TB Alliance

BPaMZ/SEM

| | |
|---|---|
| Protocol Number: | Pa-824-CL-012 |
| Title: | An Open-Label Phase 2 Trial to Evaluate the Male Reproductive Safety of a 6-month Combination Treatment for Pulmonary Tuberculosis of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) in Adult Male Participants with Drug Resistant (DR-TB) Pulmonary Tuberculosis |
| Drug(s)/Combination(s): | Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z), |
| Protocol Version/Date: | Version 4.0 / 07 APR 2022 |
| Protocol Name: | **BPaMZ/SEM** |

## PROTOCOL SIGNATURE PAGE

**Protocol Title: An Open-Label Phase 2 Trial to Evaluate the Male Reproductive Safety of a 6-month Combination Treatment for Pulmonary Tuberculosis of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) in Adult Male Participants with Drug Resistant (DR-TB) Pulmonary Tuberculosis**

**Protocol Number: Pa-824-CL-012**
**Protocol Date: 07-APR-2022**
**Protocol Name: BPaMZ/SEM**

### SPONSOR

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: April 8, 2022 | 10:17 AM EDT
3B496C3B3A6A4B0AAE32731255B7115B

Signature of Senior Medical Officer

Paul Bruinenberg, MD
Printed Name

April 8, 2022 | 10:17 AM EDT
Date

40 Wall Street, 24 FL
New York, NY, 10005
Phone: +1 646-616-8629/ +1 201-312-0988
email: 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 current Good Clinical Practice (cGCP) and local regulations.

DocuSigned by:
Pauline Howell, MD
Signer Name: Pauline Howell, MD
Signing Reason: I have reviewed this document
Signing Time: April 12, 2022 | 5:18 AM EDT
DEE8323CADED4CA7802778F22DB94A8F

Signature

Pauline Howell, MD
Printed Name

April 12, 2022 | 5:18 AM EDT
Date

# PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

**Protocol Title: An Open-Label Phase 2 Trial to Evaluate the Male Reproductive Safety of a 6-month Combination Treatment for Pulmonary Tuberculosis of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) in Adult Male Participants with Drug Resistant (DR-TB) Pulmonary Tuberculosis**

**Protocol Number:** Pa-824-CL-012

**Protocol Date: V4.0 07 APR 2022**

**Protocol Name: BPaMZ /SEM**

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

| | |
|---|---|
| AE | Adverse Event |
| AFB | Acid-Fast Bacillus |
| AIDS | Acquired Immune Deficiency Syndrome |
| ALP | Alkaline Phosphatase |
| ALT | Alanine aminotransferase |
| ART | Anti-Retroviral Therapy |
| AST | Aspartate aminotransferase |
| AUC | Area Under Concentration Time Curve |
| $AUC_{0-24}$ | Area Under Concentration Time Curve 0 to 24 hours |
| $AUC_{0-inf}$ | Area Under Concentration Time Curve extrapolated to infinity |
| $AUC_{\tau}$ | Area Under Concentration Time Curve during the dosing interval |
| B | Bedaquiline |
| BA | Bacterial Activity |
| BMI | Body Mass Index |
| BPaL | Combination of Bedaquiline plus pretomanid plus Linezolid |
| BPaMZ | Combination of Bedaquiline plus pretomanid plus moxifloxacin plus pyrazinamide |
| C | Clofazimine |
| $C_{avg}$ | Average Plasma Concentration |
| CD4 | Cluster of Differentiation 4 |
| CFU | Colony Forming Units |
| $C_{(max), (min)}$ | Plasma Concentration (maximum), (minimum) |
| CNS | Central Nervous System |
| $CO_2$ | Carbon dioxide |
| CPK | Creatine Phosphokinase |
| Ddn | Deazaflavin-dependent nitro reductase |
| DFID | Department for International Development |
| DGIS | Netherlands Ministry of Foreign Affairs |
| DMID | Division of Microbiology and Infectious Disease |
| DR-TB | Drug Resistant Tuberculosis |
| DS-TB | Drug Sensitive Tuberculosis |
| DSMC | Data Safety and Monitoring Committee |
| E | Ethambutol |
| EBA | Early Bactericidal Activity |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | electronic Case Report Form |
| ELISA | Enzyme-linked immunosorbent assay |
| EMS | Early Morning Sputum |
| EOT | End of Treatment |
| EWD | Early Withdrawal |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | Gamma Glutamyl Transferase |
| H | Isoniazid |
| HIV | Human Immunodeficiency Virus |
| HR | Isoniazid, Rifampicin |
| HRZE | Isoniazid, Rifampicin, Pyrazinamide, Ethambutol |

| | |
|---|---|
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| IRB | Institutional Review Board |
| kg | kilogram |
| LFT | Liver Function Test |
| L | Linezolid |
| LBBB | Left bundle branch block |
| LH | Luteinizing hormone |
| LLN | Lower Limit of Normal |
| LPLV | Last Patient Last Visit |
| LTFU | Lost-to-Follow-up |
| M | Moxifloxacin |
| MDR-TB | Multi Drug Resistant Tuberculosis |
| mg/dl | milligrams per deciliter |
| MGIT | Mycobacterial Growth Inhibiting Tube |
| MRHD | Maximum recommended human dose |
| ms | millisecond |
| *Mtb* | *Mycobacterium tuberculosis* |
| N/A | Not Applicable |
| NCS | Non-clinically Significant |
| NRTI | Nucleoside reverse transcriptase inhibitor |
| NTP | National TB Program |
| Pa | Pretomanid |
| Pa-824 | Pretomanid |
| PD | Pharmacodynamic |
| PDE5 | Phosphodiesterase type 5 inhibitor |
| PK | Pharmacokinetic |
| PT | Preferred Term |
| QD | Once Daily |
| R | Rifampicin |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| TB | Tuberculosis |
| TdP | Torsade de pointes |
| TEAE | Treatment Emergent Adverse Events |
| TI/NR | Treatment intolerant/ nonresponse |
| TTP | Time to Positivity |
| ULN | Upper Limit of Normal |
| USAID | United States Agency for International Development |
| µg/dl | micrograms per deciliter |
| WBC | White Blood Cell |
| WHO | World Health Organization |
| XDR-TB | extensively Drug Resistant Tuberculosis |
| Z | Pyrazinamide (tablets) |

# 1 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) |
| **Protocol Number/Title:** | An Open-Label Phase 2 Trial to Evaluate the Male Reproductive Safety of a 6-month Combination Treatment for Pulmonary Tuberculosis of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) in Adult Male Participants with Drug Resistant (DR-TB) Pulmonary Tuberculosis |
| **Treatment Indication:** | Pulmonary Tuberculosis (TB) |
| **Trial Objective(s):** | Primary Objective:<br><br>To assess the male reproductive safety of pretomanid in the regimen (BPaMZ) of Bedaquiline 200mg (200mg daily for 8 weeks then 100 mg daily for 18 weeks), together with pretomanid 200 mg (1x daily) + moxifloxacin 400 mg (1x daily) + pyrazinamide 1500 mg (1x daily) for 26 weeks in participants with Drug-resistant (DR) pulmonary TB.<br><br>Secondary objective:<br><br>To evaluate the TB treatment efficacy, safety and tolerability after 26 weeks of active treatment for TB and follow up for 52 weeks after end of the above-described treatment regimen in participants with Drug-resistant (DR) pulmonary TB.<br><br>Patient population:<br><br>DR-TB Defined as *Mycobacterium tuberculosis* that is sensitive to fluoroquinolones but<br>1. Mono-resistant to rifampicin or isoniazid, OR<br>2. Resistant to both rifampicin and isoniazid (MDR-TB) |
| **Trial Design:** | Phase 2 single arm multi-center, open-label clinical trial in DR-TB participants.<br><br>Participants will receive Bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks; together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg once daily (BPaMZ) for 26 weeks.<br><br>Participants will be followed for 52 weeks after end of treatment. |
| **Patient Population:** | A total of 20 evaluable male participants diagnosed with DR-TB who completed the trial is required. Twenty-five participants (25) will be enrolled in the trial assuming a 20% participant drop out of the trial.<br>Replacing participants who drop out of the trial may be considered.<br><br>Participants should be aged 18 years and over. |

<table>
<tr><td>Name of Sponsor/Company</td><td>Global Alliance for TB Drug Development</td></tr>
<tr><td>Name of Finished Products:</td><td>Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z)</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:<br><br>
<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>
<br>Instructions for Dosing of Test Regimen (BPaMZ):<br><br>
Treatment will be administered orally once daily, to be taken with a meal at approximately the same time each day with a full glass of water (approximately 240 ml), for 26 weeks in the following dosing scheme:<br><br>
Bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg once daily for 26 weeks (total treatment duration 6 months).<br><br>
Treatment Interruptions/Pauses<br><br>
<u>Trial Regimen:</u><br><br>
The trial treatment regimen 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.<br><br>
Action required for participants missing the following number of doses within the trial treatment regimen:<br><br>
• Up to 7 consecutive doses: restart treatment, no extension of treatment required.<br><br>
• If more than 7 to ≤ 35 consecutive doses of IMP: restart IMP and extend the IMP treatment by the number of consecutive doses missed. In this scenario, >7 missed doses between Baseline (Day 1) through week 8 inclusive i.e., bedaquiline dose of 200mg BDQ, will need to be caught up before the participant can start week 9 treatment visit. Similarly, >7 missed doses between week 9 through week 26 inclusive, i.e., bedaquiline dose of 100mg BDQ, will require a make up for completion of treatment. The final treatment visit should 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.</td></tr>
</table>

| | |
|---|---|
| **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) |
| | • Greater than 35 consecutive doses: discontinue treatment and withdraw participant from the trial.<br>• If the participant misses a total (sum) of 56 cumulative doses, discontinue treatment and withdraw participant from the trial. |

**Statistical Methods:**
A general description of the statistical methods planned to be used to analyse safety and 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.

