# A Phase 1, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics and Safety of Pretomanid in Participants with Renal Impairment Compared to Participants with Normal Renal Function

**Division of Microbiology and Infectious Diseases (DMID) Protocol Number:** 15-0037

**DMID Funding Mechanism:** Vaccine and Treatment Evaluation Units

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**Principal Investigators:** William Smith, MD and Kimberly Cruz, MD

**DMID Clinical Project Manager:** Erica Sondergaard, RN, BSN, CCRC

**Version:** 11.0

11 April 2024

# STATEMENT OF ASSURANCE

Each Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protections (OHRP) for federally funded human participants research. Each FWA will designate at least one Institutional Review Board (IRB)/Independent Ethics Committee (IEC) registered with OHRP, for which the research will be reviewed and approved by the IRB/IEC and will be participant to continuing review [45 CFR 46.103(b)]. The IRB/IEC designated under an FWA may include an institution's IRB/IEC, an independent IRB/IEC, or an IRB/IEC of another institution after establishing a written agreement with that other institution.

# STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46 (Protection of Human Subjects)
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 312 (Investigational New Drug Application [IND] Application), 21 CFR 812 (Investigational Device Exemptions)
- International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) GCP: Integrated Addendum to ICH E6(R1) Guidance for Industry, published in the Federal Register (83 FR 8882 [2018]), including the latest finalized revision
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable federal, state, and local regulations and guidance

# SIGNATURE PAGE

The signature below provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States federal regulations and ICH E6 GCP guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of participants.

Site Investigator Signature:

Signed: _____ Date: _____

William Smith, MD

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Knoxville, TN 37920

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Site Investigator Signature:

Signed: _____ Date: _____

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| | |
|---|---|
| Advantage eClinical® | Electronic Data Capture System |
| AE | Adverse Event/Adverse Experience |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| AUC | Area under the plasma concentration-time curve |
| $AUC_{\infty}$ | Area under the plasma concentration-time curve from time 0 to infinity |
| $AUC_{last}$ | Area under the plasma concentration-time curve from time 0 to the last measurement |
| A-V | Atrioventricular |
| BCG | Bacillus Calmette-Guérin |
| BDQ | Bedaquiline |
| BMI | Body Mass Index |
| BPaL | Pretomanid, Bedaquiline, and Linezolid |
| BPM | Beats Per Minute |
| BUN | Blood Urea Nitrogen |
| $C_{avg}$ | Average Concentration Over a Dosing Interval |
| CFR | Code of Federal Regulations |
| CFU | Colony Forming Unit |
| CG | Cockcroft-Gault |
| CHF | Congestive Heart Failure |
| CI | Confidence Interval |
| CKD | Chronic Kidney Disease |
| CL/F | Apparent Clearance |
| $CL_R$ | Renal Clearance |
| $C_{max}$ | Maximum plasma concentration |
| CMS | Clinical Materials Services |
| CROMS | Clinical Research Operations & Management Support |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficients of Variation |
| CYP450 | Cytochrome P450 |
| °C | Degrees Celsius |
| °F | Degrees Fahrenheit |
| DCC | Data Coordinating Center |
| DCF | Data Collection Form |
| DHHS | Department of Health and Human Services |
| dL | Deciliter |
| DMID | Division of Microbiology and Infectious Diseases, NIAID, NIH |
| DOTS | Directly Observed Therapy Short Course |
| EBA | Early Bactericidal Activity |
| ECG | Electrocardiogram |

| | |
|---|---|
| eCRF | Electronic Case Report Form |
| ED | Emergency Department |
| EDTA | Ethylenediaminetetraacetic acid |
| eGFR | Estimated Glomerular Filtration Rate |
| EHR | Electronic Health Record |
| EMA | European Medicines Agency |
| EMEA | Europe, the Middle East, and Africa |
| ESRD | End Stage Renal Disease |
| ET | Early Termination |
| FDA | Food and Drug Administration |
| FWA | Federal Wide Assurance |
| g/dL | Grams per Deciliter |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCG | Human Chorionic Gonadotropin |
| HCV | Hepatitis C virus |
| Hgb | Hemoglobin |
| HRZE | Standard Treatment with Isoniazid, Rifampin, Pyrazinamide, and Ethambutol |
| IATA | International Air Transport Association |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug Application |
| INH | Isoniazid |
| IRB | Institutional Review Board |
| kg | Kilogram |
| LLT | Low Level Term |
| LZD | Linezolid |
| µg | Microgram(s) |
| µL | Microliter(s) |
| MDRD | Modification of Diet in Renal Disease |
| MDR-TB | Multidrug-Resistant Tuberculosis |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| mg/dL | Milligram(s) per Deciliter |
| MIC | Minimum Inhibitory Concentration |
| mL | Milliliter(s) |
| mm | Millimeter(s) |

| | |
|---|---|
| mmHg | Millimeters of Mercury |
| msec | Millisecond |
| MOP | Manual of Procedures |
| Mtb | *Mycobacterium tuberculosis* |
| N | Number of Participants |
| NIAID | National Institute of Allergy and Infectious Diseases, NIH, DHHS |
| NIH | National Institutes of Health |
| NO | Nitric Oxide |
| OER | Office of Extramural Research |
| OHRP | Office for Human Research Protections |
| PHI | Personal Health Information |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| Qc | Quality Control |
| RH | Relative Humidity |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SDCC | Statistical and Data Coordinating Center |
| SMC | Safety Monitoring Committee |
| SOC | System Organ Class |
| SZD | Sutezolid |
| $t_{1/2}$ | Elimination Half-life |
| TB | Tuberculosis |
| TEAE | Treatment Emergent Adverse Event |
| TI | Treatment-intolerant |
| $T_{max}$ | Time to maximum (peak) plasma drug concentration |
| ULN | Upper Limit of Normal |
| US | United States |
| $V_d/F$ | Volume of distribution |
| WHO | World Health Organization |
| XDR-TB | Extensively Drug-Resistant TB |

# PROTOCOL SUMMARY

**Title:**

A Phase 1, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics and Safety of Pretomanid in Participants with Renal Impairment Compared to Participants with Normal Renal Function

**Design of the Study:**

This is a Phase 1, open-label, single-dose, sequential group study to compare the safety and pharmacokinetics (PK) of pretomanid in the following groups of participants: 1) participants with severe renal impairment including those with end stage renal disease (ESRD) not on dialysis, and participants with mild or moderate renal impairment, designated as Groups 2, 3, and 4, respectively; and 2) participants with normal renal function matched to the above renal impairment groups, designated as Groups 1A, 1B, and 1C, respectively.

The study will be conducted following a reduced PK study design in Part A, see Table 1 and Figure 1. Part A will enroll participants from Group 1A (i.e., 6 healthy matched controls) and Group 2 (i.e., 6 participants with severe renal impairment and ESRD, not on dialysis). A decision to proceed to Part B will be made after the PK of pretomanid, and safety in participants enrolled in Part A have been reviewed. If Part A demonstrates at least a 50% increase in pretomanid area under the plasma concentration-time curve (AUC) in Group 2 (severe renal impairments and ESRD, not on dialysis) relative to the exposures in Group 1A (matched participants with normal renal function), then the reduced PK study will extend to the full PK study to enroll participants into Part B (i.e., to investigate mild and moderate renal impairment). All Part B groups (1B, 1C, 3, and 4) will be enrolled concurrently.

If the reduced PK study shows at least a 50% increase in AUC in patients with severe renal impairment and patients with ESRD not yet on dialysis relative to the matched healthy controls, a “full PK” renal impairment study in patients with all intermediate levels of renal function impairment should be conducted. Otherwise, no further study is recommended.

**Study Population:**

Total 36 male and female adult participants ages of 18 to 85 years inclusive, including 18 participants with normal renal function matched against each of the renal impairment groups, and 18 renal

| | |
|---|---|
| | impaired participants (N=6 mild renal impairment, N=6 moderate renal impairment, and N=6 severe renal impairment) as defined by estimated glomerular filtration rate (eGFR) (see Table 1).<br><br>Six participants with normal renal function in each group (1A, 1B, 1C) will be matched by race, gender, age (± 10 years, but between 18 to 85 years of age), and body mass index (BMI) (18 to 40 kg/m$^2$) at enrollment; eGFR ≥90 mL/min as calculated by Modification of Diet in Renal Disease (MDRD) to each renal impairment Group 2, 3, and 4, respectively.<br><br>**Group 2:** Severe renal impairment: Stage 4 (eGFR 15-29 mL/min) and ESRD not on dialysis: Stage 5, MDRD (eGFR <15 mL/min).<br><br>**Group 3:** Mild renal impairment: Stage 2, MDRD (eGFR 60-89 mL/min).<br><br>**Group 4:** Moderate renal impairment: Stage 3, MDRD (eGFR 30-59 mL/min). |
| **Number of Sites:** | 2 |
| **Description of Study Product or Intervention:** | A single oral dose of pretomanid 200 mg |
| **Study Objectives:** | **Primary:**<br>• To evaluate the PK profiles of pretomanid in plasma and urine after a single oral dose of 200 mg in participants with renal impairment compared to matched healthy controls.<br><br>**Secondary:**<br>• To assess the safety profile of a single oral dose of 200 mg pretomanid in renally impaired participants compared to matched healthy controls.<br>• To evaluate the PK profiles of representative pretomanid metabolites (M19 and M50) in plasma and urine. |
| **Duration of Individual Participant Participation:** | Approximately 3 months not including the initial screening visit. |

| | |
|---|---|
| **Estimated Time to Last Participant/Last Study Day:** | Part A: 12 months<br>Part B: 18 months |

**Table 1: Study Design**

**Part A**

| Group | N | Participant Characteristics | Stage[a] | eGFR[b] mL/min |
|---|---|---|---|---|
| 1A | 6 | Healthy matched participants (controls) with normal renal function | N/A | ≥90 |
| 2 | 6 | Severe renal impairment and ESRD not on dialysis | 4<br>5 | 15-29 mL/min<br><15 mL/min |
| **Total** | **12** | | | |

**Part B**

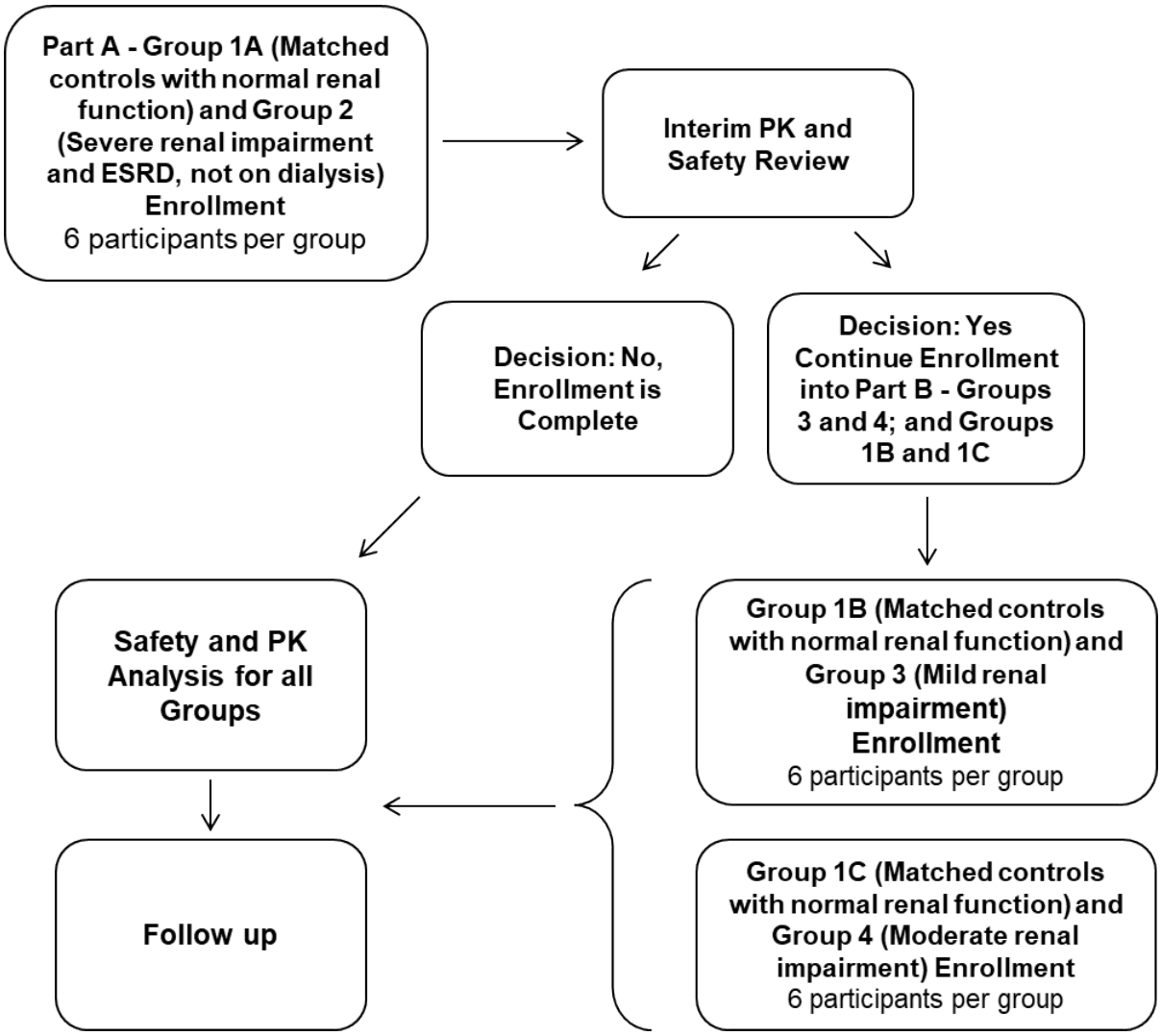
| Group | N | Participant Characteristics | Stage[a] | eGFR[b] mL/min |
|---|---|---|---|---|
| 1B | 6 | Matched participants with normal renal function | N/A | ≥90 |
| 3 | 6 | Mild renal impairment | 2 | 60-89 |
| 1C | 6 | Matched participants with normal renal function | N/A | ≥90 |
| 4 | 6 | Moderate renal impairment | 3 | 30-59 |
| **Total** | **24** | | | |

CKD=chronic kidney disease; eGFR=electronic case report form; ESRD=end stage renal disease; MDRD=Modification of Diet in Renal Disease; N/A=not applicable.

[a] *Stage based on Clinical Practice Guidelines for CKD (National Kidney Foundation, 2002) and Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function- Study Design, Data analysis and Impact on Dosing (DHHS, FDA, and CDER 2020 Draft Guidance).*

[b] *eGFR: estimated glomerular filtration rate based on an MDRD equation. Different mathematical formulas have been developed to determine eGFR. The MDRD eGFR formula was developed to adjust for body surface area and ethnicity, as well as considerations such as age and gender. In many ways the MDRD is superior to the Cockcroft-Gault calculation as it is more precise and reliable in predicting GFR. eGFR for this study is automatically calculated by clinical laboratories.*

**Figure 1: Schematic of Study Design**




ESRD=end stage renal disease; PK=pharmacokinetics
Group 1A: Matched controls to Group 2, with normal renal function
Group 2: Severe renal impairment and ESRD, not on dialysis
Group 1B: Matched controls to Group 3, with normal renal function
Group 3: Mild renal impairment
Group 1C: Matched controls to Group 4, with normal renal function
Group 4: Moderate renal impairment

# 1 KEY ROLES

| | |
|---|---|
| **Lead Principal Investigators:** | William Smith, MD<br>Alliance for Multispecialty Research (AMR)<br>1928 Alcoa Hwy, Suite 107<br>Knoxville, TN 37920<br><br>Kimberly Cruz, MD<br>Advanced Pharma CR<br>2950 NW 83rd St<br>Miami, FL 33147 |
| **DMID Clinical Project Manager:** | Erica Sondergaard, RN, BSN, CCRC |
| **Statistical and Data Coordinating Center:** | The Emmes Company, LLC |

# 2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 Background

### 2.1.1 Tuberculosis

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (Mtb) is an age-old disease and remains a major public health problem worldwide. It is estimated that one-third of the world's population is infected with Mtb, with about 10 million new cases of TB and 1.2 million deaths annually [1]. For the past 5 years, TB has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS [1]. Bacillus Calmette-Guérin (also known as BCG), an attenuated strain of *Mycobacterium bovis*, is the only available TB vaccine. The efficacy of this vaccine varies from place to place and is generally low [2, 3]. However, it is used by many countries because it protects against severe forms of TB in children [2, 3]. Therefore, TB control relies on case detection, chemoprophylaxis for newly infected individuals, and directly observed therapy short course (DOTS) for TB patients. DOTS, despite its name, is not really a short course. Under DOTS, patients are required to take multiple drugs for at least 6 months [4]. Similarly, chemoprophylaxis for newly infected individuals takes 3 to 9 months [5, 6]. Long duration of treatment is associated with increased cost for follow-up, increased side effects of drugs and increased risk of default that may lead to emergence of drug-resistant TB. The World Health Organization (WHO) reports that several countries have large numbers of patients with multidrug-resistant tuberculosis (MDR-TB), resistant to at least isoniazid (INH) and rifampin [7]. Further, less than 50% of those who started second-line drugs had successful treatment outcome [1] and the number of MDR-TB cases is increasing mainly due to lack of effective treatment [7]. In addition, several countries with high prevalence of MDR-TB also show increasing numbers of extensively drug-resistant (XDR-TB) cases. These are resistant not only to INH and rifampin, but fluoroquinolones and aminoglycosides as well. Treatment of XDR-TB is even more difficult and the outcome is unpredictable [1, 8]. Thus, MDR- and XDR-TB are global problems because of the lack of effective treatment, the need for much longer treatment with second-line or experimental drugs, and the risk of further spread through travel and immigration. This calls for enhanced efforts to develop new drugs.

Pretomanid is approved by the United States (US) Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for treating adult patients with extensively drug-resistant, treatment-intolerant (TI) or nonresponsive (NR) multidrug-resistant pulmonary TB, in combination with bedaquiline (BDQ) and linezolid (LZD) (pretomanid, bedaquiline, and linezolid [BPaL] regimen). Pretomanid is administered orally 200 mg once daily for 26 weeks; the BPaL regimen is taken with food.

### 2.1.2 Tuberculosis in Patients with Renal Impairment

Chronic kidney disease (CKD) is defined as a reduced glomerular filtration rate (GFR), increased urinary albumin excretion, or both, for 3 or more months and is an increasing public health issue with estimated prevalence of 8 to16% worldwide [9]. Patients with CKD and kidney transplant have a higher risk of developing TB compared with the general population presumably due to associated immunodeficiency [10-13]. Immunodeficiency associated with renal impairment appears to be multifactorial including defects in oxidative stress, inflammation, vitamin D deficiency, malnutrition, and functional abnormalities in immune cells, particularly B and T cells [11, 13]. Changes in immunity begin as early as Stage 3 CKD (eGFR 30-59 mL/min/1.73 $m^2$) and worsen in later stages as kidney function deteriorates and waste products accumulate.

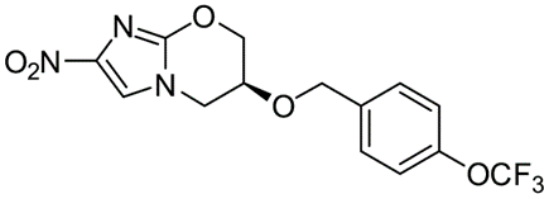
The treatment of new drug-susceptible pulmonary TB in patients with renal impairment includes 4 first-line drugs such as INH, rifampin, ethambutol, and pyrazinamide, similar to the treatment of patients with normal renal function. However, the doses of pyrazinamide and ethambutol have to be adjusted for renal function [14]. Approximately 80% of ethambutol is cleared by the kidneys and may accumulate in patients with renal impairment [15, 16]. Pyrazinamide is metabolized in the liver and its metabolites such as pyrazinoic acid and 5-hydroxy-pyrazinoic acid may accumulate in patients with renal insufficiency [15, 16]. Despite appropriate use of first-line anti-TB drugs, patients with renal impairment have worse clinical outcomes than those without renal impairment, and require close monitoring [14, 17].

### 2.1.3 Pretomanid

#### 2.1.3.1 Structure and Molecular Weight

Pretomanid, a nitroimidazooxazine, is a chemical entity with a molecular weight of 359 Daltons [18, 19]. Figure 2 shows the chemical structure.

**Figure 2: Chemical Structure of Pretomanid**



#### 2.1.3.2 Mechanism of Action

The mechanism of action of pretomanid is not fully understood, but it appears to have multiple activities. Under aerobic conditions, it inhibits Mtb cell wall biosynthesis by inhibiting the oxidation of hydroxymycolate to ketomycolate [20, 21]. Under anaerobic conditions, pretomanid generates reactive nitrogen species, including nitric oxide (NO) [22]. These known mechanisms under aerobic and anaerobic conditions explain why pretomanid has excellent early bactericidal and sterilizing activities [23, 24]. Early bactericidal activity (EBA) refers to an agent's ability to kill most of mycobacteria in the lung during the first few weeks of treatment [23]. Sterilizing activity measures the ability of the drug to kill persisting forms of Mtb, and therefore decrease relapse rates [24, 25].

#### 2.1.3.3 Microbiologic Activities *in Vitro*

In vitro studies demonstrated that the pretomanid was active against actively growing drug-sensitive Mtb isolates with the minimum inhibitory concentration (MIC) ranging from ≤0.0015 to 0.3 µg/mL [20, 21], which is comparable to the MIC of INH, one of the key first-line anti-TB drugs. Pretomanid was also tested in vitro against a broad panel of multidrug-resistant (MDR) clinical isolates of Mtb and was found to be highly active against all tested isolates with MIC <1 µg/mL [26]. Interestingly, in addition to its ability to kill actively growing Mtb, pretomanid demonstrated 85%, 89.6%, and 93.5% killing of Mtb persisting under anaerobic conditions at 2, 10, and 30 µg/mL, respectively [26].

### 2.1.4 Pre-Clinical Animal Studies

#### 2.1.4.1 Toxicology

Before advancement to human trials, the potential adverse effects of pretomanid were evaluated in repeat-dose toxicity studies up to 13 weeks in duration in mice, up to 26 weeks in duration in Sprague Dawley rats, up to 13 weeks in duration in cynomolgus monkeys. Adverse effects were uncommon at doses ≤50mg/kg [18].

#### 2.1.4.2 Pharmacokinetics

The PK profile of pretomanid following single-dose administration has been determined in mice, Sprague Dawley rats, cynomolgus monkeys, and New Zealand white rabbits, and the PK profile following repeated oral doses of pretomanid has been determined in Sprague Dawley rats and cynomolgus monkeys [18]. Systemic exposure to pretomanid following a single oral dose in mice, rats, monkeys, and rabbits increased with increasing dose, but the increase was less than dose proportional. The elimination half-life ($t_{½}$) of pretomanid following a single oral dose was approximately 3 to 7 hours in male rats, monkeys, and rabbits. The $t_{½}$ in female rats following single oral doses was longer (7 to 9 hours). In multiple studies in rats, the time to peak plasma concentration ($T_{max}$) generally ranged from 3.3 to 8 hours. In 14-day studies in rats and monkeys, pretomanid levels

in plasma were comparable on Days 1 and 14, indicating no accumulation of pretomanid after repeated dosing. Elimination kinetics in rats, rabbits, and monkeys were comparable to values observed after single doses, suggesting sustained pretomanid exposure in these animal species does not induce drug metabolic systems or other means of eliminating the drug from the body.

The elimination kinetics were determined in rats and monkeys using radiolabeled pretomanid preparations [18]. The findings suggest that pretomanid is subjected to both hepatic metabolism and renal excretion. The majority of the excretion was into urine. An average of 88.1% and 67.5% of the dose was recovered in the urine and feces for rats and monkeys, respectively.

#### 2.1.4.3 Efficacy

In a dose fractionation study in a murine model of active TB, total pretomanid doses from 144 to 4608 mg/kg were administered as 3, 4, 8, 12, 24, or 48 divided doses over 24 days beginning 2 weeks after aerosol infection with Mtb [27]. In this model, pretomanid exhibited time-dependent bactericidal activity, with a maximum observed bactericidal effect of 0.1 log colony forming unit (CFU)/day over 24 days. Lung CFU counts strongly correlated with the free drug time above MIC (T>MIC) and free drug area under the plasma concentration-time curve (AUC)/MIC, where T>MIC is the cumulative percentage of the dosing interval that the drug concentration exceeds the MIC under steady-state exposure conditions.

The effectiveness of various 3-drug combinations involving pretomanid was further evaluated in a murine model of TB. The combination of pretomanid (50 mg/kg) with BDQ and sutezolid (SZD) or LZD was superior to that of the first-line regimen for drug-susceptible TB (rifampin, pyrazinamide, and INH in reducing lung mean CFU counts in BALB/c mice infected with Mtb. The addition of SZD significantly increased the initial bactericidal activity of pretomanid + BDQ, rendering all mice culture-negative between 1 and 2 months of treatment. Although the decline in CFU counts with the 3-drug regimen containing LZD was not as rapid as that for the regimen containing SZD, the combination of LZD + BDQ + pretomanid was also significantly superior to the standard regimen after 2 months of treatment [28]. Both 3-drug combinations (pretomanid + BDQ + [SZD or LZD]) resulted in significantly fewer relapses after 3 months of treatment compared to either the first-line regimen or the 2-drug combination of pretomanid + BDQ.

### 2.1.5 Clinical Trials for Safety and Pharmacokinetics

#### 2.1.5.1 Safety

Based on unpublished safety data of the Phase 1 pooling group (i.e., pooled data from all Phase 1 studies in healthy volunteers) from the Integrated Summary of Safety for the pretomanid New Drug Application, the most frequently (≥10% of participants) reported preferred terms of treatment-emergent adverse events (TEAEs) in the all-pretomanid group (single dose or multiple doses) were headache (31.5%), nausea (11.8%), hemoglobin decreased (10.7%), and dermatitis

contact (11.4%). Hemoglobin decreased and dermatitis contact were driven by the data from the thorough QT study where multiple blood samples were taken. Participants from all the treatment groups shared the same trending with decreased hemoglobin levels. Dermatitis contact reported were associated with electrocardiogram (ECG) patches. In the control group, the only AE reported in at least 10% of participants was headache, with an incidence lower than that in the all-pretomanid group (22.9% versus 31.5%).

#### 2.1.5.2 Pharmacokinetics

The Investigator Brochure (IB) [18] includes data from the Phase 1 studies in healthy volunteers and Phase 2 studies in participants with pulmonary TB. These data indicate that the PK profile for pretomanid following oral dosing was consistent for healthy participants and participants with pulmonary TB. In both populations, pretomanid was readily absorbed after oral administration and slowly eliminated from plasma. Pretomanid plasma concentrations increased in a dose-dependent manner after single-dose administration of up to 1000 mg in healthy participants and participants with TB, but the increase was less than dose proportional, particularly at doses above 200 mg/day. The hypothesis that absorption decreases (i.e., is saturated) at high doses of pretomanid was further supported by the observations that mean apparent clearance (CL/F) and volume of distribution ($V_d$/F) at steady-state (Day 7) values increased with dose, while the mean elimination half-life ($t_{1/2}$) values remained similar across dose levels. This suggests that the apparent lack of dose proportionality in exposure is most likely related to the decreased bioavailability with increasing dose.

In both healthy participants and participants with pulmonary TB, steady-state concentrations of pretomanid in plasma were achieved within approximately 5 days of once-daily dosing, and the accumulation factor was approximately 2. Both findings support the observed elimination $t_{½}$ of approximately 18 hours in healthy participants and participants with pulmonary TB. The mean peak concentration ($C_{max}$) and AUC from time 0 to 24 hours ($AUC_{0\text{-}24hr}$) values following a 200 mg dose of pretomanid in participants with pulmonary TB ranged from 1.1 to 1.2 µg/mL and 17 to 19 µg·hr/mL, respectively, after single-dose administration and from 2.2 to 2.4 µg/mL and 38 to 40 µg·hr/mL, respectively, after 14 days of dosing.

Based on the IB [18], pretomanid is moderately absorbed following oral administration, with a $T_{max}$ of 4 to 5 hours after single- or multiple-dose administration under fasted conditions. Dosing with a high-calorie, high-fat meal increased the $T_{max}$ by approximately 1 hour, and the drug exposure was about half in the fasted state comparing with that in the fed state. It is recommended that the clinical dose of 200 mg be administered in the fed state.

Overall, oral CL/F values (~8 L/hr) for pretomanid at a 200 mg dose are considerably less than the hepatic blood flow for a 70 kg human (1450 mL/min, 87.0 L/hr), suggesting that pretomanid is not highly extracted by the liver. Furthermore, the apparent $V_d$/F after a 200 mg dose was approximately

175 L, which is considerably higher than the total volume of body water (~42 L), indicating that pretomanid is distributed out of plasma.

Pretomanid binding to human plasma protein is 86.4%, with the majority of the binding to human serum albumin [18]. In the presence of rifampicin (strong cytochrome [CYP] 3A4 inducer) and efavirenz (moderate CYP3A4 inducer), pretomanid average concentration over a dosing interval ($C_{avg}$) is reduced by 66% and 35%, respectively. Therefore, strong and moderate CYP3A4 inducers should be avoided with pretomanid.

Once-daily oral administration of pretomanid 400 mg for 14 days did not appear to significantly inhibit CYP3A4 in healthy participants, based on the results of a drug-drug interaction study with midazolam, a sensitive probe substrate for drugs metabolized by CYP3A enzymes. Results of in vitro investigations using human liver microsomes also support a low risk of drug-drug interactions with pretomanid. In 2 mass-balance studies in healthy participants [18], approximately 91% of the administered radioactive dose was recovered in the urine (65% and 53%) and feces (26% and 38%). The majority of urinary and fecal radioactivity elimination occurred within 6 to 7 days after dosing. Comparisons of plasma and whole blood total radioactivity PK parameters to plasma pretomanid PK parameters suggest that the majority of the administered dose is converted to pretomanid metabolites, after which time total radioactivity in blood is eliminated slowly from the body.

No clinically significant differences in the PK of pretomanid were observed based on sex, body weight, race, pulmonary TB status, or HIV status.

The effect of renal or hepatic impairment on the PK of pretomanid is unknown.

### 2.1.6 Efficacy Studies

#### 2.1.6.1 Efficacy As a Single Agent

Different doses of pretomanid, given as a single agent, were evaluated in 2 studies [23, 29]. In the first study, doses of 200, 600, 1000, and 1200 mg/day were used [23]. In the second study, lower doses including 50, 100, 150, and 200 mg/day were used [29]. Both studies produced a measurable decrease in sputum CFU counts over the 14-day treatment period. The results, summarized in Table 2, indicate that there were no meaningful differences among the pretomanid dose groups of 200 to 1200 mg/day also supported by formal dose trend analyses. There was a dose-related trend with respect to changes in mean logCFU values over time in the second study, with a smaller reduction seen in the 50 mg/day dose group compared with the 100, 150, or 200 mg/day dose groups. This latter study, however, was not powered to detect significant differences between the dose groups.

#### 2.1.6.2 Efficacy When Administered in a Multidrug Regimen

Three Phase 2 studies evaluated pretomanid efficacy in a multidrug regimen [18, 30-32]. The treatment regimens studied, and results are summarized in Table 2. The first multidrug regimen [30] compared 6 regimens:

- BDQ (alone).
- BDQ + pyrazinamide.
- pretomanid + BDQ.
- pretomanid + pyrazinamide.
- pretomanid + moxifloxacin + pyrazinamide.
- standard treatment regimen (INH, rifampin, pyrazinamide, and ethambutol).

In this trial, the mean daily rate of decline in logCFU in the first 14 days of treatment was highest for pretomanid + moxifloxacin + pyrazinamide combination. The second multidrug regimen [32] was a 7-arm study of the following treatments:

- pretomanid + BDQ + pyrazinamide + clofazimine.
- pretomanid + BDQ + pyrazinamide.
- pretomanid + BDQ + clofazimine.
- BDQ + pyrazinamide + clofazimine.
- pyrazinamide alone.
- clofazimine alone.
- standard treatment with INH, rifampin, and pyrazinamide.

The study showed that a regimen containing pretomanid + BDQ + pyrazinamide resulted in a marked daily rate of decline in logCFU (mean 0.167) comparable to standard treatment (mean 0.151), indicating that the pretomanid-containing regimen is a potential new TB treatment regimen. In the third trial, 3 regimens were compared, and the mean daily rate of decline of logCFU with a regimen containing pretomanid 200 mg + moxifloxacin + pyrazinamide was significantly greater than standard treatment (0.155 vs 0.112, respectively) [31].

#### 2.1.6.3 Efficacy on Drug-Resistant TB

In a Phase 2 trial by Dawson et al [31], 26 patients with MDR-TB were treated with pretomanid + moxifloxacin + pyrazinamide. The mean daily rate of decline in logCFU over 56 days in MDR-TB patients was comparable to treatment-naïve patients treated with standard treatment (0.117 vs 0.112, respectively). These results indicate that pretomanid is useful for treatment of MDR-TB.

A Phase 3, pivotal, open-label trial Nix-TB assessed the safety, tolerability, efficacy, and PK of BPaL regimen in the treatment of patients with either pulmonary XDR-TB or TI/NR MDR-TB. A total of 109 patients aged 17 to 60 years old with pulmonary XDR-TB or TI/NR MDR-TB were enrolled at 3 centers in South Africa. Patients received study treatment for a minimum of 6 months (i.e., until Week 26). If patients were culture positive or reverted to being culture positive between Month 4 and Month 6 and their clinical condition suggested they may have ongoing TB infection, the study treatment may have been extended to 9 months (i.e., Week 39) or the patient may have been withdrawn from the trial. The primary endpoint was the incidence of an unfavorable outcome, defined as treatment failure (bacteriologic or clinical) or disease relapse. Clinical treatment failure was defined as a change from the protocol-specified TB treatment as a result of a lack of clinical efficacy, retreatment for TB, or TB-related death through follow-up until 6 months after the end of treatment. The success rate was 89% at 6-month post end of treatment. FDA and EMA approval of pretomanid, in the context of the BPaL regimen, was based on the Nix-TB data [33].

**Table 2: Summary of Phase 2 studies using Pretomanid**

| Outcome measure | N* | Regimens | Results | Conclusions | Ref. |
|---|---|---|---|---|---|
| **Single Agent** | | | | | |
| Daily rate of decline in logCFU over 14 days (Mean ± SD) | 69 | Pretomanid 200 mg | 0.098 ± 0.07 | Outcome measure the same for all 4 pretomanid dosages. | [23] |
| | | Pretomanid 600 mg | | | |
| | | Pretomanid 1000 mg | | | |
| | | Pretomanid 1200 mg | | | |
| | | Standard (HRZE)¥ | 0.148 ± 0.055 | | |
| Daily rate of decline in logCFU over 14 days (Mean ± SD) | 69 | Pretomanid 50 mg | 0.063 ± 0.058 | -Dose-related trend with a smaller reduction seen in the 50 mg/day group.<br>-Study not powered to detect significant differences between the dose groups. | [29] |
| | | Pretomanid 100 mg | 0.09 ± 0.073 | | |
| | | Pretomanid 150 mg | 0.078 ± 0.074 | | |
| | | Pretomanid 200 mg | 0.112 ± 0.070 | | |
| | | Standard (HRZE)¥ | 0.177 ± 0.042 | | |
| **Multidrug Regimen** | | | | | |
| Daily rate of decline in logCFU over 14 | 85 | Bedaquiline | 0.061 ± 0.068 | -The mean decline in CFU in pretomanid + moxifloxacin + pyrazinamide group was significantly higher than the decline in all other groups | [30] |
| | | Bedaquiline + pyrazinamide | 0.131 ± 0.102 | | |
| | | Pretomanid + Bedaquiline | 0.114 ± 0.050 | | |

| Outcome measure | N* | Regimens | Results | Conclusions | Ref. |
|---|---|---|---|---|---|
| days (Mean ± SD) | | Pretomanid + