months). Approximately 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation to either BPaMZ for 4 months or HRZE/HR for 6 months.

The trial is sufficiently statistically powered to not only show superiority of 8 Weeks culture conversion but should also demonstrate non-inferiority for cure at 52 Weeks (this is in the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen).

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

  *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objectives**

  *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46, 47, 48] and full details are provided in the Statistical Analysis Plan.

As previously described in the background information, in order to telescope the time it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm and utilize data generated in non-clinical and clinical studies regarding combining of anti-tuberculosis agents which could contribute significantly to the sterilization of lesions and thus treatment shortening. Therefore, the trial design and proposed trial regimen (BPaMZ**)** which is supported with previous non-clinical and clinical studies outlined below should address the need and manner of evaluating an effective shorter regimen compared to regimes that are currently being used.

2.3.2 Trial Drug Regimen Rationale

The BPaMZ regimen has been studied singularly and in different combinations as outlined above. Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. It essentially provides protection against the development of new resistance to the B-Pa-Z drugs. Based on the exciting and promising results seen in NC-005, this regimen can be initiated in drug sensitive and drug resistant TB participants whom are sensitive to the individual drugs in the regimen (excluding extensively drug-resistant tuberculosis [XDR-TB]) and has the potential to shorten TB treatment to less than 4 months in drug sensitive TB. These are also oral regimens, removing the need for injectables as part of MDR-TB treatment and also project to be markedly less expensive than current MDR-TB therapy. Additionally, these regimens can be

administered in a fixed dose for all patients, and will therefore be simpler for health systems to deliver and patients to use.

2.4 Agents used within SimpliciTB

Bedaquiline (TMC207; Sirturo™ package insert)[7] is a novel agent approved for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[9, 10]) *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. Tb* isolates,[10, 11], and is also bactericidal against non-replicating *M. Tb.*[12] In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. Tb*.[3, 4] 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.[13] 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 DS- and MDR-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[13] and in a subsequent trial it was more active in the mouse model than HRZ.[14] Thus, a novel regimen with a 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.

Pretomanid, (Pa)[15] is a new chemical entity being developed by TB Alliance for the treatment of TB. It is 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 has been under development for several years, and entered clinical trials in 2005. Several trials of pretomanid have also been conducted previously in healthy volunteers. Collectively, these trials in participants with active TB and healthy participants have defined the efficacy, safety and pharmacokinetic features of the drug. Overall, pretomanid has mycobactericidal activity in participants and is well tolerated and bioavailable after oral dosing. Pretomanid demonstrated in vitro activity against both drug-sensitive (DS) and MDR-TB,[17] and in vivo activity in a mouse model of TB[17, 18] with a significant promise for shortening treatment of active TB.

Moxifloxacin (M)[19] is a microbial compound, approved in most countries around the world for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and soft tissue infections. Clinical studies have been carried out for many additional indications (urinary tract infections, pelvic infections, pharyngitis/tonsillitis, and tuberculosis). Moxifloxacin is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by or induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the MTB strain is susceptible or if the agent is thought to have efficacy. One of the higher generation

fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]" It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

Pyrazinamide (Z)[20] is a pyrazine analogue of nicotinamide and an approved anti-tuberculosis agent which is indicated for the initial treatment of active tuberculosis in adults and children when combined with other anti-tuberculosis agents and contributes significantly to the sterilization of lesions and thus treatment shortening.[21]

Control Group: HRZE/HR

The **HRZE/HR** combination [HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets] is approved indicated and commonly used as a 6-month treatment for drug-sensitive TB patients. Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE. Please see the HRZE package insert for more information.[22]

Additional background data supporting the combined use of new novel agents in this BPaMZ regimen for the treatment of TB:

Data from preclinical studies suggest that a regimen consisting of moxifloxacin plus pretomanid plus pyrazinamide may not only be appropriate for treating both DS and MDR-TB but may also **shorten duration of therapy**. Results from an 8-week Phase 2b SSCC trial, NC-002-(M-Pa-Z), showed that this **combination regimen** was effective as measured by time dependent decline of viable bacteria in participants with DS pulmonary TB. The combination was also shown to be safe and well tolerated supporting the evaluation of this combination in a Phase 3 trial. In this NC-002 trial 71.4% of participants with DS-TB treated with PaMZ at the 100-mg daily dose of pretomanid converted sputum to negative for *MTB* growth in liquid culture in comparison with only 37.8 % of participants treated with the HRZE control ($p<0.05$).

Studies in mice infected with *MTB* demonstrated reductions in cultured colony counts from lungs over an 8-week period when treated with the PaMZ regimen that were substantially, and statistically significantly greater, than the reductions in mice treated with an HRZ control. Experiments in mice found that mice did not relapse with MTB infection when treated with PaMZ for 4 months and followed for 3 months off treatment, in comparison to mice that required 6 months of treatment with HRZ to prevent relapse.[14]

Drug Resistant TB Background:

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in many countries. TB is the world's leading cause for mortality from infectious disease and is responsible for more deaths than HIV.[23] 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. Because of poor treatment adherence, in addition to primary transmission, **drug resistance** is becoming more common and fears of an epidemic with strains of extensively drug-resistant TB (XDR-TB) that is very difficult to treat are growing. Novel drugs and regimens for TB are needed for the growing number of patients with drug resistant-TB.

The regulatory approvals of bedaquiline and delamanid have given hope that outcomes for patients with drug resistant TB might be improved when added to background regimens.

Experience recently published from the C209 uncontrolled trial of bedaquiline given on a background of multiple drugs notes that the subset of 38 participants with XDR-TB had rates of sputum culture conversion to negative of 62.2%.[24] However, in this trial only one participant with XDR-TB was co-infected with HIV. All participants were required to have Mycobacterium tuberculosis (MTB) isolates susceptible to at least 3 drugs at enrolment and participants had a median of only 5.4 months of treatment-free follow-up. This trial added bedaquiline for 6 months to a background regimen of many drugs given for 18 months or longer. While treatment success for MDR-TB is better than for XDR-TB, **overall success in treating MDR-TB is still approximately 50%** according to the World Health Organization 2015 Global TB Report.[23] This report presented that overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, 10% failed treatment, and for 8% there was no outcome information.

With such poor historical outcomes for patients with drug resistant-TB and with the complexity, expense and toxicity of treatments for all forms of drug resistant TB, **novel drug combinations are desperately needed to improve treatment outcomes**. Linezolid was identified in a small trial as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen[25] and this drug has increasingly been added to complex regimens to treat patients with MDR-TB.

With the current availability of the following three drugs for which there is little, if any, pre-existing resistance among strains of MTB (pretomanid [Pa], bedaquiline [B], and linezolid [L]). Mice infected with MTB had relapse-free cures with 3 months of treatment with a B-Pa-L regimen. While it is not known whether that treatment duration will translate to humans, the ongoing Nix-TB clinical trial hypothesizes patients with pulmonary XDR-TB or MDR-TB not responsive to or intolerant to therapy may have relapse-free cure after as little as 6 months' treatment with the B-Pa-L regimen.[26] Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. The proposed trial [SimpliciTB] allows the opportunity to assess the efficacy, safety and tolerability of BPaMZ, a new 6 months regimen that may be administered orally once daily to treat patients with drug resistant -TB (excluding participants with XDR-TB).

Therefore, the **overall purpose** of the present proposed trial **[SimpliciTB]** is to assess the efficacy, safety and tolerability of the **BPaMZ** regime after 4 months of treatment in adult participants with drug sensitive TB and after 6 months of treatment in participants with multi drug-resistant TB. The trial will also generate data of the potential for a shorted treatment duration with the **BPaMZ** regime after 4 months compared to a 6-month **HRZE/HR** (control) treatment regime in adult participants with drug sensitive TB.

This trial will be conducted in accordance with the Protocol, ICH Guidelines for Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirement(s).

2.5 Background of Agents to be Studied in SimpliciTB

2.5.1 Bedaquiline (B)

Bedaquiline (formerly known as TMC-207; Sirturo™ package insert[7]) is approved agent for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[11] In vitro, bedaquiline potently inhibits both drug-sensitive

and drug-resistant MTB isolates,[11, 12] and is also bactericidal against non-replicating MTB[12] 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 MTB.[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.[27].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[27] and in a subsequent trial it was more active in the mouse model than HRZ.[28]. 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.

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as 200 mg daily for 8 weeks then 100 mg daily for 9 weeks in participants with DS-TB and 200 mg daily for 8 weeks then 100 mg daily for 18 weeks in participants with DR-TB. This daily dosing scheme will allow more convenient dosing that should ultimately enhance patient adherence and may allow the formulation of fixed dose combinations with other drugs. This daily dosing regimen is supported by safety and efficacy demonstrated in the NC-005 trial that administered bedaquiline 200 mg daily over 8 weeks, and by pharmacokinetic modelling and simulation of the daily dosing scheme. This supportive information is detailed below.

2.5.1.1 Bedaquiline Non-Clinical Studies

Full details of the preclinical studies are provided in the current bedaquiline Investigator's Brochure,[8] and Sirturo ™ label.[7] *In vitro* studies have demonstrated that the range of minimum inhibitory concentrations (MICs) for MTB 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 MTB. 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 MTB but 3-6 times less active than the parent compound bedaquiline. Bedaquiline demonstrated similar *in vitro* efficacy against MTB 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 International Council for Harmonisation (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.[8]

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 and ECG parameters.

Prior to the use of pretomanid in combination with bedaquiline in clinical trial NC-001, a preclinical cardiovascular safety pharmacology trial 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.[28] 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) Investigators Brochure for more detail.

2.5.1.2 Bedaquiline Clinical Studies

In the clinical studies conducted to date, a total of approximately 645 participants (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 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001, and 45 more in trial NC-003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). Four short-term Phase 2a trials enrolled treatment-naïve participants (C202, TMC207-CL001, NC-001 and NC-003). One long-term, open-label, Phase 2 trial, in MDR-TB participants (bedaquiline- TiDP13-C209) and one long-term, Phase 2b trial, consisting of 2 different stages in participants 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,[8] and Sirturo™ label.[7].

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 participants. 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 trial, 800 mg single dose in trial 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 participants and participants 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 α 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 participants 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 trial (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 trial (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. Trial C202 was a 7-day trial of three daily doses of bedaquiline (25, 100 and 400mg) in treatment-naïve participants with MDR-TB. In this trial, the 400mg dose group demonstrated positive EBA and was numerically superior to the 25 and 100mg doses. In trial TMC207-CL001, doses of 100, 200, 300 and 400mg daily (following a 2-day loading dose) were studied in participants 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 participants with TB and that higher doses appear to have greater efficacy.

A 14-day EBA regimen trial (TB Alliance Trial 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 participants 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 participants given bedaquiline 400 mg/d after a 2-day loading dose. In the cohort of 15 participants 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 participants 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 trial (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 participants 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 participants in the bedaquiline group became MGIT culture negative compared to 8.7% of participants 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 participants in the bedaquiline group and 65.2% of participants 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 participants 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 participants. Culture conversion rates after 2 weeks of treatment with bedaquiline as part of an individualized anti-tuberculosis regimen were higher in participants with lower extent of resistance of the M. Tb strain and in participants with no lung cavitation compared to participants with cavitations (in one or both lungs).

2.5.1.3 Bedaquiline Clinical Safety

In the clinical trials conducted to date, a total of approximately 645 participants (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 participants received bedaquiline in a monotherapy EBA trial of 14 days (trial TMC207-CL001) 45 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001 and 45 more in trial NC- 003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). In these trials, bedaquiline has been shown to be an effective treatment for participants 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 trial 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 trials, 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 participants) 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	**1 (1.3)**	**1 (1.0)**	**0**	**0**
Headache	1 (1.3)	1 (1.0)	0	0
Cardiac disorders	**0**	**0**	**0**	**0**
ECG QT Prolonged	0	0	0	0
Gastrointestinal disorders	**0**	**0**	**0**	**0**
Diarrhea	0	0	0	0
Vomiting	0	0	0	0
Hepatobiliary disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Transaminases increased [a]	2 (2.5)	2 (2.0)	0	0
Musculoskeletal and connective tissue disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Arthralgia	2 (2.5)	2 (2.0)	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 participants in the Any bedaquiline group and 5 participants 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 participants 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 participants (12.7%) compared to 3 placebo participants (3.7%). Based on the pooled results (Stage 1 and 2) while being followed in the placebo- controlled trial, 7 participants in the Any bedaquiline group and 1 Participant 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 haemoptysis. 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 participants 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 Participant in the bedaquiline group (pulmonary TB) and 2 participants in the Placebo group (TB-related illness and pulmonary TB) in Stage 1 died, and 4 participants in the bedaquiline group (3 participants with TB-related illness, 1 Participant motor vehicle accident) and 2 participants in the Placebo group (both TB-related illness) died after they discontinued Stage 2 of the trial. None of these participants 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, diarrhoea, blood uric acid increased, hypokalaemia, pruritus, injection site pain, insomnia, and tinnitus. From start of the trial up to the final analysis, 12 participants 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), haemoptysis, hypertension, and pyopneumothorax/respiratory failure. 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 participants 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 participants (6.9%) have died (12 participants during the trial and 4 participants 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 participants 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[7] notes that treatment initiation is not recommended in patients with:

- Heart failure;
- QTcF interval > 500 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).
- Hypokalaemia

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. If 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. participants should be monitored during treatment. Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in those participants with diminished hepatic reserve.[7]

Additional safety information from a recently completed trial

In a recently completed phase I trial not yet included in the bedaquiline Investigators Brochure that evaluated drug-drug interactions between bedaquiline and either rifampin or rifabutin, 7 participants experienced SAEs. Of those participants, 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 participant 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.

2.5.2 Pretomanid (P)

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]

2.5.2.1 Pharmacology

Key in Vitro Evaluation of Pretomanid Bactericidal Activity

Non-clinical in vitro trials demonstrated that pretomanid was active against actively growing drug- sensitive and drug-resistant MTB strains as well as against non-replicating MTB. The minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive MTB isolates *in vitro* was shown to be like the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of MTB with MIC values ranging from 0.03 to 0.53 µg/mL. The Investigator's Brochure contains further information on *in vitro* bactericidal activity.[16]

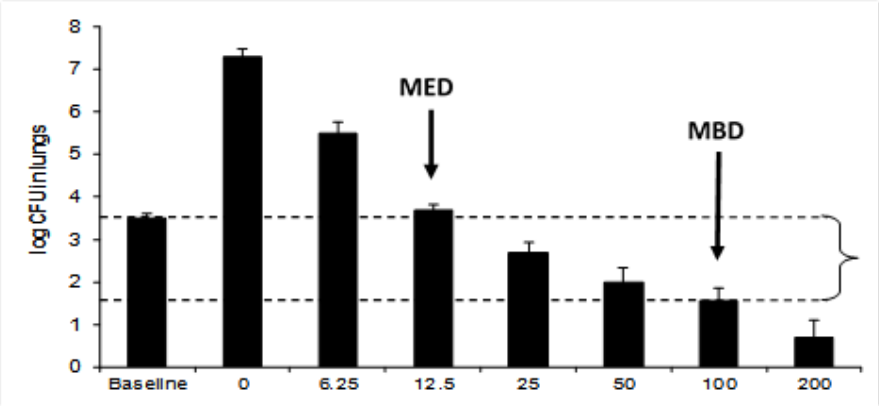
Although not thoroughly elucidated at this time, pretomanid has a novel mechanism of action that appears to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reduction of pretomanid by a deazaflavin (F420)-dependent nitroreductase has been shown to be associated with generation of reactive nitrogen species, including nitric oxide (NO),[29] although the exact target(s) of the reactive nitrogen species are not known. Transcriptional profiling trials also suggest that pretomanid affects both cell wall biosynthesis and the respiratory complex of MTB.[30, 31]

2.5.2.2 Key Non-Clinical Trials of Pretomanid

The activity of pretomanid as a single agent or as part of a multi-drug combination regimen has been examined in a number of mouse trials.[13, 14, 18, 32, 33] In a mouse model of established TB, the activity of various doses of pretomanid (given once daily, 5 days/week, for 1 month), initiated 22 days after inhalation infection with H37Rv MTB is shown in Figure 2. In this model, the minimum effective dose (MED) for pretomanid, defined as the lowest dose able to prevent the development of gross lung lesions and splenomegaly, was 12.5 mg/kg/day, while the minimum bactericidal dose (MBD), defined as the lowest dose able to reduce lung colony forming units (CFU) by 99%, was 100 mg/kg/day. Moreover, in these experiments, the activity of pretomanid at 100 mg/kg was comparable to the activity of isoniazid at 25 mg/kg.

Figure 2. Log10 CFU Counts in Lungs

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



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

2.5.2.3 Non-Clinical Toxicology and Safety

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

In the repeat-dose toxicity trials, the lowest no-observed adverse effect level (NOAELs) was 10 mg/kg/day in a 26-week trial in rats, 50 mg/kg/day in a 13-week trial in monkeys and <25 mg/kg/day (based on findings of thickening of the gastrointestinal tract at all doses) in a 9-month trial in monkeys. The major findings in safety and toxicity trials are listed below in Table 2 and are detailed in the Investigator's Brochure.[15]

Table 2. Key findings of Pretomanid in Safety and Toxicity Trials

Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behaviour at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
Testicular toxicity Although rat and rabbit embryonic development trials indicate no effects of pretomanid on foetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose toxicology trials and a Segment I fertility trial. In this fertility trial, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower dose not associated with testicular atrophy. A detailed trial in sexually mature male monkeys demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing.
Cataracts Cataracts developed in rats with prolonged daily administration of pretomanid at doses ≥100 mg/kg/day. In one 13-week trial 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 trial in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.
hERG inhibition and QT prolongation Altered ventricular repolarisation due to inhibition of hERG-mediated potassium current and manifested on the ECG as a prolonged QT interval corrected for heart rate (QTc). Pretomanid inhibited hERG current with IC50 values of approximately 6.2 µg/mL. Following a single pretomanid dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Co-administration of pretomanid with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at pretomanid doses of ≥150 mg/kg/day.

2.5.2.4 Clinical Background Information

Pretomanid has been evaluated in 8 single- and multi-dose Phase 1 trials with healthy adult male and female participants, with 163 participants receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 7 days. These Phase 1 trials have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid. Two additional Phase 1 trials Sponsored by the NIH included a Thorough QT trial and a trial of drug interactions among pretomanid, efavirenz and ritonavir/lopinavir. Further details of the trials are in the Investigator's Brochure.[15]

2.5.2.5 Pharmacokinetics

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

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

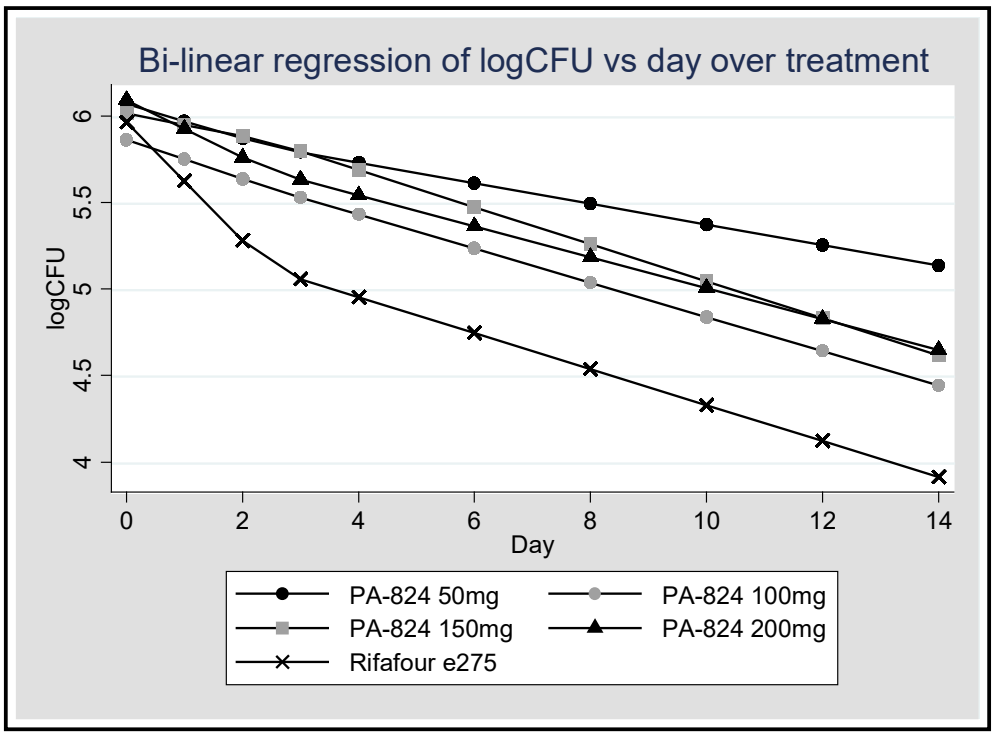
Drug interaction with efavirenz, ritonavir/lopinavir, and rifampicin: The US NIH Sponsored this drug interaction trial with rifampicin, a known hepatic enzyme inducer, and with the antiretroviral drugs efavirenz and ritonavir/lopinavir (LPV/r) in healthy participants. Participants in Arm 1 were randomised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

In conclusion, compared to pretomanid alone, plasma pretomanid values (based on geometric mean ratios) for C_{max}, $AUC_{0\text{-}24h}$, and C_{min} were reduced 28%, 35%, and 46% with efavirenz; 13%, 17%, and 21% with LPV/r; and 53%, 66%, and 85% with rifampicin, respectively.

2.5.2.6 Pretomanid Clinical Efficacy

The first two Phase 2 trials to evaluate the early bactericidal effect (EBA) of pretomanid oral monotherapy (50 to 1200 mg/day for 14 days) examined the dose-response for pretomanid in participants with newly diagnosed pulmonary TB infection. The first trial (CL-007) demonstrated good EBA, but all doses in this trial (200 to 1200 mg/day) had the same activity. The second trial (CL-010) evaluated a lower dose range (50 to 200 mg/day) and the maximum effect on EBA was seen at a dose of 100 mg/day over 14 days (Figure 3).[34]

Figure 3. Mean log Colony Forming Unit Values over Time Trial CL-010



CFU = colony-forming unit; PRETOMANID = pretomanid

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

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

2.5.2.7 Pretomanid Clinical Safety

The pretomanid Investigator's Brochure[15] provides detailed safety information.

Across the 16 clinical trials with pretomanid completed to date, a total of 649 participants have been exposed to pretomanid, including 289 healthy participants across the 10 Phase 1 trials

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

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

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

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

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

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

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

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

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

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

2.5.3 Moxifloxacin (M)

Moxifloxacin (M)[19] is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by nor induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that “all patients [with MDR-TB] should receive a Group 3 medication if the strain of MTB is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]” It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

2.2.3.1. Moxifloxacin Clinical Trials

Moxifloxacin is commonly used as second line therapy for TB (e.g. MDR- TB), and has also been evaluated in several clinical studies of participants with TB, including four 8-week treatment period Phase 2b studies (see Table 3 below).

Table 3. Summary of Phase 2b trials in which moxifloxacin were administered as part of a four-drug regimen during the intensive phase of treatment (total treatment duration: 2 months)

Trial	Design	Objective	Participants (N)	Status
Trial 27	Randomized, double-blind, controlled	To compare the sputum culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using the standard 4-drug regimen HRZE with a standard regimen with M replacing E.	336	Completed
OFLOTUB Trial	Randomized, Open label, Controlled	To compare the bactericidal activities of regimens where gatifloxacin, M, and ofloxacin were substituted for E in the 2-month initial phase of standard TB treatment with HRZE.	217	Completed
Johns Hopkins (FDA orphan drug) Trial	Randomized, double-blind, Controlled	To compare the sputum culture conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE) with a regimen with M replacing E (HRZM).	170	Completed
Trial 28	Randomized, double-blind, Controlled	To compare the culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE 5 days per week) with a regimen with M replacing H (MRZE 5 days per week).	433	Completed

2.5.3.1 Moxifloxacin Clinical Safety

In Trial 27,[35] the moxifloxacin-containing TB regimens (HRZM) were shown to be safe and well tolerated. There was no difference in SAEs between the HRZM and HRZE treatment arms, and most SAEs were hospitalizations thought to be unrelated to the trial treatment. Participants treated with the moxifloxacin-containing regimen were more likely to report nausea (22% vs. 9%, p = 0.002), but this was generally mild and did not lead to treatment discontinuation as similar proportions of participants in both groups completed trial drug treatment (88% HRZM-treated vs. 89% HRZE-treated). The one death during the first 2 months of treatment was thought to be caused by a pulmonary embolism unrelated to tuberculosis therapy.

In the OFLOTUB trial,[36] AEs and SAEs occurred with equal frequency in the four treatment arms. The most frequent AEs were raised amylase (in 41% of participants due to HIV infection), raised transaminase (10%), arthralgia (9%), anaemia (7%), hypokalaemia (6%) and vomiting (5%). No Participant was withdrawn from the trial due to an adverse event. There were 4 deaths in the trial: 2 in the control group, 1 each in the moxifloxacin and ofloxacin arms. Importantly, participants in this trial who received moxifloxacin and pyrazinamide in addition to isoniazid and rifampin had more rapid sputum clearance than participants on the four

standard first line drugs (isoniazid, rifampin, pyrazinamide and ethambutol). This difference was evident 14 days after initiation of treatment.

In the JHU trial,[37] AEs did not differ by treatment group. There were 16 SAEs (8 in each group) in 12 participants. Only 1 event was judged related to trial drug (grade 3 cutaneous reaction in the ethambutol group). Eight participants died during the trial, including 1 in each group still receiving trial phase treatment. No death was attributed to trial treatment. Only 5 participants discontinued treatment because of toxic effects; 2 participants in the moxifloxacin group stopped because of grade 2 nausea and vomiting and 1 because of grade 2 paraesthesia's and ataxia. Two participants in the E group stopped because of grade 2 rash and pruritus and 1 because of grade 3 peripheral neuropathy. There was no change in the QTc interval on serial electrocardiograms taken during the trial.

In Trial 28,[38] the proportions of participants with SAEs during the intensive phase treatment were similar between arms (isoniazid 3.9% vs. moxifloxacin 4.2%; P = 0.88). Three SAEs attributed to trial treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group. Seven participants died during the trial including 3 participants receiving the moxifloxacin treatment regimen and 4 participants receiving the isoniazid treatment regimen. The 3 moxifloxacin participants died during the intensive phase of TB treatment. Two participants died from advanced pulmonary TB judged not related to trial treatment and 1 Participant (who developed diabetic ketoacidosis considered possibly related to trial treatment) died from possible acute pulmonary embolus unrelated to trial treatment. The 4 isoniazid deaths occurred during the continuation phase, and all 4 were considered unrelated to trial treatment. Nausea was more common among participants in the moxifloxacin arm than in the isoniazid arm (19.6% vs. 11.7%, respectively; P = 0.03) although similar proportions reported vomiting. However, the proportions of participants with hepatitis, defined as serum AST 3 times or greater than the upper limit of normal, were similar between treatment arms during intensive phase (isoniazid 3.4% vs. moxifloxacin 3.3%; P = 0.93). Moxifloxacin has also been evaluated in combination with pretomanid for two weeks in participants with TB (Trial NC-001) and for 8 weeks in NC002 as reviewed above in Section 2.2.3 (Trial NC-001).

For additional information on moxifloxacin, refer to the IB[39] and the manufacturer's package insert.[19]

2.5.4 Pyrazinamide (Z)

Pyrazinamide (Z) is a standard drug used as part of the four drug HRZE regimen used for the first two months of intensive therapy for drug-sensitive TB as recommended by the WHO and many National TB programs. Please see the Package Insert[20] for more detail. Z is active against TB *in vitro* and it potentiates the bactericidal and sterilizing activity of both bedaquiline and pretomanid in mouse models of TB infection.[8, 15] Pyrazinamide enhanced the bactericidal activity of both bedaquiline and pretomanid in Trial NC-001-(J-M-Pa-Z) as noted by decreases over 14 days in the CFU counts in sputum among participants.

The pyrazinamide product label notes that pyrazinamide is contraindicated in persons with severe hepatic damage, who have shown hypersensitivity to it, and with acute gout. The most serious side effect is hepatotoxicity. Its frequency appears to be dose-related and thus liver function should be assessed before and regularly during treatment with pyrazinamide. Hyperuricemia commonly occurs and is occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other

side effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria.

Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert. [20]

2.6 Overall Benefit/Risk Assessment

Some participants with pulmonary TB in this trial will be given a regimen of **BPaMZ**. These drugs individually and in combination are known to have anti-tuberculosis activity and is not expected to have an adverse impact on the ultimate cure of TB in these participants. Based on NC-005 and other regimens using each of the regimen drugs in different combinations there is good evidence that this may be a highly effective therapy for both DS-TB and DR-TB.

For DS-TB the potential for a shorter regimen than 6 months is expected to be successful based on preclinical and clinical information as listed before. Participants in this trial will have their TB infection carefully characterized, with drug sensitivity profiles established, and they will receive treatment with trial drugs that have demonstrated activity against MTB.

Participants will receive individualized medical attention; this will allow a continuous monitoring of the health conditions of each participant, any of whom can be withdrawn at any stage of the trial and removed from trial treatment should his/her condition suggest to the Investigator that this would be in his/her best interest. Multiple blood samples will be taken for safety laboratory studies, and ECGs will be taken at multiple time points.

One concern, the combination of two agents with known QT-prolonging effects (bedaquiline and moxifloxacin), has been addressed specifically by carefully identifying and excluding participants with risk factors that might predispose them to cardiac arrhythmias, screening all participants for evidence of existing cardiac disease and monitoring all participants with ECGs throughout the trial.

The trial drugs in the proposed regimens to be tested in this trial have all demonstrated safety and efficacy in the treatment of pulmonary tuberculosis in non-clinical and clinical studies. Specifically, the regimen B-Pa-Z was generally well-tolerated and demonstrated bactericidal activity in a 14-day EBA trial. The potential risks associated with the trial drugs and regimens has been identified as outlined below and will be monitored carefully throughout the conduct of the trial.

The BPaMZ regimen is a novel regimen treatment expected to be effective, safe and well-tolerated and might even shorten the current treatment duration for patients with TB. Based on data from previous trial evaluations of key monitoring and safety information as outlined before suggests a favourable benefit-to-risk ratio trials.

Key Monitoring and Safety Information Regarding Regimen Agents

2.6.1 Bedaquiline (B)

2.6.1.1 Adverse Drug Reactions for bedaquiline

Participants in the Any bedaquiline group compared to the Any Placebo group (difference > 5.0%) had headache (23.5% versus 11.4%, respectively), nausea (35.3% versus 25.7%, respectively), arthralgia (29.4% versus 20.0%, respectively), and transaminases increased (6.9% versus 1.0%, respectively).and diarrhoea (11.4% versus 5.9%, respectively).

2.6.1.2 Cardiovascular safety

During clinical studies with bedaquiline a prolongation of QTc interval was observed. An ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.

Bedaquiline 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

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. If co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

In the DR-TB treatment arm of the present trial, moxifloxacin will be co-administered with bedaquiline. This is to prevent the development of resistance to the other drugs in the regimen in case the participant's strain of MTB is resistant to pyrazinamide. ECG assessments will be performed on all participants at screening, baseline, and at treatment visits specified in the flow chart.

2.6.1.3 Hepatic safety

Increases in transaminases were seen in clinical studies during administration of bedaquiline with the background regimen. Participants should be monitored during treatment.

Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in participants with diminished hepatic reserve.

2.6.2 Pretomanid (P)

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 diarrhoea)
- Skin and subcutaneous tissue disorders

2.6.2.1 Hepatic Safety

Hepatic enzyme increases have been seen in participants 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 NC-008 trial will include specific monitoring of hepatic enzymes.

For additional information refer to pretomanid IB.[15]

2.6.3 Moxifloxacin (M)

In the usual daily doses of 400 mg/day, moxifloxacin is well tolerated. As stated in the Package Insert[19] the most frequent individual drug related AEs observed in clinical trials with 400 mg oral moxifloxacin therapy were nausea (7.5%) and diarrhoea (5.8%). Fluoroquinolones, including moxifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages.

A known but rare side effect of fluoroquinolones, including moxifloxacin is exacerbation of myasthenia gravis. In addition, moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some participants. It should be used with caution in participants being treated concomitantly with other drugs where an additive effect on the QT interval cannot be excluded.

Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, as well as peripheral neuropathy may occur after the first or subsequent doses of moxifloxacin. For additional information, refer to the moxifloxacin package insert.[19]

2.6.4 Pyrazinamide (Z)

The dose of pyrazinamide that will be used in this trial is an approved dosage for the treatment of TB. The most serious side-effect of pyrazinamide is hepatotoxicity and its frequency appears to be dose-related. Hyperuricemia commonly occurs, occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side-effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria. Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert.[20]

2.6.5 HRZE/HR Control

The **HRZE** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets) combination will be given the first 8 weeks and the **HR** (isoniazid 75 mg plus rifampicin 150 mg combination tablets) combination will be given from Weeks 9 to 26.

Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE.

Please see the HRZE and HR Package Inserts[22, 40] for known and potential risks and benefits.

3.0 Trial Objectives

3.1 Primary Endpoint

To evaluate the time to culture negativity over 8 weeks from the start of the treatment regimens in participants with:

- Drug Sensitive TB (DS-TB)
- Drug Resistant TB (DR-TB)

DR-TB are defined as participants with:

1. *mono-resistance to rifampicin or isoniazid, OR*
2. *resistance to both rifampicin and isoniazid (DR-TB)*

3.2 Secondary Endpoints

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 52 weeks (12 months) and 104 weeks (or 24 months) weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
  - Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
  - Quantitative and qualitative ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones.
- Changes in lens opacities.

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [Cmin], maximum plasma concentration [Cmax], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of concomitant medications, including antiretroviral therapy (ART), where feasible.

Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

3.3 Exploratory Objectives

- Evaluate whether any of the secondary endpoints predicts relapse free cure.
- Subgroup analysis of populations by HIV status.

4.0 Trial Design

4.1 Summary of Trial Design

This is a Phase 2c, multi-centre, open-label, partially randomized clinical trial conducted in 3 treatment groups. Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment randomization and allocation during the treatment phase of the trial.

The trial will be performed globally at multiple centres located throughout the world.

A total of 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation, with a target of 50% of the participants being HIV positive. Up to 150 DR-TB participants will be enrolled and assigned to the treatment arm described in Table 4 below.

Refer to Section 3.0 Trial Objectives above and Section 9.3 Interim Analysis for details of the planned interim analysis and potential updates to the trial objectives and sample size.

Participants with Drug Sensitive TB (DS-TB):

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 Weeks, or HRZE/HR combination tablets daily for 26 Weeks. Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation.

Participants with Drug Resistant TB (DR-TB):

Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).

Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive.

DR participants will be treated with 6 months of BPaMZ. DS participants will be randomized using an interactive web response system (IWRS) stratifying for cavitation and HIV status to allocate participants evenly across the arms after they have given written, informed consent during the Screening Visit (Days -9 to -1).

4.2 Treatment Plan: Schedule of Assessments

- Screening Period (Day -9 to Day -1)
- Treatment Period (Day 1 to Week 17 / Week 26)
- Follow-Up Period (Week 39 to Week 104)

Refer to:

- Synopsis Flow Chart and Procedures (Section 1.2) for the timing of all procedures and laboratory samples to done at each visit.
- Trial Procedures (Section 7.0, Trial Variables and Procedures) for details regarding specific procedures or laboratory tests.

Each participant will receive up to 26 weeks of treatment. The trial IMP regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation unless an interruption/pause is required urgently for a safety concern.

All participants will enter post-treatment follow-up which continues until Week 104 after start of treatment / randomisation.

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

Table 4: Treatment Groups

	Treatment Group	Treatment Duration	No of Participants
1	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily	17 weeks (4 months)	150 DS-TB
2	**HRZE Tablets (Weeks 1-8):** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). Followed by **HR Tablets (Weeks 9-26):** (isoniazid 75 mg plus rifampicin 150 mg combination tablets).	First 8 weeks (2 months) then 17 weeks (4 months) Total 6 months	150 DS-TB
3	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily.	26 weeks (6 months)	Up to 150 DR-TB

5.0 Trial Population

The participant must meet all inclusion and no exclusion criteria within the screening period. Retesting for any laboratory or ECG parameters is allowed within the screening period. Sponsor may consider replacement of late exclusions. It is the intent of the protocol that the participants are hospitalized according to local practices and at the judgment of the treating physician / investigator.

5.1 Inclusion Criteria

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

1. Signed written consent prior to undertaking any trial-related procedures.
2. Male or female, aged 18 years or over.
3. Body weight (in light clothing and no shoes) ≥ 30 kg.

4. Sputum positive for tubercule bacilli (at least 1+ on the International Union Against Tuberculosis and Lung Disease [IUATLD]/WHO scale (Appendix 1) on smear microscopy) at the trial laboratory.
5. Disease Characteristics - Participants with one of the following pulmonary TB conditions:

   DS-TB treatment arm participants should be:

   a. sensitive to rifampicin, isoniazid and fluoroquinolones by rapid sputum-based test **AND**

   b. either newly diagnosed for TB or have a history of being untreated for at least 3 years after cure from a previous episode of TB.

   DR-TB treatment arm participants should be:

   a. Resistant to rifampicin and/or isoniazid; but sensitive to fluoroquinolones by rapid sputum-based test **AND**

   b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 3 days at start of screening.

   c. Participants with resistance to injectables by rapid sputum-based test are allowed in the trial.

   When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.

6. A chest x-ray, within 6 months prior to or during the Screening visit, which in the opinion of the Investigator is compatible with pulmonary TB.
7. Contraception:

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

   Non-childbearing potential:

   a. Participant - not heterosexually active or practice sexual abstinence; or

   b. Female participant or male participants female sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or

   c. Male participant or female participants male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening;

Effective birth control methods:

a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or

b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device.

c. Male participants' female sexual partner: Barrier method combined with hormone-based contraceptives or an intra-uterine device.

Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 6 months after the last dose of trial IMP or discontinuation from trial IMP 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 participants to prevent pregnancy.

5.2 Exclusion Criteria

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

Medical History and Concurrent Conditions:

1. Any non-TB related condition where participation in the trial, as judged by the Investigator, could compromise the well-being of the participant or prevent, limit or confound protocol specified assessments.
2. Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
3. Historical and or current use of local traditional medications/herbs which in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
4. Being, or about to be, treated for malaria.
5. Is critically ill and, in the judgment of the Investigator, has a diagnosis likely to result in death during the trial or the follow-up period.
6. TB meningitis or other forms of extrapulmonary tuberculosis with high risk of a poor outcome, or likely to require a longer course of therapy (such as TB of the bone or joint), as judged by the Investigator.
7. History of allergy or hypersensitivity to any of the trial IMP or related substances, including known allergy to any fluoroquinolone antibiotic, history of tendinopathy associated with quinolones or suspected hypersensitivity to any rifampicin antibiotics.
8. For HIV infected participants any of the following:

    a. CD4+ count <100 cells/µL
    b. Karnofsky score <60% (Appendix 5)
    c. Received intravenous antifungal medication within the last 90 days
    d. WHO Clinical Stage 4 HIV disease (Appendix 3)

9. Participants who recently started or expected to need to start ART within 1 month after randomization. Participants who have been on ARTs for more than 30 days prior to

start of the Screening visit or expected to start ART greater than 30 days after randomization may be included.

10. Having participated in other clinical trials with investigational agents within 8 weeks prior to start of trial medication or currently enrolled in an investigational trial.
11. Participants with any of the following at the Screening visit (per measurements and reading done by ECG):

    a. QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with the Sponsor Medical Monitor before enrolment.
    b. Heart failure
    c. A personal or family history of congenital QT prolongation
    d. A history of or known, untreated, ongoing hypothyroidism
    e. A history of or ongoing bradyarrhythmia
    f. A history of Torsade de Pointe

12. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening.
13. Females who have a positive pregnancy test at the Screening visit or already known to be pregnant, breast-feeding, or planning to conceive a child during the trial or within 6 months of stopping treatment. Males planning to conceive a child during the trial or within 6 months of stopping treatment.
14. Participants with lactose intolerance, lactase deficiency and/or glucose-galactose malabsorption.

<u>Previous and Concomitant Therapy</u>

15. Previous treatment for TB which includes:

    - <u>For DS-TB participants</u>: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days at the start of the Screening visit.
    - For the DR-TB participants: Previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 3 days at the start of the Screening visit.

16. Any diseases or conditions in which the use of the standard TB drugs or any of their components is contra-indicated, including but not limited to drug allergy.
17. Use of any drug within 30 days prior to randomisation known to prolong QTc interval (including, but not limited to, amiodarone, amitriptyline, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinacrine, quinidine, sotalol, sparfloxacin, thioridazine).
18. Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), as they can lead to visual opacities or cataracts.
19. For HIV infected participants:

    a. The following antiretroviral therapy (ART) should not be used with either (BPaMZ and HRZE/HR) trial regimen:

1. Stavudine
2. Didanosine
3. Triple NRTI regimen is not considered optimal for HIV treatment (poor efficacy)

b. In the case where participants are randomised to HRZE arm, rilpivirine and etravirine cannot be given with rifampicin due to drug-drug interactions. A standard NRTI backbone may be used in combination with one of the following:

1. Efavirenz requires no dose adjustment
2. Dolutegravir dose adjustment is required – double dose when co-prescribed with rifampicin.
3. Raltegravir requires no dose adjustment
4. Lopinavir/r dose adjustment is required – double dose when co-prescribed with rifampicin
5. Nevirapine requires no dose adjustment, however please note that nevirapine based regimens are associated with higher ART failure in participants having or known to have a previous viral load more than or equal to 100,000/ mL

c. In the case where participants are randomized to the BPaMZ trial regimen, a standard NRTI backbone may be combined with the following:

1. Rilpivirine
2. Dolutegravir
3. Raltegravir
4. Nevirapine
5. Lopinavir/r
6. Participants who are on efavirenz, atazanavir/r or darunavir/r at the time of screening and have an undetectable viral load, should have their ART switched to one of the agents listed above (1-5). It would be preferable to switch to another permissible ARV within the same class accompanied by the same nucleoside backbone.

d. ART regimen choice should be discussed with the Sponsor Medical Monitors if there are any concerns.

Confirmed plans to use Isoniazid prophylaxis for HIV positive participants during the treatment and follow up period is not permitted.

Diagnostic and Laboratory Abnormalities

20. Participants with the following toxicities at screening as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (Draft November 2007) (Appendix 2) where applicable:

a. platelets <75,000/mm^3
b. creatinine 1.5 times upper limit of normal [ULN])
c. eGFR ≤ 60 mL/min/
d. haemoglobin <8.0 g/dL

e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once
f. GGT: greater than 3 x ULN
g. AST:
   - ≥3.0 x ULN to be excluded;
   - results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor
h. ALT:
   - ≥3.0 x ULN to be excluded
   - greater than ULN must be discussed with and approved by the Sponsor Medical Monitor
i. ALP:
   - ≥3.0 x ULN to be excluded
   - 2.0 – <3.0 x ULN must be discussed with and approved by the Sponsor Medical Monitor
j. Total bilirubin:
   - >1.5 x ULN to be excluded;
   - Greater than 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor
k. Direct bilirubin:
   - greater than 1x ULN to be excluded

All the inclusion and none of the exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the Investigator has reason to suspect that there might be a health problem (other than TB), enrolment should only be considered after discussing the case with the Sponsor Medical monitor.

No protocol waivers will be granted by the TB Alliance.

5.3 Restrictions

Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are necessary for the participant's welfare, 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 reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected to prevent any potentially serious and/or life-threatening drug interactions.

The following recommendations should be followed with regards to concomitant medication to avoid possible drug interaction with the IMP:

Participants on a **moxifloxacin** containing treatment arm: The IMP should be taken either 4 hours before or 8 hours after taking the following products:

- An antacid, multivitamin, or other product that has magnesium, aluminium, iron or zinc

- Sucralfate
- Didanosine

Participants on the **HRZE/HR** treatment arm:

- Any aluminium-containing antacids should be taken at least one hour after the IMP dose.

The following medicinal products are prohibited from the Screening visit and during the treatment period:

- Quinolone antimalarial (e.g., chloroquine and quinacrine). Participants who have malaria at screening are to be excluded. However, if a participant develops malaria during the trial, the Investigator is advised to consult the Malaria Treatment Guidance document regarding the interaction between moxifloxacin and bedaquiline with anti-malarial drugs. Investigators may also contact the Sponsor Medical Monitor for further guidance.
- Chronic systemic glucocorticoids (topical, inhaled or intranasal glucocorticoids are allowed) due to their potential to cause visual opacities. Short term systemic glucocorticoids are allowed for emergency situations (e.g. for treatment of pulmonary exacerbation when inhaled glucocorticoids is inadequate).
- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, other quinolones, thioamides, and metronidazole.

The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible (unless this is required for emergency management of the participant). Investigators may also contact the Sponsor Medical Monitor for further guidance.

- Any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). The exception is moxifloxacin and bedaquiline administered as part of the trial IMP, with ECG monitoring, to help ensure participant safety.
- Any drug known to be hepatotoxic (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, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin,

terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).

5.4 Treatment Discontinuation and/or Early Withdrawal

Any participant for whom the Investigator decides to temporarily discontinue their IMP is to be discussed with the Sponsor Medical Monitor and, if applicable, be restarted on IMP as soon as possible.

A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following:

- Withdrawal of informed consent
- Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment
- Pregnancy
- At the specific request of the Sponsor or termination of the trial by the Sponsor
- Lost to follow-up
- When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.

A participant may withdraw from the trial at any time at his/her request (withdrawal of consent), or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative issues.

When a participant withdraws consent from the trial, no additional follow-up visits will be performed.

Participants who withdraw from the trial after having received IMP will not be replaced.

All participants withdrawn from trial and who received at least one dose of IMP will be requested to return for an Early Withdrawal visit and the applicable safety Follow-Up visits, as per the Synopsis Flow Chart and Procedures (Section 1.2 footnote c), as well as Table 5.

5.4.1 Early Withdrawal

In case of early withdrawal during the treatment or follow-up period, 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:

- Sputum sample collection x 2 (one EMS brought from home and one spot at the research site under the coaching and observation of the trial staff). If no EMS was provided by the participant, 2 spot samples may be collected at the site, at least 30 minutes apart.
- Urine pregnancy test (women of child bearing potential, whether they are sexually active or not)
- Laboratory safety sampling (including male reproductive hormone tests);
- Single 12-lead ECG

- TB Symptoms Profile
- Patient Reported Health Status Questionnaire
- Vital signs
- Full physical examination, including weight
- Ophthalmology examination, if required as described in Table 5
- IMP compliance check (if participant on IMP)
- Concomitant medications
- Adverse events

Once a participant has been withdrawn early from the trial, they will be requested to attend follow-up visits as described in Table 5:

Table 5: Follow-up Visits Required for Early Withdrawal Participants

Treatment Duration at EWD visit	**Ophthalmology Examination at EWD[a]**	**Ophthalmology Examination** **Visit 3 months after EWD Visit[a]**	**Week 52** (Month12) **Follow-up Visit**	**Week 104** (Month 24) **Follow-up Visit**
≤ 14 days	Not required	Not required	Required	Required
15 days to ≤ 12 weeks	Not required	Required	Required	Required
> 12 weeks	Required	Required	Required, if not already performed	Required

a. If an additional visit is required for an ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 3 months after the EWD visit date.

The Weeks 52 and 104 visits will be performed to collect SAE information (including verification of survival) and participant reported TB outcome information. This visit may be telephonic, a home or a site visit at Weeks 52 and/or Week 104 after the participants' start of treatment date.

5.4.2 Unscheduled Visits

Any visit which is conducted in addition to those required by the Synopsis Flow Chart and Procedures (Section 1.2), should be considered unscheduled regardless of the reason for the visit. The assessments which are undertaken as part of an Unscheduled visit should be as clinically indicated.

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

- For any medical reason, as determined by the investigator or participant.
- If both sputum samples (EMS and spot) at Week 8 or later are contaminated, the participant should return for an unscheduled visit/s to give additional sputum samples or to document that the participant is not able to produce sputum.
- If after having converted to culture negative, the participant has a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 or Week 26), the participant should return for an unscheduled visit/s to provide additional sputum samples, at a minimum of 7 days apart, or to document that the participant is not able to produce sputum sample.

Determination of the participant's primary outcome status requires sputum culture results at the following time-points during the trial:

- End of Follow-up Period (Week 52 and 104)
- Early Withdrawal, if applicable

At least one of the following criteria should be met at these time-points to confirm a participant's primary outcome status:

- 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 the participant is clinically asymptomatic

Should the participant's primary outcome not meet any of the above criteria, the Investigator should continue to recall the participant for a Unscheduled visit to collect sputum samples until the criteria is met and the primary outcome can be determined.

Additional sputum samples: Two samples at each visit – ideally, one EMS and one spot sputum at the research site under the coaching and observation of the trial staff. If no EMS was provided by the participant, 2 spot sputum samples may be collected on site, at least 30 minutes apart. Additional sputum samples should be collected at least 7 days after the previous sample.

Table 6: Summary of Scenarios Requiring Unscheduled Visits for Mycobacteriology Testing

Time-point	Scenario	Unscheduled Visit/s Required?	Comment
Week 8 or later	Both sputum cultures are contaminated	Yes	Provide additional samples until a positive or negative result is reported, or it is confirmed that the participant is unable to produce sputum
At or after the last treatment visit (Week 17 or Week 26)	Previously converted to culture negative but now has an MTB-positive culture	Yes	Provide additional samples at least 7 days after the previous sample until the result is confirmed, or it is confirmed that the participant is unable to produce sputum.

End of Follow-up Period (Week 52 and 104) Early Withdrawal, if applicable	Participant's primary outcome status cannot be confirmed by: 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	Yes	Provide additional samples at least 7 days after the previous sample until one of the criteria is met and the primary outcome status can be determined.

If the Investigator is unsure of the outcome in any of the above scenarios the Investigator should contact the Sponsor Medical Monitor to discuss and agree on how the participant is to be managed.

5.4.3 Lost-to-Follow-up

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

5.4.4 Early Withdrawal due to TB

Ultimately it is the Investigator's decision whether a participant requires early withdrawal from the trial due to a concern that the participant has symptomatic worsening of TB and/or bacteriological failure/relapse.

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

If the Investigator decides to withdraw a participant due to TB, additional sputum samples may need to be collected to ensure the participant's outcome status as determined in Section 5.5.

All early withdrawn participants who are confirmed sputum positive (two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These participants will be referred to their applicable DS/DR local community TB clinics for standard anti-tuberculosis chemotherapy according to National TB Treatment Guidelines.

The participants will be provided with a referral letter from the Investigator to take with them to their National Treatment Program (NTP) clinic and the referral letter, at a minimum, should include all treatment received by the participant and information about any suspected/confirmed adverse event/reaction related to any of the trial IMP's and or concomitant medications. A follow-up call should be made by the trial site staff to the clinic to ensure the participant attended the NTP clinic.

5.5 Participant Progress Definitions

Table 7: Participant Progress Definitions

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

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

** Early Withdrawal

5.6 Trial Stopping Rules

There are no trial specific stopping rules.

The trial or parts of the trial can be stopped by the Sponsor on advice from the Data Safety and Monitoring Committee (DSMC) after their review of applicable trial data. In addition, the Sponsor has the right to stop the trial or a specific trial site at any time, although this should only occur after consultation between the involved parties. Should this occur, the local and central Ethics Committee/Institutional Review Board (EC/IRB) and Regulatory Authorities will be informed.

Should a trial site be closed prematurely, all trial materials (except source documentation that must remain at the site) will be returned to the Sponsor or applicable vendor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Participants currently on trial IMP will receive an appropriate regimen and all participants will be referred to their applicable DS-TB/DR-TB NTP clinic.

6.0 Treatment

6.1 IMP Administration

6.1.1 Instructions for Dosing of Test Regimen (BPaMZ):

- Treatment will be orally administered once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months).

6.1.2 Instructions for Dosing Control Treatment Regimen (HRZE/HR):

- To be taken with a glass of water (approximately 240 ml).
- HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes.

HRZE/HR treatment will be administered orally once daily to DS-TB participants as follows:

Weight Band	Weight Range	Number of tablets per weight band
1	30-39 kg	2
2	40-54 kg	3
3	55-70 kg	4
4	≥ 71 kg	5

The participant's weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and dose to administer.

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

6.2 Participant Compliance

During site clinic visits, the IMP will be administered by the Investigator(s)/designated site personnel and when possible, the check for IMP compliance via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the participant has swallowed the IMP). During the trial, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how the IMP is to be taken, as well as to check the IMP cards for unused tablets in the containers at each visit during the treatment phase.

6.3 Treatment Modification(s)

The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the Investigator to identify and address the cause(s) (e.g. side effects).

Participants that do not take:

- Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required.
- If more than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been.
- If more than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial.
- If the participant misses a total (sum) of 56 cumulative missed doses, discontinue the IMP and withdraw the participant from the trial.
- If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose that was missed.

Any participant for whom the trial IMP is discontinued (including for non-adherence) will be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial IMP as soon as possible.

6.4 IMP Packaging and Labelling

The complete formulations of the IMP, bedaquiline and pretomanid, are found in the respective Investigator Brochures.[8, 15] The complete formulations of moxifloxacin, pyrazinamide, HRZE/HR are found in the Package Inserts.[19, 20, 22, 40]

The IMP will be packaged in weekly or bi-weekly cards as follows:

Week 1 to 8 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	14	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Week 9 to 17/26 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	7	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Control (HRZE/HR) Group: Dispensed *Bi-weekly*			
Weight Band	**Weight Range**	**Number of tablets per weight band**	**Number of tablets in each card**
1	30-39 kg	2	28
2	40-54 kg	3	42
3	55-70 kg	4	56
4	≥71 kg	5	70

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

The packaging of each weekly and biweekly cards will be labelled with, at a minimum, the following information:

- Name of Sponsor
- Name of medication
- Dosage, quantity and method of administration
- Reference/lot number
- The statement “For Clinical Trial Use Only”
- Space for completion of name of Investigator and site number
- MedID: medication identification number
- Storage conditions
- Period of use
- The statement “Keep out of reach of children”
- Expiry date
- Directions for use
- Space for completion of participant number and visit/date dispensed

6.5 Blinding and Procedures for Breaking the Blind

As this is an open label trial there is no need for blinding or procedures to break the blind. The trial participants, the site staff, Sponsor, and CROs will not be blinded to treatment assignment.

6.6 Handling, Storage and Accountability

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

Only participants randomised in the trial may receive trial IMP and only authorized site staff may supply or administer trial IMP. All trial IMP’s must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

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

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

Further guidance and information for the handling, storage, accountability and final disposition of unused trial IMPs are provided in the Pharmacy Manual.

7.0 Trial Variables and Procedures

The Synopsis Flowchart and Procedures in (Section 1.2) should be referenced for timing, sequence of assessments, and specific procedures.

7.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected:

- Written Informed Consent
- Visit dates
- Participant disposition
- Demography (date of birth, race and gender)
- Inclusion and exclusion criteria
- Clinically significant medical and TB treatment history (including past and current TB diagnosis, smoking and alcohol use)
- Screening coached spot sputum samples:
    - Smear microscopy for acid-fast bacilli
    - Rapid molecular tests for isoniazid, rifampicin, fluoroquinolones resistance (Hain MTBDRplus and HainMTBRsl)
    - Liquid Culture (MGIT) for Mycobacterium tuberculosis (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive.
- Urine pregnancy test: women of childbearing potential only, whether they are sexually active or not (non-childbearing potential for a female participant is defined as having bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months).
- Serology: HIV and CD4 count. Where required by regulatory authorities or ethics committees, a separate (EC/IRB approved) HIV informed consent form will be obtained from participants:
    - Prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the participant, HIV counselling that is provided to the participant by the trial site should be clearly documented in the participant's medical records/source. Participants have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the participant's medical records/source.
- Karnofsky Score (Appendix 5). Only for HIV positive participants.
- Chest X-Ray: A chest X-ray digital image within 6 months prior to or during the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor; this process will be documented in the Chest X-Ray / Radiology Manual. The investigator is responsible for review and analysis of the chest X-ray for participant's inclusion.
- Method of birth control: male and female participants and their sexual partners
- IMP details: randomization
- IMP compliance and actual dosing
- Concomitant medications

7.2 Efficacy Variables and Procedures

Two spot sputum samples are collected, one EMS brought from home or collected in the hospital ward (only if the participant is hospitalised) and one spot sputum sample collected at

the research site under the coaching and observation of the trial staff or, if no EMS sample was provided by the participant, 2 samples may be collected on site at least 30 minutes apart. The mycobacteriology sampling methodology and requirements will be described in a separate document, the Mycobacteriology Laboratory Manual, which will be provided prior to the trial start. Sputum samples may not be obtained by induction.

The following analyses will be performed:

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

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

- Bacteriologic failure/relapse
- Time to sputum culture conversion
- Number of participants with sputum culture conversion

Every effort must 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 participant who never achieves culture negative status due to the inability to produce sputum, but has completed Week 17 or Week 26 and post treatment completion follow-up (Weeks 39 to 104) and is without clinical or biological evidence of relapse, will be considered to have a favourable outcome.

TB Symptoms Profile:

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

Patient Reported Health Status Variables and Procedures:

- The Patient Reported Health Status variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2). Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire (Appendix 7). 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 trial Participant Questionnaires Guideline which will be provided prior to the trial start.

7.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2) and assessed for evaluation of the safety endpoints:

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

  - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, ALP, AST, ALT, lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO_2, creatine phosphokinase (CPK). GGT is only routinely included at the Screening visit (Day -9 to -1).
  - When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].
  - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator
- 12-lead ECG:
  - Investigator assessment: normal or abnormal
  - Central cardiologist assessment: heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.
  - Methodology:
    - Timing (Synopsis Flow Chart and Procedures, Section 1.2) and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start
    - ECGs are to be recorded for 10 seconds
    - ECGs are to be performed during a single visit
    - ECGs should be done before any phlebotomy when both included in a visit
    - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch)

- ECGs to be performed prior to pre- and post-dose PK sampling as described below:
  - Day 1: pre-dose (within 2 hours prior to dosing)
  - Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
  - Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
  - Week 12: pre-dose (within 2 hours prior to dosing)
  - Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose

- Vital signs:
  - Vital signs (should be done before any phlebotomy in light clothing and with no shoes)
  - Systolic and diastolic blood pressure (mmHg) to be measured in a supine position (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 (beats per minute)
  - Respiratory rate (breaths per minute)
  - Axillary body temperature (°C)
- Physical Examination:
  - Height (m) is measured at the screening visit only
  - Full (complete) and limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded
  - Weight (kg) (in light clothing and with no shoes)

  - Using the variables of weight and height, the body mass index (BMI) will be calculated
- Ophthalmology Slit Lamp Examination:
  - To be done by an Ophthalmologist trained on Age-Related Eye Disease Scale 2 (AREDS2) assessment. The ophthalmology slit lamp methodology and requirements will be described in a separate document, the Ophthalmology Guideline. The following analyses will be performed: AREDS2 opacity typing and grading.
- Adverse events
- Investigator assessment:
  - The Investigator will review the participant status at specified visits in the Synopsis Flow Chart and Procedures (Section 1.2), including any time the Investigator determines that the participant fulfils the criteria for the primary outcome of treatment failure. The Investigator will assess whether TB treatment is considered a "success" or "failure". If it is considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration.

7.4 PK Variables and Procedures

Plasma concentrations from sparse sampling (Synopsis Flow Chart and Procedures, Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin and pyrazinamide to further evaluate the effects of covariates on model parameters in this trial population.

PK data from the current trial may be combined with prior data to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{min}, C_{max}, AUC_{τ}, C_{mean}, and time above minimum inhibitory concentration) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.

7.5 Mycobacteriology Characterization Variable and Procedures

- Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative);
- MTB confirmed positive cultures (after the participant has previously converted to negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.
- Refer to the Mycobacteriology Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for:

- Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);
- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid and moxifloxacin
- Drug Susceptibility Testing for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing (WGS), and the comparison of sequences from baseline and relapse isolates.

If the participant's culture converts to negative and has a MTB positive culture at or after the last visit of the treatment period (Week 17 and Week 26), the MTB cultures will be tested at the trial mycobacteriology laboratories using Hain MTBDR*plus* and HainMTBR*sl* to detect resistance to isoniazid, rifampicin, fluoroquinolones and injectables.

All MTB isolates must be stored be stored at the local mycobacteriology laboratories, until trial closure. In addition, MTB isolates as well as extracted MTB DNA from the applicable baseline and follow-up cultures will be stored at the central mycobacteriology laboratory for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure.

8.0 Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

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

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

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

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or

hospitalisation but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse. A "suspected transmission of infectious agent by a medicinal product" is also considered a serious adverse event under the SAE criterion "Other medically important condition".

8.1.3 Attribution/Causality

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

Table 8: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An AE, which is not related to the use of the drug.
Unlikely	An AE 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 AE, 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 AE, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by de-challenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An AE, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

8.1.4 Severity

Table 9: Definitions for Adverse Event Severity Gradings

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

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

8.2 Reporting

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

All AEs will be collected by the Investigator from the time a participant signs the Informed Consent Form through to their Week 104 follow-up visit. The exception to this is early withdrawal participants who will only have SAEs collected from their time of early withdrawal to their Week 104 follow-up visit at the timepoints specified in the Synopsis Flow Chart and Procedures (Section 1.2) and recorded in the CRF.

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

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

The Sponsor/Investigator/designee will inform Regulatory Authorities and/or EC/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 EC/IRB.

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

reasonably related to the trial IMP or trial participation, the Investigator must promptly notify the Sponsor, EC/IRB and regulatory authorities in an expedited basis, in accordance with local requirements and ICH GCP Guidelines.

8.2.1 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- The end of the follow-up period; and
- 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 Investigator. However, this will have to be agreed upon with the Sponsor Medical Monitor.

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

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

New or updated SAE information will be recorded in the originally completed CRF and submitted to the Sponsor within 24 hours of receipt, per the eCRF completion guidelines.

8.2.2 Clinical Laboratory Adverse Events

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

8.2.3 Disease Symptoms During Trial

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

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

it will be recorded as an adverse event. If there is:

- no change; and
- the Investigator assesses the symptom as due to the participant's TB; and

- not clinically significant;

it will not be recorded as an AE and this will be noted in the participant's source documentation. All TB related symptoms that meet SAE criteria will be recorded and reported as a SAE.

8.2.4 Overdose

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

8.2.5 Drug Interaction

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

8.2.6 Pregnancy

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

If a pregnancy is suspected while the participant is receiving IMP, the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner and the participant withdrawn from the trial and referred to the NTP for further management.

Protocol-required procedures for trial discontinuation and follow-up will be performed unless contraindicated by the pregnancy.

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

8.3 Monitoring for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in the preclinical toxicity studies of the Investigator's Brochures[8, 15] and Package Inserts.[19, 20, 22, 40]

AEs still ongoing at the end of the treatment period in the trial will be followed until satisfactory clinical resolution or stabilization, or until the end of the follow-up period and until all queries on these AEs have been resolved.

Grade 3 and Grade 4 laboratory abnormalities, and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.

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

8.3.1 ALT, AST and Bilirubin Elevations

The Investigator should refer to the Hepatotoxicity Management Guideline, to appropriately monitor significant elevations of AST, ALT or Bilirubin. A separate Hepatoxicity Management Guideline document has been developed to aid investigators in the management of participants.

When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

8.3.2 Lipase

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

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

8.3.3 Musculoskeletal System and Cardiac Muscle Myalgia

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

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

8.3.4 Cardiac Rhythm Disturbances

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

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

<u>QTc prolongation</u>

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

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

8.4 Safety Monitoring by Data Monitoring Committee

A Data Safety Monitoring Committee (DSMC) will be appointed for the trial. The primary responsibility of the DSMC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial participants by monitoring participant safety, assess participant risk versus benefit, and assess data quality and general evaluation of the trial progress. Its activities will be delineated in a DSMC Charter that will define the membership, responsibilities and the scope and frequency of data reviews.

The DSMC will operate on a conflict-free basis independently of the Sponsor and the trial team. It will comprise at least 3 voting members that include at least 2 clinicians and one statistician.

The DSMC may have an organizational meeting prior to commencement of the trial. The DSMC will have meetings where it will review unblinded data during a closed session. These meetings will be planned at regular intervals.

The Sponsor or the DSMC may convene ad hoc meetings based on rates of SAEs and/or to review results of the futility analysis, or if safety concerns arise during the trial. After its assessment, the DSMC will recommend to the Sponsor continuation, modification or termination of the clinical trial.

9.0 Statistical Analysis

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

There will be 3 data analyses and trial reports generated for this trial:

1. When all participants have completed 8 weeks (2 months) of treatment from baseline.
2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy.
3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.

9.1 Analysis Populations

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

- The ITT population is defined as all randomized participants excluding late screening failures. Late screening failures are participants withdrawn from treatment because they were found to be ineligible (late exclusions from the trial), based on data collected *prior to randomization*.

- The mITT population is defined as the ITT population with extra exclusions (described in the SAP).
- The PP population is defined as the mITT population with extra exclusions (described in the SAP).
- The mITT analysis will be considered primary, with consistent findings required from the other main analysis populations to support the primary conclusion.

9.2 Sample Size

For the primary endpoint, time-to-culture conversion at 8 weeks,150 participants per arm (DS-TB participants) will provide at more than 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 90% power to detect a HR of least 2. This sample size also allows for one planned interim analysis of the primary endpoint (See Section 9.4.1)

For the key secondary endpoint of clinical outcome at 12 months from randomization, 150 patients per arm will provide 74% power based on assumptions using data from the largest most recent and completed phase 3 TB treatment trial which used the same control arm.[41] That is, assuming 16% unfavourable (see Section 9.4.2) in the control arm and 13% unassessable (see Section 9.6) at 52 weeks post randomization. A 12% margin of non-inferiority was chosen to preserve at least 75% of the estimated control arm effect against placebo (estimated to be 54%)[41, 42] which is considered an acceptable proportion on which to declare non-inferiority of the test regimen.

9.3 Interim Analyses

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

  *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objectives**

  *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised

arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46,47,48] and full details are provided in the Statistical Analysis Plan.

9.4 Primary and Secondary Efficacy Endpoint Analysis

9.4.1 Primary Efficacy Endpoint, Time to Culture Conversion at 8 Weeks

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

Participants will be classified as being culture positive, culture negative, dead or unassessable at 8 weeks. The proportion culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis and groups compared using a hazard ratio and 95% confidence interval.

Non-inferiority of the key secondary endpoint of clinical outcome will be assessed using the upper bound of the one-sided 97.5% confidence interval for the difference between the proportion of participants who are classified as having an unfavourable status on the intervention less the control regimen. If the upper bound of the one-sided 97.5% confidence limit for this difference in proportions is less than 12% (the margin of inferiority) the intervention will be non-inferior to the control arm.

9.4.2 Key Secondary Efficacy Endpoint, Clinical Outcome at 52 Weeks from Randomization

For the key secondary endpoint of clinical outcome (bacteriologic failure or relapse or clinical failure), participants will be classified as having a favourable, unfavourable or unassessable outcome status which will be defined in detail in the SAP. In general, participants achieving and maintaining culture negative status without any additional treatment will be considered favourable; participants who fail on treatment or relapse in follow-up will be considered unfavourable and participants who are not assessable (and who have not already been declared as unfavourable) will be considered unassessable and excluded from the analysis.

9.4.3 Other Secondary Efficacy Endpoints

The secondary efficacy endpoints and analyses are as follows are:

- Clinical outcome (bacteriologic failure or relapse or clinical failure) at 104 weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight will be summarised and presented.
- Proportion of participants experiencing a change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status will be summarised and presented.

9.5 Safety and Tolerability Assessments

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.

9.6 Pharmacokinetics

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

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

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., C_{min}, C_{max}, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so, too, will the effects of concomitant medications including ART, as feasible. Data from other trials may be included to enhance the model-based analysis.

Detailed plans for the PopPK analysis will be outlined in a separate modelling plan, and results will be reported in separate modelling report.

9.7 Pharmacokinetics/Pharmacodynamics

Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate. Planning details and results will be included in the separate modelling plan and report.

10.0 Records Management

10.1 Data Collection

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

10.2 Source Documents

Source documents are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary

for the reconstruction and evaluation of the trial. Source documents will include, but are not limited to, progress notes, in-patient hospital records, electronic data, screening logs, and recorded data from automated instruments.

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

10.3 File Management at the Trial Centre

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

10.4 Records Retention at the Trial Centre

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

11.0 Quality Control and Assurance

11.1 Site Procedures

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

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

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

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

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

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

11.2 Monitoring

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

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

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

11.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol and GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the trial site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly.

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

11.4 Auditing

For 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 about accuracy, adequacy and consistency, and to assure that trials are in accordance with the guidelines. Having the highest quality data from trials is an essential aspect of drug development.

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The

auditors or inspectors may also review site SOPs, training records, site facilities and other trial related systems/processes.

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

12.0 Ethics and Regulatory

12.1 Basic Principles

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

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

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

12.3 Regulatory Authorities

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

12.4 Informed Consent

Written informed consent will be obtained from all participants (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment procedures) are performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for 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 part of the research.

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

the international GCP and must adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The trial will be included and updated in the appropriate Country registry and referenced in the informed consent forms (ICF).

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

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

The monitor will inspect the original completed ICFs for all participants.

12.5 Confidentiality

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

13.0 Publication Policy

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

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

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory Investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors.[43]

Because the trial is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the Trial must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy . Specifically, (a) all peer-reviewed published research relating to the trial must be submitted for publication by TB Alliance through the Chronos Open Access Publishing Service established

by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy.

14.0 Protocol Amendment Policy

Any change to the protocol will be affected by means of a protocol amendment. Any changes which affect participant safety or welfare will be submitted to the EC/IRB and Regulatory Authorities prior to implementation. The Investigator, EC/IRB, and Sponsor must agree on all amendments. No amendment will be implemented until approved by the relevant authorities and/or EC/IRB and signed by all required parties. Exceptions to this are when the Investigator considers that the participant's safety is compromised.

Protocol amendments detailing minor administrative changes should be submitted by the Investigator to the EC/IRB and Regulatory Authorities, either for notification purposes or approval as appropriate.

15.0 Sponsor, Financial Aspects, Insurance and Indemnity

The trial Sponsor is the TB Alliance (TBA). The TB Alliance is a not for profit, product development partnership accelerating the discovery and development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies for those HIV-TB participants currently on such therapies and improve treatment of latent infection.

The TB Alliance works with public and private partners worldwide. It is committed to ensuring that approved new regimens are affordable, adopted and available to those who need them.

The TB Alliance operates with funding mainly from the Bill & Melinda Gates Foundation, the Netherlands Ministry of Foreign Affairs (DGIS), the United Kingdom Department for International Development (DFID), and the United States Agency for International Development (USAID).

The participants will not receive any incentives for their involvement in the trial. The Sponsor has made provision to reimburse the participants for out-of-pocket expenses such as travelling to and from the trial site and other miscellaneous costs as a result of their trial participation.

The Sponsor certifies that it has liability insurance coverage for itself and will provide an associated certificate upon request. The insurance does not relieve the Investigators of the obligation to maintain their own liability insurance as required by applicable law. The Sponsor does not assume any obligation for the medical treatment of other injuries and illnesses.

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Appendices

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	scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

Reference: The Public Health Service National Tuberculosis Reference Laboratory and the National Laboratory Network. Minimum Requirements, Role and Operation in a Low-Income Country. International Union Against Tuberculosis and Lung Disease 1998.

Appendix 2: Division of Microbiology and Infectious Disease (DMID) Toxicity Table

Source: U.S. National Institute of Allergy and Infectious Diseases, DMID, November 2007 (Draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of Acquired Immune Deficiency Syndrome (AIDS), NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the DMID and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 /mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures

Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day

Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent ; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatienttreatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient - no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

GASTROINTESTINAL

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	Subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia

Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint 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: Who Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection
Asymptomatic Acute retroviral syndrome
Clinical Stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical Stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections
Clinical Stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for >1 month Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) Persistent oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anemia (hemoglobin <8 g/dL) Neutropenia (neutrophils <500 cells/µL) Chronic thrombocytopenia (platelets <50,000 cells/µL)
Clinical Stage 4
HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Cryptococcosis, extrapulmonary (including meningitis) Disseminated nontuberculosis mycobacteria infection Progressive multifocal leukoencephalopathy Candida of the trachea, bronchi, or lungs Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis) Recurrent nontyphoidal Salmonella bacteremia Lymphoma (cerebral or B-cell non-Hodgkin) Invasive cervical carcinoma

Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy
Symptomatic HIV-associated cardiomyopathy
Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

REF: World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children; 2007*

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: Cardiovascular Safety

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

All-important abnormalities from the ECG readings will be reported.

The percentage of participants with increases in QTc of <30, 30-60, or > 60 ms from baseline will also be tabulated at each time point.

Abnormality Code	ECG parameter			
	HR	PR	QRS	QTcorrected
Abnormalities on actual values				
“Abnormally low”	≤ 50 bpm	NAP	≤ 50 ms	-
“Abnormally high”	≥ 120 bpm	≥ 210 ms	≥ 120 ms	-
“]450 ms, 480 ms]	-	-	-	450 ms < QTc ≤ 480 ms
“]480 ms, 500 ms]	-	-	-	480 ms < QTc ≤ 500 ms
“More than 500 ms	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline				
“[30; 60] ms”	-	-	-	[30; 60] ms
“> 60 ms”	-	-	-	> 60 ms

Appendix 5: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Description		%
Able to carry on normal activity and to work; no special care needed.	Normal no complaints; no evidence of disease.	100
	Able to carry on normal activity; minor signs or symptoms of disease.	90
	Normal activity with effort; some signs or symptoms of disease.	80
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	Cares for self; unable to carry on normal activity or to do active work.	70
	Requires occasional assistance, but is able to care for most of his personal needs.	60
	Requires considerable assistance and frequent medical care.	50
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	Disabled; requires special care and assistance.	40
	Severely disabled; hospital admission is indicated although death not imminent.	30
	Very sick; hospital admission necessary; active supportive treatment necessary.	20
	Moribund; fatal processes progressing rapidly.	10
	Dead	0

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109.

TB ALLIANCE

Protocol Amendment or Administrative Change

Lead Trial Number	Trial Name
NC-008	SimpliciTB

x Protocol Russia Amendment Number 1, Dated 25/JAN/2019, Incorporating Protocol V3.0/14January2019
☐ Protocol Administrative Change Number _ _, Dated _ _/_ _ _/_ _ _ _

Summary - Protocol section changed		Does amendment / administrative change affect any of the elements listed?	
		YES	NO
A	Purpose of trial	☐	x
B	Design of trial	☐	x
C	Informed consent	x	☐
D	Recruitment procedure	☐	x
E	Measures of efficacy	☐	x
F	Schedule of samples	☐	x
G	Addition or deletion of tests or measures	x	☐
H	Number of participants	x	☐
I	Age range of participants	☐	x
J	Inclusion criteria	x	☐
K	Exclusion criteria	x	☐
L	Safety monitoring	x	☐
M	Duration of exposure to the investigational medicinal product(s)	☐	x
N	Change of posology of the investigational medicinal product(s)	☐	x
O	Change of comparator	☐	x
P	Statistical analysis	x	☐

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Protocol Amendment or Administrative Change

TB ALLIANCE

Reasons for Protocol Amendment or Administrative Change:

1	**Change:** All references to The Global Alliance for TB Drug Development have been changed to TB Alliance (TBA). The correct and current TBA logo has been placed into the header of the protocol, on the cover page.
2	**Delete:** Lead Investigator signature filed, as there has not been in the past and won't be in the future, a SimpliciTB Lead Investigator. This is to prevent unnecessary RA and EC queries, as experienced with the review and approval cycles of the prior Protocol Versions 1.0 and 2.0.
3	**Add:** Abbreviations and Definition of Terms - DST, Drug Susceptibility Testing
4	**Add:** Abbreviations and Definition of Terms - HR, Hazard Ratio
5	**Change:** Abbreviations and Definition of Terms - LTFU, previously described as Long-Term Follow-up, changed to Lost to Follow-up in the section
6	**Add**: Abbreviations and Definition of Terms - WGS, Whole Genome Sequencing.
7	**Delete:** 1.1 Synopsis Summary, Section Trial Objective(s) - description and treatment duration from the as it is not applicable to this section.
8	**Add:** 1.1 Synopsis Summary, Statistical Methods – description of abbreviated definitions from the SAP to provide further clarity
9	**Clarify:** 1.1 Synopsis Summary and Protocol Section 6.1.2 Instructions for Dosing Control Treatment Regimen (HRZE/HR) - The participants weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and HRZE and HR does to administer, to ensure optimal dosing at these 2 time-points when changing from HRZE to HR.
10	**Clarify:** 1.1 Synopsis Summary and Protocol Section 6.3 Treatment Modification(s) – If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose that was missed, as the Bedaquiline dose (BPaMZ treatment regime) changes from 200mg to 100 mg at Week 9, and from HRZE to HR at Week 9 (HRZE/HR treatment regime). The term 'greater than' has been replaced with 'if more than' for clarity.
11	**Change:** 1.1 Synopsis, Statistical Methods and Protocol Section 9.0 Statistical Analysis - the Statistical Analysis Plan (SAP) will be written and signed of prior to the interim analysis.
12	**Change:** 1.1 Synopsis, Statistical Methods and Protocol Section 9.3 Interim Analysis - There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size: If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the study on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The study efficacy objectives will be updated as follows: - **Primary Objective:** *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.* - **Secondary Objective:** *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

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	To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework and full details are provided in the Statistical Analysis Plan.
13	**Delete:** Synopsis, Trial Duration – removed reference to 3 database locks as it is not applicable to the trial duration.
14	**Clarify:** 1.2 Synopsis Flow Chart and Procedures - Week 1 occurs on Day 8 and not Day 7 (Day 7 deleted), as per Protocol Memo 1 dated 11 May 2018, to ensure that 7 days of IMP are administered to the participant between Day 1 / Baseline and Week 1.
15	**Change:** 1.2 Synopsis and Flow Chart (foot note) General: vital signs and blood draws (removed ECGs) are to be performed before dosing, unless otherwise specified. Vital signs and or ECGs should be done before blood draws (safety and PK) on days with those assessments.
16	**Change:** Synopsis and Flow Chart (foot note, a) – Screening assessments must occur during the Screening period (Day -9 to -1) before Day 1 (Baseline). This has been amended for clarity.
17	**Clarify:** 1.2 Synopsis and Flow Chart (foot note, f) that rifampicin resistance testing includes Hain MTBDRPlus and Hain MTBRsl.
18	**Clarify:** 1.2 Synopsis and Flow Chart (foot note, f) that unscheduled visits referenced in this section, are for the collection of additional sputum samples.
19	**Change:** 1.2 Synopsis and Flow Chart (foot note, f) if sputum samples collected at Week 8 or later (remove reference to Weeks 17, 26, 52 and 104) are contaminated the participant return for an unscheduled visit.
20	**Change:** 1.2 Synopsis and Flow Chart (foot note, g) Rapid molecular tests will be done for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period) and Drug Susceptibility Testing will be done for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide only, in liquid culture
21	**Add:** 1.2 Synopsis and Flow Chart (foot note, n) – Additional single 12-lead ECGs to be performed prior to pre- and post-dose PK sampling to observe the cardiac safety profile at defined timepoints after dosing, over time, on these days (weeks 2, 8 and 17).
22	**Add:** 1.2 Synopsis and Flow Chart (foot note, s) Blood draws for PK samples collected pre and post-dose must be done after the ECG is performed, as previously ECG's were only performed pre-dose.
23	**Add:** 1.2 Synopsis and Flow Chart (foot note, s) PK samples at Weeks 39, 65, 78 and 104 are to be obtained at any time on the day of the scheduled visit, and only bedaquiline and M2 will be measured.
24	**Add:** 1.2 Synopsis and Flow Chart (foot note, s) and Protocol Section 7.4 PK Variables and Procedures - If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.
25	**Clarify:** 1.2 Synopsis and Flow Chart (foot note, v) the Investigator Assessment, per the Synopsis and Flow Chart, is only performed at Week 52 and 104 or anytime the Investigator determines that the participant fulfills the criteria for outcome of treatment failure.
26	**Add:** 1.2 Synopsis and Flow Chart (additional foot note, x) and Protocol Section 7.1 Demographic and Background Variables and Procedures - The Karnofsky Score is only to be performed on HIV+ participants.
27	**Clarify:** Protocol Section 3.1 Primary Endpoint - To evaluate the time to culture negativity over 8 weeks from the start of the following treatment regimens in participants with: Drug Sensitive TB (DS-TB) and Drug Resistant TB (DR-TB). DR-TB are defined as participants with: mono-resistance to rifampicin or isoniazid, OR resistance to both rifampicin and isoniazid (DR-TB). The treatment allocation descriptions have been removed as they are irrelevant to this section.

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28	**Clarify:** Protocol Section 3.2 Secondary Endpoints, PK and PD - Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., **minimum plasma concentration** [Cmin], **maximum plasma concentration** [Cmax], **area under curve** over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide.
29	**Clarify:** Protocol Section 4.1 Summary of Trial Design - Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment **randomisation** and allocation (as all DR-TB participants are allocated and not randomised, to only receive 6 months BPaMZ) during the treatment phase of the trial.
30	**Clarify:** Protocol Section 4.1 has been re-written to state that DS participants will be randomized (either to HRZE/HR or 4 months BPaMZ) and all DR participants will be allocated and not randomized to 6 months BPaMZ.
31	**Change:** Protocol Section 5.1 Inclusion Criteria #5 has been changed to the following for the DS-TB treatment arm participants: sensitive to rifampicin, isoniazid **and fluoroquinolones** by rapid sputum-based test.
32	**Change:** Protocol Section 5.1 Inclusion Criteria #5 has been changed to not (late) exclude DS-TB participants who are randomized to the trial due to being sensitive to rifampicin and isoniazid by rapid molecular sputum-based test, however on receipt of the rifampicin and or isoniazid phenotypic resistance testing in liquid culture this shows they are rifampicin or isoniazid resistant.
33	Change: Protocol Section 5.1 Inclusion Criteria #5 has been changed for the DR-TB treatment arm participants, as follows: - Resistant to rifampicin and/or isoniazid; **but sensitive to fluoroquinolones by rapid sputum-based test AND** - Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than **3 days** (previously, was 7 days) at start of screening. - **Participants with resistance to injectables by rapid sputum-based test are allowed in the trial**. - When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.
34	**Change:** Protocol Section 5.1 Inclusion Criteria #7, Contraception – Contraception has been updated to require that both the female trial participants and the male trial participants' female sexual partners, use the same type of contraception: Barrier method combined with hormone-based contraceptives or an intra-uterine device. Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 6 months (previously stated in this section as 3 months) after the last dose of trial IMP or discontinuation from trial IMP in case of premature discontinuation, to ensure consistency throughout the protocol, as per Section 5.2 Exclusion Criteria #13 that also references a period of 6 months.
35	**Add:** Protocol Section 5.2 Exclusion Criteria #3 - Historical and or current use of local traditional medications/herbs which in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
36	**Delete:** Protocol Section 5.2 Exclusion Criteria #9 - Resistant to fluoroquinolones (rapid, sputum-based molecular screening tests). If they are randomised into the trial due to being sensitive to fluoroquinolones by rapid sputum-based test, however on receipt of the moxifloxacin phenotypic resistance testing in liquid culture they are found to be fluoroquinolones resistant, they will be excluded as late exclusions. This criterion is already stipulated in the updated Inclusion Criteria #5.

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37	**Change:** Protocol Section 5.2 Exclusion Criteria #15, 16, 17 and 18, as these criteria are consolidated and described more specifically in the updated Exclusion Criteria #15, including an update to a limit of **3 days** previous DR-TB/MDR-TB treatment regimen for the DR-TB participants.
38	**Clarify:** Protocol Section 5.2 Exclusion Criteria #18 (previously #21) has been corrected, as follows: Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), **as they can lead to** visual opacities or cataracts.
39	**Add:** Protocol Section 5.2 Exclusion Criteria #19 (previously #22) has been extended to provide additional instructions wrt ART for HIV infected participants.
40	**Delete:** Protocol Section 5.2 Exclusion Criteria #20 (previously #24) has been updated to remove the DMID grade for platelets, haemoglobin, AST, ALT, ALP and total bilirubin to provide clarity and remove ambiguity. The actual values of these laboratory results remain unchanged.
41	**Delete:** Protocol Section 5.3 Restrictions – 1st paragraph, 2nd sentence has been updated to be keep the participant's welfare as the primary concern: However, if concomitant medications are necessary for the participant's welfare, they may be given at the discretion of the Investigator.
42	**Clarify:** Protocol Section 5.3 Restrictions – The section that describes medications that should be avoided has been updated to state the following: The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible (**unless this is required for emergency management of the participant**). Investigators may also contact the Sponsor Medical Monitor for further guidance.
43	**Delete:** Protocol Section 5.3 Restrictions – 'contraceptive pill' has been deleted from the list of medications to be avoided, since it is a contraceptive requirement (Inclusion Criteria #7) to participate in this trial.
44	**Change:** Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal, as the criteria for late exclusion based on phenotypic DST and whole genome sequencing has been amended.
45	**Delete:** Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal – the following 2 reasons for withdrawal have been removed, due to the updated Inclusion Criteria #5: - Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum-based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result. - Early withdrawal due to TB (removed as this is now detailed in the additional criteria listed in item #44 above)
46	**Clarify:** Protocol Section 5.4.2 Unscheduled Visits has been updated to provide additional clarity, as follows: - Addition of the following reason: For any medical reason, as determined by the Investigator or participant. - End of Treatment Period (Week 17 or 26) has been removed from the timepoint at which sputum cultures are assessed for the primary outcome status, as this was incorrectly stated in the previous protocol - General rewording of this section to provide clarity to the Investigator on when Unscheduled Assessments should occur - Addition of Table 6: Summary of Scenarios Requiring Unscheduled Visit for Mycobacteriology Testing to aid the Investigator's understanding of the Unscheduled Assessment requirements. - Last sentence has been updated to indicate that the …'Investigator **should** (previously documented as, 'is to') contact the Sponsor Medical Monitor to discuss'…
47	**Clarify:** Protocol Section 5.4.4 Early Withdrawal due to TB – last paragraph has been updated to ensure that the Investigator provides a referral letter and at a minimum should include all treatment received by the participant and information about any suspected/confirmed adverse event/reaction related to any of the trial IMP's and or concomitant medications. A follow-up call **should** (previously stated as 'will') be made by the trial site staff to the clinic to ensure the participant attended the NTP clinic.

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48	**Clarify:** Protocol Section 7.1 Demographic and Background Variables and Procedures – The following 2 descriptions of testing as documented in Section 7.5 Mycobacteriology Characterization Variable and Procedures: - Rapid molecular tests for isoniazid, rifampicin, fluoroquinolones resistance (Hain MTBDRplus and HainMTBRsl) - Liquid Culture (MGIT) for Mycobacterium tuberculosis (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive. **Delete:** Protocol Section 7.1 Demographic and Background Variables and Procedures - Gene Xpert, as this was incorrectly included in the previous version of the protocol.
49	**Clarify:** Protocol Section 7.1 Demographic and Background Variables and Procedures – method of birth control: make and female participants and their **sexual** partners
50	**Clarify:** Protocol Section 7.5 Mycobacteriology Characterization Variable and Procedures – exact wording documented in 1.2 Synopsis and Flowchart (footnote, g) to ensure consistency of procedure description. **Delete:** 'Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be sub-cultured and sent to the central microbiology laboratory from the applicable local microbiology laboratory, for relevant participants / no positive cultures from screening through week 4', because only assessments perform from the Screening visit will be used for this trial. **Change:** Protocol Section 7.5 Mycobacteriology Characterization Variable and Procedures – all MTB isolates (not just those obtained at Baseline / Day 1, as previously documented) must be stored…
51	**Clarify:** Protocol Section 8.2.1 Follow-up of Adverse Events – reference to the reporting requirements is now referenced as the eCRF Guidelines (incorrectly referenced as SAE Completion Guidelines, in the previous version of the protocol).
52	**Clarify:** Protocol Section 8.2.6 Pregnancy – reporting required at any time during the trial.
53	**Delete:** Protocol Section 8.3 Monitoring for Specific Toxicities – 8.3.3 Neurological, has been removed, as it is not a requirement given the safety profiles of the BPaMZ and or HRZE/HR trial regimens.
54	**Add:** (moved from the Synopsis): Protocol Section 9.0 Statistical Analysis – added the following: There will be 3 data analyses and trial reports generated for this trial: - When all participants have completed 8 weeks (2 months) of treatment from baseline. - When all participants have completed 52 weeks (12 months) follow-up from start of therapy. - When all participants have completed 104 weeks (24 months) follow-up from start of therapy.
55	**Delete:** Protocol Section 11.3 Protocol Deviations – reference to the Monitoring Plan has been removed as the Investigator is not provided with this plan, and therefore would not deviate from this plan.
56	**Delete:** Removal of the following appendixes and references in the protocol, as these appendixes are now included in separate trial documents, and provided to the Investigator: - Appendix 6 TB Symptom Profile is documented in the 'Participant Questionnaires Guideline' - Appendix 7 Patient Reported Health Status is documented in the 'Participant Questionnaires Guideline' - Appendix 8 Liver Toxicity Management documented in 'Hepatoxicity Management Guideline'

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57	**Clarify:** Protocol Section 5.2 Exclusion Criteria – with the addition of criteria #3, deletion of #9, 15, 16 the numbering of the Exclusion Criteria has had to change.
58	**Change:** Tables – with the addition of Table #6, subsequent table numbering updated
59	**Change:** all references to the 2 treatment periods of Week 17 (4-month treatment arm) and Week 26 (6-month treatment arm) are stated as either Week 17 or Week 26, only.
60	**Change:** all references to 'study' have been changed to 'trial' for consistency.
61	**Change:** all references to 'patient' (where applicable) have been changed to 'participant' for consistency.
62	**Change:** all references to B-Pa-M-Z have been changed to BPaMZ.
63	**Change:** all references to 'therapy' has been changed to 'treatment' for consistency.
64	**Change:** all references to early morning sample or early morning sputum, has been changed to EMS, Early Morning Sputum, per the 'Abbreviations and Definition of Terms'.
65	**Change:** all references to Drug Resistant TB (DR-TB) and Drug Sensitive TB (DS-TB), are documented as either DS-TB or DR TB, per the 'Abbreviations and Definition of Terms'.
66	**Change:** all references to trial medication and or study medication, has been changed to 'trial IMP' where appropriate, per the 'Abbreviations and Definition of Terms'.
67	**Delete:** all references to study time points in 'months'. All study time points are only referenced in weeks.
68	Administrative changes, including spelling, grammar, format, use of 'Abbreviations and Definition of Terms' in the protocol body, have been implemented and updated throughout the entire document.

#	Section	Previous Text Russia Version 1.0 dated 21-Feb-18	Amended Text Version 2.0 dated 15-Jan-19 Additional text - bold font. Deleted text – strike-through.	Reason for Change Insert reason # from table above
1	Cover Page	Global Alliance for TB Drug Development TB ALLIANCE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT	TB Alliance TB ALLIANCE	1

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2	Protocol signature page	**LEAD INVESTIGATOR** I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations. Signature Printed Name Date	~~**LEAD INVESTIGATOR**~~ ~~I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein and in accordance to the principles of Good Clinical Practice (GCP) and local regulations.~~ ~~Signature~~ ~~Printed Name~~ ~~Date~~	2
3	Abbreviations and Definitions of Terms	No previous text	**DST Drug Susceptibility Testing**	3
4	Abbreviations and Definitions of Terms	No previous text	**HR Hazard Ratio**	4
5	Abbreviations and Definitions of Terms	LTFU Long term follow-up	**LTFU Lost to Follow-up**	5
6	Abbreviations and Definitions of Terms	No previous text	**WGS Whole Genome Sequencing**	6

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7	1.1 Synopsis Summary, Trial Objectives	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with: **Drug Sensitive TB (DS-TB)** – BPaMZ given for 17 Weeks (4 months), or – Standard HRZE/HR treatment given for 26 weeks (6 months) **Drug Resistant TB (DR-TB)** – BPaMZ given for 26 Weeks (6 months) **DR-TB Defined as participants with** 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with: Drug Sensitive TB (DS-TB) – ~~BPaMZ given for 17 Weeks (4 months), or~~ – ~~Standard HRZE/HR treatment given for 26 weeks (6 months)~~ Drug Resistant TB (DR-TB) – ~~BPaMZ given for 26 Weeks (6 months)~~ DR-TB Defined as participants with 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)	7

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8	1.1 Synopsis Summary, Statistical Methods	No previous text to describe the abbreviated SAP definitions	**Abbreviated Definitions, full definitions will be described in the Statistical Analysis Plan (SAP):** • **Bacteriologic failure: During the treatment period, failure to attain or maintain culture conversion to negative.** • **Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status, with culture conversion to positive status with a strain of *Mycobacterium tuberculosis* (MTB) genetically identical to the infecting strain at baseline.** • **Clinical failure: A change from protocol-specified TB treatment to a new regimen before end of protocol specified treatment due to treatment failure, retreatment for TB during follow up, or TB-related death.** **Note:** ○ **Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.** ○ **Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit.**	8

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9	1.1 Synopsis Summary, Positive Control Product, Dose and Mode of Administration and Protocol Section 6.1.2	No previous text	**The participant's weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and HRZE and HR dose to administer.**	9
10	1.1 Synopsis Summary, Treatment Interruptions /Pauses and Protocol Section 6.3	• Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required. • Greater than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been. • Greater than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial. • If the participant misses a total (sum) of 56 cumulative missed doses, discontinue the IMP and withdraw participant from the trial.	• Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required. • ~~Greater~~ **If more** than 7 to ≤ 35 consecutive doses **missed, before the end of the treatment period (Week 17/26)**: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been. • ~~Greater~~ **If more** than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial. • If the participant misses a total (sum) of 56 cumulative missed doses, discontinue the IMP and withdraw **the** participant from the trial. **If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose that was missed.**	10

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11	1.1 Synopsis, Statistical Methods and Protocol Section 9.0 Statistical Analysis	A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the statistical analysis plan (SAP,) which will be written and signed off prior to the first participant enrolled in the trial.	A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP) which will be written and signed off **prior to the interim analysis.**	11

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12	1.1 Synopsis, Statistical Methods and Protocol Sections 2.3.1 Trial Design Rationale, and 9.3 Interim Analysis	No previous text	**Interim Analysis** **There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:** **If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the study on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The study efficacy objectives will be updated as follows:** - **Primary Objective** ***To determine the incidence of bacteriologic failure or relapse or clinical failure at 52 weeks from the start of treatment / randomisation.*** - **Secondary Objective** ***To evaluate the time to culture negativity over 8 weeks, from the start of treatment / randomisation.*** **All other study objectives will remain unchanged.**	12

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			To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework and full details are provided in the Statistical Analysis Plan.	
13	1.1 Synopsis, Trial Duration	Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until week 104 from start of treatment. Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms is complete. There will be 3 database locks, data analyses and trial reports generated for this trial: 1. When all participants have completed 8 weeks (2 months) of treatment from baseline. 2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy. 3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.	Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until week 104 from start of treatment. Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms is complete. ~~There will be 3 database locks, data analyses and trial reports generated for this trial:~~ ~~1. When all participants have completed 8 weeks (2 months) of treatment from baseline.~~ ~~2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy.~~ ~~3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.~~	13
14	1.2 Synopsis Flow Chart and Procedures	**1.2 Synopsis Flow Chart and Procedures** Period: Screen-ing[a]; Treatment Visit[b]: Day -9 to -1; Day 1 (Baseline)[d]; Day 7 (Week 1); Week 2; Week 3; Week 4; Week 5; Week 6; Week 7; Week 8; Week 12	**1.2 Synopsis Flow Chart and Procedures** Period: Screen-ing[a]; Treatment Visit[b]: Day -9 to -1; Day 1 (Baseline)[d]; Week 1; Week 2; Week 3; Week 4; Week 5; Week 6; Week 7; Week 8; Week 12	14

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15	1.2 Synopsis Flow Chart and Procedures (foot notes), General	GENERAL: Vital signs, ECGs and blood draws are to be performed pre-dosing unless otherwise specified. Vital signs and/or ECGs should be done prior to blood draws (safety and PK) on days with those assessments.	GENERAL: Vital signs~~, ECGs~~ and blood draws are to be performed **before** dosing unless otherwise specified. Vital signs and/or ECGs should be done **before** blood draws (safety and PK) on days with those assessments.	15
16	1.2 Synopsis Flow Chart and Procedures (foot note a)	Screening: Screening assessments can occur on different days, within nine days before Day 1 dosing (randomisation).	Screening: Screening assessments can occur on different days, within nine days before Day 1 ~~dosing~~ **(**~~randomisation~~ **Baseline).**	16
17	1.2 Synopsis Flow Chart and Procedures (foot notes, f)	Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance	Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance **(Hain MTBDRplus and Hain MTBRsl);**	17
18	1.2 Synopsis Flow Chart and Procedures (foot notes, f)	Baseline to Week 104, including any Unscheduled visits:	**Day 1 (**Baseline**)** to Week 104 **and** ~~including any~~ Unscheduled visits **for additional sputum samples:**	18
19	1.2 Synopsis Flow Chart and Procedures (foot notes, f)	If both sputum samples at Weeks 8, 17 (4-month treatment arm), 26 (6-month treatment arm), 52 or 104 are contaminated, the participant should return for an unscheduled visit(s) to give additional samples or to document that the participant is not able to produce sputum.	If both sputum samples at Weeks 8 **or later**~~, 17 (4-month treatment arm), 26 (6-month treatment arm), 52 or 104~~ are contaminated, the participant should return for an unscheduled visit(s) to give additional samples or to document that the participant is not able to produce sputum.	19

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20	1.2 Synopsis Flow Chart and Procedures (foot notes, g)	Mycobacterial Characterization - MTB isolates will be processed for: - Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin; - Drug Susceptibility Testing for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, pyrazinamide and second line TB drugs including, but not limited to fluoroquinolones, and injectables using an indirect susceptibility test in liquid culture; - Extraction of organismal (MTB) DNA for whole genome sequencing, and comparison of sequences from baseline and relapse isolates.	Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for: - **Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);** - Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin; - Drug Susceptibility Testing (DST) for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, ~~and second line TB drugs including, but not limited to fluoroquinolones, and injectables using an indirect susceptibility test in pyrazinamide~~ in liquid culture; - Extraction of organismal (MTB) DNA for whole genome sequencing **(WGS),** and comparison of sequences from baseline and relapse isolates.	20
21	1.2 Synopsis Flow Chart and Procedures (foot notes, n) and Protocol Section 7.3 Safety and Tolerability Assessments	Single 12-Lead ECG: To every extent possible, this should be performed at approximately the same time of day as the trial procedures (+/-1 hour). Central ECG analysis will be performed. Results from central reading of Day -9 to -1 (Screening) ECG must be used to determine eligibility.	Single 12-Lead ECG: **ECGs to be performed prior to pre- and post-dose PK sampling as described below:** • **Day 1: pre-dose (within 2 hours prior to dosing)** • **Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose** • **Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose** • **Week 12: pre-dose (within 2 hours prior to dosing)** • **Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose** Central ECG analysis will be performed. Results from central reading of ~~Day -9 to -1 (Screening)~~ Screening ECG must be used to determine eligibility.	21

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22	1.2 Synopsis Flow Chart and Procedures (foot notes, s)	Pharmacokinetic (PK) Sampling: This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE-HR treatment arm. Blood draws for PK samples collected pre-dose must be done after the ECG is performed.	Pharmacokinetic (PK) Sampling: This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE/HR treatment arm. Blood draws for PK samples collected pre- **and post-dose** must be done after the ECG is performed.	22
23	1.2 Synopsis Flow Chart and Procedures (foot notes, s)	Weeks 39, 65, 78 and 104: PK samples are to be obtained at any time on the day of the scheduled visit.	Weeks 39, 65, 78 and 104: PK samples are to be obtained at any time on the day of the scheduled visit, **and only bedaquiline and M2 will be measured**.	23
24	1.2 Synopsis Flow Chart and Procedures (foot notes, s) and Protocol Section 7.4 PK Variables and Procedures	No previous text	**If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.**	24
25	1.2 Synopsis Flow Chart and Procedures (foot notes, v)	Investigator Assessment: Investigator to review participant status and assess whether IMP or TB treatment at current visit is considered a “success” or “failure”. If considered a failure, the Investigator should specify if based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed, as shown on the flowchart, and at any time Investigator determines that participant fulfils criteria for outcome of treatment failure.	Investigator Assessment: Investigator to review the participant status and assess whether IMP or TB treatment at ~~current visit~~ **Week 52 and 104** is considered a “success” or “failure”. If considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed~~, as shown on the flowchart,~~ **at Week 52 and 104, <u>and at any time</u>** the Investigator determines that the participant fulfils the criteria for outcome of treatment failure.	25

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26	1.2 Synopsis Flow Chart and Procedures (foot notes, x), and Protocol section 7.1	No previous text	**Karnofsky Score: Only to be performed on HIV+ participants.**	26
27	Protocol Section 3.1 Primary Objective	Primary Objectives To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with: Drug Sensitive TB (DS-TB) – BPaMZ given for 17 Weeks (4 months) – Standard HRZE/HR treatment given for 26 weeks (6 months) Drug Resistant TB (DR-TB) – BPaMZ given for 26 Weeks (6 months) DR-TB are defined as participants with: 1. *mono-resistance to rifampicin or isoniazid, OR* 2. *resistance to both rifampicin and isoniazid (DR-TB)*	Primary **Endpoints** To evaluate **the time to culture negativity over 8 weeks from the start of the following treatment regimens in participants with** ~~the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the following treatment regimens in participants with~~: - Drug Sensitive TB (DS-TB) ~~– BPaMZ given for 17 Weeks (4 months)~~ ~~– Standard HRZE/HR treatment given for 26 weeks (6 months)~~ - Drug Resistant TB (DR-TB) ~~– BPaMZ given for 26 Weeks (6 months)~~ DR-TB are defined as participants with: 2. *mono-resistance to rifampicin or isoniazid, OR* 2. *resistance to both rifampicin and isoniazid (DR-TB)*	27

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28	Protocol Section 3.2 Secondary Objectives, PK and PD	Secondary Objectives Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., Cmin, Cmax, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide.	Secondary **Endpoints** Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., **minimum plasma concentration** [Cmin], **maximum plasma concentration** [Cmax], **area under curve over a dosing interval** [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide.	28
29	Protocol Section 4.1 Summary of Trial Design	Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment allocation during the treatment phase of the trial.	Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment **randomisation and** allocation during the treatment phase of the trial.	29

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30	Protocol Section 4.1 Summary of Trial Design, 6th paragraph	Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive. An interactive web response system (IWRS) will be used which will utilize a dynamic randomization system using cavitation with a random element to allocate participants evenly across the arms by HIV status and type of TB (DS versus DR) after they have given written, informed consent during the Screening Visit (Days -9 to -1) and met all eligibility criteria.	Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive. ~~An interactive web response system (IWRS) will be used which will utilize a dynamic randomization system using cavitation with a random element to allocate participants evenly across the arms by HIV status and type of TB (DS versus DR) after they have given written, informed consent during the Screening Visit (Days -9 to -1) and met all eligibility criteria.~~ **DR participants will be treated with 6 months of BPaMZ**. **DS participants will be randomised** using ~~a~~ **an interactive web response system (IWRS) stratifying for cavitation and HIV status to allocate participants evenly across the arms after they have given written, informed consent during the Screening Visit (Days -9 to -1).**	30
31	Protocol Section 5.1, Inclusion Criteria #5	DS-TB treatment arm participants should be: sensitive to rifampicin and isoniazid by rapid sputum-based test	DS-TB treatment arm participants should be: sensitive to rifampicin, isoniazid **and fluoroquinolones** by rapid sputum-based test.	31
32	Protocol Section 5.1, Inclusion Criteria #5	If they are randomised into the trial due to being sensitive to rifampicin and isoniazid by rapid molecular sputum-based test, however on receipt of the rifampicin and/or isoniazid phenotypic resistance testing in liquid culture this shows they are rifampicin or isoniazid resistant, they will be: - Excluded as late exclusions; - Possibly replaced as determined by the Sponsor.	~~If they are randomised into the trial due to being sensitive to rifampicin and isoniazid by rapid molecular sputum-based test, however on receipt of the rifampicin and/or isoniazid phenotypic resistance testing in liquid culture this shows they are rifampicin or isoniazid resistant, they will be:~~ ~~- Excluded as late exclusions;~~ ~~- Possibly replaced as determined by the Sponsor.~~	32

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33	Protocol Section 5.1, Inclusion Criteria #5	DR-TB treatment arm participants should be: a. Resistant to rifampicin and/or isoniazid. b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 7 days at start of screening.	DR-TB treatment arm participants should be: a. Resistant to rifampicin and/or isoniazid; **but sensitive to fluoroquinolones by rapid sputum-based test AND** b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than ~~7~~ **3** days at start of screening. c. **Participants with resistance to injectables by rapid sputum-based test are allowed in the trial.** **When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.**	33

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34	Protocol Section 5.1 Inclusion Criteria #7, Contraception	Effective birth control methods: a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female participant. c. Male participants' female sexual partner: Double barrier method or hormone-based contraceptives or an intra-uterine device for the female partner. Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 12 weeks after the last dose of trial medication or discontinuation from trial medication in case of premature discontinuation.	Effective birth control methods: a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device ~~for the female participant~~. c. Male participants' female sexual partner: ~~Double~~ Barrier method **combined with** hormone-based contraceptives or an intra-uterine device ~~for the female partner~~. Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for **6 months** ~~12 weeks~~ after the last dose of trial IMP or discontinuation from trial IMP in case of premature discontinuation.	34
35	Protocol Section 5.2 Exclusion Criteria #3	No previous text	**Historical and or current use of local traditional medications/herbs which in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.**	35

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36	Protocol Section 5.2 Exclusion Criteria #9 (previous protocol)	Resistant to fluoroquinolones (rapid, sputum-based molecular screening tests) - If they are randomised into the trial due to being sensitive to fluoroquinolones by rapid sputum-based test, however on receipt of the moxifloxacin phenotypic resistance testing in liquid culture they are found to be fluoroquinolones resistant, they will be excluded as late exclusions.	~~Resistant to fluoroquinolones (rapid, sputum-based molecular screening tests)~~ ~~- If they are randomised into the trial due to being sensitive to fluoroquinolones by rapid sputum-based test, however on receipt of the moxifloxacin phenotypic resistance testing in liquid culture they are found to be fluoroquinolones resistant, they will be excluded as late exclusions.~~	36
37	Protocol Section 5.2 Exclusion Criteria #15, 16, 17, 18 (previous protocol)	15. Previous treatment with pretomanid or bedaquiline. 16. Previous treatment for TB which includes, but is not limited to, gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole. 17. For DS-TB participants: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days prior to randomization 18. For the DR-TB participants: Previous treatment for DR-TB/MDR-TB, although may have been on a DR/MDR-TB treatment regimen for no longer than 7 days at start of screening.	~~Previous treatment with pretomanid or bedaquiline.~~ ~~Previous treatment for TB which includes, but is not limited to, gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.~~ **15. Previous treatment for TB:** For DS-TB participants: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days at the start of the Screening visit. For the DR-TB participants: Previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than **3** days at the start of the Screening visit.	37

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38	Protocol Section 5.2 Exclusion Criteria # 18	Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), due to visual opacities or cataracts.	Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), ~~due to~~ **as they can lead to** visual opacities or cataracts.	38

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39	Protocol Section 5.2 Exclusion Criteria # 19	For HIV infected participants, only the following types of ART are permissible: a. Lopinavir/ritonavir-based regimen consisting of lopinavir/ritonavir in combination with any two NRTI. TDF/ABC and FTC/3TC. b. Integrase inhibitor (e.g., dolutegravir) in combination with TDF/ABC and FTC/3TC. c. In participants who have viral load suppressed on efavirenz at the time of screening, their ART can be changed to rilpivirine in combination with TDF/ABC and FTC/3TC. If possible, the same nucleoside backbone should be used. d. Nevirapine (NVP) based regimen consisting of NVP in combination with any two nucleosidase reverse transcriptase inhibitors (NRTIs) tenofovir (TDF)/abacavir (ABC) and emtricitabine (FTC)/lamivudine (3TC). In the case where participants are randomized to a rifampicin containing regime: a. EFV can be used with rifampicin. b. LPV needs to be double dosed. c. Rilpivirine cannot be given with rifampicin	For HIV infected participants ~~only the following types of ART are permissible~~: **a. The following antiretroviral therapy (ART) should not be used with either (BPaMZ and HRZE/HR) trial regimen:** **1. Stavudine** **2. Didanosine** **3. Triple NRTI regimen is not considered optimal for HIV treatment (poor efficacy)** **b.** In the case where participants are randomised to HRZE arm, **<u>rilpivirine and etravirine cannot be given</u> with rifampicin due to drug-drug interactions. A standard NRTI backbone may be used in combination with one of the following:** **1. Efavirenz requires no dose adjustment** **2. Dolutegravir dose adjustment is required – double dose when co-prescribed with rifampicin.** **3. Raltegravir requires no dose adjustment** **4. Lopinavir/r dose adjustment is required – double dose when co-prescribed with rifampicin** **5. Nevirapine requires no dose adjustment, however please note that nevirapine based regimens are associated with higher ART failure in participants having or known to have a previous viral load more than or equal to 100,000/ mL** **c. In the case where participants are randomized to the BPaMZ trial regimen, a standard NRTI backbone may be combined with the following:**	39

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			1. Rilpivirine **2. Dolutegravir** **3. Raltegravir** **4. Nevirapine** **5. Lopinavir/r** **6. <u>Participants who are on efavirenz, atazanavir/r or darunavir/r at the time of screening and have an undetectable viral load</u>, should have their ART switched to one of the agents listed above (1-5). It would be preferable to switch to another permissible ARV within the same class accompanied by the same nucleoside backbone.** **d. ART regimen choice should be discussed with the Sponsor Medical Monitors if there are any concerns.** **Confirmed plans to use Isoniazid prophylaxis for HIV positive participants during the treatment and follow up period is not permitted.**	

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40	Protocol Section 5.2 Exclusion Criteria, Diagnostic and Laboratory Abnormalities, Item #20 (Previously #24)	a. platelets grade 2 or greater (<100,000/mm^3) b. creatinine grade 2 or greater (>1.5 times upper limit of normal [ULN]) c. eGFR ≤ 60 mL/min/m^2 d. haemoglobin grade 2 or greater (≤8.0 g/dL) e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once f. GGT: greater than 3 x ULN g. AST: • grade 3 or greater (≥3.0 x ULN) to be excluded; • results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor h. ALT: • grade 3 or greater (≥3.0 x ULN) to be excluded • greater than ULN must be discussed with and approved by the Sponsor Medical Monitor i. ALP: • grade 3 or greater (≥3.0 x ULN) to be excluded • grade 2 (2.0 – <3.0 x ULN) must be discussed with and approved by the Sponsor Medical Monitor j. Total bilirubin: • >1.5 x ULN to be excluded; • 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor k. Direct bilirubin: • greater than 1x ULN to be excluded	a. platelets ~~grade 2 or greater (<100~~<75,000/mm^3~~)~~ b. creatinine ~~grade 2 or greater (~~>1.5 times upper limit of normal (~~[~~ULN~~]~~) c. eGFR ≤ 60 mL/min~~/m^2~~ d. haemoglobin ~~grade 2 or greater (≤~~<8.0 g/dL~~)~~ e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once f. GGT: greater than 3 x ULN g. AST: • ~~grade 3 or greater (~~≥3.0 x ULN~~)~~ to be excluded; • results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor h. ALT: • ~~grade 3 or greater (~~≥3.0 x ULN~~)~~ to be excluded • greater than ULN must be discussed with and approved by the Sponsor Medical Monitor i. ALP: • ~~grade 3 or greater (~~≥3.0 x ULN~~)~~ to be excluded • ~~grade 2 (~~2.0 – <3.0 x ULN~~)~~ must be discussed with and approved by the Sponsor Medical Monitor j. Total bilirubin: • >1.5 x ULN to be excluded; • **greater than** 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor k. Direct bilirubin: • greater than 1x ULN to be excluded	40
41	Protocol Section 5.3 Restrictions	Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are necessary for the participant's welfare and are unlikely to	Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are necessary for the participant's welfare ~~and are unlikely to~~	41

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		interfere with the IMP, they may be given at the discretion of the Investigator.	~~interfere with the IMP~~, they may be given at the discretion of the Investigator.	
42	Protocol Section 5.3 Restrictions	The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible unless discussed with the Sponsor Medical Monitor:	The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible **(unless this is required for emergency management of the participant**~~) unless discussed with the Sponsor Medical Monitor~~**. Investigators may also contact the Sponsor Medical Monitor for further guidance.**	42
43	Protocol Section 5.3 Restrictions	Any drug known to be hepatotoxic (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…	Any drug known to be hepatotoxic (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~~…	43

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44	Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal	A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following: • Withdrawal of informed consent • Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment. • Pregnancy • At the specific request of the Sponsor or termination of the trial by the Sponsor. • Lost to follow-up • Drug-Sensitive TB treatment arms: participants, who have been randomised onto the trial as a rifampicin sensitive participant on the rapid sputum based test result, who on receipt of the rifampicin resistance testing using an indirect susceptibility test in liquid culture, shows a rifampicin resistant result. • Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result.	A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following: • Withdrawal of informed consent • Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment • Pregnancy • At the specific request of the Sponsor or termination of the trial by the Sponsor • Lost to follow-up • ~~Drug-Sensitive TB treatment arms: participants, who have been randomised onto the trial as a rifampicin sensitive participant on the rapid sputum based test result, who on receipt of the rifampicin resistance testing using an indirect susceptibility test in liquid culture, shows a rifampicin resistant result.~~ • ~~Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result.~~ • **When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that**	44

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			participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.	
45	Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal	- Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum-based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result. - Early withdrawal due to TB (see Section 5.4.4)	~~- Participants, who have been randomised onto the trial as fluoroquinolone sensitive on the rapid sputum-based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture; this shows a fluoroquinolone resistant result.~~ ~~- Early withdrawal due to TB (see Section5.4.4)~~	45

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46	Protocol Section 5.4 Treatment Discontinuation and/or Early Withdrawal	The following situation/s would require an unscheduled visit/s: - If both sputum samples (Early Morning and Spot) at Week 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum. - If there is a MTB confirmed positive culture at or after the end of treatment at Week 17 (4-month treatment) or Week 26 (6-month treatment), the participant should return for an Unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the participant is not able to produce sputum. If no early morning sputum sample was provided by the participant, 2 samples may be collected at the site, at least 30 minutes apart. Table 6 is a new table and did not previously exist in Protocol Russia V1.0. If the Investigator is unsure of the outcome in any of the above scenarios the Investigator is to contact the Sponsor Medical Monitor and discuss and agree on how the participant is to be managed.	The following situation/s would require an unscheduled visit/s: **- For any medical reason, as determined by the Investigator or participant.** **-** If both sputum samples (EMS and spot sputum sample) at Week 8 or later are contaminated, the participant should return for an unscheduled visit/s to give 2 (EMS and spot sputum sample, at each visit ~~under the coaching and observation of the trial staff~~) additional sputum samples or to document that the participant is not able to produce sputum. - ~~If there is a MTB confirmed positive culture~~ **If after having converted to culture negative**, **the participant has a MTB confirmed positive culture at or after the last visit of the treatment period** (Week 17 or Week 26) ~~Week 17 (4-month treatment) or Week 26 (6-month treatment)~~, the participant should return for Unscheduled visit/s to provide 2 **(EMS and spot sputum sample, at each visit)** additional sputum samples ~~under the coaching and observation of the trial staff~~), at a minimum of 7 days apart, or to document that the participant is not able to produce a sputum sample. **Table 6: Summary of Scenarios Requiring Unscheduled Visits for Mycobacteriology Testing** **Time-point** / **Scenario** / **Unscheduled Visit/s Required?** / **Comment** **Week 8 or later** / **Both sputum cultures are contaminated** / **Yes** / **Provide additional samples until a positive or negative result is reported, or it is confirmed that the participant is unable to produce sputum** **At or after the last treatment visit (Week 17 or Week 26)** / **Previously converted to culture negative but now has an MTB-positive culture** / **Yes** / **Provide additional samples at least 7 days after the previous sample until the result is confirmed, or it is confirmed that the**	46

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<tr><th>#</th><th>Section</th><th>Previous Text
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<table>
<tr><td></td><td></td><td></td><td>participant is unable to produce sputum.</td></tr>
<tr><td>End of Follow-up Period (Week 52 and 104) Early Withdrawal, if applicable</td><td>Participant's primary outcome status cannot be confirmed by: 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</td><td>Yes</td><td>Provide additional samples at least 7 days after the previous sample until one of the criteria is met and the primary outcome status can be determined.</td></tr>
</table>

If the Investigator is unsure of the outcome in any of the above scenarios, the Investigator should ~~is to~~ contact the Sponsor Medical Monitor to discuss and agree on how the participant is to be managed.
</td><td></td></tr>
<tr><td>47</td><td>Protocol Section 5.4.4 Early Withdrawal due to TB</td><td>The participants will be provided with a referral letter from the Investigator to take with them to the TB clinic. A follow-up call will be made by the trial site staff to the clinic to ensure the participant attended the clinic.</td><td>The participant will be provided with a referral letter from the Investigator to take with them ~~to the TB clinic~~ their National Treatment Program (NTP) clinic and the referral letter, at a minimum, should include all treatment received by the participant and information about any suspected/confirmed adverse event/reaction related to any of the trial IMP's and or concomitant medications. A follow-up call ~~will~~ should be made by the trial site staff to the clinic to ensure the participant attended the NTP clinic.</td><td>47</td></tr>
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48	Protocol Section 7.1 Demographic and Background Variables and Procedures	Screening coached spot sputum samples: ○ Smear microscopy for acid-fast bacilli ○ Gene Xpert, Hain Assay MTBDRplus or equivalent to determine MTB complex and rifamycin resistance	Screening coached spot sputum samples: ○ Smear microscopy for acid-fast bacilli ○ ~~Gene Xpert~~ **Rapid molecular tests for isoniazid, rifampicin, fluoroquinolones resistance** (Hain MTBDRplus and **HainMTBRsl**) ○ **Liquid Culture (MGIT) for Mycobacterium tuberculosis (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive.**	48
49	Protocol Section 7.1 Demographic and Background Variables and Procedures	Method of birth control: male and female participants and their partners	Method of birth control: male and female participants and their **sexual** partners	49

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50	Protocol Section 7.5 Mycobacteriology Characterisation Variable and Procedures	Mycobacteriology Characterization Variable and Procedures The following Mycobacterial Characterization variables will be collected: Positive Culture (for MTB) from: • Day 1 or if Day 1 is not available, first positive result between screening through Week 4 • Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be sub-cultured and sent to the central microbiology laboratory from the applicable local microbiology laboratory, for relevant participants / no positive cultures from screening through week 4 • When applicable, at last visit of the treatment period (Week 17 for the 4-month treatment arm and Week 26 for the 6-month treatment arm) or visits with positive cultures, during the post-treatment follow-up period The MTB isolates will be processed at the central microbiology laboratory for: • MIC against bedaquiline, pretomanid and moxifloxacin • Drug Susceptibility Testing in liquid culture for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide, and second line TB drugs including but not limited to fluoroquinolones, and injectables • Extraction of organismal (MTB) DNA for whole genome sequencing, and the comparison of sequences from baseline and relapse isolates.	Mycobacteriology Characterization Variable and Procedures ~~The following Mycobacterial Characterization variables will be collected:~~ ~~Positive Culture (for MTB) from:~~ • **Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative).** • ~~Pre-screening culture that was used for the tests that qualified the participant for inclusion into the trial to be sub-cultured and sent to the central microbiology laboratory from the applicable local microbiology laboratory, for relevant participants / no positive cultures from screening through week 4~~ • **MTB confirmed positive cultures (after the participant has previously converted to negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.** • **Refer to the Mycobacteriology Laboratory Manual for full details.** **Mycobacterial Characterization** - MTB isolates **(from the first MTB positive culture)** will be processed for: • **Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);** • **Minimum Inhibitory Concentration** (MIC) against bedaquiline, pretomanid, and moxifloxacin; • DST ~~in liquid culture~~ for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, and	50

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#	Section	Previous Text Russia Version 1.0 dated 21-Feb-18	Amended Text Version 2.0 dated 15-Jan-19 Additional text - bold font. Deleted text – strike-through.	Reason for Change Insert reason # from table above
		All Day 1 (Baseline) MTB isolates and isolates from positive cultures to be stored at the local and central microbiology laboratories, until trial closure. Extracted MTB DNA to be stored at the central microbiology laboratory until trial closure. The extracted MTB DNA and isolates will then be stored for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure. The MTB isolates will be processed at the trial microbiology laboratories for positive MTB complex at/after the last visit of the treatment period (Week 17 for the 4-month treatment arm and Week 26 for the 6-month treatment arm) via Hain MTBDR*plus* and HainMTBR*sl*.	pyrazinamide, ~~and second line TB drugs including but not limited to fluoroquinolones, and injectables~~ **in liquid culture**; • Extraction of organismal (MTB) DNA for whole genome sequencing **(WGS),** and comparison of sequences from baseline and relapse isolates. **If the participant's culture converts to negative and has a MTB positive culture at or after the last visit of the treatment period (Week 17 and Week 26), the MTB cultures** ~~isolates will be processed~~ **will be tested at the trial mycobacteriology laboratories** ~~for positive MTB complex~~ **using Hain MTBDR*plus* and HainMTBR*sl* to detect resistance to isoniazid, rifampicin, fluoroquinolones and injectables.** All ~~Day 1 (Baseline)~~ MTB isolates and isolates from positive cultures to must be stored at the local mycobacteriology laboratories, until trial closure. **In addition**, MTB ~~DNA~~ **isolates as well as extracted MTB DNA from the applicable baseline and follow-up cultures** will be stored at the central mycobacteriology laboratory for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure.	
51	Protocol Section 8.2.1 Follow-up of Adverse Events	New or updated information will be recorded in the originally completed CRF and submitted to the Sponsor within 24 hours of receipt, per SAE reporting guidelines.	New or updated SAE information will be recorded in the originally completed CRF and submitted to the Sponsor within 24 hours of receipt, per the ~~SAE~~ **eCRF Completion Guideline.**	51

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52	Protocol Section 8.2.6 Pregnancy	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: • Any time during the trial • Within 6 months after the last dose of IMP	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) **at any time during the trial.** ~~for the following time-periods:~~ ~~• Any time during the trial~~ ~~• Within 6 months after the last dose of IMP~~	52
53	Protocol Section 8.3 Monitoring for Specific Toxicities	Neurological Participants co-administration with a serotonergic agent, including anti-depressants, should be monitored closely for signs of serotonin syndrome. The Investigator should determine whether the full regimen or the concomitant agent should be discontinued for those who experience signs or symptoms of serotonin syndrome such as cognitive dysfunction, hyperrexia, hyperreflexia and incoordination.	~~Neurological~~ ~~Participants co-administration with a serotonergic agent, including anti-depressants, should be monitored closely for signs of serotonin syndrome. The Investigator should determine whether the full regimen or the concomitant agent should be discontinued for those who experience signs or symptoms of serotonin syndrome such as cognitive dysfunction, hyperrexia, hyperreflexia and incoordination.~~	53
54	Protocol Section 9.0 Statistical Analysis	Statistical Analysis The statistical analysis plan (SAP), which will contain details of the analyses specified in this section, will be written and signed off prior to first patient randomized.	Statistical Analysis The statistical analysis plan (SAP), which will contain details of the analyses specified in this section, will be written and signed off prior to **the interim analysis.** **There will be 3 data analyses and trial reports generated for this trial:** **- When all participants have completed 8 weeks (2 months) of treatment from baseline.** **- When all participants have completed 52 weeks (12 months) follow-up from start of therapy.** **- When all participants have completed 104 weeks (24 months) follow-up from start of therapy.**	54

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55	Protocol Section 11.3 Protocol Deviations	A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Monitoring Plan requirements.	A protocol deviation is any noncompliance with the clinical trial protocol **and** GCP ~~or Monitoring Plan requirements~~.	55
56	Appendix 6 Appendix 7 Appendix 8	TB Symptom Profile **TUBERCULOSIS SYMPTOM PROFILE (V3)** This questionnaire asks about symptoms that patients with tuberculosis may or may not experience. Please read each symptom carefully and think about your experience **during the past 7 days** when you make your response. Then tick (☑) one box for each symptom. If you **did not** experience the symptom **during the past 7 days**, please tick (☑) "None" for that symptom. If you **did** experience the symptom **during the past 7 days**, please tick (☑) whether the intensity of the symptom you experienced was "Mild", "Moderate" or "Severe". **TB Symptom** — **Rate your experience of each symptom over the past 7 days.** Feeling feverish: ☐ None ☐ Mild ☐ Moderate ☐ Severe Feeling chills: ☐ None ☐ Mild ☐ Moderate ☐ Severe Excessive sweating: ☐ None ☐ Mild ☐ Moderate ☐ Severe Shortness of breath: ☐ None ☐ Mild ☐ Moderate ☐ Severe Chest pain: ☐ None ☐ Mild ☐ Moderate ☐ Severe Feeling unwell: ☐ None ☐ Mild ☐ Moderate ☐ Severe Tiredness/weakness: ☐ None ☐ Mild ☐ Moderate ☐ Severe Cough: ☐ None ☐ Mild ☐ Moderate ☐ Severe Coughing up mucus: ☐ None ☐ Mild ☐ Moderate ☐ Severe Coughing up blood: ☐ None ☐ Mild ☐ Moderate ☐ Severe **During the past 7 days**, how would you rate your appetite? ☐ Good ☐ Fair ☐ Poor Approved, Issued Date 09-Apr-2012 Patient Reported Health Status Questionnaire	~~TB Symptom Profile~~ ~~Patient Reported Health Status Questionnaire~~	56

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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 ❑

2

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		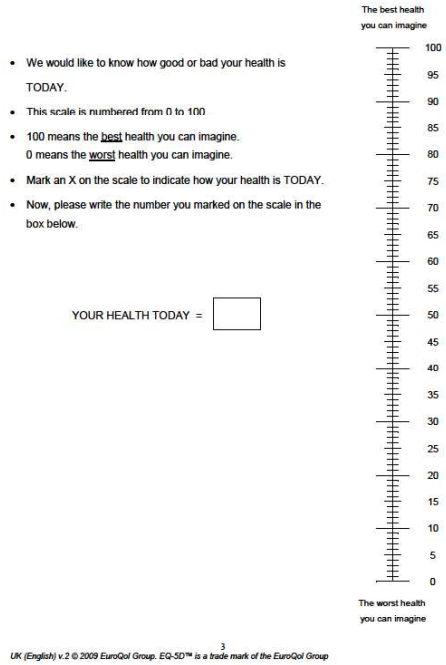 The best health you can imagine 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 The worst health you can imagine • We would like to know how good or bad your health is TODAY. • This scale is numbered from 0 to 100. • 100 means the best health you can imagine. 0 means the worst health you 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 = 3 UK (English) v.2 © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group Liver Toxicity Management Standard anti-TB chemotherapy is known to cause derangement of liver function tests in a substantial number of patients. In many cases this will be asymptomatic and self-limiting. In some cases, severe hepatitis and even fulminant liver failure and death can occur. In pre-marketing clinical trials of new drugs and regimens it is especially important to identify and carefully manage	~~Liver Toxicity Management~~ ~~Standard anti-TB chemotherapy is known to cause derangement of liver function tests in a substantial number of patients. In many cases this will be asymptomatic and self-limiting. In some cases, severe hepatitis and even fulminant liver failure and death can occur.~~ ~~In pre-marketing clinical trials of new drugs and regimens it is especially important to identify and carefully manage any trial participants who are at risk of progression to~~	

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		any trial participants who are at risk of progression to serious liver injury. The observation of altered liver function to a degree that has a high risk of progressing to liver failure as been referred to informally as Hy's Law;[44, 45]; this reflects that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components: 1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo. 2. Among trial participants showing such aminotransferase (AT) elevations, often with ATs much greater than 3x ULN, one or more also show elevation of serum total bilirubin (TBL) to >2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase (ALP)). 3. No other reason can be found to explain the combination of increased AT and total bilirubin level (TBL), such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury. During the trial, liver function will be monitored regularly with clinical assessment and blood tests in trial participants and this will assist in follow up laboratory measurements that can document either resolution of abnormalities or signal the potential for drug-induced liver injury (DILI). In a clinical trial of new drugs and combinations it is especially important for Investigators to follow closely any participants who have evidence of hepatic inflammation or potential toxicity. The	~~serious liver injury. The observation of altered liver function to a degree that has a high risk of progressing to liver failure as been referred to informally as Hy's Law;[44, 45]; this reflects that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components:~~ ~~4. 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.~~ ~~5. Among trial participants showing such aminotransferase (AT) elevations, often with ATs much greater than 3x ULN, one or more also show elevation of serum total bilirubin (TBL) to >2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase (ALP)).~~ ~~6. No other reason can be found to explain the combination of increased AT and total bilirubin level (TBL), such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.~~ ~~During the trial, liver function will be monitored regularly with clinical assessment and blood tests in trial participants and this will assist in follow up laboratory measurements that can document either resolution of abnormalities or signal the potential for drug-induced liver injury (DILI). In a clinical trial of new drugs and combinations it is especially important for Investigators to follow closely any participants who have evidence of hepatic inflammation or potential toxicity. The following procedure describes the management of~~	

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		following procedure describes the management of deranged liver function tests in trial participants. Procedure Blood tests for liver function will be taken routinely at screening (Day -9 to -1) and at the specific time points designated in the protocol, and at Early Withdrawal. If at any other visit the clinician suspects derangement of liver function, e.g. the participant describes nausea and vomiting, right upper abdominal pain or is jaundiced, blood should be taken for liver function tests and the participant comprehensively assessed for evidence of hepatitis or hepatic impairment and any potentially contributing causes. Suspected liver toxicity (or elevated liver enzymes detected in the absence of symptoms) must be taken seriously and detailed guidance will be provided in a separate document, Management of Hepatotoxicity Guideline. Investigators should refer to this document as a guide to management in cases of suspected or proven liver toxicity. Importantly, the Sponsor Medical Monitor is available to provide further assistance if there is any uncertainty or additional questions. The laboratory source (print-out of any results) should be stored alongside or transcribed into the clinical source document. Each abnormal value should be marked as clinically significant (CS) or non-clinically significant (NCS); the assessment of significance is at the discretion of the Investigator. All clinically significant abnormal results must be recorded as Adverse Events in the eCRF and graded clinically as per the DMID adult toxicity table grading, (Appendix 2). Assessments and decision making for elevations in aminotransferase values	~~deranged liver function tests in trial participants.~~ ~~Procedure~~ ~~Blood tests for liver function will be taken routinely at screening (Day -9 to -1) and at the specific time points designated in the protocol, and at Early Withdrawal. If at any other visit the clinician suspects derangement of liver function, e.g. the participant describes nausea and vomiting, right upper abdominal pain or is jaundiced, blood should be taken for liver function tests and the participant comprehensively assessed for evidence of hepatitis or hepatic impairment and any potentially contributing causes.~~ ~~Suspected liver toxicity (or elevated liver enzymes detected in the absence of symptoms) must be taken seriously and detailed guidance will be provided in a separate document, Management of Hepatotoxicity Guideline. Investigators should refer to this document as a guide to management in cases of suspected or proven liver toxicity. Importantly, the Sponsor Medical Monitor is available to provide further assistance if there is any uncertainty or additional questions.~~ ~~The laboratory source (print-out of any results) should be stored alongside or transcribed into the clinical source document. Each abnormal value should be marked as clinically significant (CS) or non-clinically significant (NCS); the assessment of significance is at the discretion of the Investigator. All clinically significant abnormal results must be recorded as Adverse Events in the eCRF and graded clinically as per the DMID adult toxicity table grading, (Appendix 2). Assessments and decision making for elevations in aminotransferase values~~	

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		or bilirubin of various levels of concern are detailed below:	~~or bilirubin of various levels of concern are detailed below:~~	
		Elevated liver enzymes considered of clinical significance, but not accompanied by other signs and symptoms, should be reported as an adverse event and should usually be recorded as elevated liver enzymes. If the term "hepatitis" is used, the Safety Data Manager will question the site for additional evidence to support the diagnosis, such as clinical signs and serological or biopsy data. While a liver biopsy is not required to make a diagnosis of hepatitis, the term "hepatitis" should be reserved in most instances for cases where there is supportive evidence beyond a liver enzyme abnormality. However, if the Investigator will confirm the diagnosis of hepatitis just on the basis of clinical signs and laboratory values the diagnosis will be accepted. Should other symptoms or signs be present, these should also be recorded as adverse events.	~~Elevated liver enzymes considered of clinical significance, but not accompanied by other signs and symptoms, should be reported as an adverse event and should usually be recorded as elevated liver enzymes. If the term "hepatitis" is used, the Safety Data Manager will question the site for additional evidence to support the diagnosis, such as clinical signs and serological or biopsy data. While a liver biopsy is not required to make a diagnosis of hepatitis, the term "hepatitis" should be reserved in most instances for cases where there is supportive evidence beyond a liver enzyme abnormality. However, if the Investigator will confirm the diagnosis of hepatitis just on the basis of clinical signs and laboratory values the diagnosis will be accepted. Should other symptoms or signs be present, these should also be recorded as adverse events.~~	
		Temporarily Stopping and Restarting Trial Medication	~~Temporarily Stopping and Restarting Trial Medication~~	
		Liver function tests that are improving should be repeated regularly, such as every 3 days for the first week then once a week until they return to near baseline values for the participant. Manage the participant symptomatically as required using medications that are not potentially hepatotoxic and discontinue any concomitant drugs, if clinically warranted, that may be hepatotoxic. Infection control issues must be carefully managed whilst TB medications are being withheld, especially if the participant is still culture positive for acid fast bacilli.	~~Liver function tests that are improving should be repeated regularly, such as every 3 days for the first week then once a week until they return to near baseline values for the participant. Manage the participant symptomatically as required using medications that are not potentially hepatotoxic and discontinue any concomitant drugs, if clinically warranted, that may be hepatotoxic. Infection control issues must be carefully managed whilst TB medications are being withheld, especially if the participant is still culture positive for acid fast bacilli.~~	
		If trial medication has been temporarily stopped, once the liver function values have decreased	~~If trial medication has been temporarily stopped, once the liver function values have decreased~~	

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		substantially a decision must be made about further TB management. This will be dependent on the clinical context and a decision must be made in discussion with the Sponsor Medical Monitor. Investigational treatment can only be restarted if the Sponsor Medical Monitor is in agreement with the plan. In all cases treatment should be recommenced under close supervision for any evidence of recurrent liver function abnormalities. If there is a further significant elevation of hepatic enzymes or bilirubin or symptoms of clinical concern after resumption of trial medication, the trial medication should be withdrawn permanently. Participants who permanently discontinue trial medication should be managed as clinically indicated according to local National TB Programme guidelines. The Sponsor Medical Monitor can be contacted for further advice when referring to the National Treatment Program. The Sponsor Medical Monitor is available to assist the Investigators in both the management of liver toxicity and decisions regarding the holding or re-introduction of trial medication. Investigators must involve the Sponsor Medical Monitor in any decisions regarding medication hold or re-start, and there should always be a low threshold for contacting the Sponsor Medical Monitor in cases of elevated liver enzymes.	~~substantially a decision must be made about further TB management. This will be dependent on the clinical context and a decision must be made in discussion with the Sponsor Medical Monitor. Investigational treatment can only be restarted if the Sponsor Medical Monitor is in agreement with the plan. In all cases treatment should be recommenced under close supervision for any evidence of recurrent liver function abnormalities.~~ ~~If there is a further significant elevation of hepatic enzymes or bilirubin or symptoms of clinical concern after resumption of trial medication, the trial medication should be withdrawn permanently. Participants who permanently discontinue trial medication should be managed as clinically indicated according to local National TB Programme guidelines. The Sponsor Medical Monitor can be contacted for further advice when referring to the National Treatment Program.~~ ~~The Sponsor Medical Monitor is available to assist the Investigators in both the management of liver toxicity and decisions regarding the holding or re-introduction of trial medication. Investigators must involve the Sponsor Medical Monitor in any decisions regarding medication hold or re-start, and there should always be a low threshold for contacting the Sponsor Medical Monitor in cases of elevated liver enzymes.~~	

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I agree to the terms of this Protocol Russia Amendment #1.

DocuSigned by: Morounfolu Olugbosi Signer Name: Morounfolu Olugbosi Signing Reason: I approve this document Signing Time: 1/25/2019 6:46:43 AM EST 3DABF6C3410E4B8F85E1D6E511FA5A5F	Morounfolu Olugbosi	January 25, 2019 | 3:46 AM PST
Signature of Study Physician	Printed name	Date

Principal Investigator

I hereby confirm I have read the above Protocol Amendment or Protocol Administrative Change and agree to conduct this clinical trial as outlined in the above. I will provide copies of the Protocol Amendment or Protocol Administrative Change and access to all of the information required to conduct the clinical trial according to the above Protocol Amendment or Protocol Administrative Change to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature of Principal Investigator	Printed name	Date

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ID: 8028570c-617d-4406-b419-ac9d8a5cc392

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Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/25/2019 6:07:00 AM
Certified Delivered	Security Checked	1/25/2019 6:46:23 AM
Signing Complete	Security Checked	1/25/2019 6:46:47 AM
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Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
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Protocol Number:	NC-008 (BPaMZ)
Title:	An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).
Drug(s)/Combination(s):	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Version/Date:	Russia V3.0 / 1 October 2019, Incorporating Protocol V4.0 / 30 September 2019
Protocol Name:	SimpliciTB

PROTOCOL SIGNATURE PAGE

Protocol Title: An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).

Protocol Number: **NC-008 (BPaMZ)**

Protocol Date: **Russia V3.0 / 1 October 2019, Incorporating Protocol V4.0 / 30 September 2019**

Protocol Name: **SimpliciTB**

SPONSOR: **TB Alliance**

I agree to the terms of this trial protocol.

DocuSigned by:
Morounfolu Olugbosi
Signer Name: Morounfolu Olugbosi
Signing Reason: I approve this document
Signing Time: October 2, 2019 | 10:05 AM PDT
3DABF6C3410E4B8F85E1D6E511FA5A5F

Signature of Study Physician

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PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).

Protocol Number: **NC-008 (BPaMZ)**

Protocol Date: **Russia V3.0 / 1 October 2019, Incorporating Protocol V4.0 / 30 September 2019**

Protocol Name: **SimpliciTB**

I hereby confirm that I have read the above protocol and agree to conduct this clinical trial as outlined in the above protocol. I will provide copies of the protocol and access to all the information required to conduct the clinical trial according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

_____ _____
Signature Printed Name

_____
Date

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Abbreviations and Definition of Terms

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AFB	Acid-fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AREDS2	Age Related Eye Disease Scale 2
ART	Anti-Retroviral Therapy
AST	Aspartate aminotransferase
AUC_{τ}	Area Under Curve over a dosing interval
B	Bedaquiline
BA	Bacterial activity
BMI	Body Mass Index
BPaMZ	Combination of bedaquiline plus pretomanid plus moxifloxacin plus pyrazinamide
C	Clofazimine
CFU	Colony Forming Units
$C_{(max), (min)}$	plasma Concentration (maximum), (minimum)
CO_2	Carbon dioxide
CPK	Creatine Phosphokinase
CYP3A4	Cytochrome P450 3A4
DMID	Division of Microbiology and Infection Disease
DNA	Deoxyribonucleic Acid
DR-TB	Drug-resistant tuberculosis For this particular protocol defined as TB participants with 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB) (participants with fluoroquinolone resistance are excluded)
DS-TB	Drug-sensitive tuberculosis
DSMC	Data Safety and Monitoring Committee
DST	Drug Susceptibility Testing
E	Ethambutol
EBA	Early Bactericidal Activity
EC	Ethics Committee
ECG	Electrocardiogram
EFV	Efavirenz
(e)CRF	(electronic) Case Report Form
EMS	Early Morning Sputum
EWD	Early Withdrawal
FTC	Emtricitabine
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
H	Isoniazid
HR	Hazard Ratio
hERG	Human *Ether-à-go-go* Related Gene
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
HR	Isoniazid plus rifampicin combination tablet

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent to Treat
IUATLD	International Union Against Tuberculosis and Lung Disease
IWRS	Interactive Web Randomization System
kg	Kilogram
L	Linezolid
LH	Luteinizing hormone
LLN	Lower Limit of Normal
LPV	Lopinavir
LTFU	Lost to follow-up
M	Moxifloxacin
MBD	Minimum Bactericidal Dose
MIC	Minimum Inhibitory Concentration
MTB	*Mycobacterium tuberculosis*
MDR-TB	Multi Drug Resistant Tuberculosis
MGIT	Mycobacterial Growth Inhibiting Tube
mITT	Modified Intent to Treat
ms	millisecond
NVP	Nevirapine
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
NRTI	(Triple) Nucleosidase Reverse Transcriptase Inhibitor
Pa	Pretomanid
PD	Pharmacodynamic
PP	Per Protocol
PK	Pharmacokinetic
PR	PR interval
R	Rifampicin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSCC	Serial sputum colony counting
TB	Tuberculosis
TDF	Tenofovir
TEAE	Treatment Emergent Adverse Events
TTP	Time to Positivity
ULN	Upper Limit of Normal
WGS	Whole Genome Sequencing
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis
µg(/ml)	micrograms (per millilitre)
Z	Pyrazinamide (tablets)

1.0 Synopsis

1.1 Synopsis Summary

Synopsis	Description
Name of Sponsor/Company	TB Alliance
Name of Finished Products	Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Protocol Number/Title	NC-008 (BPaMZ) An Open-Label, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month Treatment of HRZE/HR (Control) in Adult Participants with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis (DS-TB) and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB)
Treatment Indication	Pulmonary Tuberculosis (TB)
Trial Objective(s)	To evaluate the efficacy, safety and tolerability at 8 weeks (2-months), 52 weeks (12-months), and 104 Weeks (24-months) post the start of the treatment regimens in participants with Drug Sensitive TB (DS-TB) and Drug Resistant TB (DR-TB). DR-TB is defined as participants with: 1. mono-resistance to rifampicin or isoniazid, OR 2. resistance to both rifampicin and isoniazid (MDR-TB)
Trial Design	Phase 2c multi-centre, open-label, partially randomized clinical trial in Drug Sensitive-TB (DS-TB) and Drug Resistant-TB (DR-TB) participants. All participants will enter post-treatment follow-up which continues until Week 104 from start of treatment / randomisation. **Participants with DS-TB:** Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 weeks (4 months), or HRZE/HR tablets daily for 26 weeks (6 months). Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation. **Participants with DR-TB:** Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td>Participant Population</td><td>Up to 450 male and female participants, diagnosed with DS-TB or DR-TB, aged 18 years and over with a target of up to 50% being HIV positive.

300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation.

Up to 150 DR-TB participants will be enrolled.</td></tr>
<tr><td>Test Product, Dose and Mode of Administration</td><td>The Test Product (BPaMZ) consists of a combination of the following products and will be supplied as:
<table>
<tr><th>Product</th><th>Tablet Strength</th><th>Abbreviation</th></tr>
<tr><td>Bedaquiline</td><td>100 mg</td><td>(B)</td></tr>
<tr><td>Pretomanid</td><td>200 mg</td><td>(Pa)</td></tr>
<tr><td>Moxifloxacin</td><td>400 mg</td><td>(M)</td></tr>
<tr><td>Pyrazinamide</td><td>500 mg</td><td>(Z)</td></tr>
</table>
Instructions for Dosing BPaMZ:

Investigational Medicinal Product (IMP) will be administered orally once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months) in the following dosing schemes:

Participants with DS TB:
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 17 weeks (total treatment duration 4 months)

OR

Participants with DR-TB:
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 26 weeks (Total treatment duration 6 months).</td></tr>
<tr><td>Positive Control Product, Dose and Mode of Administration</td><td>The Control Treatment Regimen (HRZE/HR) will be supplied as:

HRZE Tablets: isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets. This combination will be given for the first 8 weeks.

AND

HR Tablets: isoniazid 75 mg plus rifampicin 150 mg combination tablets. This combination will be given from Weeks 9 to 26.</td></tr>
</table>

<table>
<tr><th>Synopsis</th><th>Description</th></tr>
<tr><td></td><td>
Instructions for Dosing Control Treatment Regimen

To be taken with a glass of water (approximately 240 ml). HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes:

Treatment will be administered orally once daily to the HRZE/HR randomized DS-TB participants as follows:

Weeks 1-26: HRZE/HR tablets daily dose per the participant’s weight as follows:
<table>
<tr><th>Weight Band</th><th>Weight Range</th><th>Number of tablets</th></tr>
<tr><td>1</td><td>30-39 kg</td><td>2</td></tr>
<tr><td>2</td><td>40-54 kg</td><td>3</td></tr>
<tr><td>3</td><td>55-70 kg</td><td>4</td></tr>
<tr><td>4</td><td>≥ 71 kg</td><td>5</td></tr>
</table>
The participant’s weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and HRZE and HR dose to administer.

Vitamin B6 daily supplement to be taken with the HRZE/HR treatment, as per each country’s TB Treatment Guidelines.
</td></tr>
<tr><td>Treatment Interruptions/Pauses</td><td>
For All Trial Regimens
The trial treatment regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor’s Medical Monitor prior to implementation, unless an interruption/pause is required urgently for a safety concern.
Action required for participants missing the following number of doses within the trial treatment regimens:

Up to 7 consecutive doses: restart treatment, no extension of treatment required.
If more than 7 and to ≤ 35 consecutive doses missed, before the end of the treatment period (Week 17/26): restart treatment, extend the treatment by the number of consecutive doses missed. In this case, the last visit of the treatment period should also be pushed out to the date of the last dose
If more than 35 consecutive doses: discontinue treatment and withdraw participant from the trial
If the participant misses a total of 56 cumulative missed doses, discontinue the IMP and withdraw the participant from the trial.

</td></tr>
</table>

Synopsis	Description
	• If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose, that was missed. Any participant for whom the trial IMP is discontinued (including for non-adherence) should be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial IMP as soon as possible.

Statistical Methods:
A general description of the statistical methods planned to be used to analyse efficacy data is outlined below. Specific details will be provided in the statistical analysis plan (SAP,) which will be written and signed off prior to the interim analysis.

Criteria for Evaluation

Primary Endpoint

The primary efficacy endpoint will be time to culture negativity over 8 weeks. The primary hypothesis to be evaluated is:

- In the participants with DS-TB in the experimental BPaMZ treatment regimen, the time to culture negativity by 8 weeks will be superior, compared to the participants who are treated with the standard HRZE/HR regimen.

Secondary Endpoints

- A key secondary efficacy endpoint will be the proportion of participants experiencing bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks.

The hypothesis to be evaluated for this endpoint is:

- In the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE/HR regimen.

Abbreviated Definitions, full definitions will be described in the Statistical Analysis Plan (SAP):

- Bacteriologic failure: During the treatment period, failure to attain or maintain culture conversion to negative.
- Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status, with culture conversion to positive status with a strain of *Mycobacterium tuberculosis* (MTB) genetically identical to the infecting strain at baseline.
- Clinical failure: A change from protocol-specified TB treatment to a new regimen before end of protocol specified treatment due to treatment failure, retreatment for TB during follow up, or TB-related death.

Synopsis	Description

Note:

- Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.
- Participants who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit.

Other Secondary Endpoints

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 104 weeks from the start of treatment.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of treatment.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
- Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
- Quantitative and qualitative electrocardiogram (ECG) results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones.
- Changes in lens opacities.

These data will be presented as descriptive analyses, and no inferential tests will be carried out.

Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD):

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [Cmin], maximum plasma concentration [Cmax], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide.

Effects of baseline covariates on exposure will be assessed; so too, will the effects of concomitant medications, including antiretroviral therapy (ART), where feasible. Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

Synopsis	Description

Exploratory Objectives:

Evaluate whether any of the secondary endpoints predict relapse free cure. Subgroup analysis of populations by HIV status will be performed.

No formal statistical comparisons will be made for the participants enrolled with DR-TB. The responses of participants with DR-TB receiving BPaMZ will be compared for consistency with those responses of the DS-TB participants on the same regimen.

Sample Size

Primary endpoint: 150 participants per arm (DS-TB patients) will provide at least 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks.

Additional efficacy parameters will be evaluated including the incidence of bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks and 104 weeks from the start of treatment. Time to unfavourable outcome from assignment of trial treatment through follow-up as a function of time will be analysed using Kaplan-Meier analysis.

Interim Analysis

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

  *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objective**

  *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

Synopsis	Description
To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46,47,48] and full details are provided in the Statistical Analysis Plan.	
Trial Duration: Approximately 4 years (18-month enrolment period for DS-TB participants, up to 26 week-treatment, and follow-up until 104 weeks from start of treatment). Depending on the DR-TB recruitment rate, enrolment into this arm may continue after enrolment into the DS-TB arms are complete.	

1.2 Synopsis Flow Chart and Procedures

Period	Screen-ing[a]	Treatment															Follow-Up[c]					
Visit[b]	Day -9 to -1	Day 1 (Baseline)[d]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 17 *4-mth treatment*[e]	Week 17 *6-mth treatment*[e]	Week 22	Week 26 *4-mth treatment*[e]	Week 26 *6-mth treatment*[e]	Week 39	Week 52	Week 65	Week 78	Week 104	Early Withdrawal[c]
Visit Window[v]	N/A	+/- 3 Days									+/- 5 Days						+/- 14 Days					
Written Informed Consent	X																					
Demography	X																					
Medical/Treatment/ Smoking History	X																					
Inclusion/Exclusion	X	X																				
Sputum Sampling[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Status[h] and CD4 Count[i]	X																					
Karnofsky Score[x]	X																					
Urine Drug Screen[j]	X																					
Urine Pregnancy Test[k]	X	X								X		X	X		X	X						X
Laboratory Safety Test[l]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X						X
Male Reproductive Hormone Tests[m]	X	X										X				X	X					X
12-lead ECG[n]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X					X
Chest X-Ray[o]	X																					
TB Symptoms Profile	X	X		X		X				X		X	X		X	X		X			X	X
Patient Reported Health Status	X	X		X		X				X		X	X		X	X		X			X	X
Vital Signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination[p]	X											X			X	X	X					X
Physical Examination – full[q]	X	X										X				X						X
Physical Examination – limited[r]			X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Pharmacokinetic Sampling[s]		X		X						X	X	X	X				X		X	X	X	
IMP Randomization/ Assignment[t]		X																				
IMP Compliance Check[u]			X	X	X	X	X	X	X	X	X	X	X	X[e]		X						X[t]
Concomitant Medications	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
Investigator Assessment[v]																		X			X	

GENERAL: Vital signs and blood draws are to be performed before dosing, unless otherwise specified. Vital signs and/or ECGs should be done before blood draws (safety and PK) on days with those assessments.

a. **Screening:** Screening assessments can occur on different days within nine days before to Day 1 (Baseline).

b. **Visit Schedule (due to unforeseen circumstances):** If the duration of treatment is extended due to dose interruptions / pauses (7 to ≤ 35 consecutive doses), the last visit of the corresponding treatment period should also be pushed out to the date of the last dose. It is not necessary to have an unscheduled visit at the time that the last visit of the treatment period would have been scheduled on.

c. **Follow-up Visits for Early Withdrawal Participants:** Once a participant has been permanently withdrawn from the trial, they will be required to attend an Early Withdrawal visit (Week 52, if not already performed) and Week 104 follow-up visits. The Week 52 and Week 104 visits will be performed to collect Serious Adverse Event (SAE) information (including verification of survival) and the participant reported TB outcome information only, and may be performed telephonically, at home or a site visit. Visits will occur at Week 52 and/or Week 104 after the participant's start of treatment date. Refer to Table 5 for additional guidance.

d. **Day 1 (Baseline):** All procedures are to be completed before dosing.

e. **Last Visit of the Treatment Period:** Investigational Medicinal Product (IMP) Compliance Check is not performed at the Week 22 visit for participants who have completed treatment at Week 17.

f. **Sputum Sampling:** The sputum sampling methodology/requirements and tests will be described in a separate document, the Mycobacteriology Laboratory Manual.

- Screening (Days -9 to -1). Two spot sputum samples taken 30 minutes apart will be collected at the research site under the coaching and observation of the trial staff. The following analyses will be performed on the first of these samples:
  - Smear microscopy for acid-fast bacilli (AFB);
  - Rapid molecular tests for fluoroquinolones, isoniazid and rifampicin resistance (Hain MTBDplus and Hain MTBRsl);
  - Liquid Culture (MGIT) for *Mycobacterium tuberculosis* (MTB), followed by a speciation test to detect the presence or absence of MTB and obtain the time to positivity (TTP) when positive.
  - The second sample is collected as a back-up sample to the first sample in case it is technically not possible to obtain a result/s from the first sample. If the Screening spot sputum smear shows an indeterminate result or is AFB negative, the test may be repeated on the back-up sample or on a freshly collected spot sputum, and then that result will be used.
- Day 1 (Baseline) to Week 104 and Unscheduled visits for additional sputum samples:
  - Two sputum samples are collected, ideally one Early Morning Sputum (EMS) brought from home and one spot sputum sample at the research site, under the coaching and observation of the trial staff. If the participant forgets to bring in the EMS, then two spot sputum samples are to be collected at the site, at least 30 min apart, and this altered sample collection is captured within case report form (CRF).

- If both sputum cultures at Weeks 8 or later are contaminated, the participant should return for an unscheduled visit(s) to give additional sputum samples or to document that the participant is not able to produce a sputum sample.

- If after having converted to culture negative, and the participant has a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 or Week 26), the participant should return for an unscheduled visit/s to provide additional sputum samples, at a minimum of 7 days apart, or to document that the participant is not able to produce a sputum sample.
- Additional samples may be required to define a participants' primary outcome status as described in Sections 5.4.2 and 7.2.
- Liquid Culture (MGIT) for MTB, followed by a speciation test to detect the presence or absence of MTB and obtain TTP when positive, will be performed on all samples.

g. **Mycobacteriology Characterisation Tests performed:**

- Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative);
- MTB confirmed positive cultures (after the participant has previously converted to culture negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.
- Refer to Mycobacteriology Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for:

- Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);
- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid, and moxifloxacin;
- Drug Susceptibility Testing (DST) for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing (WGS), and comparison of sequences from baseline and relapse isolates.

h. **HIV Testing:** If HIV status is a confirmed known positive, a repeated HIV test is not needed provided that a documented HIV test result (ELISA, Western Blot or Electro-Chemiluminescence) is available. If the HIV status is unknown or suspected negative, a HIV test will be requested. If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 4 weeks prior to screening, it should not be repeated if documentation of testing method and negative HIV results can be provided. Repeated HIV testing, during the Screening period is permitted for indeterminate HIV results.

i. **CD4 Count:** Required for all HIV-positive participants.

j. **Urine Drug Screen:** Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates, at Screening only. Investigator to utilize this result to determine whether participant meets Exclusion Criteria 2. Positive results will not automatically exclude a participant from the trial.

k. **Urine Pregnancy Test:** Women of childbearing potential only, whether they are sexually active or not.

l. **Safety Laboratory Assessments**: The safety laboratory sampling methodology and requirements will be described in a separate document, the Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:

- Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count).
- Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/carbon dioxide [CO_2], creatine phosphokinase [CPK]). GGT is only routinely included at the Screening visit (Day -9 to -1).
- 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.
- When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator should request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].
- Hepatitis A, B and C serology test to be performed at Day 1 (baseline) or where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Russia Protocol V3.0.

m. **Male Reproductive Hormone Tests:** Testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin B to be done on male participants in ALL treatment groups.

n. **Single 12-Lead ECG:** ECGs to be performed prior to pre- and post-dose PK sampling as described below:

- Day 1: pre-dose (within 2 hours prior to dosing)
- Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 12: pre-dose (within 2 hours prior to dosing)
- Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose

Central ECG analysis will be performed. Results from central reading of Screening ECG must be used to determine eligibility.

o. **Chest X-Ray:** A chest x-ray (digital image only) within 6 months prior to or at the Screening visit, will be obtained and read locally by the Investigator or designee. Digital images will be provided to the Sponsor and this process will be described in a separate document, the Radiology Manual.

p. **Slit Lamp Ophthalmic Examination**: Slit lamp examination will be done at the Screening visit, the last visit of the treatment period (Week 17 or 26) and at Week 39 for both treatment groups. An additional slit lamp at Week 26 will be done for the 4-month treatment group. Slit lamp ophthalmology examination will be performed by an

Ophthalmologist with AREDS2 training. Ophthalmology examinations may occur at any time within the window period for the applicable visit i.e. they do not have to be performed on the same day as the trial procedures.

q. **Physical Examination, Full:** Height (m) will only be collected at Screening.

r. **Physical Exam, Limited:** Limited physical exams will include weight and gross neurological, pulmonary, cardiovascular and abdominal exam(s).

s. **Pharmacokinetic (PK) Sampling:** This process will be described in a separate document, the PK Sampling Manual. No PK samples will be collected for the HRZE/HR treatment arm. Blood draws for PK samples collected pre-and post-dose must be done after the ECG is performed. The dates and times of IMP taken prior to all pre-dose PK samples will be collected. Specific PK blood draws will be obtained as follows:

- *Day 1: pre-dose (within 2 hours prior to dosing)
- Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
- Week 12: pre-dose (within 2 hours prior to dosing)
- Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose
- Weeks 39, 65, 78 and 104 (for bedaquiline, bedaquiline metabolite M2): PK samples are to be obtained at any time on the day of the scheduled visit.

Only bedaquiline and M2 will be measured.

If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.

* Where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Russia Protocol V3.0.

t. **Investigational Medicinal Product (IMP) Randomization/Assignment:** Randomization/Assignment may occur once all the Screening results are available and the Investigator has determined that the participant is eligible for the trial.

u. **IMP/Compliance Check:** IMP administration will be supervised per local site practice to assure compliance to the regimen. Performed at all visits and Early Withdrawal (EWD), if during the treatment period.

v. **Investigator Assessment:** Investigator to review the participant status and assess whether IMP or TB treatment at Week 52 and 104 is considered a “success” or “failure”. If considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration. Investigator Assessment to be completed, at Week 52 and 104, and at any time the Investigator determines that the participant fulfils the criteria for outcome of treatment failure.

w. **Visit Windows**: The windows noted on the flowchart for timing of visit also apply to the timing *within a visit.* Procedures should be performed within +/- 3 days of scheduled visit from Day 1 to Week 8 or +/- 5 Days of scheduled visit from Week 12 to Week 26 or +/- 14 days of scheduled visit at or after Week 39. Sites should make every effort to ensure all procedures are done on the same day, when possible.

x. **Karnofsky Score**: Only to be performed on HIV+ participants.

2.0 Introduction and Rationale

2.1 Tuberculosis Disease

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in the developing countries of Africa, Asia and South America. TB is currently one of the top three killer infectious diseases, 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 40 years and are relatively ineffective in controlling TB as a public health problem. 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 participants, treatment takes 6 months or more to complete. This, long duration treatment **plus side effects**, result in poor adherence which particularly occurs after the second month of treatment.

The current TB treatment regimens and treatments for drug-sensitive TB are decades old. The available treatments have a lengthy duration of treatment, involve multi-drug therapy, and require large commitments of resources and infrastructure. High rates of noncompliance are common, which often results in increased mortality and chronic, infectious, drug-resistant cases. The present TB epidemic and the challenge of current treatment options demonstrate the clear need for effective novel TB drugs and **drug regimens** that are safe for drug sensitive and drug resistant TB disease and that are well-tolerated and will shorten the current treatment duration for patients.

The full application of the Directly Observed Treatment, Short-Course strategy is becoming more and more difficult in the developing countries of the world that are also battling to control the HIV-epidemic. Because of poor treatment adherence, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB are growing. Since the discovery of the rifamycins,[1] and their introduction into standard antituberculosis regimens, very few new classes of drugs have been evaluated with a view to their registration as antituberculosis agents. On December 28, 2012 the U.*S.* Food and Drug Administration approved bedaquiline (B) as part of combination therapy to treat adults with multi-drug resistant (MDR) pulmonary tuberculosis (TB) when other alternatives are not available. 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.

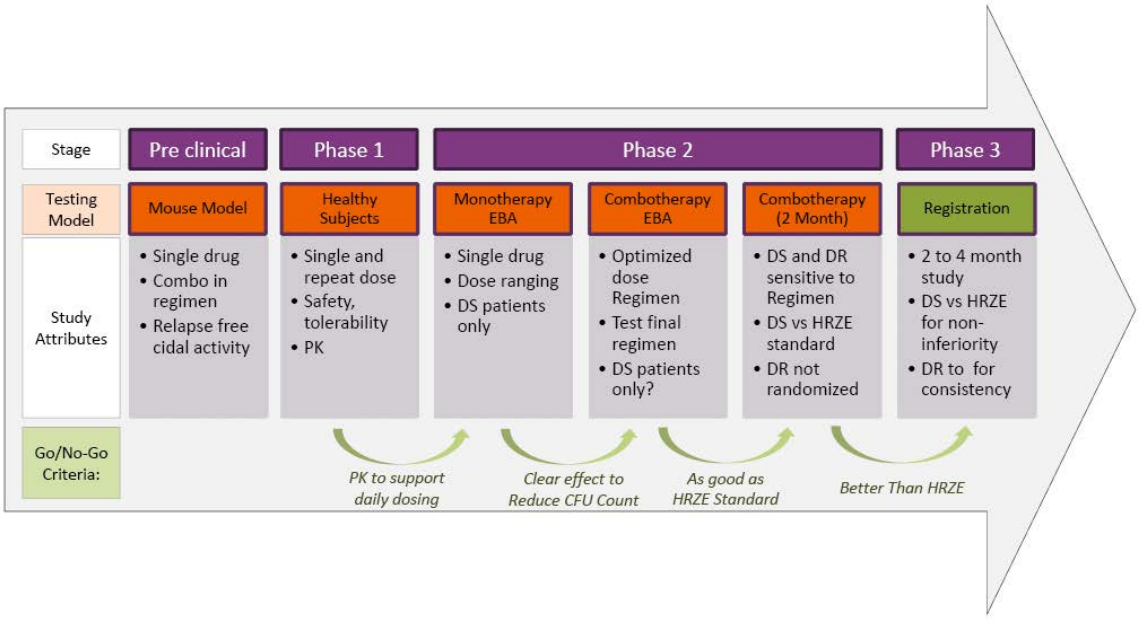
New combination regimens are desperately needed for two reasons: to shorten treatment to a duration more easily manageable by patients and public health services, and to provide more efficacious, safer and better tolerated, affordable treatments for the growing number of patients suffering from multidrug-resistant and extensively drug-resistant tuberculosis.

2.2 Tuberculosis Clinical Research

TB currently must be treated with multiple drugs to achieve maximal efficacy and prevent resistance. To transform treatment, novel TB regimens are needed. To telescope the time, it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm. This approach tests promising combinations of drugs together to find the most impactful treatment once the individual drug candidates have been tested in a robust pre-clinical program and the establishment of the individual drug candidates' safety and efficacy have been evaluated. It evaluates novel combinations of TB drugs — instead of single drugs — as part of a single development program, enabling the development of novel TB drug

regimens that have potential to transform treatment for drug-sensitive and drug-resistant tuberculosis. This approach offers the potential to reduce the time previously needed to develop a novel treatment regimen by up to 75%, shortening the clinical development from decades to years. The steps followed in this development model are shown in Figure 1 Between each step on the unified development pathway a decision is made as to whether to proceed.

Figure 1. Unified Drug Sensitive/Drug Resistant Regimen Development Path



Early Bactericidal Activity (EBA) Trials

EBA trials are the backbone clinical trials to quantify the bactericidal action of anti-tuberculosis agents alone or in combination by either trialling the fall in the number of colony forming units (CFU) or measuring the TTP in liquid culture of *M. tuberculosis* (*MTB*) present in the sputum of participants with microscopy smear-positive pulmonary TB. EBA trials have been conducted over 2, 5, 7 and 14 days.[2]. A review of EBA trials conducted on the key anti-TB drugs has shown the value these trials offer to demonstrate the early anti-TB effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in participants.[3]

8-week Bactericidal Activity (BA) Trials

EBA methodology of quantitative colony counting on solid medium has been adapted to Phase 2, 8-week TB treatment trials based on serial sputum colony counting (SSCC) or measurement of TTP liquid culture to provide a more sensitive efficacy endpoint than the previously used binary endpoint of rate of sputum conversion measured after 8 weeks of treatment.[4-6] Such trials are conducted to provide data on which to base the selection of treatment-shortening regimens.

2.3 Trial Rationale

The SimpliciTB NC-008 (BPaMZ) trial will evaluate and support that, in additional to previous studies evaluated with BPaMZ, this drug regimen (BPaMZ) will be safe and effective, is well-tolerated and could potentially shorten the current treatment duration compared to the standard HRZE/HR treatment for patients with drug sensitive TB disease. This trial will also evaluate if the BPaMZ drug regimen given for 6 months will be safe and effective in drug resistant TB disease.

Therefore, the trial design addresses the need to find and evaluate a potentially effective and shorter regimen compared to regimens (standard HRZE/HR) that are currently being used.

2.3.1 Trial Design Rationale

The SimpliciTB NC-008 (BPaMZ) trial is a Phase 2c multi-centre, open-label, partially randomized clinical trial in DS-TB and DR-TB participants. This trial is to evaluate the combination regimen of **Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) plus Pyrazinamide (Z)**, (BPaMZ), in participants with pulmonary TB.

All participants will enter post-treatment follow-up which continues until Week 104 after start of treatment / randomisation.

Participants with DS-TB:

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either:

- BPaMZ daily for 17 weeks (4 months),

OR

- HRZE/HR combination tablets daily for 26 weeks (6 months).

Participants will be stratified for co-infection with HIV and cavitation.

Participants with DR-TB are defined as:

1. mono-resistance to rifampicin or isoniazid, OR

2. resistance to both rifampicin and isoniazid (multi-drug resistant tuberculosis [MDR-TB])

Up to 150 participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months). Approximately 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation to either BPaMZ for 4 months or HRZE/HR for 6 months.

The trial is sufficiently statistically powered to not only show superiority of 8 Weeks culture conversion but should also demonstrate non-inferiority for cure at 52 Weeks (this is in the participants with DS-TB in the experimental BPaMZ treatment regimen, the proportion experiencing an unfavourable outcome will be non-inferior compared to the participants who are treated with the standard HRZE regimen).

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

  *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objectives**

  *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46, 47, 48] and full details are provided in the Statistical Analysis Plan.

As previously described in the background information, in order to telescope the time it takes to develop novel, tolerable multi-drug treatments, it is necessary to use the regimen development paradigm and utilize data generated in non-clinical and clinical studies regarding combining of anti-tuberculosis agents which could contribute significantly to the sterilization of lesions and thus treatment shortening. Therefore, the trial design and proposed trial regimen (BPaMZ**)** which is supported with previous non-clinical and clinical studies outlined below should address the need and manner of evaluating an effective shorter regimen compared to regimes that are currently being used.

2.3.2 Trial Drug Regimen Rationale

The BPaMZ regimen has been studied singularly and in different combinations as outlined above. Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. It essentially provides protection against the development of new resistance to the B-Pa-Z drugs. Based on the exciting and promising results seen in NC-005, this regimen can be initiated in drug sensitive and drug resistant TB participants whom are sensitive to the individual drugs in the regimen (excluding extensively drug-resistant tuberculosis [XDR-TB]) and has the potential to shorten TB treatment to less than 4 months in drug sensitive TB. These are also oral regimens, removing the need for injectables as part of MDR-TB treatment and also project to be markedly less expensive than current MDR-TB therapy. Additionally, these regimens can be

administered in a fixed dose for all patients, and will therefore be simpler for health systems to deliver and patients to use.

2.4 Agents used within SimpliciTB

Bedaquiline (TMC207; Sirturo™ package insert)[7] is a novel agent approved for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[9, 10]) *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. Tb* isolates,[10, 11], and is also bactericidal against non-replicating *M. Tb.*[12] In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. Tb*.[3, 4] 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.[13] 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 DS- and MDR-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[13] and in a subsequent trial it was more active in the mouse model than HRZ.[14] Thus, a novel regimen with a 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.

Pretomanid, (Pa)[15] is a new chemical entity being developed by TB Alliance for the treatment of TB. It is 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 has been under development for several years, and entered clinical trials in 2005. Several trials of pretomanid have also been conducted previously in healthy volunteers. Collectively, these trials in participants with active TB and healthy participants have defined the efficacy, safety and pharmacokinetic features of the drug. Overall, pretomanid has mycobactericidal activity in participants and is well tolerated and bioavailable after oral dosing. Pretomanid demonstrated in vitro activity against both drug-sensitive (DS) and MDR-TB,[17] and in vivo activity in a mouse model of TB[17, 18] with a significant promise for shortening treatment of active TB.

Moxifloxacin (M)[19] is a microbial compound, approved in most countries around the world for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and soft tissue infections. Clinical studies have been carried out for many additional indications (urinary tract infections, pelvic infections, pharyngitis/tonsillitis, and tuberculosis). Moxifloxacin is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by or induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the MTB strain is susceptible or if the agent is thought to have efficacy. One of the higher generation

fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]" It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

Pyrazinamide (Z)[20] is a pyrazine analogue of nicotinamide and an approved anti-tuberculosis agent which is indicated for the initial treatment of active tuberculosis in adults and children when combined with other anti-tuberculosis agents and contributes significantly to the sterilization of lesions and thus treatment shortening.[21]

Control Group: HRZE/HR

The **HRZE/HR** combination [HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets] is approved indicated and commonly used as a 6-month treatment for drug-sensitive TB patients. Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE. Please see the HRZE package insert for more information.[22]

Additional background data supporting the combined use of new novel agents in this BPaMZ regimen for the treatment of TB:

Data from preclinical studies suggest that a regimen consisting of moxifloxacin plus pretomanid plus pyrazinamide may not only be appropriate for treating both DS and MDR-TB but may also **shorten duration of therapy**. Results from an 8-week Phase 2b SSCC trial, NC-002-(M-Pa-Z), showed that this **combination regimen** was effective as measured by time dependent decline of viable bacteria in participants with DS pulmonary TB. The combination was also shown to be safe and well tolerated supporting the evaluation of this combination in a Phase 3 trial. In this NC-002 trial 71.4% of participants with DS-TB treated with PaMZ at the 100-mg daily dose of pretomanid converted sputum to negative for *MTB* growth in liquid culture in comparison with only 37.8 % of participants treated with the HRZE control ($p<0.05$).

Studies in mice infected with *MTB* demonstrated reductions in cultured colony counts from lungs over an 8-week period when treated with the PaMZ regimen that were substantially, and statistically significantly greater, than the reductions in mice treated with an HRZ control. Experiments in mice found that mice did not relapse with MTB infection when treated with PaMZ for 4 months and followed for 3 months off treatment, in comparison to mice that required 6 months of treatment with HRZ to prevent relapse.[14]

Drug Resistant TB Background:

Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in many countries. TB is the world's leading cause for mortality from infectious disease and is responsible for more deaths than HIV.[23] 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. Because of poor treatment adherence, in addition to primary transmission, **drug resistance** is becoming more common and fears of an epidemic with strains of extensively drug-resistant TB (XDR-TB) that is very difficult to treat are growing. Novel drugs and regimens for TB are needed for the growing number of patients with drug resistant-TB.

The regulatory approvals of bedaquiline and delamanid have given hope that outcomes for patients with drug resistant TB might be improved when added to background regimens.

Experience recently published from the C209 uncontrolled trial of bedaquiline given on a background of multiple drugs notes that the subset of 38 participants with XDR-TB had rates of sputum culture conversion to negative of 62.2%.[24] However, in this trial only one participant with XDR-TB was co-infected with HIV. All participants were required to have Mycobacterium tuberculosis (MTB) isolates susceptible to at least 3 drugs at enrolment and participants had a median of only 5.4 months of treatment-free follow-up. This trial added bedaquiline for 6 months to a background regimen of many drugs given for 18 months or longer. While treatment success for MDR-TB is better than for XDR-TB, **overall success in treating MDR-TB is still approximately 50%** according to the World Health Organization 2015 Global TB Report.[23] This report presented that overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, 10% failed treatment, and for 8% there was no outcome information.

With such poor historical outcomes for patients with drug resistant-TB and with the complexity, expense and toxicity of treatments for all forms of drug resistant TB, **novel drug combinations are desperately needed to improve treatment outcomes**. Linezolid was identified in a small trial as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen[25] and this drug has increasingly been added to complex regimens to treat patients with MDR-TB.

With the current availability of the following three drugs for which there is little, if any, pre-existing resistance among strains of MTB (pretomanid [Pa], bedaquiline [B], and linezolid [L]). Mice infected with MTB had relapse-free cures with 3 months of treatment with a B-Pa-L regimen. While it is not known whether that treatment duration will translate to humans, the ongoing Nix-TB clinical trial hypothesizes patients with pulmonary XDR-TB or MDR-TB not responsive to or intolerant to therapy may have relapse-free cure after as little as 6 months' treatment with the B-Pa-L regimen.[26] Moxifloxacin has been added to the B-Pa-Z regimen because of the high rate of pyrazinamide resistance seen in MDR-TB participants in the NC-002 trial. The proposed trial [SimpliciTB] allows the opportunity to assess the efficacy, safety and tolerability of BPaMZ, a new 6 months regimen that may be administered orally once daily to treat patients with drug resistant -TB (excluding participants with XDR-TB).

Therefore, the **overall purpose** of the present proposed trial **[SimpliciTB]** is to assess the efficacy, safety and tolerability of the **BPaMZ** regime after 4 months of treatment in adult participants with drug sensitive TB and after 6 months of treatment in participants with multi drug-resistant TB. The trial will also generate data of the potential for a shorted treatment duration with the **BPaMZ** regime after 4 months compared to a 6-month **HRZE/HR** (control) treatment regime in adult participants with drug sensitive TB.

This trial will be conducted in accordance with the Protocol, ICH Guidelines for Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirement(s).

2.5 Background of Agents to be Studied in SimpliciTB

2.5.1 Bedaquiline (B)

Bedaquiline (formerly known as TMC-207; Sirturo™ package insert[7]) is approved agent for TB treatment. As detailed in the Investigator's Brochure,[8] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase.[11] In vitro, bedaquiline potently inhibits both drug-sensitive

and drug-resistant MTB isolates,[11, 12] and is also bactericidal against non-replicating MTB[12] 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 MTB.[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.[27].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[27] and in a subsequent trial it was more active in the mouse model than HRZ.[28]. 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.

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary tuberculosis by the following scheme: 400mg once daily for Days 1-14 followed by 200mg three times per week for the remainder of treatment. In this trial bedaquiline will be administered as 200 mg daily for 8 weeks then 100 mg daily for 9 weeks in participants with DS-TB and 200 mg daily for 8 weeks then 100 mg daily for 18 weeks in participants with DR-TB. This daily dosing scheme will allow more convenient dosing that should ultimately enhance patient adherence and may allow the formulation of fixed dose combinations with other drugs. This daily dosing regimen is supported by safety and efficacy demonstrated in the NC-005 trial that administered bedaquiline 200 mg daily over 8 weeks, and by pharmacokinetic modelling and simulation of the daily dosing scheme. This supportive information is detailed below.

2.5.1.1 Bedaquiline Non-Clinical Studies

Full details of the preclinical studies are provided in the current bedaquiline Investigator's Brochure,[8] and Sirturo ™ label.[7] *In vitro* studies have demonstrated that the range of minimum inhibitory concentrations (MICs) for MTB 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 MTB. 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 MTB but 3-6 times less active than the parent compound bedaquiline. Bedaquiline demonstrated similar *in vitro* efficacy against MTB 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 International Council for Harmonisation (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.[8]

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 and ECG parameters.

Prior to the use of pretomanid in combination with bedaquiline in clinical trial NC-001, a preclinical cardiovascular safety pharmacology trial 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.[28] 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) Investigators Brochure for more detail.

2.5.1.2 Bedaquiline Clinical Studies

In the clinical studies conducted to date, a total of approximately 645 participants (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 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001, and 45 more in trial NC-003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). Four short-term Phase 2a trials enrolled treatment-naïve participants (C202, TMC207-CL001, NC-001 and NC-003). One long-term, open-label, Phase 2 trial, in MDR-TB participants (bedaquiline- TiDP13-C209) and one long-term, Phase 2b trial, consisting of 2 different stages in participants 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,[8] and Sirturo™ label.[7].

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 participants. 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 trial, 800 mg single dose in trial 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 participants and participants 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 α 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 participants 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 trial (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 trial (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. Trial C202 was a 7-day trial of three daily doses of bedaquiline (25, 100 and 400mg) in treatment-naïve participants with MDR-TB. In this trial, the 400mg dose group demonstrated positive EBA and was numerically superior to the 25 and 100mg doses. In trial TMC207-CL001, doses of 100, 200, 300 and 400mg daily (following a 2-day loading dose) were studied in participants 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 participants with TB and that higher doses appear to have greater efficacy.

A 14-day EBA regimen trial (TB Alliance Trial 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 participants 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 participants given bedaquiline 400 mg/d after a 2-day loading dose. In the cohort of 15 participants 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 participants 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 trial (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 participants 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 participants in the bedaquiline group became MGIT culture negative compared to 8.7% of participants 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 participants in the bedaquiline group and 65.2% of participants 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 participants 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 participants. Culture conversion rates after 2 weeks of treatment with bedaquiline as part of an individualized anti-tuberculosis regimen were higher in participants with lower extent of resistance of the M. Tb strain and in participants with no lung cavitation compared to participants with cavitations (in one or both lungs).

2.5.1.3 Bedaquiline Clinical Safety

In the clinical trials conducted to date, a total of approximately 645 participants (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 participants received bedaquiline in a monotherapy EBA trial of 14 days (trial TMC207-CL001) 45 participants received bedaquiline, either as monotherapy (B) or in combination with other agents (B-Pa or B-Z) in trial NC-001 and 45 more in trial NC- 003 (B-Pa-Z, B-Pa-C, B-Pa-Z-C). In these trials, bedaquiline has been shown to be an effective treatment for participants 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 trial 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 trials, 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 participants) 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	**1 (1.3)**	**1 (1.0)**	**0**	**0**
Headache	1 (1.3)	1 (1.0)	0	0
Cardiac disorders	**0**	**0**	**0**	**0**
ECG QT Prolonged	0	0	0	0
Gastrointestinal disorders	**0**	**0**	**0**	**0**
Diarrhea	0	0	0	0
Vomiting	0	0	0	0
Hepatobiliary disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Transaminases increased [a]	2 (2.5)	2 (2.0)	0	0
Musculoskeletal and connective tissue disorders	**2 (2.5)**	**2 (2.0)**	**0**	**0**
Arthralgia	2 (2.5)	2 (2.0)	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 participants in the Any bedaquiline group and 5 participants 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 participants 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 participants (12.7%) compared to 3 placebo participants (3.7%). Based on the pooled results (Stage 1 and 2) while being followed in the placebo- controlled trial, 7 participants in the Any bedaquiline group and 1 Participant 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 haemoptysis. 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 participants 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 Participant in the bedaquiline group (pulmonary TB) and 2 participants in the Placebo group (TB-related illness and pulmonary TB) in Stage 1 died, and 4 participants in the bedaquiline group (3 participants with TB-related illness, 1 Participant motor vehicle accident) and 2 participants in the Placebo group (both TB-related illness) died after they discontinued Stage 2 of the trial. None of these participants 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, diarrhoea, blood uric acid increased, hypokalaemia, pruritus, injection site pain, insomnia, and tinnitus. From start of the trial up to the final analysis, 12 participants 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), haemoptysis, hypertension, and pyopneumothorax/respiratory failure. 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 participants 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 participants (6.9%) have died (12 participants during the trial and 4 participants 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 participants 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[7] notes that treatment initiation is not recommended in patients with:

- Heart failure;
- QTcF interval > 500 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).
- Hypokalaemia

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. If 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. participants should be monitored during treatment. Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in those participants with diminished hepatic reserve.[7]

Additional safety information from a recently completed trial

In a recently completed phase I trial not yet included in the bedaquiline Investigators Brochure that evaluated drug-drug interactions between bedaquiline and either rifampin or rifabutin, 7 participants experienced SAEs. Of those participants, 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 participant 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.

2.5.2 Pretomanid (P)

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]

2.5.2.1 Pharmacology

Key in Vitro Evaluation of Pretomanid Bactericidal Activity

Non-clinical in vitro trials demonstrated that pretomanid was active against actively growing drug- sensitive and drug-resistant MTB strains as well as against non-replicating MTB. The minimum inhibitory concentration (MIC) of pretomanid against a variety of drug-sensitive MTB isolates *in vitro* was shown to be like the MIC of isoniazid (MIC of pretomanid, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). Pretomanid was efficacious *in vitro* against drug-resistant clinical isolates of MTB with MIC values ranging from 0.03 to 0.53 µg/mL. The Investigator's Brochure contains further information on *in vitro* bactericidal activity.[16]

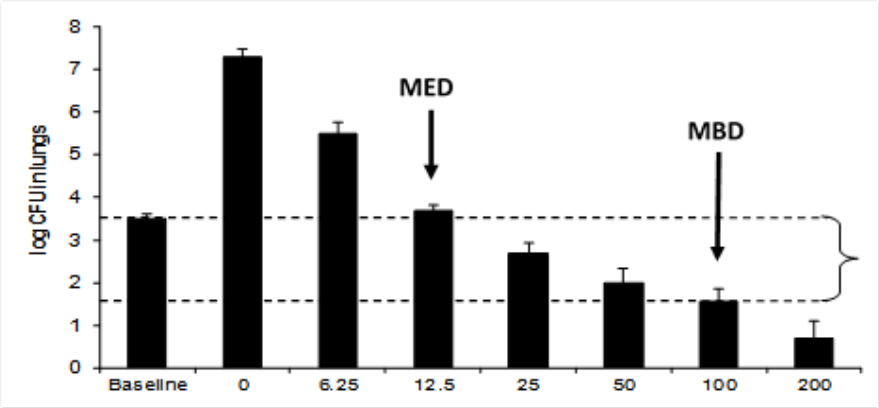
Although not thoroughly elucidated at this time, pretomanid has a novel mechanism of action that appears to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reduction of pretomanid by a deazaflavin (F420)-dependent nitroreductase has been shown to be associated with generation of reactive nitrogen species, including nitric oxide (NO),[29] although the exact target(s) of the reactive nitrogen species are not known. Transcriptional profiling trials also suggest that pretomanid affects both cell wall biosynthesis and the respiratory complex of MTB.[30, 31]

2.5.2.2 Key Non-Clinical Trials of Pretomanid

The activity of pretomanid as a single agent or as part of a multi-drug combination regimen has been examined in a number of mouse trials.[13, 14, 18, 32, 33] In a mouse model of established TB, the activity of various doses of pretomanid (given once daily, 5 days/week, for 1 month), initiated 22 days after inhalation infection with H37Rv MTB is shown in Figure 2. In this model, the minimum effective dose (MED) for pretomanid, defined as the lowest dose able to prevent the development of gross lung lesions and splenomegaly, was 12.5 mg/kg/day, while the minimum bactericidal dose (MBD), defined as the lowest dose able to reduce lung colony forming units (CFU) by 99%, was 100 mg/kg/day. Moreover, in these experiments, the activity of pretomanid at 100 mg/kg was comparable to the activity of isoniazid at 25 mg/kg.

Figure 2. Log10 CFU Counts in Lungs

After One Month of Daily Treatment with the Indicated Dose (in mg/kg) of Pretomanid



Arrows denote the minimum effective dose (MED) and minimum bactericidal dose (MBD).

2.5.2.3 Non-Clinical Toxicology and Safety

Pretomanid has been evaluated in an ICH recommended battery of safety pharmacology trials, in repeat-dose toxicity trials in rats (2 to 26 weeks) and cynomolgus monkeys (7 days to 9 months), in 8 genotoxicity trials, and in fertility and teratology trials in rats and rabbits.

In the repeat-dose toxicity trials, the lowest no-observed adverse effect level (NOAELs) was 10 mg/kg/day in a 26-week trial in rats, 50 mg/kg/day in a 13-week trial in monkeys and <25 mg/kg/day (based on findings of thickening of the gastrointestinal tract at all doses) in a 9-month trial in monkeys. The major findings in safety and toxicity trials are listed below in Table 2 and are detailed in the Investigator's Brochure.[15]

Table 2. Key findings of Pretomanid in Safety and Toxicity Trials

Nervous system-related effects. Rats given single oral pretomanid doses had decreased body tone, touch responses and decreased grooming behaviour at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of pretomanid had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of pretomanid had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
Testicular toxicity Although rat and rabbit embryonic development trials indicate no effects of pretomanid on foetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose toxicology trials and a Segment I fertility trial. In this fertility trial, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower dose not associated with testicular atrophy. A detailed trial in sexually mature male monkeys demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing.

Cataracts
Cataracts developed in rats with prolonged daily administration of pretomanid at doses ≥100 mg/kg/day. In one 13-week trial 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 trial in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.
hERG inhibition and QT prolongation
Altered ventricular repolarisation due to inhibition of hERG-mediated potassium current and manifested on the ECG as a prolonged QT interval corrected for heart rate (QTc). Pretomanid inhibited hERG current with IC50 values of approximately 6.2 µg/mL. Following a single pretomanid dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Co-administration of pretomanid with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at pretomanid doses of ≥150 mg/kg/day.

2.5.2.4 Clinical Background Information

Pretomanid has been evaluated in 8 single- and multi-dose Phase 1 trials with healthy adult male and female participants, with 163 participants receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 7 days. These Phase 1 trials have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid. Two additional Phase 1 trials Sponsored by the NIH included a Thorough QT trial and a trial of drug interactions among pretomanid, efavirenz and ritonavir/lopinavir. Further details of the trials are in the Investigator's Brochure.[15]

2.5.2.5 Pharmacokinetics

Several Phase 1 trials have evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid and have demonstrated that pretomanid has a half-life of approximately 18 hours, which supports daily dosing, and an effect of food with the 200-mg dose that increases total exposure by 88%. Interaction trials with midazolam, efavirenz and ritonavir/lopinavir demonstrate effects that are not likely to be clinically significant.

Drug interaction with midazolam: Trial CL-006 was an open-label, fixed-sequence drug-drug interaction trial to evaluate the effects of multiple-dose administration of pretomanid on the PK of midazolam, a sensitive probe substrate and representative compound for drugs metabolised by CYP3A enzymes. Dosing with pretomanid at 400 mg/day for 14 days (to steady state) had minimal effect on the PK of midazolam and its 1-hydroxy metabolite as assessed by measurement of the Day 17: Day 1 ratios of maximum concentration (C_{max}, AUC_{0-t}, and AUC_{0-inf}. The C_{max} and AUC values for midazolam after co-administration with pretomanid were approximately 85% of those observed after treatment with midazolam alone. Furthermore, midazolam and 1-hydroxy midazolam time to maximum concentration (T_{max}) and half-life ($t_{1/2}$) values were not different in the presence or absence of pretomanid. Therefore, 14 days' dosing with 400 mg/day pretomanid does not appear to significantly inhibit CYP3A4 in humans.

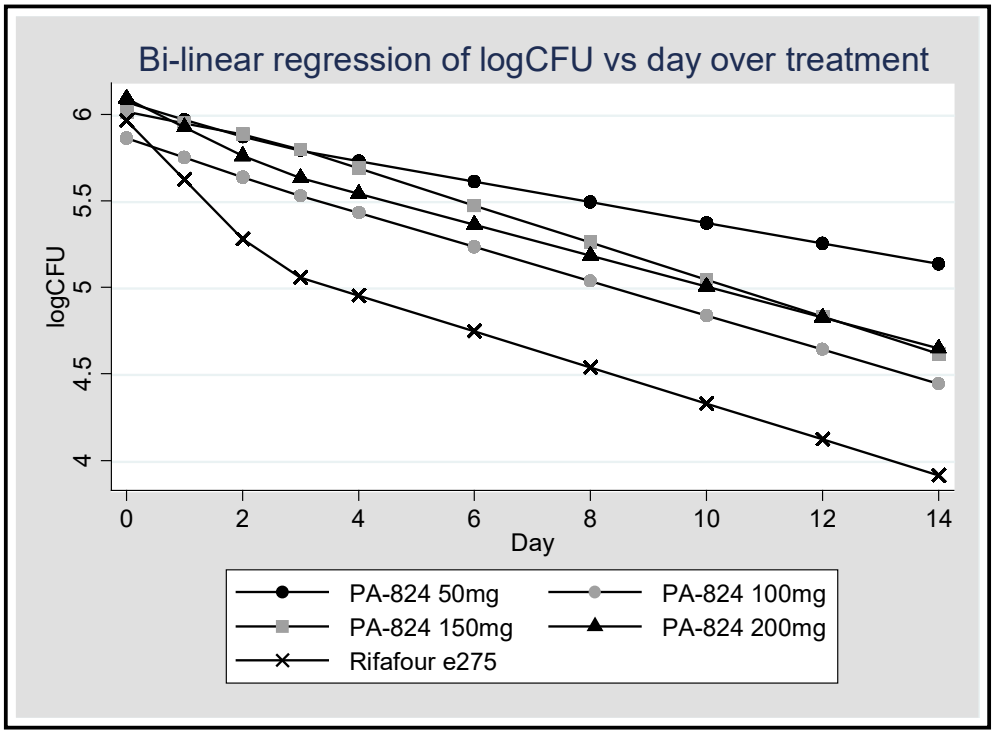
Drug interaction with efavirenz, ritonavir/lopinavir, and rifampicin: The US NIH Sponsored this drug interaction trial with rifampicin, a known hepatic enzyme inducer, and with the antiretroviral drugs efavirenz and ritonavir/lopinavir (LPV/r) in healthy participants. Participants in Arm 1 were randomised to Sequence 1 (pretomanid 200 mg once daily for 7 days, two-week washout period, efavirenz (EFV) 600 mg once daily for 14 days, then both drugs for 7 days) or Sequence 2 (Treatment 1B: EFV, then EFV + pretomanid, washout, and pretomanid). Results indicate that comparing pretomanid given with EFV versus pretomanid alone in 16 participants, the geometric mean ratio (GMR) for C_{max} was 0.71, the GMR for AUC_{0-24h} was 0.65, and the GMR for C_{min} was 0.54. Concentrations of EFV when given with pretomanid versus given alone were similar. Participants in Arm 2 were randomised to Sequence 1 (pretomanid 200 mg once daily for 7 days, then a 2-week washout period, then LPV/r 400/100 mg twice daily for 14 days, then LPV/r + pretomanid together for 7 days) or Sequence 2 (LPV/r, then LPV/r + pretomanid, washout, then pretomanid alone). Comparing pretomanid + LPV/r versus pretomanid- alone from 16 PK-evaluable participants, the GMR for C_{max} was 0.87, for AUC_{0-24h} was 0.83, and for C_{min} was 0.78. In Arm 3, participants received pretomanid for 7 days, then rifampicin 600 mg for 7 days, then pretomanid + rifampicin together for 7 days. Comparing pretomanid + rifampicin versus pretomanid alone from 16 PK-evaluable participants, the GMR for C_{max}, AUC_{0-24h}, and C_{min} were 0.47, 0.34, and 0.15, respectively.

In conclusion, compared to pretomanid alone, plasma pretomanid values (based on geometric mean ratios) for C_{max}, AUC_{0-24h}, and C_{min} were reduced 28%, 35%, and 46% with efavirenz; 13%, 17%, and 21% with LPV/r; and 53%, 66%, and 85% with rifampicin, respectively.

2.5.2.6 Pretomanid Clinical Efficacy

The first two Phase 2 trials to evaluate the early bactericidal effect (EBA) of pretomanid oral monotherapy (50 to 1200 mg/day for 14 days) examined the dose-response for pretomanid in participants with newly diagnosed pulmonary TB infection. The first trial (CL-007) demonstrated good EBA, but all doses in this trial (200 to 1200 mg/day) had the same activity. The second trial (CL-010) evaluated a lower dose range (50 to 200 mg/day) and the maximum effect on EBA was seen at a dose of 100 mg/day over 14 days (Figure 3).[34]

Figure 3. Mean log Colony Forming Unit Values over Time Trial CL-010



CFU = colony-forming unit; PRETOMANID = pretomanid

* Day 0 = (Day -2 + Day -1)/2 = baseline measurement

Pretomanid has been evaluated in patients with TB as monotherapy for a maximum duration of 14 days, the longest considered acceptable for a TB patient to be treated in a clinical trial with a single drug. Trials of pretomanid for both 14 days and for up to 6 months, in combination with either bedaquiline and/or linezolid, are described below.

2.5.2.7 Pretomanid Clinical Safety

The pretomanid Investigator's Brochure[15] provides detailed safety information.

Across the 16 clinical trials with pretomanid completed to date, a total of 649 participants have been exposed to pretomanid, including 289 healthy participants across the 10 Phase 1 trials and 360 participants with newly diagnosed smear positive pulmonary TB across 5 Phase 2 trials. Among the 289 healthy participants, 174 received exposure to a single dose of pretomanid ranging from 50 to 1500 mg and 115 received exposures to repeated daily doses of pretomanid (50 to 1000 mg) for up to 14 days. The 360 participants with newly diagnosed smear positive pulmonary TB were exposed to pretomanid either as a single agent at daily doses of 50 to 1200 mg for 14 days or in combination with other anti-TB agents (bedaquiline, moxifloxacin, pyrazinamide, linezolid and/or clofazimine) at a dose of 100 mg or 200 mg for up to 26 weeks. The overall safety profile determined from the clinical trials completed to date indicates pretomanid is well tolerated in healthy adults and in TB patients when administered alone and in combination with moxifloxacin, pyrazinamide, bedaquiline and clofazimine.

Pretomanid is an investigational drug and there is limited experience in humans; the safety database is being developed and Investigators should be vigilant to any adverse events noted in clinical trials. Across these trials, the most common side effects or AEs associated with pretomanid exposure include:

- Headache
- Stomach discomfort (nausea, vomiting, flatulence, and/or diarrhoea)
- Skin and subcutaneous tissue disorders

The only adverse drug reaction identified in clinical trials completed to date as likely caused by pretomanid is blood creatinine increased. A trial of the effects of repeat doses of pretomanid in healthy volunteers determined that the drug does not adversely affect glomerular filtration rate, effective renal plasma flow or filtration fraction and the elevations in serum creatinine reverse.

The following parameters will be followed with particular care in the Phase 3 development program:

- Hepatic Safety – Specific guidelines are included in the protocol to assure close surveillance and careful management of participants who have elevations in aminotransferases and/or bilirubin. Serious liver injury, including death in 3 participants taking a combination of pretomanid, pyrazinamide and moxifloxacin, has occurred during clinical trials and the risk of liver injury may be higher for participants taking a combination of pretomanid and pyrazinamide than it is for the standard HRZE treatment. Therefore, close monitoring of liver function is required for participants who are administered pretomanid, especially when combined with pyrazinamide. Administration of the regimen of PaMZ has been associated with death in 3 participants associated with hepatic injury. Furthermore, the HRZE control regimen, and both pyrazinamide and moxifloxacin, has been associated with drug induced liver injury and in rare cases hepatic necrosis. Consequently, hepatic safety will be under close surveillance in all clinical trials.

- Ophthalmologic Evaluations – while the detailed examinations in Phase 2 have not raised concern for humans, ophthalmologic examinations, with slit lamp exam and grading of lens opacities, will continue in all human trials that involve exposure to pretomanid longer than 14 days. These examinations will be conducted at baseline, near the end of the dosing period and 3 months after the end of trial drug exposure. These examinations are to follow up on the finding of cataracts in rats exposed to pretomanid in clinical trials.

- Cardiovascular Safety – All participants will have ECGs taken at baseline and at multiple time points during the trial. Although the Thorough QT Trial in healthy participants found that pretomanid did not increase corrected QT intervals in a clinically meaningful way and did not add to the known effect of moxifloxacin, the ECGs will be carefully monitored during Phase 3. All ECGs will be interpreted and conduction intervals will be confirmed by a central cardiology service.

- Central Nervous System Safety –While pretomanid alone or combined in various regimens has been well tolerated overall, one participant in Trial NC-002 of the Pa-M-Z regimen had a seizure without any prior seizure history, and some animals in toxicology trials have had seizures at high drug exposures. Consequently, close surveillance will be made of

participants in the Phase 3 trial for seizures or any central nervous system adverse events of potential concern.

Of note, preclinical toxicology trials found that rats, but not primates, had testicular toxicity when treated with pretomanid. Clinical evaluations of potential testicular toxicity in Phase 2 trials have evaluated over 300 participants exposed to pretomanid over 2-6 months with evaluations of testosterone, LH, or Inhibin B (2 trials) or FSH values (3 trials) at baseline and after daily dosing of regimens containing pretomanid in various combinations with moxifloxacin, pyrazinamide and bedaquiline. A review of data from the 3 trials by an independent reproductive endocrine expert concluded that, based on the hormone evaluations to date, there is no evidence that pretomanid is a testicular toxicant in men at the doses and exposure times evaluated.

2.5.3 Moxifloxacin (M)

Moxifloxacin (M)[19] is an **8-methoxyquinolone** whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by nor induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg. **Moxifloxacin** while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxacin in the category of Group 3 drugs and notes that “all patients [with MDR-TB] should receive a Group 3 medication if the strain of MTB is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.[5]” It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different **four-month long** regimens.

2.2.3.1. Moxifloxacin Clinical Trials

Moxifloxacin is commonly used as second line therapy for TB (e.g. MDR- TB), and has also been evaluated in several clinical studies of participants with TB, including four 8-week treatment period Phase 2b studies (see Table 3 below).

Table 3. Summary of Phase 2b trials in which moxifloxacin were administered as part of a four-drug regimen during the intensive phase of treatment (total treatment duration: 2 months)

Trial	Design	Objective	Participants (N)	Status
Trial 27	Randomized, double-blind, controlled	To compare the sputum culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using the standard 4-drug regimen HRZE with a standard regimen with M replacing E.	336	Completed
OFLOTUB Trial	Randomized, Open label, Controlled	To compare the bactericidal activities of regimens where gatifloxacin, M, and ofloxacin were substituted for E in the 2-month initial phase of standard TB treatment with HRZE.	217	Completed
Johns Hopkins (FDA orphan drug) Trial	Randomized, double-blind, Controlled	To compare the sputum culture conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE) with a regimen with M replacing E (HRZM).	170	Completed
Trial 28	Randomized, double-blind, Controlled	To compare the culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE 5 days per week) with a regimen with M replacing H (MRZE 5 days per week).	433	Completed

2.5.3.1 Moxifloxacin Clinical Safety

In Trial 27,[35] the moxifloxacin-containing TB regimens (HRZM) were shown to be safe and well tolerated. There was no difference in SAEs between the HRZM and HRZE treatment arms, and most SAEs were hospitalizations thought to be unrelated to the trial treatment. Participants treated with the moxifloxacin-containing regimen were more likely to report nausea (22% vs. 9%, p = 0.002), but this was generally mild and did not lead to treatment discontinuation as similar proportions of participants in both groups completed trial drug treatment (88% HRZM-treated vs. 89% HRZE-treated). The one death during the first 2 months of treatment was thought to be caused by a pulmonary embolism unrelated to tuberculosis therapy.

In the OFLOTUB trial,[36] AEs and SAEs occurred with equal frequency in the four treatment arms. The most frequent AEs were raised amylase (in 41% of participants due to HIV infection), raised transaminase (10%), arthralgia (9%), anaemia (7%), hypokalaemia (6%) and vomiting (5%). No Participant was withdrawn from the trial due to an adverse event. There were 4 deaths in the trial: 2 in the control group, 1 each in the moxifloxacin and ofloxacin arms. Importantly, participants in this trial who received moxifloxacin and pyrazinamide in addition to isoniazid and rifampin had more rapid sputum clearance than participants on the four

standard first line drugs (isoniazid, rifampin, pyrazinamide and ethambutol). This difference was evident 14 days after initiation of treatment.

In the JHU trial,[37] AEs did not differ by treatment group. There were 16 SAEs (8 in each group) in 12 participants. Only 1 event was judged related to trial drug (grade 3 cutaneous reaction in the ethambutol group). Eight participants died during the trial, including 1 in each group still receiving trial phase treatment. No death was attributed to trial treatment. Only 5 participants discontinued treatment because of toxic effects; 2 participants in the moxifloxacin group stopped because of grade 2 nausea and vomiting and 1 because of grade 2 paraesthesia's and ataxia. Two participants in the E group stopped because of grade 2 rash and pruritus and 1 because of grade 3 peripheral neuropathy. There was no change in the QTc interval on serial electrocardiograms taken during the trial.

In Trial 28,[38] the proportions of participants with SAEs during the intensive phase treatment were similar between arms (isoniazid 3.9% vs. moxifloxacin 4.2%; P = 0.88). Three SAEs attributed to trial treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group. Seven participants died during the trial including 3 participants receiving the moxifloxacin treatment regimen and 4 participants receiving the isoniazid treatment regimen. The 3 moxifloxacin participants died during the intensive phase of TB treatment. Two participants died from advanced pulmonary TB judged not related to trial treatment and 1 Participant (who developed diabetic ketoacidosis considered possibly related to trial treatment) died from possible acute pulmonary embolus unrelated to trial treatment. The 4 isoniazid deaths occurred during the continuation phase, and all 4 were considered unrelated to trial treatment. Nausea was more common among participants in the moxifloxacin arm than in the isoniazid arm (19.6% vs. 11.7%, respectively; P = 0.03) although similar proportions reported vomiting. However, the proportions of participants with hepatitis, defined as serum AST 3 times or greater than the upper limit of normal, were similar between treatment arms during intensive phase (isoniazid 3.4% vs. moxifloxacin 3.3%; P = 0.93). Moxifloxacin has also been evaluated in combination with pretomanid for two weeks in participants with TB (Trial NC-001) and for 8 weeks in NC002 as reviewed above in Section 2.5.3 (Trial NC-001).

For additional information on moxifloxacin, refer to the IB[39] and the manufacturer's package insert.[19]

2.5.4 Pyrazinamide (Z)

Pyrazinamide (Z) is a standard drug used as part of the four drug HRZE regimen used for the first two months of intensive therapy for drug-sensitive TB as recommended by the WHO and many National TB programs. Please see the Package Insert[20] for more detail. Z is active against TB *in vitro* and it potentiates the bactericidal and sterilizing activity of both bedaquiline and pretomanid in mouse models of TB infection.[8, 15] Pyrazinamide enhanced the bactericidal activity of both bedaquiline and pretomanid in Trial NC-001-(J-M-Pa-Z) as noted by decreases over 14 days in the CFU counts in sputum among participants.

The pyrazinamide product label notes that pyrazinamide is contraindicated in persons with severe hepatic damage, who have shown hypersensitivity to it, and with acute gout. The most serious side effect is hepatotoxicity. Its frequency appears to be dose-related and thus liver function should be assessed before and regularly during treatment with pyrazinamide. Hyperuricemia commonly occurs and is occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other

side effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria.

Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert. [20]

2.6 Overall Benefit/Risk Assessment

Some participants with pulmonary TB in this trial will be given a regimen of **BPaMZ**. These drugs individually and in combination are known to have anti-tuberculosis activity and is not expected to have an adverse impact on the ultimate cure of TB in these participants. Based on NC-005 and other regimens using each of the regimen drugs in different combinations there is good evidence that this may be a highly effective therapy for both DS-TB and DR-TB.

For DS-TB the potential for a shorter regimen than 6 months is expected to be successful based on preclinical and clinical information as listed before. Participants in this trial will have their TB infection carefully characterized, with drug sensitivity profiles established, and they will receive treatment with trial drugs that have demonstrated activity against MTB.

Participants will receive individualized medical attention; this will allow a continuous monitoring of the health conditions of each participant, any of whom can be withdrawn at any stage of the trial and removed from trial treatment should his/her condition suggest to the Investigator that this would be in his/her best interest. Multiple blood samples will be taken for safety laboratory studies, and ECGs will be taken at multiple time points.

One concern, the combination of two agents with known QT-prolonging effects (bedaquiline and moxifloxacin), has been addressed specifically by carefully identifying and excluding participants with risk factors that might predispose them to cardiac arrhythmias, screening all participants for evidence of existing cardiac disease and monitoring all participants with ECGs throughout the trial.

The trial drugs in the proposed regimens to be tested in this trial have all demonstrated safety and efficacy in the treatment of pulmonary tuberculosis in non-clinical and clinical studies. Specifically, the regimen B-Pa-Z was generally well-tolerated and demonstrated bactericidal activity in a 14-day EBA trial. The potential risks associated with the trial drugs and regimens has been identified as outlined below and will be monitored carefully throughout the conduct of the trial.

The BPaMZ regimen is a novel regimen treatment expected to be effective, safe and well-tolerated and might even shorten the current treatment duration for patients with TB. Based on data from previous trial evaluations of key monitoring and safety information as outlined before suggests a favourable benefit-to-risk ratio trials.

Key Monitoring and Safety Information Regarding Regimen Agents

2.6.1 Bedaquiline (B)

2.6.1.1 Adverse Drug Reactions for bedaquiline

Participants in the Any bedaquiline group compared to the Any Placebo group (difference > 5.0%) had headache (23.5% versus 11.4%, respectively), nausea (35.3% versus 25.7%, respectively), arthralgia (29.4% versus 20.0%, respectively), and transaminases increased (6.9% versus 1.0%, respectively).and diarrhoea (11.4% versus 5.9%, respectively).

2.6.1.2 Cardiovascular safety

During clinical studies with bedaquiline a prolongation of QTc interval was observed. An ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.

Bedaquiline 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

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. If co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

In the DR-TB treatment arm of the present trial, moxifloxacin will be co-administered with bedaquiline. This is to prevent the development of resistance to the other drugs in the regimen in case the participant's strain of MTB is resistant to pyrazinamide. ECG assessments will be performed on all participants at screening, baseline, and at treatment visits specified in the flow chart.

2.6.1.3 Hepatic safety

Increases in transaminases were seen in clinical studies during administration of bedaquiline with the background regimen. Participants should be monitored during treatment.

Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in participants with diminished hepatic reserve.

2.6.2 Pretomanid (P)

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 diarrhoea)
- Skin and subcutaneous tissue disorders

2.6.2.1 Hepatic Safety

Hepatic enzyme increases have been seen in participants 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 NC-008 trial will include specific monitoring of hepatic enzymes.

For additional information refer to pretomanid IB.[15]

2.6.3 Moxifloxacin (M)

In the usual daily doses of 400 mg/day, moxifloxacin is well tolerated. As stated in the Package Insert[19] the most frequent individual drug related AEs observed in clinical trials with 400 mg oral moxifloxacin therapy were nausea (7.5%) and diarrhoea (5.8%). Fluoroquinolones, including moxifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages.

A known but rare side effect of fluoroquinolones, including moxifloxacin is exacerbation of myasthenia gravis. In addition, moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some participants. It should be used with caution in participants being treated concomitantly with other drugs where an additive effect on the QT interval cannot be excluded.

Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, as well as peripheral neuropathy may occur after the first or subsequent doses of moxifloxacin. For additional information, refer to the moxifloxacin package insert.[19]

2.6.4 Pyrazinamide (Z)

The dose of pyrazinamide that will be used in this trial is an approved dosage for the treatment of TB. The most serious side-effect of pyrazinamide is hepatotoxicity and its frequency appears to be dose-related. Hyperuricemia commonly occurs, occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side-effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria. Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert.[20]

2.6.5 HRZE/HR Control

The **HRZE** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets) combination will be given the first 8 weeks and the **HR** (isoniazid 75 mg plus rifampicin 150 mg combination tablets) combination will be given from Weeks 9 to 26.

Participants with DS-TB that are randomized to the **HRZE/HR control arm** in this trial will be given standard weight-adjusted doses of HRZE.

Please see the HRZE and HR Package Inserts[22, 40] for known and potential risks and benefits.

3.0 Trial Objectives

3.1 Primary Endpoint

To evaluate the time to culture negativity over 8 weeks from the start of the treatment regimens in participants with:

- Drug Sensitive TB (DS-TB)
- Drug Resistant TB (DR-TB)

DR-TB are defined as participants with:

1. *mono-resistance to rifampicin or isoniazid, OR*
2. *resistance to both rifampicin and isoniazid (DR-TB)*

3.2 Secondary Endpoints

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 52 weeks (12 months) and 104 weeks (or 24 months) weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight.
- Change from baseline in TB symptoms.
- Change from baseline in Participant Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, seriousness, leading to early withdrawal, and leading to death.
  - Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
  - Quantitative and qualitative ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed. QT/QTc intervals, change from baseline, will be categorized as these will be centrally read.
- Changes in male reproductive hormones.
- Changes in lens opacities.

These data will be presented as descriptive analyses, and no inferential tests will be carried out.

Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD):

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., minimum plasma concentration [Cmin], maximum plasma concentration [Cmax], area under curve over a dosing interval [AUC]) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so too, will the effects of concomitant medications, including antiretroviral therapy (ART), where feasible.

Data from other trials may be included to enhance the model-based analysis. Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate.

3.3 Exploratory Objectives

- Evaluate whether any of the secondary endpoints predicts relapse free cure.
- Subgroup analysis of populations by HIV status.

4.0 Trial Design

4.1 Summary of Trial Design

This is a Phase 2c, multi-centre, open-label, partially randomized clinical trial conducted in 3 treatment groups. Participants, trial Investigators and staff, including laboratory staff, will not be blinded to treatment randomization and allocation during the treatment phase of the trial.

The trial will be performed globally at multiple centres located throughout the world.

A total of 300 DS-TB participants (150 per treatment arm) will be randomized and stratified for co-infection with HIV and cavitation, with a target of 50% of the participants being HIV positive. Up to 150 DR-TB participants will be enrolled and assigned to the treatment arm described in Table 4 below.

Refer to Section 3.0 Trial Objectives above and Section 9.3 Interim Analysis for details of the planned interim analysis and potential updates to the trial objectives and sample size.

Participants with Drug Sensitive TB (DS-TB):

Participants with DS-TB will be randomized to one of two treatment arms. These participants will receive either BPaMZ daily for 17 Weeks, or HRZE/HR combination tablets daily for 26 Weeks. Participants will be stratified for co-infection with human immunodeficiency virus (HIV) and cavitation.

Participants with Drug Resistant TB (DR-TB):

Participants with DR-TB will be assigned to receive BPaMZ daily for 26 weeks (6 months).

Eligible participants who meet all the inclusion criteria and none of the exclusion criteria, aged 18 and over, male or female will be assigned to one of the 3 treatment groups with a target of 50% of the participants being HIV positive.

DR participants will be treated with 6 months of BPaMZ. DS participants will be randomized using an interactive web response system (IWRS) stratifying for cavitation and HIV status to allocate participants evenly across the arms after they have given written, informed consent during the Screening Visit (Days -9 to -1).

4.2 Treatment Plan: Schedule of Assessments

- Screening Period (Day -9 to Day -1)
- Treatment Period (Day 1 to Week 17 / Week 26)
- Follow-Up Period (Week 39 to Week 104)

Refer to:

- Synopsis Flow Chart and Procedures (Section 1.2) for the timing of all procedures and laboratory samples to done at each visit.
- Trial Procedures (Section 7.0, Trial Variables and Procedures) for details regarding specific procedures or laboratory tests.

Each participant will receive up to 26 weeks of treatment. The trial IMP regimens may require interruptions/pauses due to toxicities. All dose interruptions/pauses should be discussed with the Sponsor's Medical Monitor prior to implementation unless an interruption/pause is required urgently for a safety concern.

All participants will enter post-treatment follow-up which continues until Week 104 after start of treatment / randomisation.

Participants will receive daily dosing, orally. They will be randomized to one of the following arms:

Table 4: Treatment Groups

	Treatment Group	Treatment Duration	No of Participants
1	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily	17 weeks (4 months)	150 DS-TB
2	**HRZE Tablets (Weeks 1-8):** (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets). Followed by **HR Tablets (Weeks 9-26):** (isoniazid 75 mg plus rifampicin 150 mg combination tablets).	First 8 weeks (2 months) then 17 weeks (4 months) Total 6 months	150 DS-TB
3	Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily.	26 weeks (6 months)	Up to 150 DR-TB

5.0 Trial Population

The participant must meet all inclusion and no exclusion criteria within the screening period. Retesting for any laboratory or ECG parameters is allowed within the screening period. Sponsor may consider replacement of late exclusions. It is the intent of the protocol that the participants are hospitalized according to local practices and at the judgment of the treating physician / investigator.

5.1 Inclusion Criteria

Participants are required to meet all the following inclusion criteria during the screening period to be randomized.

1. Signed written consent prior to undertaking any trial-related procedures.
2. Male or female, aged 18 years or over.
3. Body weight (in light clothing and no shoes) ≥ 30 kg.

4. Sputum positive for tubercule bacilli (at least 1+ on the International Union Against Tuberculosis and Lung Disease [IUATLD]/WHO scale (Appendix 1) on smear microscopy) at the trial laboratory.
5. Disease Characteristics - Participants with one of the following pulmonary TB conditions:

   DS-TB treatment arm participants should be:

   a. sensitive to rifampicin, isoniazid and fluoroquinolones by rapid sputum-based test **AND**

   b. either newly diagnosed for TB or have a history of being untreated for at least 3 years after cure from a previous episode of TB.

   DR-TB treatment arm participants should be:

   a. Resistant to rifampicin and/or isoniazid; but sensitive to fluoroquinolones by rapid sputum-based test **AND**

   b. Should not have had previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 3 days at start of screening.

   c. Participants with resistance to injectables by rapid sputum-based test are allowed in the trial.

   When Phenotypic DST and / or whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.

6. A chest x-ray, within 6 months prior to or during the Screening visit, which in the opinion of the Investigator is compatible with pulmonary TB.
7. Contraception:

   Be of non-childbearing potential **<u>or</u>** using effective methods of birth control, as defined below:

   Non-childbearing potential:

   a. Female participant or male participants female sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or

   b. Male participant

   Effective birth control methods:

   a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or

b. Female participant: Barrier method combined with hormone-based contraceptives or an intra-uterine device.

c. Male participants' female sexual partner: Barrier method combined with hormone-based contraceptives or an intra-uterine device.

Both male and female participants must be willing to continue practicing birth control methods and are not planning to conceive throughout treatment and for 6 months after the last dose of trial IMP or discontinuation from trial IMP 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 participants to prevent pregnancy.

5.2 Exclusion Criteria

Participants will be excluded from participation if they meet any of the following criteria:

Medical History and Concurrent Conditions:

1. Any non-TB related condition where participation in the trial, as judged by the Investigator, could compromise the well-being of the participant or prevent, limit or confound protocol specified assessments.
2. Abuse of alcohol or illegal drugs that in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
3. Historical and or current use of local traditional medications/herbs which in the opinion of the Investigator would compromise the participants' safety or ability to follow through with all protocol-specified restrictions, visits and evaluations.
4. Being, or about to be, treated for malaria.
5. Is critically ill and, in the judgment of the Investigator, has a diagnosis likely to result in death during the trial or the follow-up period.
6. TB meningitis or other forms of extrapulmonary tuberculosis with high risk of a poor outcome, or likely to require a longer course of therapy (such as TB of the bone or joint), as judged by the Investigator.
7. History of allergy or hypersensitivity to any of the trial IMP or related substances, including known allergy to any fluoroquinolone antibiotic, history of tendinopathy associated with quinolones or suspected hypersensitivity to any rifampicin antibiotics.
8. For HIV infected participants any of the following:

    a. CD4+ count <100 cells/µL
    b. Karnofsky score <60% (Appendix 5)
    c. Received intravenous antifungal medication within the last 90 days
    d. WHO Clinical Stage 4 HIV disease (Appendix 3)

9. Participants who recently started or expected to need to start ART within 1 month after randomization. Participants who have been on ARTs for more than 30 days prior to start of the Screening visit or expected to start ART greater than 30 days after randomization may be included.

10. Having participated in other clinical trials with investigational agents within 8 weeks prior to start of trial medication or currently enrolled in an investigational trial.

11. Participants with any of the following at the Screening visit (per measurements and reading done by ECG):

    a. QTcF interval on ECG >500 msec. Participants with QTcF > 450 must be discussed with the Sponsor Medical Monitor before enrolment.
    b. Heart failure
    c. A personal or family history of congenital QT prolongation
    d. A history of or known, untreated, ongoing hypothyroidism
    e. A history of or ongoing bradyarrhythmia
    f. A history of Torsade de Pointe

12. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening.
13. Females who have a positive pregnancy test at the Screening visit or already known to be pregnant, breast-feeding, or planning to conceive a child during the trial or within 6 months of stopping treatment. Males planning to conceive a child during the trial or within 6 months of stopping treatment.
14. Participants with lactose intolerance, lactase deficiency and/or glucose-galactose malabsorption.

<u>Previous and Concomitant Therapy</u>

15. Previous treatment for TB which includes:

    - <u>For DS-TB participants</u>: Previous treatment for tuberculosis within 3 years prior to the Screening visit. Participants who have previously received isoniazid prophylactically may be included in the trial if that treatment is/was discontinued at least 7 days at the start of the Screening visit.
    - For the DR-TB participants: Previous treatment for DR-TB/MDR-TB, although may have been on a DR-TB/MDR-TB treatment regimen for no longer than 3 days at the start of the Screening visit.

16. Any diseases or conditions in which the use of the standard TB drugs or any of their components is contra-indicated, including but not limited to drug allergy.
17. Use of any drug within 30 days prior to randomisation known to prolong QTc interval (including, but not limited to, amiodarone, amitriptyline, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinacrine, quinidine, sotalol, sparfloxacin, thioridazine).
18. Use of systemic glucocorticoids within one year of the start of the Screening visit (topical, inhaled or intranasal glucocorticoids are allowed), as they can lead to visual opacities or cataracts.
19. For HIV infected participants:

    a. The following antiretroviral therapy (ART) should not be used with either (BPaMZ and HRZE/HR) trial regimen:

        1. Stavudine
        2. Didanosine
        3. Triple NRTI regimen is not considered optimal for HIV treatment (poor efficacy)

b. In the case where participants are randomised to HRZE arm, rilpivirine and etravirine cannot be given with rifampicin due to drug-drug interactions. A standard NRTI backbone may be used in combination with one of the following:

   1. Efavirenz requires no dose adjustment
   2. Dolutegravir dose adjustment is required – double dose when co-prescribed with rifampicin.
   3. Raltegravir requires no dose adjustment
   4. Lopinavir/r dose adjustment is required – double dose when co-prescribed with rifampicin
   5. Nevirapine requires no dose adjustment, however please note that nevirapine based regimens are associated with higher ART failure in participants having or known to have a previous viral load more than or equal to 100,000/ mL

c. In the case where participants are randomized to the BPaMZ trial regimen, a standard NRTI backbone may be combined with the following:

   1. Rilpivirine
   2. Dolutegravir
   3. Raltegravir
   4. Nevirapine
   5. Lopinavir/r
   6. Participants who are on efavirenz, atazanavir/r or darunavir/r at the time of screening and have an undetectable viral load, should have their ART switched to one of the agents listed above (1-5). It would be preferable to switch to another permissible ARV within the same class accompanied by the same nucleoside backbone.

d. ART regimen choice should be discussed with the Sponsor Medical Monitors if there are any concerns.

Confirmed plans to use Isoniazid prophylaxis for HIV positive participants during the treatment and follow up period is not permitted.

Diagnostic and Laboratory Abnormalities

20. Participants with the following toxicities at screening as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (Draft November 2007) (Appendix 2) where applicable:

    a. platelets <75,000/mm^3
    b. creatinine 1.5 times upper limit of normal [ULN])
    c. eGFR ≤ 60 mL/min/
    d. haemoglobin <8.0 g/dL
    e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once
    f. GGT: greater than 3 x ULN
    g. AST:
       - ≥3.0 x ULN to be excluded;

- results between 1.5 x ULN and 3 x ULN must be discussed with and approved by the Sponsor Medical Monitor

h. ALT:
- ≥3.0 x ULN to be excluded
- greater than ULN must be discussed with and approved by the Sponsor Medical Monitor

i. ALP:
- ≥3.0 x ULN to be excluded
- 2.0 – <3.0 x ULN must be discussed with and approved by the Sponsor Medical Monitor

j. Total bilirubin:
- >1.5 x ULN to be excluded;
- Greater than 1 – 1.5 x ULN must be discussed with and approved by the Sponsor Medical Monitor

k. Direct bilirubin:
- greater than 1x ULN to be excluded

All the inclusion and none of the exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the Investigator has reason to suspect that there might be a health problem (other than TB), enrolment should only be considered after discussing the case with the Sponsor Medical monitor.

No protocol waivers will be granted by the TB Alliance.

5.3 Restrictions

Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are necessary for the participant's welfare, 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 reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected to prevent any potentially serious and/or life-threatening drug interactions.

The following recommendations should be followed with regards to concomitant medication to avoid possible drug interaction with the IMP:

Participants on a **moxifloxacin** containing treatment arm: The IMP should be taken either 4 hours before or 8 hours after taking the following products:

- An antacid, multivitamin, or other product that has magnesium, aluminium, iron or zinc
- Sucralfate
- Didanosine

Participants on the **HRZE/HR** treatment arm:

- Any aluminium-containing antacids should be taken at least one hour after the IMP dose.

The following medicinal products are prohibited from the Screening visit and during the treatment period:

- Quinolone antimalarial (e.g., chloroquine and quinacrine). Participants who have malaria at screening are to be excluded. However, if a participant develops malaria during the trial, the Investigator is advised to consult the Malaria Treatment Guidance document regarding the interaction between moxifloxacin and bedaquiline with anti-malarial drugs. Investigators may also contact the Sponsor Medical Monitor for further guidance.
- Chronic systemic glucocorticoids (topical, inhaled or intranasal glucocorticoids are allowed) due to their potential to cause visual opacities. Short term systemic glucocorticoids are allowed for emergency situations (e.g. for treatment of pulmonary exacerbation when inhaled glucocorticoids is inadequate).
- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, other quinolones, thioamides, and metronidazole.

The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible (unless this is required for emergency management of the participant). Investigators may also contact the Sponsor Medical Monitor for further guidance.

- Any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). The exception is moxifloxacin and bedaquiline administered as part of the trial IMP, with ECG monitoring, to help ensure participant safety.
- Any drug known to be hepatotoxic (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, co-trimoxazole, darunavir, delavirdine, diclofenac, doxycycline, enalapril, fluconazole, fluoxetine, fosamprenavir, furosemide, gliclazide, glimeperide, glipizide, ibuprofen, irbesartan, ketoconazole, lisinopril, loperamide, losartan, methotrexate, metolazone, mirtazepine, nitrofurantoin, omeprazole, other non-steroidal anti-inflammatory drugs, paroxetine, phenobarbital, phenothiazines, phenytoin, pravastatin, probenecid, prochlorperazine, risperidone, rosuvastatin, sertraline, simeprevir, simvastatin, sodium valproate, sotalol, sulfasalazine, sumatriptan, tamsulosin, terbinafine, tetracycline, theophyllin/uniphyllin, tipranavir, tolazamide, tolbutamide, topiramate, trazodone, tricyclic antidepressants, trimethoprim, verapamil).

5.4 Treatment Discontinuation and/or Early Withdrawal

Any participant for whom the Investigator decides to temporarily discontinue their IMP is to be discussed with the Sponsor Medical Monitor and, if applicable, be restarted on IMP as soon as possible.

A participant must be prematurely withdrawn from the trial (during the trial treatment or follow-up periods) because of the following:

- Withdrawal of informed consent
- Investigator considers that for safety reasons it is in the best interest of the participant that he/she be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment
- Pregnancy
- At the specific request of the Sponsor or termination of the trial by the Sponsor
- Lost to follow-up
- When Phenotypic DST and / or whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.

A participant may withdraw from the trial at any time at his/her request (withdrawal of consent), or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative issues.

When a participant withdraws consent from the trial, no additional follow-up visits will be performed.

Participants who withdraw from the trial after having received IMP will not be replaced.

All participants withdrawn from trial and who received at least one dose of IMP will be requested to return for an Early Withdrawal visit and the applicable safety Follow-Up visits, as per the Synopsis Flow Chart and Procedures (Section 1.2 footnote c), as well as Table 5.

5.4.1 Early Withdrawal

In case of early withdrawal during the treatment or follow-up period, 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:

- Sputum sample collection x 2 (one EMS brought from home and one spot at the research site under the coaching and observation of the trial staff). If no EMS was provided by the participant, 2 spot samples may be collected at the site, at least 30 minutes apart.
- Urine pregnancy test (women of child bearing potential, whether they are sexually active or not)
- Laboratory safety sampling (including male reproductive hormone tests);
- Single 12-lead ECG
- TB Symptoms Profile
- Patient Reported Health Status Questionnaire
- Vital signs
- Full physical examination, including weight

- Ophthalmology examination, if required as described in Table 5
- IMP compliance check (if participant on IMP)
- Concomitant medications
- Adverse events

Once a participant has been withdrawn early from the trial, they will be requested to attend follow-up visits as described in Table 5:

Table 5: Follow-up Visits Required for Early Withdrawal Participants

Treatment Duration at EWD visit	**Ophthalmology Examination at EWD[a]**	**Ophthalmology Examination** **Visit 3 months after EWD Visit[a]**	**Week 52** (Month12) **Follow-up Visit**	**Week 104** (Month 24) **Follow-up Visit**
≤ 14 days	Not required	Not required	Required	Required
15 days to ≤ 12 weeks	Not required	Required	Required	Required
> 12 weeks	Required	Required	Required, if not already performed	Required

a. If an additional visit is required for an ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 3 months after the EWD visit date.

The Weeks 52 and 104 visits will be performed to collect SAE information (including verification of survival) and participant reported TB outcome information. This visit may be telephonic, a home or a site visit at Weeks 52 and/or Week 104 after the participants' start of treatment date.

5.4.2 Unscheduled Visits

Any visit which is conducted in addition to those required by the Synopsis Flow Chart and Procedures (Section 1.2), should be considered unscheduled regardless of the reason for the visit. The assessments which are undertaken as part of an Unscheduled visit should be as clinically indicated.

The following situation/s would require an unscheduled visit/s:

- For any medical reason, as determined by the investigator or participant.
- If both sputum samples (EMS and spot) at Week 8 or later are contaminated, the participant should return for an unscheduled visit/s to give additional sputum samples or to document that the participant is not able to produce sputum.
- If after having converted to culture negative, the participant has a MTB confirmed positive culture at or after the last visit of the treatment period (Week 17 or Week 26), the participant should return for an unscheduled visit/s to provide additional sputum samples, at a minimum of 7 days apart, or to document that the participant is not able to produce sputum sample.

Determination of the participant's primary outcome status requires sputum culture results at the following time-points during the trial:

  - End of Follow-up Period (Week 52 and 104)
  - Early Withdrawal, if applicable

At least one of the following criteria should be met at these time-points to confirm a participant's primary outcome status:

- 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 the participant is clinically asymptomatic

Should the participant's primary outcome not meet any of the above criteria, the Investigator should continue to recall the participant for a Unscheduled visit to collect sputum samples until the criteria is met and the primary outcome can be determined.

Additional sputum samples: Two samples at each visit – ideally, one EMS and one spot sputum at the research site under the coaching and observation of the trial staff. If no EMS was provided by the participant, 2 spot sputum samples may be collected on site, at least 30 minutes apart. Additional sputum samples should be collected at least 7 days after the previous sample.

Table 6: Summary of Scenarios Requiring Unscheduled Visits for Mycobacteriology Testing

Time-point	Scenario	Unscheduled Visit/s Required?	Comment
Week 8 or later	Both sputum cultures are contaminated	Yes	Provide additional samples until a positive or negative result is reported, or it is confirmed that the participant is unable to produce sputum
At or after the last treatment visit (Week 17 or Week 26)	Previously converted to culture negative but now has an MTB-positive culture	Yes	Provide additional samples at least 7 days after the previous sample until the result is confirmed, or it is confirmed that the participant is unable to produce sputum.

Time-point	Scenario	Unscheduled Visit/s Required?	Comment
End of Follow-up Period (Week 52 and 104) Early Withdrawal, if applicable	Participant's primary outcome status cannot be confirmed by: 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	Yes	Provide additional samples at least 7 days after the previous sample until one of the criteria is met and the primary outcome status can be determined.

If the Investigator is unsure of the outcome in any of the above scenarios the Investigator should contact the Sponsor Medical Monitor to discuss and agree on how the participant is to be managed.

5.4.3 Lost-to-Follow-up

Every reasonable attempt must be made to minimise Lost-to-Follow-up (LTFU) participants. A minimum of three contact attempts (telephonic/home visit) will be made for participants who do not arrive for their scheduled trial visits. If these attempts are unsuccessful the participant will be considered LTFU. All attempts to contact the participant must be clearly documented in the participant's source documents.

5.4.4 Early Withdrawal due to TB

Ultimately it is the Investigator's decision whether a participant requires early withdrawal from the trial due to a concern that the participant has symptomatic worsening of TB and/or bacteriological failure/relapse.

Early withdrawal is usually not indicated for a single positive culture. Should a participant have a single positive culture result after being culture negative, the Investigator is to evaluate whether the participant has signs and symptoms suggestive of active inadequately treated TB and whether it is in the participants best interest that he/she be withdrawn. Prior to early withdrawal of a participant due to TB, the Investigator must discuss the participant with the Sponsor Medical Monitor, unless the Investigator cannot contact the Sponsor Medical Monitor

and considers that early withdrawal must occur immediately due to immediate safety concerns with respect to the participant.

If the Investigator decides to withdraw a participant due to TB, additional sputum samples may need to be collected to ensure the participant's outcome status as determined in Section 5.5.

All early withdrawn participants who are confirmed sputum positive (two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These participants will be referred to their applicable DS/DR local community TB clinics for standard anti-tuberculosis chemotherapy according to National TB Treatment Guidelines.

The participants will be provided with a referral letter from the Investigator to take with them to their National Treatment Program (NTP) clinic and the referral letter, at a minimum, should include all treatment received by the participant and information about any suspected/confirmed adverse event/reaction related to any of the trial IMP's and or concomitant medications. A follow-up call should be made by the trial site staff to the clinic to ensure the participant attended the NTP clinic.

5.5 Participant Progress Definitions

Table 7: Participant Progress Definitions

Status	Treatment	Follow-Up
Screen Failure	Participants from whom informed consent is obtained and is documented in writing (i.e., participant signs an informed consent form) but who are not randomized	
Completed Treatment / Completed Follow-Up*	Participants who complete the full course of IMP	Participants who complete all follow-up visits
Completed Treatment / Discontinued Follow-Up	Participants who complete the full course of IMP	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)
Completed Treatment / Lost to Follow-Up	Participants who complete the full course of IMP	Participants who are unable to be contacted on or before their final visit
Discontinued Treatment / Completed FU	Participants who discontinue IMP prior to completion of the protocol-defined treatment course	Participants who complete all applicable follow-up visits
Discontinued Treatment / Discontinued Follow-Up**	Participants who discontinue IMP prior to completion of the protocol-defined treatment course	Participants who do not complete all applicable follow-up visits, regardless of the reason (excluding LTFU)
Lost to Follow-Up	Participants who are unable to be contacted on or before their final treatment visit and it cannot be confirmed whether treatment was completed	

* Note that this includes treatment failures who complete all applicable follow-up visits

** Early Withdrawal

5.6 Trial Stopping Rules

There are no trial specific stopping rules.

The trial or parts of the trial can be stopped by the Sponsor on advice from the Data Safety and Monitoring Committee (DSMC) after their review of applicable trial data. In addition, the Sponsor has the right to stop the trial or a specific trial site at any time, although this should only occur after consultation between the involved parties. Should this occur, the local and central Ethics Committee/Institutional Review Board (EC/IRB) and Regulatory Authorities will be informed.

Should a trial site be closed prematurely, all trial materials (except source documentation that must remain at the site) will be returned to the Sponsor or applicable vendor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Participants currently on trial IMP will receive an appropriate regimen and all participants will be referred to their applicable DS-TB/DR-TB NTP clinic.

6.0 Treatment

6.1 IMP Administration

6.1.1 Instructions for Dosing of Test Regimen (BPaMZ):

- Treatment will be orally administered once daily, to be taken during breakfast, with a full glass of water (approximately 240 ml), for 17 weeks (4 months) or 26 weeks (6 months).

6.1.2 Instructions for Dosing Control Treatment Regimen (HRZE/HR):

- To be taken with a glass of water (approximately 240 ml).
- HRZE or HR should not be taken with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) in the following dosing schemes.

HRZE/HR treatment will be administered orally once daily to DS-TB participants as follows:

Weight Band	Weight Range	Number of tablets per weight band
1	30-39 kg	2
2	40-54 kg	3
3	55-70 kg	4
4	≥ 71 kg	5

The participant's weight at the Screening (HRZE) and Week 8 (HR) visits will be used to determine which weight band and dose to administer.

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

6.2 Participant Compliance

During site clinic visits, the IMP will be administered by the Investigator(s)/designated site personnel and when possible, the check for IMP compliance via the hand-and-mouth procedure (both the hand and the mouth of the participant will be checked to ensure that the

participant has swallowed the IMP). During the trial, sites will be responsible for ensuring participants are taking IMP correctly and are fully trained on how the IMP is to be taken, as well as to check the IMP cards for unused tablets in the containers at each visit during the treatment phase.

6.3 Treatment Modification(s)

The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the Investigator to identify and address the cause(s) (e.g. side effects).

Participants that do not take:

- Up to 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required.
- If more than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. The final treatment visit should also be pushed out to the date of last dose. It is not necessary to have an unscheduled visit at the time when the end of treatment visit would have been.
- If more than 35 consecutive doses of IMP, discontinue IMP and withdraw participant from the trial.
- If the participant misses a total (sum) of 56 cumulative missed doses, discontinue the IMP and withdraw the participant from the trial.
- If more than 7 to ≤ 35 consecutive doses are missed, these must be made up with the same treatment combination or dose that was missed.

Any participant for whom the trial IMP is discontinued (including for non-adherence) will be discussed with the Sponsor Medical Monitor and, if applicable, the participant will be restarted on trial IMP as soon as possible.

6.4 IMP Packaging and Labelling

The complete formulations of the IMP, bedaquiline and pretomanid, are found in the respective Investigator Brochures.[8, 15] The complete formulations of moxifloxacin, pyrazinamide, HRZE/HR are found in the Package Inserts.[19, 20, 22, 40]

The IMP will be packaged in weekly or bi-weekly cards as follows:

Week 1 to 8 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	14	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Week 9 to 17/26 Cards: Dispensed *Weekly*			
IMP	**Strength**	**Number of tablets**	**Abbreviation**
Bedaquiline	100 mg	7	B
Pretomanid	200 mg	7	Pa
Moxifloxacin	400 mg	7	M
Pyrazinamide	500 mg	21	Z

Control (HRZE/HR) Group: Dispensed *Bi-weekly*			
Weight Band	**Weight Range**	**Number of tablets per weight band**	**Number of tablets in each card**
1	30-39 kg	2	28
2	40-54 kg	3	42
3	55-70 kg	4	56
4	≥71 kg	5	70

A daily supplement of Vitamin B6 will be provided by the trial site to participants randomised to the HRZE/HR treatment arm, per each country's National TB Treatment Guideline.

The packaging of each weekly and biweekly cards will be labelled with, at a minimum, the following information:

- Name of Sponsor
- Name of medication
- Dosage, quantity and method of administration
- Reference/lot number
- The statement "For Clinical Trial Use Only"
- Space for completion of name of Investigator and site number
- MedID: medication identification number
- Storage conditions
- Period of use
- The statement "Keep out of reach of children"
- Expiry date
- Directions for use
- Space for completion of participant number and visit/date dispensed

6.5 Blinding and Procedures for Breaking the Blind

As this is an open label trial there is no need for blinding or procedures to break the blind. The trial participants, the site staff, Sponsor, and CROs will not be blinded to treatment assignment.

6.6 Handling, Storage and Accountability

The Investigator or designee must confirm that the appropriate temperature conditions as per details on IMP labelling, have been maintained during transit for all trial IMP received and any discrepancies are reported and resolved before use of the trial IMP.

Only participants randomised in the trial may receive trial IMP and only authorized site staff may supply or administer trial IMP. All trial IMP's must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for trial IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Upon completion or termination of the trial, all unused and/or partially used IMPs must either be returned to Sponsor (or designated vendor: who will arrange for destruction) or destroyed at site as agreed by the Sponsor, after final accountability has been confirmed.

The Investigator/designee will immediately inform the Sponsor of any quality issues arising with respect to the trial IMP. The Sponsor will take whatever action is required should such a situation arise.

Further guidance and information for the handling, storage, accountability and final disposition of unused trial IMPs are provided in the Pharmacy Manual.

7.0 Trial Variables and Procedures

The Synopsis Flowchart and Procedures in (Section 1.2) should be referenced for timing, sequence of assessments, and specific procedures.

7.1 Demographic and Background Variables and Procedures

The following demographic and background variables will be collected:

- Written Informed Consent
- Visit dates
- Participant disposition
- Demography (date of birth, race and gender)
- Inclusion and exclusion criteria
- Clinically significant medical and TB treatment history (including past and current TB diagnosis, smoking and alcohol use)
- Screening coached spot sputum samples:
    - Smear microscopy for acid-fast bacilli
    - Rapid molecular tests for isoniazid, rifampicin, fluoroquinolones resistance (Hain MTBDRplus and HainMTBRsl)
    - Liquid Culture (MGIT) for Mycobacterium tuberculosis (MTB), followed by a speciation test to detect presence or absence of MTB and obtain time to positivity (TTP) when positive.
- Urine pregnancy test: women of childbearing potential only, whether they are sexually active or not (non-childbearing potential for a female participant is defined as having bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months).
- Serology: HIV and CD4 count. Where required by regulatory authorities or ethics committees, a separate (EC/IRB approved) HIV informed consent form will be obtained from participants:
    - Prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained counsellors if they have indicated as such on the HIV consent form. If requested by the participant, HIV counselling that is provided to the participant by the trial site should be clearly documented in the participant's medical records/source. Participants have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the participant's medical records/source.
- Karnofsky Score (Appendix 5). Only for HIV positive participants.
- Chest X-Ray: A chest X-ray digital image within 6 months prior to or during the Screening visit, will be obtained and read locally by the Investigator or designee. Digital

images will be provided to the Sponsor; this process will be documented in the Chest X-Ray / Radiology Manual. The investigator is responsible for review and analysis of the chest X-ray for participant's inclusion.

- Method of birth control: male and female participants and their sexual partners
- IMP details: randomization
- IMP compliance and actual dosing
- Concomitant medications

7.2 Efficacy Variables and Procedures

Two spot sputum samples are collected, one EMS brought from home or collected in the hospital ward (only if the participant is hospitalised) and one spot sputum sample collected at the research site under the coaching and observation of the trial staff or, if no EMS sample was provided by the participant, 2 samples may be collected on site at least 30 minutes apart. The mycobacteriology sampling methodology and requirements will be described in a separate document, the Mycobacteriology Laboratory Manual, which will be provided prior to the trial start. Sputum samples may not be obtained by induction.

The following analyses will be performed:

- Liquid culture (MGIT), to detect presence or absence of MTB and obtain the TTP followed by a speciation test when applicable, to confirm MTB.

Using these observed variables, the following derived variables will be assessed for evaluation of the efficacy endpoints:

- Bacteriologic failure/relapse
- Time to sputum culture conversion
- Number of participants with sputum culture conversion

Every effort must 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 participant who never achieves culture negative status due to the inability to produce sputum, but has completed Week 17 or Week 26 and post treatment completion follow-up (Weeks 39 to 104) and is without clinical or biological evidence of relapse, will be considered to have a favourable outcome.

TB Symptoms Profile:

- The TB Symptoms Profile will record participants' ratings of the severity of common TB symptoms.

Patient Reported Health Status Variables and Procedures:

- The Patient Reported Health Status variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2). Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire. 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 trial Participant Questionnaires Guideline which will be provided prior to the trial start.

7.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the Synopsis Flow Chart and Procedures (Section 1.2) and assessed for evaluation of the safety endpoints:

- The safety laboratory sampling methodology and requirements will be described in a separate document, the Safety Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
    - Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count)
    - Clinical Chemistry (albumin, serum urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, ALP, AST, ALT, lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, glucose, bicarbonate/CO_2, creatine phosphokinase (CPK). GGT is only routinely included at the Screening visit (Day -9 to -1).
    - When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator can request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].
    - Hepatitis A, B and C serology test to be performed at Day 1 (baseline) or where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Russia Protocol V3.0
    - 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 ECG:
    - Investigator assessment: normal or abnormal
    - Central cardiologist assessment: heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.
    - Methodology:
        - Timing (Synopsis Flow Chart and Procedures, Section 1.2) and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start
        - ECGs are to be recorded for 10 seconds
        - ECGs are to be performed during a single visit
        - ECGs should be done before any phlebotomy when both included in a visit
        - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch)
    - ECGs to be performed prior to pre- and post-dose PK sampling as described below:
        - Day 1: pre-dose (within 2 hours prior to dosing)
        - Week 2: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
        - Week 8: pre-dose (within 2 hours prior to dosing), 1.5–3 hours post-dose and 4-6 hours post-dose
        - Week 12: pre-dose (within 2 hours prior to dosing)
        - Week 17 or at early withdrawal if prior to week 17: pre-dose (within 2 hours prior to dosing) and 1.5–3 hours post-dose

- Vital signs:
  - Vital signs (should be done before any phlebotomy in light clothing and with no shoes)
  - Systolic and diastolic blood pressure (mmHg) to be measured in a supine position (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 (beats per minute)
  - Respiratory rate (breaths per minute)
  - Axillary body temperature (°C)
- Physical Examination:
  - Height (m) is measured at the screening visit only
  - Full (complete) and limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded
  - Weight (kg) (in light clothing and with no shoes)
  - Using the variables of weight and height, the body mass index (BMI) will be calculated
- Ophthalmology Slit Lamp Examination:
  - To be done by an Ophthalmologist trained on Age-Related Eye Disease Scale 2 (AREDS2) assessment. The ophthalmology slit lamp methodology and requirements will be described in a separate document, the Ophthalmology Guideline. The following analyses will be performed: AREDS2 opacity typing and grading.
- Adverse events
- Investigator assessment:
  - The Investigator will review the participant status at specified visits in the Synopsis Flow Chart and Procedures (Section 1.2), including any time the Investigator determines that the participant fulfils the criteria for the primary outcome of treatment failure. The Investigator will assess whether TB treatment is considered a “success” or “failure”. If it is considered a failure, the Investigator should specify if the assessment is based on bacteriology and/or clinical deterioration and/or radiological deterioration.

7.4 PK Variables and Procedures

Plasma concentrations from sparse sampling (Synopsis Flow Chart and Procedures, Section 1.2) will be used to update population PK models for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin and pyrazinamide to further evaluate the effects of covariates on model parameters in this trial population.

PK data from the current trial may be combined with prior data to enhance this population PK analysis. The models will be used to estimate individual exposure metrics (e.g., C_{min}, C_{max}, AUC_{τ}, C_{mean}, and time above minimum inhibitory concentration) for subsequent analyses exploring relationships between drug exposure and efficacy and safety endpoints.

If IMP is not administered during Week 2, 8 and or 17, then only a single PK sample is required to be obtained at any time during the visit assessment.

7.5 Mycobacteriology Characterization Variable and Procedures

- Day 1 (Baseline) sputum sample (or any positive sample from Screening to Week 4, if the baseline cultures are contaminated or negative);

- MTB confirmed positive cultures (after the participant has previously converted to negative) at or after the last visit of the treatment period (Week 17 or Week 26) or visits with positive cultures, during the post-treatment follow-up period.
- Refer to the Mycobacteriology Laboratory Manual for full details.

Mycobacterial Characterization - MTB isolates (from the first MTB positive culture) will be processed for:

- Rapid molecular tests for fluoroquinolones, injectables, isoniazid and rifampicin resistance (only on MTB positive cultures in the follow-up period);
- Minimum Inhibitory Concentration (MIC) against bedaquiline, pretomanid and moxifloxacin
- Drug Susceptibility Testing for streptomycin, rifampicin, isoniazid, ethambutol, moxifloxacin and pyrazinamide in liquid culture;
- Extraction of organismal (MTB) DNA for whole genome sequencing (WGS), and the comparison of sequences from baseline and relapse isolates.

If the participant's culture converts to negative and has a MTB positive culture at or after the last visit of the treatment period (Week 17 and Week 26), the MTB cultures will be tested at the trial mycobacteriology laboratories using Hain MTBDR*plus* and HainMTBR*sl* to detect resistance to isoniazid, rifampicin, fluoroquinolones and injectables.

All MTB isolates must be stored be stored at the local mycobacteriology laboratories, until trial closure. In addition, MTB isolates as well as extracted MTB DNA from the applicable baseline and follow-up cultures will be stored at the central mycobacteriology laboratory for potential further work to advance new assay tools and understanding of MTB as a pathogen for a maximum of 5 years after trial closure.

8.0 Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

Any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a trial treatment whether or not considered related to trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a trial treatment, whether or not related to the trial treatment.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening (any event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation; In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred, or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity; the term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect; or
- Is a medically important event

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse. A "suspected transmission of infectious agent by a medicinal product" is also considered a serious adverse event under the SAE criterion "Other medically important condition".

8.1.3 Attribution/Causality

- The Investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE
- The Investigator will use clinical judgment to determine the relationship

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial IMP administration will be considered and investigated
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor/designee. However, it is very important that the Investigator always assesses causality for every event before the initial transmission of the SAE data to the Sponsor/designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment

Table 8: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An AE, which is not related to the use of the drug.
Unlikely	An AE 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 AE, 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 AE, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by de-challenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An AE, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

8.1.4 Severity

Table 9: Definitions for Adverse Event Severity Gradings

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-Threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

See Appendix 2 for full DMID Toxicity Tables. Above ratings should be used to estimate the grade for abnormalities NOT found elsewhere in the Toxicity Tables.

8.2 Reporting

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

All AEs will be collected by the Investigator from the time a participant signs the Informed Consent Form through to their Week 104 follow-up visit. The exception to this is early withdrawal participants who will only have SAEs collected from their time of early withdrawal to their Week 104 follow-up visit at the timepoints specified in the Synopsis Flow Chart and Procedures (Section 1.2) and recorded in the CRF.

Medical occurrences that begin after obtaining informed consent will be recorded as AEs. If an AE started before signing of the informed consent, but is ongoing at trial start, it should be recorded as medical history. If the pre-existing medical occurrence worsens during the trial, an AE will be recorded.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of the information becoming known to the Investigator, as noted in the SAE reporting guidelines. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of information becoming known to the Investigator.

The Sponsor/Investigator/designee will inform Regulatory Authorities and/or EC/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 EC/IRB.

Investigators are not obligated to actively seek AE or SAE information in former trial participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be

reasonably related to the trial IMP or trial participation, the Investigator must promptly notify the Sponsor, EC/IRB and regulatory authorities in an expedited basis, in accordance with local requirements and ICH GCP Guidelines.

8.2.1 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- The end of the follow-up period; and
- 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 Investigator. However, this will have to be agreed upon with the Sponsor Medical Monitor.

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. The Investigator should contact the Sponsor/designee to discuss appropriate medical follow-up if consultation is required.

If a participant dies during participation in the trial or during a recognized follow-up period, the Investigator will provide the Sponsor/representative with a copy of any post-mortem findings, including histopathology.

New or updated SAE information will be recorded in the originally completed CRF and submitted to the Sponsor within 24 hours of receipt, per the eCRF completion guidelines.

8.2.2 Clinical Laboratory Adverse Events

Changes in the results of the clinical laboratory assessment results and which the Investigator determines are clinically significant will be reported as AEs. It is the Investigators' responsibility to review the results of all laboratory tests as they become available. This review must be documented by the Investigators' dated signature on the laboratory report. For each abnormal laboratory test result, the Investigator needs to ascertain and document if this is a clinically significant change from baseline for that individual participant. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is determined by the Investigator to be a clinically significant change from baseline for that participant, it is considered to be an AE.

8.2.3 Disease Symptoms During Trial

Symptoms of the disease under trial (Tuberculosis) experienced by the participant while on the trial will be assessed by the Investigator. If the symptom has:

- worsened while the participant is in the trial; and
- the Investigator assesses it as clinically significant;

it will be recorded as an adverse event. If there is:

- no change; and
- the Investigator assesses the symptom as due to the participant's TB; and

- not clinically significant;

it will not be recorded as an AE and this will be noted in the participant's source documentation. All TB related symptoms that meet SAE criteria will be recorded and reported as a SAE.

8.2.4 Overdose

Overdose of the IMP experienced by the participant while on the trial, will be assessed by the Investigator to determine whether the overdose led to an adverse event, including if the taking of the suspected medicine led to suicidal intention and subsequent overdose of the suspected medicine, or other medication. In this case it will be recorded as an adverse event. If it does not lead to an adverse event, it will not be recorded as an AE and this will be noted in the participant's source documentation.

8.2.5 Drug Interaction

If the Investigator becomes aware that the participant has experienced a drug interaction which has resulted in an adverse event, it will be recorded as an adverse event.

8.2.6 Pregnancy

The Investigator will immediately notify the Sponsor of any pregnancy that is discovered during IMP administration or which started during IMP administration. Pregnancy forms will be completed for all pregnancies reported during the clinical trial, as defined below. In addition, the Investigator will report to the Sponsor any follow up information regarding the outcome of the pregnancy, including perinatal and neonatal outcome. Infants will be followed-up 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) at any time during the trial.

If a pregnancy is suspected while the participant is receiving IMP, the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner and the participant withdrawn from the trial and referred to the NTP for further management.

Protocol-required procedures for trial discontinuation and follow-up will be performed unless contraindicated by the pregnancy.

Pregnancy reporting **will follow the same timelines for a SAE** (see above). Instructions and forms will be provided separately. SAE reporting will also occur if the pregnancy outcome is a congenital anomaly. This will follow the reporting procedures described above for SAE reporting.

8.3 Monitoring for Specific Toxicities

Monitoring for specific toxicities is based upon target organs as defined in the preclinical toxicity studies of the Investigator's Brochures[8, 15] and Package Inserts.[19, 20, 22, 40]

AEs still ongoing at the end of the treatment period in the trial will be followed until satisfactory clinical resolution or stabilization, or until the end of the follow-up period and until all queries on these AEs have been resolved.

Grade 3 and Grade 4 laboratory abnormalities, and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.

Note: For Grade 3 or 4 laboratory toxicities, participants should have a confirmatory measurement within 48 hours, where possible. The recommendations for managing participants below assumes that the laboratory abnormalities of concern have been confirmed.

8.3.1 ALT, AST and Bilirubin Elevations

The Investigator should refer to the Hepatotoxicity Management Guideline, to appropriately monitor significant elevations of AST, ALT or Bilirubin. A separate Hepatoxicity Management Guideline document has been developed to aid investigators in the management of participants.

When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator should request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].

8.3.2 Lipase

Grade 3 (> 2.0 to ≤ 5.0 x ULN) or Grade 4 (> 5.0 x ULN):

- Contact the Sponsor Medical Monitor to review. Participants with confirmed Grade 3 or 4 elevations of lipase, the Investigator should consider pausing the full regimen, pending further evaluation.

8.3.3 Musculoskeletal System and Cardiac Muscle Myalgia

Grade 2 (muscle tenderness at a site other than sites of injection and/or venepuncture or with moderate impairment of activity) or Grade 3 (severe muscle tenderness with marked impairment of activity) or Grade 4 (frank myonecrosis):

- Participants with Grade 2 signs and symptoms should be followed closely. Participants with Grade 3 or 4 signs and symptoms should be discussed with the Sponsor Medical Monitor to consider pausing trial IMP, pending further evaluation.

8.3.4 Cardiac Rhythm Disturbances

Cardiac rhythm disturbances that are Grade 3 (recurrent, persistent, symptomatic arrhythmia requiring treatment) or Grade 4 (unstable dysrhythmia requiring treatment):

- Participants should be monitored closely. The Investigator should discuss with the Sponsor Medical Monitor to consider pausing the full regimen, pending further evaluation.

<u>QTc prolongation</u>

If QTcF is equal to or greater than 500 msec, the ECG should be repeated and serum electrolytes should be evaluated. If the second ECG also has a QTcF of > 500 msec, the Sponsor Medical Monitor should be consulted to consider pausing the full regimen, pending further evaluation.

New left bundle branch block (LBBB) or Mobitz type 2 or complete heart block. Recordings with artifacts that interfere with the interpretation of the ECG should be repeated to confirm the findings. If the finding is from the centralized ECG machine reading the result is to be checked and confirmed by the Investigator. If this is confirmed by the Investigator, dosing is to be paused until the reading has been confirmed by the central cardiologist and the participant is to be treated per the Investigator's clinical judgment. If it is confirmed by the central cardiologist, the participant is to be withdrawn from the full regimen. Contact Sponsor Medical Monitor to review.

8.4 Safety Monitoring by Data Monitoring Committee

A Data Safety Monitoring Committee (DSMC) will be appointed for the trial. The primary responsibility of the DSMC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial participants by monitoring participant safety, assess participant risk versus benefit, and assess data quality and general evaluation of the trial progress. Its activities will be delineated in a DSMC Charter that will define the membership, responsibilities and the scope and frequency of data reviews.

The DSMC will operate on a conflict-free basis independently of the Sponsor and the trial team. It will comprise at least 3 voting members that include at least 2 clinicians and one statistician.

The DSMC may have an organizational meeting prior to commencement of the trial. The DSMC will have meetings where it will review unblinded data during a closed session. These meetings will be planned at regular intervals.

The Sponsor or the DSMC may convene ad hoc meetings based on rates of SAEs and/or to review results of the futility analysis, or if safety concerns arise during the trial. After its assessment, the DSMC will recommend to the Sponsor continuation, modification or termination of the clinical trial.

9.0 Statistical Analysis

The statistical analysis plan (SAP), which will contain details of the analyses specified in this section, will be written and signed off prior to the interim analysis.

There will be 3 data analyses and trial reports generated for this trial:

1. When all participants have completed 8 weeks (2 months) of treatment from baseline.
2. When all participants have completed 52 weeks (12 months) follow-up from start of therapy.
3. When all participants have completed 104 weeks (24 months) follow-up from start of therapy.

9.1 Analysis Populations

There will be three main analyses of the primary efficacy endpoint: An intent to treat (ITT) analysis; a modified intent to treat (mITT) analysis and a per protocol (PP) analysis

- The ITT population is defined as all randomized participants excluding late screening failures. Late screening failures are participants withdrawn from treatment because they were found to be ineligible (late exclusions from the trial), based on data collected *prior to randomization*.

- The mITT population is defined as the ITT population with extra exclusions (described in the SAP).
- The PP population is defined as the mITT population with extra exclusions (described in the SAP).
- The mITT analysis will be considered primary, with consistent findings required from the other main analysis populations to support the primary conclusion.

9.2 Sample Size

For the primary endpoint, time-to-culture conversion at 8 weeks,150 participants per arm (DS-TB participants) will provide at more than 90% power (5% 2-sided significance) to detect a hazard ratio (HR) of at least 2 assuming 50% of control participants are culture negative by 8 weeks. If only 25% of the control arm remain culture positive at 8 weeks, then this sample size will still retain more than 90% power to detect a HR of least 2. This sample size also allows for one planned interim analysis of the primary endpoint (See Section 9.4.1)

For the key secondary endpoint of clinical outcome at 12 months from randomization, 150 patients per arm will provide 74% power based on assumptions using data from the largest most recent and completed phase 3 TB treatment trial which used the same control arm.[41] That is, assuming 16% unfavourable (see Section 9.4.2) in the control arm and 13% unassessable (see Section 9.6) at 52 weeks post randomization. A 12% margin of non-inferiority was chosen to preserve at least 75% of the estimated control arm effect against placebo (estimated to be 54%)[41, 42] which is considered an acceptable proportion on which to declare non-inferiority of the test regimen.

9.3 Interim Analyses

There is one planned interim efficacy analysis which will occur after approximately 60 assessable participants have been randomised to the control arm and have reached the 8-week primary endpoint. Time to culture negative status in liquid media up to 8 weeks will be analysed using a Cox regression model, censoring for death and lost to follow up/withdrawal to estimate the hazard ratio (HR). Following a review of these interim findings, the following considerations will be given to modify the trial objectives and sample size:

If the observed HR (time to culture negativity, experimental arm vs. HRZE control arm) is >2, the sample size may be increased to adequately power the trial on the key secondary efficacy endpoint (clinical and microbiological outcome at 52 weeks from randomization), which will then become the primary efficacy endpoint. The trial efficacy objectives will be updated as follows:

- **Primary Objective**

  *To determine the incidence of bacteriologic failure or relapse or clinical failure at **52 weeks** from the start of treatment / randomisation.*

- **Secondary Objectives**

  *To evaluate the time to culture negativity **over 8 weeks,** from the start of treatment / randomisation.*

All other trial objectives will remain unchanged.

To achieve 90% power and overall 5% 2-sided significance after adjusting for the interim analysis, this will mean increasing the sample size to 225 participants per randomised

arm, i.e., to a total of 450 DS-TB participants (and up to 225 DR-TB participants). This adaptation is based on the Multi-arm Multi-stage (MAMS) framework [46,47,48] and full details are provided in the Statistical Analysis Plan.

9.4 Primary and Secondary Efficacy Endpoint Analysis

9.4.1 Primary Efficacy Endpoint, Time to Culture Conversion at 8 Weeks

The primary analysis will be conducted using culture results from liquid culture (MGIT) media.

Participants will be classified as being culture positive, culture negative, dead or unassessable at 8 weeks. The proportion culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis and groups compared using a hazard ratio and 95% confidence interval.

Non-inferiority of the key secondary endpoint of clinical outcome will be assessed using the upper bound of the one-sided 97.5% confidence interval for the difference between the proportion of participants who are classified as having an unfavourable status on the intervention less the control regimen. If the upper bound of the one-sided 97.5% confidence limit for this difference in proportions is less than 12% (the margin of inferiority) the intervention will be non-inferior to the control arm.

9.4.2 Key Secondary Efficacy Endpoint, Clinical Outcome at 52 Weeks from Randomization

For the key secondary endpoint of clinical outcome (bacteriologic failure or relapse or clinical failure), participants will be classified as having a favourable, unfavourable or unassessable outcome status which will be defined in detail in the SAP. In general, participants achieving and maintaining culture negative status without any additional treatment will be considered favourable; participants who fail on treatment or relapse in follow-up will be considered unfavourable and participants who are not assessable (and who have not already been declared as unfavourable) will be considered unassessable and excluded from the analysis.

9.4.3 Other Secondary Efficacy Endpoints

The secondary efficacy endpoints and analyses are as follows are:

- Clinical outcome (bacteriologic failure or relapse or clinical failure) at 104 weeks from the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy.
- Change from baseline in weight will be summarised and presented.
- Proportion of participants experiencing a change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status will be summarised and presented.

9.5 Safety and Tolerability Assessments

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 any AE occurring or worsening with an onset date on or after the date of the first dose of the study medication and within 14 days after the date of the last dose. Any adverse event that started beyond this timeframe and assessed as possibly related to study drug is considered 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.

9.6 Pharmacokinetics

For each analyte and each scheduled sampling time/window, the plasma concentration will be summarized by descriptive statistics including the mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and geometric CV (%).

In addition, mean and/or median concentration-versus-time graphs will be provided, with error bars and/or scatter plots as appropriate.

Plasma concentrations from sparse sampling will be used to update existing population PK models and derive exposure metrics (e.g., C_{min}, C_{max}, AUC) for bedaquiline and its M2 metabolite, pretomanid, moxifloxacin, and pyrazinamide. Effects of baseline covariates on exposure will be assessed; so, too, will the effects of concomitant medications including ART, as feasible. Data from other trials may be included to enhance the model-based analysis.

Detailed plans for the PopPK analysis will be outlined in a separate modelling plan, and results will be reported in separate modelling report.

9.7 Pharmacokinetics/Pharmacodynamics

Relationships will be explored between drug exposure and efficacy and safety endpoints. These exploratory PK/PD analyses may include HIV status as a covariate. Planning details and results will be included in the separate modelling plan and report.

10.0 Records Management

10.1 Data Collection

All relevant CRF/eCRF pages will be completed for each participant who receives any amount of IMP, depending on visits attended. For screening failure participants, specific eCRF pages will be completed as described in the eCRF Completion Guidelines. For participants who are prematurely withdrawn, all the visits the participant attended including withdrawal and follow-up visits need to be completed.

10.2 Source Documents

Source documents are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents will include, but are not

limited to, progress notes, in-patient hospital records, electronic data, screening logs, and recorded data from automated instruments.

All source documents pertaining to this trial will be maintained by the Investigators. The Investigator must permit trial related monitoring, audits, Independent Ethics Committee/Institutional Review Board (EC/IRB) review and regulatory inspections providing authorized personnel direct access to source documents, including documents required to confirm inclusion/exclusion and relevant in-patient records while participants are on trial treatment.

10.3 File Management at the Trial Centre

It is the responsibility of the Investigators to ensure that the trial centre files are maintained in accordance with International Good Clinical Practice Guidelines and the ethical principles that have their origin in the Declaration of Helsinki.

10.4 Records Retention at the Trial Centre

The Investigator is obliged to retain records and data from the trial for safety reasons and for audit and inspection after trial completion. The essential documents should be retained for not less than 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. Investigator should notify the Sponsor/designees prior to destroying any records pertaining to the trial.

11.0 Quality Control and Assurance

11.1 Site Procedures

The Investigator undertakes to perform the clinical trial in accordance with this protocol, local regulations, International GCP, and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator undertakes to complete the CRFs according to the Sponsor's requirements, in a timely, accurate and legible manner. CRF entries will be verifiable to source documentation other than the CRF.

Site Standard Operating Procedures (SOPs), where available, will be adhered to for all clinical and bioanalytical activities relevant to the quality of the trial. Participant compliance will be monitored throughout the trial.

The Investigator will sign and date any analysis results (e.g., laboratory, ECG, etc.) to verify that the results have been reviewed.

The Investigator may appoint other sub-Investigators to assist with the trial. However, the Investigator maintains responsibility for the trial and will supervise the sub-Investigators. Written EC/IRB approval of the trial will be obtained prior to involvement in the trial.

The Investigator will ensure that all site personnel are adequately trained in GCP, local regulations, the protocol, IBs/package inserts and all trial procedures and requirements.

11.2 Monitoring

The Investigator is responsible for the validity of all data collected at the clinical site and must accept the various monitoring procedures employed by the Sponsor. The purpose of monitoring is to verify that the rights and well-being of human participants are protected; that trial data are accurate, complete and verifiable with source data; and that the trial is conducted in compliance with the protocol, International GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

Monitors assigned by the Sponsor will conduct regular site visits before, during and after the trial for monitoring various aspects of the trial, and to assure appropriate conduct of the trial in accordance with ICH GCP. Visits will take place usually within a predetermined interval, but this may vary during the trial. The Investigator and site staff will allow the trial monitor and authorized representatives of the Sponsor to (1) inspect all CRFs, written informed consent documents and corresponding source documents (e.g., original medical records), patient records and laboratory raw data, site SOPs, training records, facilities and other trial related systems/processes, and (2) access clinical supplies, dispensing and storage areas. The Investigator and site staff should also (1) agree to assist with monitoring activities if requested and (2) provide adequate time and space for monitoring visits.

The monitor will query any missing, confusing, spurious, or otherwise ambiguous data with the Investigator. All queries should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor's signature and Investigator or designee's confirmation signature.

11.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol and GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the trial site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in trial source documents and reported to Sponsor/designee. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/trial staff is responsible for knowing and adhering to their IRB requirements.

11.4 Auditing

For 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 about accuracy, adequacy and consistency, and to assure that trials are in accordance with the guidelines. Having the highest quality data from trials is an essential aspect of drug development.

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The auditors or inspectors may also review site SOPs, training records, site facilities and other trial related systems/processes.

In the event of the site being notified of a Regulatory Inspection, the Sponsor will help with preparation. It is essential that the Sponsor be notified of the inspection as soon as possible.

12.0 Ethics and Regulatory

12.1 Basic Principles

This research will be carried out in accordance with International GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

12.2 Independent Ethics Committee/Institutional Review Board (EC/IRB) Review

The protocol and required trial related documents will be reviewed by the sites respective EC/IRB. The trial will not start until the EC/IRB has approved the protocol, written informed consent, any written information to be provided to the participant or any modification thereof, plus any other trial related documents required for review. The EC/IRB shall be constituted and shall operate in accordance with International GCP, the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will maintain an accurate and complete record of all submissions made to, and responses from the IRB/EC. The records should be filed in the Investigator's Trial File, and copies will be sent to the Sponsor.

12.3 Regulatory Authorities

The Regulatory Authorities will receive the protocol, amendments, reports on SAEs, and the Integrated Clinical Trial Report according to national regulations. As required by local legislation, written approval will be obtained from the Regulatory Authorities prior to commencement of the trial and implementation of e.g. amendments as applicable.

12.4 Informed Consent

Written informed consent will be obtained from all participants (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment procedures) are performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for 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 part of the research.

The Investigators have both ethical and legal responsibility to ensure that each participant being considered for inclusion in this trial is given a full explanation of the protocol. Participants must be informed that their participation is voluntary. The Investigator or his/her representative will explain the nature of the trial to the participant or his/her legally authorized representative and answer all questions regarding the trial. This shall be documented on a written informed consent form that shall be approved by the same EC/IRB responsible for approval of this protocol. Each informed consent form shall include the elements required by the international GCP and must adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The trial will be included and updated in the appropriate Country registry and referenced in the informed consent forms (ICF).

Once the appropriate essential information has been provided to the participant and fully explained by the Investigators (or qualified designees) and it is felt that the participant understands the implications of participating, the EC/IRB approved written ICF will be signed

and dated by both the participant and the person obtaining consent (Investigators or designees), and by any other parties required by the EC/IRB. Ongoing participants must be re-consented to the most current version of the ICF(s) during their participation in the trial.

The original signed ICFs will be kept with the trial records and a copy of ICF will be provided to the participant or the participant's legally authorized representative. Another copy of the signed ICF and a source document identifying the trial and recording the dates of participation will be placed in the participant's medical record.

The monitor will inspect the original completed ICFs for all participants.

12.5 Confidentiality

All site staff, the Sponsor, and any Sponsor representatives will preserve the confidentiality of all participants taking part in the trial, in accordance with International GCP, applicable local legislation/regulations. Subject to the requirement for source data verification by the trial personnel by reference to the participant's notes, confidentiality of all participant identities will be maintained. Unique identifiers will be used on the CRF and in all trial correspondence, as permitted. No material bearing a participant's name will be kept on file by the Sponsor. The written informed consent will contain a clause granting permission for review of the participants' source data by the Sponsor or designees.

13.0 Publication Policy

The definition of publication for this purpose is any public presentation of the data emerging from this trial.

All unpublished information given to the Investigator by the Sponsor shall not be published or disclosed to a third party, other than to the responsible EC/IRB, within the understanding of the confidentiality of their nature, without the prior written consent of the Sponsor.

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between Sponsor and Investigator(s), including site clinical and laboratory Investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors.[43]

Because the trial is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the Trial must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy . Specifically, (a) all peer-reviewed published research relating to the trial must be submitted for publication by TB Alliance through the Chronos Open Access Publishing Service established by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy.

14.0 Protocol Amendment Policy

Any change to the protocol will be affected by means of a protocol amendment. Any changes which affect participant safety or welfare will be submitted to the EC/IRB and Regulatory Authorities prior to implementation. The Investigator, EC/IRB, and Sponsor must agree on all amendments. No amendment will be implemented until approved by the relevant authorities and/or EC/IRB and signed by all required parties. Exceptions to this are when the Investigator considers that the participant's safety is compromised.

Protocol amendments detailing minor administrative changes should be submitted by the Investigator to the EC/IRB and Regulatory Authorities, either for notification purposes or approval as appropriate.

15.0 Sponsor, Financial Aspects, Insurance and Indemnity

The trial Sponsor is the TB Alliance (TBA). The TB Alliance is a not for profit, product development partnership accelerating the discovery and development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies for those HIV-TB participants currently on such therapies and improve treatment of latent infection.

The TB Alliance works with public and private partners worldwide. It is committed to ensuring that approved new regimens are affordable, adopted and available to those who need them.

The TB Alliance operates with funding mainly from the Bill & Melinda Gates Foundation, the Netherlands Ministry of Foreign Affairs (DGIS), the United Kingdom Department for International Development (DFID), and the United States Agency for International Development (USAID).

The participants will not receive any incentives for their involvement in the trial. The Sponsor has made provision to reimburse the participants for out-of-pocket expenses such as travelling to and from the trial site and other miscellaneous costs as a result of their trial participation.

The Sponsor certifies that it has liability insurance coverage for itself and will provide an associated certificate upon request. The insurance does not relieve the Investigators of the obligation to maintain their own liability insurance as required by applicable law. The Sponsor does not assume any obligation for the medical treatment of other injuries and illnesses.

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Appendices

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	scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli per field in at least 20 fields	+++

Reference: The Public Health Service National Tuberculosis Reference Laboratory and the National Laboratory Network. Minimum Requirements, Role and Operation in a Low-Income Country. International Union Against Tuberculosis and Lung Disease 1998.

Appendix 2: Division of Microbiology and Infectious Disease (DMID) Toxicity Table

Source: U.S. National Institute of Allergy and Infectious Diseases, DMID, November 2007 (Draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of Acquired Immune Deficiency Syndrome (AIDS), NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the DMID and modified to better meet the needs of participants 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	> 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	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life- threatening arrhythmia

Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening
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
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	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent ; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatienttreatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient - no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3- 4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	Subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint 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 -	38.6 - 39.5 C or 101.6 -	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: Who Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection
Asymptomatic Acute retroviral syndrome
Clinical Stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical Stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections
Clinical Stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for >1 month Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) Persistent oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anemia (hemoglobin <8 g/dL) Neutropenia (neutrophils <500 cells/µL) Chronic thrombocytopenia (platelets <50,000 cells/µL)
Clinical Stage 4
HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Cryptococcosis, extrapulmonary (including meningitis) Disseminated nontuberculosis mycobacteria infection Progressive multifocal leukoencephalopathy Candida of the trachea, bronchi, or lungs Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis) Recurrent nontyphoidal Salmonella bacteremia Lymphoma (cerebral or B-cell non-Hodgkin) Invasive cervical carcinoma

Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy
Symptomatic HIV-associated cardiomyopathy
Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

REF: World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children; 2007*

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: Cardiovascular Safety

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

All-important abnormalities from the ECG readings will be reported.

The percentage of participants with increases in QTc of <30, 30-60, or > 60 ms from baseline will also be tabulated at each time point.

Abnormality Code	ECG parameter			
	HR	PR	QRS	QTcorrected
Abnormalities on actual values				
“Abnormally low”	≤ 50 bpm	NAP	≤ 50 ms	-
“Abnormally high”	≥ 120 bpm	≥ 210 ms	≥ 120 ms	-
“]450 ms, 480 ms]	-	-	-	450 ms < QTc ≤ 480 ms
“]480 ms, 500 ms]	-	-	-	480 ms < QTc ≤ 500 ms
“More than 500 ms	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline				
“[30; 60] ms”	-	-	-	[30; 60] ms
“> 60 ms”	-	-	-	> 60 ms

Appendix 5: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Description		%
Able to carry on normal activity and to work; no special care needed.	Normal no complaints; no evidence of disease.	100
	Able to carry on normal activity; minor signs or symptoms of disease.	90
	Normal activity with effort; some signs or symptoms of disease.	80
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	Cares for self; unable to carry on normal activity or to do active work.	70
	Requires occasional assistance, but is able to care for most of his personal needs.	60
	Requires considerable assistance and frequent medical care.	50
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	Disabled; requires special care and assistance.	40
	Severely disabled; hospital admission is indicated although death not imminent.	30
	Very sick; hospital admission necessary; active supportive treatment necessary.	20
	Moribund; fatal processes progressing rapidly.	10
	Dead	0

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109.

Protocol Amendment or Administrative Change

TB ALLIANCE

Trial Number	Trial Name
NC-008	SimpliciTB

X Protocol Russia Amendment Number 2 Dated 01/OCT/2019, Incorporating Protocol V4.0 Dated 30/SEP/2019
☐ Protocol Administrative Change Number _ _, Dated _ _/_ _ _/_ _ _ _

Summary - Protocol section changed		Does amendment / administrative change affect any of the elements listed?	
		YES	**NO**
A	Purpose of trial	☐	X
B	Design of trial	☐	X
C	Informed consent	☐	X
D	Recruitment procedure	☐	X
E	Measures of efficacy	☐	X
F	Schedule of samples	☐	X
G	Addition or deletion of tests or measures	X	☐
H	Number of participants	☐	X
I	Age range of participants	☐	X
J	Inclusion criteria	☐	X
K	Exclusion criteria	☐	X
L	Safety monitoring	X	☐
M	Duration of exposure to the investigational medicinal product(s)	☐	☐
N	Change of posology of the investigational medicinal product(s)	☐	X
O	Change of comparator	☐	X
P	Statistical analysis	☐	X

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Reasons for Protocol Amendment or Administrative Change:

1	Change:	TB Alliance logo has been changed on page 1, due to updated company logo that was implemented in Jul 2019.
2	Clarify:	Per Memo #3, Slit lamp ophthalmic examination to be performed at Week 17 and 26 for the 4-month treatment arm, and only at Week 26 for the 6-month treatment arms (Section 1.2, Synopsis Flow Chart and Procedures update, only) to ensure consistency with protocol Section 1.2 Flow Chart and Procedures footnote p.
3	Clarify:	Per Memo #5, ECG to be performed at Week 12 (Section 1.2, Synopsis Flow Chart and Procedures update, only) to ensure consistency with the protocol Section 1.2 Flow Chart and Procedures footnote n, and Section 7.3 Safety and Tolerability Assessments.
4	Clarify:	Per Memo #6, Male Reproductive Hormone testing to be performed at the end of each 4 and 6-month treatment period (Section 1.2, Synopsis Flow Chart and Procedures update, only) in alignment with the protocol intention to perform this assessment at the end of each treatment period.
5	Clarify:	Per Memo #7, Male Reproductive Hormone testing to be performed at the early withdrawal visit (Section 1.2, Synopsis Flow Chart and Procedures update, only), to ensure consistency with the Section 5.4.1 Early Withdrawal.
6	Clarify:	Per Memo #8, pregnancy testing is to be performed on all female participants of childbearing potential. Females of non-childbearing potential are: Female participant or male participants' female sexual partner – bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months (Inclusion criteria #5.1.7 updated, only), to ensure consistency with the Section 1.2 Synopsis and Flow Chart and Procedures footnote k, Section 5.4.1 Early Withdrawal (urine pregnancy test) and Section 7.1 Demographic and Background Variables and Procedures (urine pregnancy test).
7	Change:	'When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator **should** (changed from 'can') request additional tests…' (Section 1.2, Synopsis Flow Chart and Procedures footnote l; Section 7.3 Safety and Tolerability Assessments; Section 8.3.1 ALT, AST and Bilirubin Elevations) to improve safety monitoring and management of participants.
8	Add:	Hepatitis A, B and C serology test to be performed at Day 1 (baseline) or where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Protocol V4.0, to improve safety monitoring and management of participants (Section 1.2, Synopsis Flow Chart and Procedures footnote l; Section 7.3 Safety and Tolerability Assessments).
9	Add:	'Where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C result for all participants already enrolled prior to Protocol V4.0', to improve safety monitoring and management of participants (Section 1.2, Synopsis Flow Chart and Procedures footnote s).
10	Add:	'When Phenotypic DST and **/ or** whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results'… wording updated, as Phenotypic DST results are

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		more readily available when this review and decision needs to be made, on an ongoing basis (Section 5.1.5 Inclusion Criteria and 5.4 Treatment Discontinuation and/or Early Withdrawal).
11	Change:	Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening with an onset date on or after the date of the first dose of the study medication and **within 14 days after the date of the last dose,** changed from …'until the last scheduled visit / assessment / measurement'… in Section 9.5 Safety and Tolerability Assessments, to be consistent with the Statistical Analysis Plan (SAP) definition of TEAEs.

#	Section	Previous Text Version 3.0, dated 14-Jan-19	Amended Text Version 4.0, dated 30-Sep-19 **Additional text - bold font.** Deleted text – ~~strike-through.~~	Reason for Change Insert reason # from table above
1	Page 1, title page	TB ALLIANCE	TB Alliance	1
2	Section 1.2 Synopsis Flow Chart and Procedures	X-mark present at Week 17 for the 6-month treatment arms	**X-mark has been removed from Week 17 for the 6-month treatment arms**, for the Ophthalmic examination assessment	2
3	Section 1.2 Synopsis Flow Chart and Procedures	X-mark not present	**X-mark has been included at Week 12**, for the assessment of the 12-lead ECG	3
4	Section 1.2 Synopsis Flow Chart and Procedures	X-marks present at Week 17 for the 6-month treatment arms, and at Week 26 for the 4-month treatment arm	**X-mark has been included at Week 17 for the 4-month and at Week 26 for the 6-month treatment arms**, for the assessment of the Male Reproductive Hormone Tests	4
5	Section 1.2 Synopsis Flow Chart and Procedures	X-mark not present	**X-mark has been included at Early Withdrawal**, for the assessment of the Male Reproductive Hormone Tests	5

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#	Section	Previous Text Version 3.0, dated 14-Jan-19	Amended Text Version 4.0, dated 30-Sep-19 **Additional text - bold font.** Deleted text – ~~strike-through.~~	Reason for Change Insert reason # from table above
6	Inclusion Criteria #5.1.7	a. Participant - not heterosexually active or practice sexual abstinence; or b. Female participant or male participants female sexual partner – bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or c. Male participant or female participants male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening;	~~a. Participant - not heterosexually active or practice sexual abstinence; or~~ b. Female participant or male participants female sexual partner – bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or ~~c.~~ Male participant ~~or female participants male sexual partner - vasectomised or has had a bilateral orchidectomy at least three months prior to screening;~~	6
7	Section 1.2, Synopsis Flow Chart and Procedures footnote l; Section 7.3 Safety and Tolerability Assessments; Section 8.3.1 ALT, AST and Bilirubin Elevations	When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator should request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].	When managing participants with elevated liver enzymes at an Unscheduled visit, the investigator ~~can~~ **should** request additional tests, in addition to the repeat LFT [e.g. Gamma Glutamyl Transferase (GGT), screening for Hepatitis A, B, C; to assist in ruling out other causes of a dysfunctional liver test (e.g. alcohol induced hepatic cell injury, hepatobiliary disease, hepatic viral infection)].	7

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#	Section	Previous Text Version 3.0, dated 14-Jan-19	Amended Text Version 4.0, dated 30-Sep-19 **Additional text - bold font.** Deleted text – ~~strike-through.~~	Reason for Change Insert reason # from table above
8	Section 1.2, Synopsis Flow Chart and Procedures footnote l; Section 7.3 Safety and Tolerability Assessments	No previous text	**Hepatitis A, B and C serology test to be performed at Day 1 (baseline) or where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis A, B and C serology result for all participants already enrolled prior to Protocol V4.0**	8
9	Section 1.2, Synopsis Flow Chart and Procedures footnote s	No previous text	**Where available, the backup PK sample at Day 1 (pre-dose) will be used to obtain a hepatitis serology result for all participants already enrolled prior to Protocol V4.0**	9
10	Section 5.1.5 Inclusion Criteria and 5.4 Treatment Discontinuation and/or Early Withdrawal	When Phenotypic DST and whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.	When Phenotypic DST and **/ or** whole genome sequencing (WGS) results on baseline samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the Sponsor Medical Monitor in consultation with the Investigator to determine whether that participant is unlikely to respond to treatment and should therefore be removed from the trial and given alternative treatment. If a participant is removed from the trial for such a reason, they will be classified as a late exclusion.	10

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#	Section	Previous Text Version 3.0, dated 14-Jan-19	Amended Text Version 4.0, dated 30-Sep-19 **Additional text - bold font.** Deleted text – ~~strike-through.~~	Reason for Change Insert reason # from table above
11	Section 9.5 Safety and Tolerability Assessments	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.	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.~~ **any AE occurring or worsening with an onset date on or after the date of the first dose of the study medication and within 14 days after the date of the last dose**. **Any adverse event that started beyond this timeframe and assessed as possibly related to study drug is considered treatment-emergent**	11

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I agree to the terms of this Protocol Amendment or Administrative Change.

DocuSigned by:
Morounfolu Olugbosi
Signer Name: Morounfolu Olugbosi
Signing Reason: I approve this document
Signing Time: October 2, 2019 | 1:10 AM PDT
3DABF6C3410E4B8F85E1D6E511FA5A5F

Signature of Study Physician	Morounfolu Olugbosi Printed name	October 2, 2019 | 1:10 AM PDT Date

Principal Investigator

I hereby confirm I have read the above Protocol Amendment or Protocol Administrative Change and agree to conduct this clinical trial as outlined in the above. I will provide copies of the Protocol Amendment or Protocol Administrative Change and access to all of the information required to conduct the clinical trial according to the above Protocol Amendment or Protocol Administrative Change to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature of Principal Investigator	Printed name	Date

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To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an e-mail to christi.baine@tballiance.org and in the body of such request you must state your e-mail address, full name, US Postal address, and telephone number. We will bill you for any fees at that time, if any.
To withdraw your consent with Global Alliance for TB Drug Development-Sub Account
To inform us that you no longer want to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your DocuSign account, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
ii. send us an e-mail to christi.baine@tballiance.org and in the body of such request you must state your e-mail, full name, IS Postal Address, telephone number, and account number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will

have the right to withdraw your consent.

Acknowledging your access and consent to receive materials electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.

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