**Sample Size:**

Sequential assessment of semen parameters in a cohort of 20 men followed for 26 weeks on treatment.

**Objective of the trial**:
This study is intended to rule out clinically significant severe adverse effects on testicular function.

**Criteria for Evaluation:**

**Primary Endpoint:**

- Change from baseline in total sperm count at 26 weeks.

**Secondary Endpoint(s):**

- Change from baseline in total sperm count at 13 and 44 weeks.
- The change from baseline in male reproductive hormones at Week 2, 4, 8, 12, 16, 26, 35, 44, 52, 65, 78, and at early withdrawal. Reproductive hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), Inhibin B and testosterone).

**Other Secondary Endpoints:**

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at78 weeks after the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at Week 4, 8, 12, 16, 22, 26, 35,44, 52, 65 and 78.

**Safety and Tolerability:**

- Change in weight from baseline.
- 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.

| | |
|---|---|
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| **Name of Finished Products:** | Bedaquiline tablets (B), pretomanid tablets (Pa), moxifloxacin tablets (M), pyrazinamide tablets (Z) |

- Quantitative and qualitative electrocardiogram (ECG) results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval, including observed QT/QTc intervals and change from baseline) will be categorized.

**Trial Duration:**

| | |
|---|---|
| Estimated date of first Participant enrolled: | Quarter 3Q2021 |
| Estimated date of last Participant enrolled: | Quarter 4Q2022 |
| Estimated date of last Participant completed: | Quarter 2Q2023 |

**Duration of trial:**

Approximately 3 years: up to 52 weeks enrollment period plus up to 2-week screening period plus 26 weeks treatment and 52 weeks follow-up after stop of treatment.

### 1.1.1 Synopsis Flow Chart and Procedures

| | Period | Screening | | Treatment | | | | | | | | | | | | | Follow Up | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Footnote | Visit | Day -21 to -1 | Day 1 (Baseline) | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 12 | Week 12 to 13 | Week 16 | Week 22 | Week 26 (EOT) | Week 26 to 27 | Week 35 | Week 44 | Week 44 to 45 | Week 52 | Week 65 | Week 78 | Early Withdrawal |
| a | Visit Window | N/A | +/- 3 days | | | | | | | | +/-7 days | | | | | | +/-14 days | | | | | | |
| | Written Informed Consent | X | | | | | | | | | | | | | | | | | | | | | |
| | Demography/Medical Treatment/Smoking History | X | | | | | | | | | | | | | | | | | | | | | |
| | Inclusion/Exclusion | X | X | | | | | | | | | | | | | | | | | | | | |
| b | Sputum Sampling | X | X | | | X | | | | X | X | | X | X | X | | X | X | | X | X | X | X |
| c | HIV Status and CD4 Count | X | | | | | | | | | | | | | | | | | | | | | |
| d | Urine Drug Screen | X | | | | | | | | | | | | | | | | | | | | | |
| e | Safety Laboratory Test | X | X | X | X | X | X | X | X | X | X | | X | X | X | | | | | | | | X |
| f | Semen Sampling | QX | BX | | | | | | | | | XX[f] | | | | XX[f] | | | XX[f] | | | | XX[f] |
| g | Male Reproductive Hormone Tests | X | | X | | X | | | | X | X | | X | | X | | X | X | | X | X | X | X |
| h | 12-Lead ECG | X | X | X | X | X | X | X | X | X | X | | X | | X | | | X | | | | | X |
| i | Chest X-Ray | 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 |
| j | Physical Exam – Full | X | X | | | | | | | | | | | | | | | | | | | | X |
| j | Physical Exam – Limited | | | X | X | X | X | X | X | X | X | | X | X | X | | X | X | | X | X | X | |

| | Period | Screening | | Treatment | | | | | | | | | | | | | Follow Up | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Footnote | Visit | Day -21 to -1 | Day 1 (Baseline) | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 12 | Week 12 to 13 | Week 16 | Week 22 | Week 26 (EOT) | Week 26 to 27 | Week 35 | Week 44 | Week 44 to 45 | Week 52 | Week 65 | Week 78 | Early Withdrawal |
| a | Visit Window | N/A | +/- 3 days | | | | | | | | +/-7 days | | | | | | +/-14 days | | | | | | |
| k | Pharmacokinetic Sampling | | | X | | X | | | | X | X | | X | X | X | | | X | | | | | X |
| l | IMP Assignment | | X | | | | | | | | | | | | | | | | | | | | |
| m | IMP dispensing and compliance Check | | | X | X | X | X | X | X | X | X | | X | X | X | | | | | | | | X |
| | Concomitant Medications | 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 |
| n | Investigator Assessment | | | | | | | | | | | | | | X | | | X | | | | X | X |
| o | Paternity Questionnaire | | | | | | | | | | | | | | | | | | | | | 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.**

**b. Visit Schedule**

i. **Screening Visit**
Screening assessments may occur over several days prior to Day 1 of dosing (i.e., not all screening procedures must be performed on the same day).

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

iii. **Unscheduled Visits (due to unforeseen circumstances)**
If the duration of treatment is extended due to dose interruptions / pauses, the last visit of the treatment period and all subsequent visits 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.

iv. **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 visit. At Early Withdrawal visit, we will collect Serious Adverse Event (SAE) information (including verification of survival) and participant reported TB outcome information only and may be telephonic, at home or a site visit.

v. **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 +/- 7 Days of scheduled visit from Week 9 to Week 26 or +/- 14 days of scheduled visit at or after Week 30. Sites should make every effort to ensure all procedures are done on the same day, when possible.

**b. Sputum Sampling & Mycobacteriology Characterization**

The sputum sampling methodology/requirements and tests will be described in a separate document, the Mycobacteriology Laboratory Manual.

i. **Screening, Days -21 to -1**
Two spot sputum samples taken at least 30 minutes apart will be collected 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 rifampicin and isoniazid resistance;
- Rapid molecular tests for fluoroquinolone resistance;
- Liquid Culture (MGIT) for *Mycobacterium tuberculosis* (*Mtb*) with identification to detect the presence or absence of *Mtb* and obtain the time to positivity (TTP) when positive and not contaminated;

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 -21 to -1 (Screening) spot sputum shows a negative or indeterminate molecular test result, the back-up sample or a newly collected spot sputum may be used.

ii. **Baseline to Week 78, including Early Withdrawal and Unscheduled Visits**

- Two spot sputum samples taken at least 30 minutes apart will be collected under the coaching and observation of the trial staff.
- If there is an *Mtb* positive culture (after the participant has previously converted to culture negative) at or after the last visit of the treatment period (Week 26), 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 participant sputum outcome status.

The following analyses will be performed on these samples:

- Liquid Culture (MGIT) for *Mtb*, followed by an identification test to detect presence or absence of *Mtb* and obtain the time to positivity (TTP) when culture positive and not contaminated will be performed on all samples.
- Susceptibility Testing for bedaquiline (B), moxifloxacin (M), pyrazinamide (Z) and pretomanid (Pa) on the following cultures:
  - The 1st positive non-contaminated *Mtb* positive culture from Screening up to Week 4;
  - On *Mtb* positive cultures, after the participant has previously converted to culture negative at or after the last visit of the treatment period (Week 26);
  - At Early Withdrawal;
  - At Bacteriological failure, which is defined as failing to attain culture negative status at or before the end of treatment (Week 26). The last available positive culture will be used for susceptibility testing e.g., the Early Withdrawal or Week 26 culture of a participant who withdrew and/or started re-treatment before the Week 78 visit or the Week 78 culture of a participant who has not started re-treatment.

**c. HIV Testing & CD4 Count**

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.

CD4 count is required for HIV-positive participants.

**d. Urine Drug Screening**

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

**e. 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 (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count).
- Clinical Chemistry (albumin, 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]).
- 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. Only at screening and Baseline-Day 1).

- When managing participants with elevated liver enzymes, refer to the Hepatotoxicity Manual.
- Hepatitis B and C test to be performed during screening visit.

**f. Semen Sampling (Two semen samples within a 14 day window)**

A single qualifying semen sample (QX) during screening. (Days -13 to -1) is required during screening to determine whether a participant qualifies for the Male Fertility Analysis per the inclusion/exclusion criteria.

48 hours of sexual abstinence is required prior to obtaining semen sample (QX). Sexual abstinence is the practice of refraining from all sexual intercourse, including masturbation.

There is allowance for repeat collection of a qualifying semen sample (QX) for cases of sample handling or collection errors (e.g., spillage of sample by participant or by site staff prior to shipment of sample to lab, or sample gets misplaced/lost prior to shipment).

Qualifying semen sample (QX) will be reviewed by an andrologist prior to enrollment.

Another semen sample (BX) will be collected on Day 1, or Day 2. These two samples (QX and BX) are averaged to make up the baseline semen sample for the analyses.

**All semen samples must be separated by no less than 48 hours and preceded by no less than 48 hours of sexual abstinence.**

At week 12-13, week 26-27, and week 44-45 timepoint two (XX) semen samples must be collected within those weeks. These two (XX) samples will be averaged to make up the week 12, week 26 and week 44 semen sample values.

For week 12-13, week 26-27 and week 44-45 timepoints, a 14-day collection window is allowed with the aim of the (XX) semen samples to have about a 7-day separation between samples for these timepoints.

Early withdrawal: After 18 weeks of treatment at any early withdrawal thereafter, two (XX) semen samples must be collected. These two samples per timepoint will also be averaged to make up the early withdrawal week semen sample value.

**g. Male Reproductive Hormone Tests**

Total Testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin B. Sample timepoints will be required at screening and at week 2, 4, 8, 12, 16, 26, 35, 44. 52, 65, 78 and at early withdrawal.

**h. 12-Lead ECG**

**Single 12-Lead ECG:** To every extent possible, this should be performed at approximately the same time every day during trial procedures (+-1 hour).

At visits when pre-dose PK samples are also scheduled, i.e., Weeks 2, 4, 8, 12, 16, 26, ECGs should be performed prior to PK sampling. PK samples will also be collected at Week 44 and Early Withdrawal.

**i. Chest X-Ray**

A chest x-ray (digital image only) within 6 months prior to screening or during day -21 to day -1, will be obtained and read locally by the Investigator or designee to confirm TB.

A chest x-ray (digital image only) at Week 26 EOT will be obtained and read locally by the investigator or designee to confirm TB treatment outcome.

**j. Physical Examination**

- Physical – Full: Height (m) will only be collected at Day -21 to -1 (Screening).
- Physical Exam – Limited: Limited physical exams will include weight and gross neurological, pulmonary, cardiovascular and abdominal exam(s).

**k. Pharmacokinetic (PK) Sampling**

This process will be described in the safety laboratory manual. Blood draws for PK samples collected pre-dose must be done after the ECG is performed. The dates and times of the doses of IMP taken prior to all pre-dose PK samples will be collected. Specific Pretomanid PK blood draws will be obtained pre-dose (within 2 hours prior to dosing at weeks 2, 4, 8, 12, 16, 22, 26, 44 or at early withdrawal if prior to week 26).

**l. Investigational Medicinal Product (IMP) Randomization/Assignment**

Enrolment may occur once all the Screening results are available, and the Investigator has determined that the participant is eligible for the trial.

**m. 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.

**n. Investigator Assessment**

Investigator to review participant status and assess whether IMP 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.

**o. Paternity Questionnaire**

Collect information regarding fathering of children during and after the trial

# 2 Introduction and Rationale

Tuberculosis (TB) in humans is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (*Mtb*), which typically affects the lungs (pulmonary TB) but can affect other sites as well (extrapulmonary TB). While incidence rates and mortality for TB have been falling, it remains the ninth leading cause of death worldwide, the world's leading cause of death from a single infectious disease and is responsible for more deaths than human immunodeficiency virus (HIV). In 2018, 10.0 million (range, 9.0 - 11.1 million) new cases of TB were reported. (World Health Organization [WHO] Global TB Report 2019) [(1)].

The current TB treatment regimens have a lengthy duration of treatment, involve multi-drug therapy, many tolerability issues, and require large commitments of resources and infrastructure. High rates of noncompliance are common, which often results in increased mortality, chronic, infectious, and drug-resistant cases. The present TB epidemic and treatment conditions demonstrate the clear need in patients with drug-sensitive or drug-resistant TB for novel drugs and drug regimens that will shorten the current treatment duration and be safe and well tolerated. In addition, new TB drugs and regimens should also be affordable, easy to adopt and implement, suitable for pediatric use and for co-administration with antiretroviral therapy in individuals co-infected with *Mtb* and HIV. Following the declaration of TB as a global emergency by the 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.

There are several drugs which are in different stages of development but only a few have advanced to phase 3 clinical trials and are being tested alone or in combination with other anti-TB drugs[(2)]. Pretomanid (Pa-824) is one of these new drugs and recently received U.S. approval (on 14$^{th}$ August 2019) in a combination regimen with Bedaquiline and Linezolid (BPaL) for people with XDR-TB or treatment-intolerant/non-responsive MDR-TB. Pretomanid is also being developed for the treatment of drug sensitive (DS)- and Drug Resistant (DR)-TB. Study NC-008 (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) is currently ongoing.

## 2.1 Trial Rationale

Pretomanid is being used in an antimicrobial combination regime(s) to treat patients with pulmonary tuberculosis. The primary purpose of the Male Reproductive Safety – "**BPaMZ/SEM**"- clinical study is to evaluate the potential effect of Pretomanid on human testicular function whilst being used in a 6 months antimicrobial combination regime consisting of Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) and Pyrazinamide (Z) (BPaMZ).

## Background

The findings of testicular toxicity in animal species have been a challenge in pharmaceutical drug development [2]. As an example, over the Past 10 years formal studies have been conducted on the effects of PDE5 inhibitors on human semen and spermatogenesis [3,4]. Studies of the effects of these drugs on semen parameters in humans are challenging to implement and have generally been evaluated in patients but also in healthy young male volunteers who have been administered the drug daily for 6-12 months.

Pretomanid is a new antimicrobial compound recently approved to be used in a 6-month antimicrobial combination regime [Bedaquiline (B) plus Pretomanid (Pa) plus Linezolid (L) [BPaL] regime] to treat patients with XDR pulmonary tuberculosis. Pretomanid is also being studied for the treatment of TB in a 4 month and 6 months antimicrobial combination regime consisting of Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) and Pyrazinamide (Z) (BPaMZ) in drug sensitive (DS)- and Drug Resistant (DR) -TB. The primary purpose of this male reproductive safety study (Pa-824-CL012 – "**BPaMZ/SEM**"-) is to evaluate the potential effect of once-a-day pretomanid (200mg) on human testicular function whilst being dosed as an antimicrobial regimen consisting of Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) and Pyrazinamide (Z) (BPaMZ) for 6 months in DR-TB patients.

In nonclinical toxicology studies of PA-824 (Pretomanid), testicular degeneration/atrophy has occurred in rats with repeated doses of PA-824 (Pa) at ≥30 mg/kg/day but did not occur in monkeys at any dose level. Testicular effects showed evidence of being partially reversible, albeit very slowly, in rats dosed for 7 days, but not in rats dosed for 14 days. As would be expected, there was a dose-related decrease in fertility in male rats at ≥30 mg/kg/day that was associated with decreased sperm count and motility. This effect on fertility in male rats was partially reversible. Repeat toxicology studies were conducted in the monkey (0, 50, 150, 300 mg/kg/day for 3 months; 20-week recovery period) to further explore the male reproductive system effects of PA-824. In this trial direct testes effects (semen morphology, organ weights, histopathology), or effects on hormones [testosterone, follicle-stimulating hormone (FSH), inhibin-B]) were not observed at any point during dosing or during the 20-week recovery period.

In follow-up to the non-clinical findings, males in the 8-week Phase 2 Trial NC-002-(M-Pa-Z) were evaluated by plasma sampling for the reproductive hormones Luteinizing Hormone (LH), FSH and Testosterone at baseline and at the end of the treatment period. If the trial drug regimen caused testicular toxicity, the most sensitive measure from these hormones would be an increase in levels of FSH. Among participants in the M-$Pa_{100}$-Z group the mean baseline FSH was 9.027 U/L which decreased to 8.338 U/L at the end of therapy (N=21 with samples at baseline and Day 56). Among participants in the M-$Pa_{200}$-Z group the mean baseline FSH was 6.531 U/L at baseline, and this decreased to a mean of 6.061 at the end of therapy (N=19 with samples at baseline and Day 56). Men in the rifampicin 150 mg plus isoniazid 75 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets (HRZE) control group had a mean baseline of 7.394 U/L which decreased to 6.714 at the end of therapy (N=23 with samples at baseline and Day 56). This gives relative reassurance that pretomanid is not likely to cause testicular toxicity in men.

## Trial Design Rationale

The primary purpose of this Male Reproductive Safety – "**BPaMZ/SEM**"- clinical study is to generate data to evaluate the potential effect of once daily 200mg Pretomanid on human testicular function whilst being dosed for 6 months in patients with Drug Resistant (DR-TB) Pulmonary Tuberculosis. The 6 months dosing period covers current use of pretomanid is an approved antimicrobial regimen for the treatment of TB. (Pretomanid in combination regimen with Bedaquiline and Linezolid (BPaL) for people with XDR-TB or treatment-intolerant/non-responsive MDR-TB). It is not feasible to evaluate the potential testicular toxicity of once daily 200mg Pretomanid in this BPaL regime, as Linezolid has shown toxicity on testicular function in non-clinical studies. Therefore, the study will be conducted using the antimicrobial regimen consisting of Bedaquiline (B) plus Pretomanid (Pa) plus Moxifloxacin (M) and Pyrazinamide (Z) (BPaMZ) for 6 months in DR-TB patients. Participants will also be followed up to 18 weeks post dose to evaluate and ensure coverage of potential recovery of semen parameters which encompasses one and one-half cycles (cycle length is around 75 days) of the seminiferous epithelium. This also includes epididymal transit time (since we are sampling and evaluating semen), which adds another ~10 days. Thus, in days 75 + 37.5 + 10 = 122.5 days or 17.5 weeks, therefore 18 weeks should be sufficient for follow-up period.

The safety of pretomanid has been tested in 10 single- and multi-dose Phase I studies with healthy adult male and female participants, receiving single oral doses of pretomanid ranging from 50 to 1500 mg and multiple oral doses ranging from 200 to 1000 mg/day given for up to eight days. Pretomanid has also been studied in combination regimens in patients for up to 9 months in Phase 2 and 3 studies. For this study adult male DR-TB patients who can complete the trial will be required.

For assessment of the male reproductive safety profile the following parameters will be evaluated in adult male participants with Drug Resistant (DR-TB) Pulmonary Tuberculosis.

For assessment of the male reproductive safety profile the following parameters will be evaluated.

## Primary Endpoint

Change from baseline in total sperm count at 26 weeks.

## Secondary Endpoints

Change from baseline in total sperm count at 13 and 44 weeks:

A key secondary endpoint will be the change from baseline (at screening) in male reproductive hormones at Week 2, 4, 8,12,16, 26, 35, 44, 52, 65, 78, and at early withdrawal. Reproductive hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), Inhibin B and testosterone.

**Other Secondary Endpoints:** For assessment (other secondary endpoints) of the Pulmonary Tuberculosis the following parameters will evaluated.

**Efficacy:**

- Incidence of bacteriologic failure or relapse or clinical failure at 78 weeks after the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at Week 4, 8, 12, 16, 22, 26, 35, 44, 52, 65 and 78.

**Safety and Tolerability:**

- Change in weight from baseline.
- 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 and change from baseline) will be categorized.

Obtaining findings of testicular toxicity has been a challenge in pharmaceutical drug development and the evaluations of the above reproductive parameters will give us important and adequate insight as we continue to develop pretomanid.

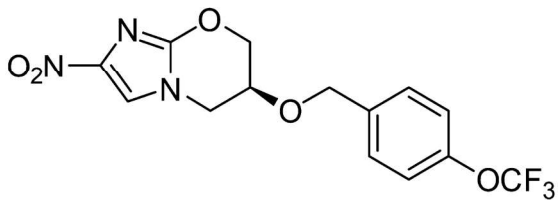
## 2.2 Drugs used in the TB Antimicrobial BPaMZ regimen

### 2.2.1 Pretomanid [5]

#### *2.2.1.1 Structure and Mechanism of Action*

Pretomanid, a nitroimidazooxazine, with a molecular weight of 359 daltons [5,6]. Figure 1 shows the chemical structure.

*Figure 1: Chemical Structure of Pretomanid*




Pretomanid kills actively replicating *Mycobacterium tuberculosis (Mtb*) by inhibiting mycolic acid biosynthesis thereby blocking cell wall production. Under hypoxic conditions, against non-replicating bacteria, pretomanid acts as a respiratory poison following nitric oxide release.
All these activities require nitro-reduction of pretomanid within the mycobacterial cell by the deazaflavin-dependent nitro reductase (Ddn), which is dependent on the reduced form of the

cofactor F420. Reduction of F420 is accomplished by the F420-dependent glucose-6-phosphate dehydrogenase, Fgd1.

#### *2.2.1.2 Nonclinical Studies*

Pretomanid has demonstrated in vitro activity against *Mtb* complex, including genetically diverse clinical isolates, and mono resistant and polyresistant/multidrug resistant (MDR) *Mtb*, with the exception of delamanid-resistant *Mtb* where cross-resistance has been observed for pretomanid against some but not all tested delamanid-resistant strains. This indicates that pretomanid activity is not affected by *Mtb* phylogeny, or *Mtb* resistance phenotype, apart from delamanid-resistance in some cases.

Pretomanid has also demonstrated anti-*Mtb* activity as both a monotherapy and as part of combination regimens in animal models of TB. Regimens with pretomanid plus bedaquiline, including BPaL, the regimen that also included linezolid, demonstrated efficacy superior to the combination of rifampicin, isoniazid, and pyrazinamide (RHZ).

No central nervous system (CNS), cardiovascular, or respiratory effects were seen at pretomanid exposures consistent with those seen in humans at the maximum recommended human dose (MRHD) in a series of safety pharmacology studies in rats and monkeys; effects were evident at pretomanid exposures that were >3-fold higher than those seen with the MHRD.
No mutagenic or clastogenic effects were detected in both an in vitro bacterial reverse mutation assay and an in vitro mammalian chromosome aberrations assay using a Chinese hamster ovary cell line. Pretomanid was negative for clastogenicity in a mouse bone marrow micronucleus assay.

Cataracts were observed in rats treated with pretomanid at doses of 300 mg/kg/day for 13 weeks or 100 mg/kg/day for 26 weeks. There were no cataracts observed in rats given oral pretomanid at 30 mg/kg/day (approximately twice the human exposure for a 200 mg dose) for 26 weeks.
In a 13-week monkey toxicity study, no cataracts were observed at the end of 13-week dosing, but at the end of the 13-week recovery two animal showed cataracts in the 400/300 mg/kg group. In a subsequent study, cataracts were not observed following 13-week treatment with up to 300 mg/kg/day oral pretomanid or during the 20-week post treatment recovery period. No cataracts were observed in monkeys given oral pretomanid at 100 mg/kg/day for 39 weeks with a 12-week post treatment recovery.

Testicular toxicity was observed in repeat-dose toxicity studies in rats and mice, but not monkeys.

Pretomanid was not teratogenic, and no peri-postnatal effects occurred at doses that did not also produce maternal toxicity in rats.

Pretomanid has phototoxic potential at high doses in rats.

#### *2.2.1.3 Pharmacokinetics*

Important drivers of pharmacokinetic (PK) variability are dosing with or without food, and co-administration of medications that induce CYP3A4.

Bioavailability in the fasted state was about half that in the fed state, when administered at the clinical dose of 200 mg. Pretomanid should be administered in the fed state.

In the presence of rifampicin and efavirenz, pretomanid average concentration over a dosing interval (Cavg) was reduced 66% and 35%, respectively. Such strong and moderate CYP3A4 inducers should be avoided with pretomanid.

No clinically significant differences in the pharmacokinetics of pretomanid were observed based on sex, body weight, race (black, Caucasian, or other), pulmonary TB status, or human immunodeficiency status (HIV) status. The effect of renal or hepatic impairment on the pharmacokinetics of pretomanid is unknown.

#### *2.2.1.4 Efficacy and clinical studies*

As a single agent, pretomanid showed mycobactericidal activity over 14 days spanning a wide range of doses from 50 to 1200 mg/day: 200, 600, 1000, and 1200 mg/day were tested in CL-007; and 50, 100, 150, and 200 mg/day were tested in CL-010. The bactericidal activity of pretomanid was similar for all doses tested except 50 mg, which showed less activity than the higher doses.

As treatment of TB requires a combination of multiple drugs, pretomanid was also tested in different combination regimens, measuring bactericidal efficacy over 14 days of treatment in the NC-001 and NC-003 studies, to inform the selection of candidate regimens for later stage clinical development. All pretomanid-containing arms in these two studies showed bactericidal activity. The two best regimens were the combination of pretomanid, moxifloxacin, and pyrazinamide (PaMZ) in NC-001 and the combination of bedaquiline, pretomanid, and pyrazinamide (BPaZ) in NC-003. Both PaMZ and BPaZ showed daily reductions in colony-forming unit (CFU) counts that were like or greater than those in subjects administered the standard-of-care 4-drug regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE).

PaMZ and BPaZ were further tested over an 8-week treatment period in studies NC-002 and NC-005. In NC-002, subjects with DS-TB were treated with PaMZ, with either 100 or 200 mg/day pretomanid doses. The same combination with 200 mg/day pretomanid was tested in MDR-TB subjects. Results indicated that the bactericidal activity of the 200 mg pretomanid regimen was significantly greater than that of HRZE. In contrast, no significant differences were observed between the 100 mg pretomanid regimen and HRZE.

In NC-005, DS-TB subjects were treated with BPaZ with bedaquiline administered as either a loading dose (400 mg/day) for 14 days, followed by 3 times a week at 200 mg/day, or administered consistently at 200 mg/day. Data from this study demonstrated significantly greater bactericidal activity for the BPaZ regimen than for HRZE. The efficacy of the regimen with bedaquiline at 200 mg/day was like the efficacy of the regimen with bedaquiline administered as recommended per label (i.e., loading dose and then 3 times a week). In this study, one study arm of MDR-TB subjects was treated with BPaZ (bedaquiline at 200 mg/day) plus moxifloxacin (BPaMZ). The BPaMZ regimen in MDR-TB subjects showed the greatest bactericidal activity and the shortest time to culture conversion among all treatment arms, although conclusions for this population were limited by the absence of a randomized control arm.[7]

The Phase 3 study NC-006 tested the combination PaMZ in DS-TB subjects under 3 different dosing schedules: 6 months with pretomanid at 200 mg/day, 4 months with pretomanid at 100

mg/day, or 4 months with pretomanid at 200 mg/day. An MDR-TB population was also treated with PaMZ for 6 months (pretomanid at 200 mg/day). This study was placed on partial clinical hold in 2015 due to deaths associated with hepatotoxicity. Following investigations, the partial clinical hold was lifted on 17 August 2016. However, due to delays in enrollment and the promising results of other pretomanid-containing drug regimens, TB Alliance chose not to re-open enrollment when the partial clinical hold was removed, but the already enrolled subjects (N = 284) were followed to the study endpoints. With this reduced sample size, the study failed to demonstrate noninferiority in the efficacy of the PaMZ regimens compared with the efficacy of the standard-of-care regimen (HRZE) at 6 months.

In Nix-TB, the first clinical trial ever to evaluate the 3-drug, all-oral, 6-month BPaL regimen, approximately 90% of subjects with highly resistant TB achieved relapse-free cure status 6 months after the end of treatment. The Nix-TB rate of favorable outcomes is like the rates of treatment success for DS-TB (World Health Organization [WHO] 2018). The study met the prespecified threshold for success, with the lower bound of the confidence interval (CI) for a favorable outcome far exceeding 50%. Furthermore, the percentage of patients who had a favorable status following this 6-month regimen was substantially higher than the rate of favorable outcomes in the reported literature with existing regimens lasting 18 months or longer. Nix-TB received FDA approval of pretomanid in the BPaL regimen combination in August 2019.

Favorable outcome rates were similar for patients with XDR-TB or treatment intolerant/ nonresponse (TI/NR) MDR-TB and across subgroups defined by demographic and baseline disease characteristics and the linezolid treatment regimen (600 mg twice daily [BID], as was originally implemented, or 1200 mg once daily [QD], after a protocol amendment).

Patients on the BPaL regimen converted to culture-negative status quickly, with a median time of less than 6 weeks. Patients improved clinically; a reduction of TB symptoms and increased body weight accompanied the change in TB status. Most patients remained relapse-free at 6 months after the end of treatment with preliminary 24-month data indicating that virtually all patients with culture conversion remained relapse free.

Another Phase 3 study, ZeNix, with the BPaL regimen, is ongoing. The objective of this study is to optimize the treatment duration and dosage of linezolid, in MDR, pre-extensively drug resistant (XDR) and XDR patients. A Phase 2c study, SimpliciTB, also known as NC-008, is also ongoing to further study the BPaMZ regimen in both drug susceptible (DS) and drug resistant (DR) patients. At the time of the IB update, the efficacy data from both studies are not yet available and thus, are not incorporated.

At the time of IB data cut-off data, 26 May 2019, pretomanid, either alone or as part of a combination regimen, has been used in at least 26 clinical trials sponsored by either TB Alliance or another entity in more than 1,664 subjects.

As both ZeNix and SimpliciTB are still ongoing, detailed safety data from these two studies are not incorporated into this IB. Safety data for pretomanid are summarized based on 1,153 subjects from the other 19 trials, including 208 subjects with either extensively drug resistant tuberculosis (XDR-

TB) or MDR-TB, 656 subjects with drug susceptible (DS)-TB, and 289 healthy volunteers. Safety data are summarized in Section 5.3 of the investigator brochure.

#### 2.2.1.4.1 Safety

The adverse drug reactions were identified from the pooled safety database of reported AEs in the Phase 1 studies where placebo arm was available, and Phase 2/3 clinical studies where a standard of care arm was available, with data from other non-controlled studies, including results from exposure/response modeling of Nix-TB as supporting evidence. Adverse drug reactions for pretomanid include the following:

- Mild to Moderate (G1 to G2) nausea (preferred term [PT]) and vomiting (PT).
- G1 and G2 rash (grouped terms, including the following PTs; rash; rash popular; rash maculopapular; rash erythematous; and rash vesicular).
- Transaminases increased (grouped terms, including the following PTs: transaminases abnormal; transaminases increased; ALT abnormal; AST abnormal; ALT elevated; AST elevated; hepatic enzyme increased; hepatic enzyme abnormal; liver function test abnormal; liver function test increased; hepatic function abnormal).

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 trial will include specific monitoring of hepatic enzymes.

For additional information refer to pretomanid IB. [5]

### 2.2.2 Information regarding other compounds used with in the BPaMZ

#### *2.2.2.1 Bedaquiline [8,9]*

**Bedaquiline** (TMC207; Sirturo™ package insert) [8] is a novel agent approved for TB treatment. As detailed in the Investigator's Brochure, [9] Bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate synthase. [10, 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.*[13] In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampcin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. Tb*.[14, 15] 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.[16] 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[16] and in a subsequent trial it was more active in the mouse model than HRZ.[17] 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.

#### *2.2.2.1.1 Clinical Studies*

In the clinical studies conducted to date, a total of approximately 645 participants (including 265 DR-TB patients) 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). In the Nix-TB (B-Pa-L) trial, 109 participants received Bedaquiline that led to an FDA approval in August 2019. 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. Full details of the completed clinical studies are provided in the current bedaquiline IB,[9] and Sirturo™ label.[8].

#### 2.2.2.1.2 Safety

#### *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).

#### 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
- A history of or ongoing hypothyroidism
- A history of or ongoing bradyarrhythmia
- A history of TdP
- Concomitant administration of fluoroquinolone antibiotics that have a greater potential for significant QT prolongation (i.e., gatifloxacin, moxifloxacin and sparfloxacin)

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 this 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.

### 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.

#### *2.2.2.2 Moxifloxacin [18, 19]*

**Moxifloxacin** (M)[18] 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.[20]" 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.

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.

In the usual daily doses of 400 mg/day, moxifloxacin is well tolerated. As stated in the Package Insert [18] 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.[18]

For additional information on moxifloxacin, refer to the IB[19] and the manufacturer's package insert.[18]

#### *2.2.2.3 Pyrazinamide*

**Pyrazinamide** (Z)[21] 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.[22]

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. 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.[9, 5] 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 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 appear to be dose related. The pyrazinamide investigator brochure 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, 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 investigator brochure.[23]

## 2.3 Overall Benefit/Risk Assessment

The primary purpose of the Male Reproductive Safety – "**BPaMZ/SEM**"- clinical study is to evaluate the potential effect of pretomanid on human testicular function whilst being used in a 6-month antimicrobial combination regime. All participants in this trial will be given an antibiotic treatment regimen consisting of a 6-month Combination Treatment for Pulmonary Tuberculosis of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ). These drugs individually and in combination are not expected to have an adverse impact on Male Reproductive Safety, based on nonclinical and available clinical data. Similarly, 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. The same BPaMZ regime is also being studied in another ongoing clinical study NC-008 (the SimpliciTB study) This 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 trial will also evaluate if this drug regimen (BPaMZ) given for 6 months will be safe and effective in drug resistant TB disease.

In addition to treating participant's pulmonary tuberculosis in the planned BPaMZ-SEM study we plan to assess the male reproductive safety profile of pretomanid with the same regimen (BPaMZ).

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.

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.

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 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 suggests an overall favourable benefit-to-risk ratio.

# 3 Trial Objectives

## 3.1 Primary Objective:

To assess the male reproductive safety of pretomanid in the regimen (BPaMZ) of bedaquiline 200mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg (1x daily) + moxifloxacin 400 mg (1x daily) + pyrazinamide 1500 mg (1x daily) for 26 weeks in participants with Drug-resistant (DR) pulmonary TB.

## 3.2 Secondary Objective:

To evaluate the efficacy, safety and tolerability after 26 weeks of active treatment for TB and follow up for 52 weeks after start of the above-described treatment regimen in participants with Drug-resistant (DR) pulmonary TB.

# 4 Trial Endpoints

## 4.1 Primary Endpoint

- Change from baseline in total sperm count at 26 weeks.

## 4.2 Secondary Endpoints

- Change from baseline in total sperm count at 13 and 44 weeks.
- A key secondary endpoint will be the change from baseline in male reproductive hormones at Week 2, 4, 8,12,16, 26, 35, 44, 52, 65, 78, and at early withdrawal. Reproductive hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), Inhibin B and testosterone.

## 4.3 Other Secondary Endpoints:

**Efficacy:**

- Incidence of bacteriologic failure or relapse or clinical failure at 44 weeks after the start of therapy.
- Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at Week 4, 8, 12, 16, 22, 26, 35, 44, 52, 65, and 78.

**Safety and Tolerability:**

- Change in weight from baseline.
- 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 and change from baseline) will be categorized.

**Pharmacokinetics (PK):**

Plasma concentration of pretomanid from sparse sampling will be summarized as descriptive statistics.

# 5 Trial Design

## 5.1 Summary of Trial Design

This is a Phase 2, multi-center, open-label clinical trial in DR-TB in male participants aged 18 years and older.

The trial requires 20 evaluable and eligible male participants who meet all the inclusion criteria and none of the exclusion criteria diagnosed with DR-TB. All participants will receive the same regimen of BPaMZ once daily for 26 weeks. All participants must give written informed consent at screening visit (-21 day) to participate in this trial and continue with screening procedures during the screening period (Day -21 to Day -1).

## 5.2 Treatment Plan: Schedule of Assessments

- Screening Period (Day -21 to Day -1)
- Treatment Period (Day 1 to Week 26)
- Follow -up Period (Week 26 to Week 78)

Refer to:

- Trial Flow Chart (Section 1.1) for the timing of all procedures and laboratory samples to done at each visit.
- Trial Procedures (Section 8) for details regarding specific procedures or laboratory tests.

The Test Treatment Regimen, BPaMZ consists of a combination of the following products:

**Table 1: Products**

| Product | Tablet Strength | Abbreviation |
|---|---|---|
| Bedaquiline | 100 mg | (B) |
| Pretomanid | 200 mg | (Pa) |
| Moxifloxacin | 400 mg | (M) |
| Pyrazinamide | 500 mg | (Z) |

Participants will receive Bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg once daily (BPaMZ) for 26 weeks.

Participants will enter post- treatment follow-up which continues until Week 78.

# 6 Trial Population

Participant must meet all inclusion and no exclusion criteria within the screening period. The screening period of -21 to -1 days provides flexibility for allowed retesting of applicable mycobacteriology, safety, or ECG parameters. Only one qualifying semen sample during screening is allowed within the -13 to -1 day period. Refer to Trial Flow Chart (Section 1.1) footnote f for further details. Sponsor may consider replacements of withdrawn participants.

**No protocol waivers will be granted by the TB Alliance**

## 6.1 Inclusion Criteria

Participants are required to meet all the following inclusion criteria during the screening period to be enrolled. Patients must abstain from ejaculation for at least 2 days prior to screening clinic visit.

1. Understands study procedures and voluntarily provides written informed consent prior to the start of any study-specific procedures.

2. Male gender 18 years or over.
3. Body weight (in light clothing and no shoes) ≥ 45kg.
4. A positive molecular test for tuberculosis in sputum either at screening or within one month prior to enrollment.
5. Disease Characteristics:
    - Participants must have been diagnosed with TB prior to or at screening.
    - Participants' TB should be resistant to rifampicin and/or isoniazid (historical evidence of resistance to rifampicin and/or isoniazid is acceptable within 3 months prior to screening), and susceptible to fluoroquinolones by rapid sputum-based tests
    - Participants who have had previous treatment for DR-TB for more than 3 months at start of screening should be discussed with the medical monitor.
6. A chest x-ray, within 6 months prior to or at the screening visit, which in the opinion of the Investigator is compatible with pulmonary TB.
7. Participants will be required to use a double contraceptive method during the whole treatment duration and 18 weeks post dose.
8. Can comply with the protocol and the assessments therein, including all restrictions.

## 6.2 Exclusion Criteria

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

### *Medical History and Concurrent Conditions:*

1. Resistant to fluoroquinolones by rapid molecular test.
2. History of male infertility or vasectomy.
3. Unable to produce semen sample.
4. Evidence at screening of azoospermia.
5. Known erectile dysfunction that would prevent ejaculation.
6. Historical or active disease process of the male reproductive tract that would compromise sperm production. e.g., Tuberculous epididymitis.
7. History of any illness that, in the opinion of the Investigator, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
8. 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.
9. Being, or about to be, treated for malaria.
10. 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.
11. 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.

12. 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.
13. For HIV infected participants any of the following:
    a) CD4+ count <100 cells/μL
    b) Received intravenous antifungal medication within the last 90 days
14. Participants with newly diagnosed tuberculosis and HIV that require initiation of appropriate HIV therapy before participants has received at least 2 weeks of an antituberculosis regimen.
15. 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 enrollment.
    b. Heart failure
    c. A personal or family history of congenital QT prolongation
    d. A history of or known, untreated, ongoing hypothyroidism, except for well treated hypothyroidism.
    e. A history of or ongoing bradyarrhythmia
    f. A history of Torsade de Pointe
16. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening.
17. Receiving any form of hormone or hormone-like (nutraceuticals) therapy, except for well treated hypothyroidism.
18. Received Pretomanid and/or Delamanid to treat TB.
19. Known chronic hepatitis B or C.

### *Previous and Concomitant Therapy*

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. For HIV infected participants:
    a. The following antiretroviral therapy (ART) should not be used:
        1. Stavudine
        2. Zidovudine
        3. Didanosine
        4. Triple NRTI regimen is not considered optimal for HIV treatment (poor efficacy)

b. 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.

c. 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*

22. 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. 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
    g. ALT:
       - ≥3.0 x ULN to be excluded
       - greater than ULN must be discussed with and approved by the Sponsor Medical Monitor
    h. 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
    i. Total bilirubin:
       - >1.5 x ULN to be excluded
       - Greater than ULN must be discussed with and approved by the Sponsor Medical Monitor
    j. Direct bilirubin:
       - greater than 1x ULN to be excluded

k. Positive hepatitis B surface Ag, or hepatitis C antibody

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.

## 6.3 Restrictions

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

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

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

**Moxifloxacin**: 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

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.
- 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 except moxifloxacin, thioamides, and metronidazole.

The following medicinal products should be avoided from Day 1 (Baseline visit) and during the treatment period as much as possible. 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, 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).

## Discontinuation from Treatment/Trial

The following may result in the discontinuation of trial treatment:

- Withdrawal of informed consent.
- Investigator considers that for safety reasons it is in the best interest of the participant that he be withdrawn, including a concern that the participant has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment.
- Adverse event resulting in death.
- Lost to follow-up.
- Termination of the trial by the sponsor.

A participant may withdrawal 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 withdrawals consent for the trial, no additional follow-up visits will be performed.

Participants who withdraw from the trial before 9 months maybe replaced and should be discussed with the Sponsor medical monitor.

All Participants withdrawal 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 1.1.1).

### 6.3.1 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:

- Two Spot sputum samples at least 30 minutes apart will be collected under the coaching and observation of the trial staff.
- Semen sampling collection: one pair of semen samples one week apart, each sample must be collected at least 2 days after abstinence from ejaculation.
- Laboratory safety sampling (including male reproductive hormone tests: LH, FSH, inhibin B and testosterone)
- Pharmacokinetic sampling (pre-dose within 2 hours prior to dosing)
- Single 12-lead ECG
- Vital signs
- Full physical examination, including weight
- IMP compliance check (if participant on IMP)
- Concomitant medications
- Adverse Events

### 6.3.2 Unscheduled Visits

Any visit which is conducted in addition to those required by the Synopsis Flow Chart and Procedures (Section 1.1.1), should be considered unscheduled regardless of the reason for the visit. The assessments which are undertaken as part of an Unscheduled visit should be as clinically indicated.

If the duration of treatment is extended due to dose interruptions/pauses, the last visit of the 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 treatment period would have been.

### 6.3.3 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.

### 6.3.4 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 converted to 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 1.1.1.

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 DR local community TB clinics for standard anti-tuberculosis chemotherapy according to local treatment guidelines.

The participant will be provided with a referral letter from the Investigator to take with them to their local treatment 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 their local treatment clinic.

## 6.4 Participant Progress Definitions

**Table 2: 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 entered into the study | |
| **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

## 6.5 Trial Stopping Rules

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 DR-TB NTP clinic.

For potential stopping rules regarding reproductive safety, refer to safety monitoring Section 9.4.

# 7 Treatment

## 7.1 IMP Administration

- Treatment will be administered orally once daily, to be taken with a meal approximately the same time each day with a glass of water (approximately 240 ml) for 26 weeks in the following dosing scheme:
    - Bedaquiline 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg once daily for 26 weeks (total treatment duration 6 months).

## 7.2 Participant Compliance

During treatment 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.

## 7.3 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).

A 'dose of IMP' is defined as the correct medication strength of bedaquiline + pretomanid + moxifloxacin + pyrazinamide as required to be taken for the day per protocol.

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. In this scenario, missed doses between Baseline (Day 1) through week 8 inclusive i.e., bedaquiline dose of 200mg BDQ, will need to be caught up before the participant can start week 9 treatment visit. Similarly, missed doses between week 9 through week 26 inclusive, i.e., bedaquiline dose of 100mg BDQ, will require a make up for completion of treatment. The final treatment visit should 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.

All missed doses should be completed as part of the BPaMZ regimen (i.e., do not complete missed doses as monotherapy).

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.

## 7.4 IMP Packaging and Labelling

The complete formulations of the IMP, namely Bedaquiline and pretomanid are found in the respective Investigator Brochures. [9, 5, 23] The complete formulations of bedaquiline, moxifloxacin and pyrazinamide are found in the Package Inserts. [8, 18, 21]

The IMP will be packaged in weekly cards as follows:

| Week 1 to 8 Cards: Dispensed treatment | | | |
|---|---|---|---|
| **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 26 Cards: Dispensed treatment | | | |
|---|---|---|---|
| **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 |

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

- Name, address 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.
- Kit number, as applicable.
- The statement “Keep out of reach of children” as applicable.
- Storage conditions.
- Period of Use.
- Expiry Date.
- Directions for use.
- Space for completion of participant number and visit/date dispensed.

## 7.5 Method of Treatment Assignment

All participants will receive the same regimen of BPaMZ.

## 7.6 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.

## 7.7 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 at treatment visits. 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.

# 8 Trial Variables and Procedures

The Synopsis Flow Chart and Procedures (Section 1.1.1) should be referenced for timing, sequence of assessments, and specific procedures.

## 8.1 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)
- **Semen Sampling: Single semen sample required at screening to determine whether participant qualifies for the study**
- Male Reproductive Hormones (LH, FSH, inhibin B, testosterone)
- Two spot sputum samples taken at least 30 minutes apart will be collected under the coaching and observation of the trial staff:
    - Smear microscopy for Acid-Fast Bacilli (AFB).
    - Rapid molecular tests for isoniazid, rifampicin, fluoroquinolones resistance *Mtb*.
    - Liquid Culture (MGIT) for *Mycobacterium tuberculosis* (*Mtb*), with speciation to detect presence or absence *of Mtb* and obtain time to positivity (TTP) when positive and not contaminated.
    - Second sample is a back-up sample in case it is not possible to obtain a result/s from the first sample. If initial screening sputum shows a negative or indeterminate molecular test result, the test may be repeated on the back-up sample or a newly collected spot sputum can be used.
- 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.

- 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. A chest X-ray digital image will also be obtained and read locally by the Investigator or designee at Week 26 EOT. Digital images will be provided to the Sponsor. The investigator is responsible for review and analysis of the chest X-ray for participant's inclusion.
- Urine drug test
- Concomitant medications

## 8.2 Trial Variables and Procedures

### 8.2.1 Semen Sample Test Parameters

48 hours of sexual abstinence is required prior to obtaining each semen sample during the trial. Sexual abstinence is the practice of refraining from all sexual intercourse, including masturbation. A single qualifying semen sample (QX) during screening (Days -13 to -1) is required during screening to determine whether a participant qualifies for the Male Fertility Analysis per the inclusion/exclusion criteria. There is allowance for repeat of collection of a qualifying semen sample (QX) for cases of sample handling or collection errors (e. g., spillage of sample by participant or by site staff prior to shipment of sample to lab, or sample gets misplaced/lost prior to shipment).

Qualifying semen sample (QX) will be reviewed by an andrologist prior to enrollment.

Another semen sample (BX) will be collected on Day 1, or Day 2. These two samples (QX and BX) are averaged to make up the baseline semen sample for the analyses. All semen samples must be separated by no less than 48 hours and preceded by no less than 48 hours of sexual abstinence.

At week 12-13, week 26-27, and week 44-45 timepoint two (XX) semen samples must be collected within those weeks. These two (XX) samples per timepoint will be averaged to make up the week 12, week 26 and week 44 semen sample values.

For week 12-13, week 26-27 and week 44-45 timepoints, a 14-day collection window is allowed with the aim of the (XX) semen samples to have about a 7-day separation between samples for these timepoints.

Early withdrawal: After 18 weeks of treatment at any early withdrawal thereafter, two (XX) semen samples must be collected. These two samples per timepoint will be averaged to make up the early withdrawal week semen sample value.

Analyses will be performed on the total sperm count.

The semen sampling and methodology follow the WHO requirements for the examination and processing of human semen[24]. This can be found in the safety and/or andrology laboratory manual.

### 8.2.2 Laboratory Male Reproductive Hormone Blood Sample Test Parameters

The following male reproductive hormones will be assessed at the time points described in Synopsis Flow Chart and Procedures (Section 1.1.1):

- Serum Endocrinology: LH, FSH, inhibin B and testosterone and total testosterone

### 8.2.3 TB Efficacy Variables and Procedures

Refer to Section 8.1 for Screening sample collection and analyses. At baseline and subsequent visits, refer to Section 1.1.1 (Synopsis Flow Chart and Procedures). Two spot sputum samples are collected at least 30 minutes apart at the research site under the coaching and observation of the trial staff.

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 when culture positive and not contaminated followed by a speciation test when applicable:
- Susceptibility Testing for bedaquiline (B), moxifloxacin (M), pyrazinamide (Z) and pretomanid (Pa) on the following cultures:
    - The 1st positive, non-contaminated *Mtb* positive culture from Screening up to week 4;
    - On *Mtb* positive cultures, after the participant has previously converted to culture negative at or after the last visit of the treatment period (Week 26);
    - At Early Withdrawal;
    - At bacteriological failure is defined as failing to attain culture negative status at or before the end of treatment (Week 26). The last available positive culture will be used for susceptibility testing e.g. the Early Withdrawal or Week 26 culture of a participant who withdrew and/or started re-treatment before the Week 78 visit, or the Week 78 culture of a participant who has not started re-treatment.

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 and post treatment follow-up (Weeks 35 to 78) and is without clinical or biological evidence of relapse, will be considered to have a favourable outcome.

## 8.3 Safety and Tolerability Assessments

The following safety and tolerability variables will be collected at the time points described in the Synopsis Trial Flow chart and Procedures (Section 1.1.1) 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 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).
  - Hepatitis B and C test.
  - **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) At screening and baseline-Day1. Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator.
- Single 12 lead Electrocardiogram (ECG):
  - Investigator Assessment: Normal, Abnormal
  - Methodology:
    - Timing and registration technique for ECGs will be standardized for all participants;
    - Participants should be lying down (recumbent) for at least 5 minutes prior to each 12-lead ECG evaluation;
    - ECGs are to be recorded for 10 seconds;
    - All ECGs are to be performed in single
    - ECGs should be done before any labs when both included in a visit
    - For each participant, the ECGs should, to every extent possible, be collected at approximately the same time of day (+/- 1 hours) and in the same fed/fast state throughout the trial (e.g. 4 hours after lunch).
    - ECGs are to be performed at Screening, Day 1, Weeks 2 through 8, Week 12, Week 16, Week 26, Week 44, if applicable, at Early Withdrawal. At visits when pre-dose PK samples are also scheduled, I.e., Weeks 2, 4, 8, 12, 16, 26, ECGs should be performed prior to PK sampling.
- Vital Signs
  - Vital signs, including weight (should be done before any labs)
  - Systolic and diastolic blood pressure (mmHg) to be measured supine (after 5 minutes of rest) using an appropriately sized cuff, and using the same type of sphygmomanometer, if possible, by the same observer, at each relevant visit.
  - Heart rate (bpm)

    - Respiratory rate (breaths per minute)
- Axillary/aural/other body temperature (°C)
- Physical Exam
    - Height is measured at screening only.
    - Full (complete) and Limited (gross neurological, pulmonary, cardiovascular and abdominal) examinations will be performed, and any clinically significant findings will be recorded.
    - Weight (kg) (in light clothing with no shoes).
    - Using the observed variables weight and height, calculated body mass index (BMI) will be derived.
- Adverse Events
- Investigator Assessment:
    - The Investigator will review the participant status at specified visits in the Synopsis Flow Chart and Procedures (Section 1.1.1), 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.

## 8.4 PK Variables and Procedures

Plasma concentrations from sparse sampling (Synopsis Flow Chart and Procedures, Section 1.1.1) will be summarized as descriptive statistics.

## 8.5 Mycobacteriology Characterization Variable and Procedures

Refer to the Mycobacteriology Laboratory Manual for full details.

- The 1st positive, non-contaminated *Mtb* positive culture from Screening to Week 4;
- *Mtb* positive cultures (after the participant has previously converted to negative) at or after the last visit of the treatment period (Week 26);
- At Early Withdrawal;
- At bacteriological failure, which is defined as failing to attain culture negative status at or before the end of treatment (Week 26). The last available positive culture will be used for susceptibility testing e.g., the Early Withdrawal or Week 26 culture of a participant who withdrew and/or started re-treatment before the Week 78 visit, or the Week 78 culture of a participant who has not started re-treatment.

Mycobacterial Characterization - *Mtb* isolates (from the first *Mtb* positive culture) will be processed for:

- Susceptibility Testing for bedaquiline (B), moxifloxacin (M), pyrazinamide (Z) and pretomanid (Pa).

All *Mtb* isolates must be stored at the local mycobacteriology laboratories, until trial closure.

# 9 Adverse Events

## 9.1 Definitions

### 9.1.1 Adverse Event (AE)

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

### 9.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

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

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

### 9.1.3 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 assess 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 considering follow-up information and send a SAE follow-up report with the updated causality assessment.

**Table 3: 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). |

### 9.1.4 Severity

**Table 4: 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.

## 9.2 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 78 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 78 follow-up visit at the timepoints specified in the Synopsis Flow Chart and Procedures (Section 1.1.1) 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 study, and adverse event will be recorded.

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

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

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

Reporting of expedited safety reports such as SUSARs (or IND safety reports as applicable) to the sites, RA and ECs (where it is the Sponsor responsibility) will cease 30 days after LPLV for the primary endpoint is completed, unless there is a specific local requirement that would go beyond this time point. Distribution of aggregated safety reports and investigator brochures to relevant destinations will cease once LPLV of the entire study is completed.

### 9.2.1 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.

### 9.2.2 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 an adverse event.

### 9.2.3 Disease under Study

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.

#### 9.2.4 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.

#### 9.2.5 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.

### 9.3 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[5, 9, 19, 23] and Package Inserts. [8, 18, 21]

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 recommendation for managing participants below assumes the laboratory abnormalities of concern have been confirmed.

#### 9.3.1 ALT, AST and Bilirubin

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)].

### 9.3.2 Lipase

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

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

### 9.3.3 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.

### 9.3.4 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.

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 artefacts that interfere with the interpretation of the ECG should be repeated to confirm the findings. If the finding is from the 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 and the participant is to be treated per the Investigator's clinical judgment. If it is the investigator judgement to withdraw the participant from the full regimen, the Sponsor Medical Monitor should be contacted for further review.

## 9.4 Safety Monitoring

**Medical Monitoring:**

During the conduct of the study, it is the responsibility of the sponsor-appointed medical monitor of the study to consult with the investigator(s) and fertility experts regarding any medical concerns or questions that arise. When requested by an investigator, the Medical Monitor discusses and reviews potential participants and helps the investigator ensure that only participants who are appropriate and who meet the protocol inclusion and exclusion criteria are enrolled in the study. The Medical Monitor also ensures that the protocol-specified procedures are followed, especially safety and tolerability data, and that there are no potential safety concerns. The Medical Monitor will review all SAE's regarding this study and any Severe AEs and clinically significant safety concerns.

Regarding the reproductive safety of this study, a reproductive safety monitoring committee will be formed consisting of three fertility experts – these fertility experts should have previously served on a reproductive safety monitoring committee – and the medical monitor. This reproductive safety monitoring committee will convene after the first 4 patients enrolled and then quarterly thereafter to review the reproductive parameters.

**Stopping rules:**

Stopping rules will be developed with the help and guidance of the fertility experts after the first 4 patients are enrolled and sufficient information is available about the baseline sperm counts seen for this population.

Regarding the nonreproductive safety of this study, this will be monitored by the medical monitor together with the NC-008 safety monitoring committee (comprising the medical monitors and sponsor study physician for the trial). This NC-008 safety monitoring committee is an appointed group of physicians that are currently monitoring study NC-008. In this study (NC-008) patients with pulmonary TB are being treated with the same (BPaMZ) antibiotic treatment regime. The Medical Monitor will participate in teleconferences with this NC-008 safety monitoring committee to review all SAE and Severe AEs regarding this and any safety concerns that are new or are being tracked.

**Paternity Questionnaire:**

This questionnaire is aimed at collecting additional data on male reproduction after treatment completion of this regimen containing pretomanid. The questionnaire at week 78 or early withdrawal. Will include a general question whether the participant has fathered any children during or after treatment with the pretomanid-containing regimen

If yes, the number of children and the month and year of their birth will be obtained.
A completed questionnaire will be entered into the database for all participants. Data will be analyzed descriptively based on the data collected in this trial.

Data collected may be added to the ongoing paternity survey of male reproduction which is currently being collected from previous and ongoing TB Alliance trials with pretomanid containing regimens (i.e., STAND, Nix-TB, SimpliciTB and ZeNix). See Appendix 5 for the questionnaire questions.

## 10 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.

### 10.1 Analysis Population

Semen Analysis Population will include data from all participants who receive at least one dose of IMP.

TB Efficacy Analysis Population will include data from all participants who receive at least one dose of IMP.

Safety and tolerability population will include data from participants who received at least one dose of IMP.

## 10.2 Sample Size

To assess the male reproductive safety profile of pretomanid in the regimen (BPaMZ) of Bedaquiline 200mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg (1x daily) + moxifloxacin 400 mg (1x daily) + pyrazinamide 1500 mg (1x daily) for 26 weeks in participants with Drug-sensitive (DS) or Drug-resistant (DR) pulmonary TB.

The sample size is not based on formal statistical considerations. It is based on practicality of enrolment and to rule out any severe effect of the regimen on semen parameters.

## 10.3 Interim Analyses

No formal interim analyses are planned.

## 10.4 Primary and Secondary Endpoint Analysis

Analyses will be performed at 26, 44 and 78 weeks. The Statistical Analysis Plan (SAP) will outline the data endpoints that will be included in each analysis.

### 10.4.1 Primary Endpoint Analysis

- Change from baseline in total sperm count at 26 weeks

### 10.4.2 Secondary Endpoints

- Change from baseline in total sperm count at 13 and 44 weeks
- A key secondary endpoint will be the change from baseline in male reproductive hormones at Week 2, 4, 8, 12, 16, 26, 35, 44, 52, 65, 78, and at early withdrawal. Reproductive hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), Inhibin B and testosterone.

### 10.4.3 Other Secondary Endpoints

#### 10.4.3.1 Efficacy (TB)

##### 10.4.3.1.1 Clinical Outcome at 78 Weeks

For the secondary endpoint of clinical outcome (bacteriologic failure or relapse or clinical failure), participants will be classified as having a favourable, unfavourable, or un-assessable 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 un-assessable and excluded from the analysis.

##### 10.4.3.1.2 Culture Conversion to Negative Status at Week 4, 8, 12, 17, 22 and 26

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 78 weeks from start of therapy.

## 10.5 Safety and Tolerability Analysis

- The incidence of all-cause mortality will be summarized.
- All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by Preferred Term within each MedDRA System Organ Class (SOC).
- Treatment-emergent adverse events (TEAEs) are defined as AEs which started at or after the first administration of IMP and includes those events started prior to the first administration of IMP but which worsened after the first intake. Adverse events starting after the last administration of IMP until the last scheduled visit/assessment/measurement will be regarded as treatment emergent.
- The incidence of the following events will be summarized for further medical analysis:
    - Incidence of TEAEs;
    - Incidence of TEAEs by Severity;
    - Incidence of TEAEs by DMID toxicity grade;
    - Incidence of Drug-Related TEAEs;
    - Incidence of Serious TEAEs;
    - Incidence of TEAEs Leading to Early Withdrawal;
    - Incidence of TEAEs leading to Death.

## 10.6 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.

## 10.7 Pharmacokinetics/Pharmacodynamics

Relationships may be explored between drug exposure and efficacy and safety endpoints, as appropriate. If so, planning details and results will be included in a separate modelling plan and report.

# 11 Records Management

## 11.1 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.

## 11.2 Source Documents

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

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

## 11.3 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.

## 11.4 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 sponsor/designees prior to destroying any records pertaining to the trial.

# 12 Quality Control and Assurance

## 12.1 Site Procedures

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

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

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

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

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

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

## 12.2 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 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.

## 12.3 Protocol Deviations

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

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

## 12.4 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 regarding accuracy, adequacy, and consistency, and to assure that studies are in accordance with the guidelines. Having the highest quality data from studies is an essential aspect of drug development.

The Investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The

audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred. The auditors or inspectors may also review site SOPs, training records, site facilities and other trial related systems/processes.

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

# 13 Ethics and Regulatory

## 13.1 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.

## 13.2 Independent Ethics Committee/Institutional Review Board (IEC/IRB) Review

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

## 13.3 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.

## 13.4 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 part of the research.

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

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

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

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

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

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

### 13.5 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.

## 14 Publication Policy

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

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

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

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

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

## 15 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 IEC/IRB and Regulatory Authorities prior to implementation. The Investigator, IEC/IRB, and Sponsor must agree on all amendments. No amendment will be implemented until approved by the relevant Authorities and/or IEC/IRB and signed by all required parties. Exceptions to this are when the Investigator considers that the participant's safety is compromised.

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

## 16 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 because 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.

## 17 References

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## Appendix 1: The IUATLD Scale

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

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

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

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

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

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

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

### ESTIMATING SEVERITY GRADE

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

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

### SERIOUS OR LIFE-THREATENING AEs

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

### COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of 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 is 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; out participant treatment or hospitalization possible | end organ damage or hospitalization required |
| **Hypotension** | transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, no treatment required | symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment | requires IV fluids; no hospitalization required | mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment |
| **Pericarditis** | minimal effusion | mild/moderate asymptomatic effusion, no treatment | symptomatic effusion; pain; EKG changes | tamponade; pericardiocentesis or surgery required |
| **Hemorrhage, Blood Loss** | microscopic/occult | mild, no transfusion | gross blood loss; 1-2 units transfused | massive blood loss; > 3 units transfused |

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

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

| NEUROLOGICAL | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| **Neuro-Cerebellar** | slight incoordination dysdiadochokinesis | intention tremor, dysmetria, slurred speech; nystagmus | locomotor ataxia | incapacitated |
| **Psychiatric** | mild anxiety or depression | moderate anxiety or depression; therapy required; change in normal routine | severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation | acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations |
| **Muscle Strength** | Participative 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; prurits | 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% cannot work | unable to care for self |

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

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

## Appendix 4: Cardiovascular Safety

Vital Signs

The following abnormalities will be defined for vital signs:

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

ECG

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 | QT Corrected |
| 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: Paternity Questionnaire**

# Paternity Questionnaire

Please answer the following questions:

Did you father a child(ren) after your start of the trial?

| | |
|---|---|
| Yes ☐☐ | No ☐☐ |

- If yes, how many? _____
- What month and year was/were your child(ren) born?
  (Add more lines if necessary)
  - Child 1: MMM/YYYY
  - Child 2: MMM/YYYY
  - Child 3: MMM/YYYY

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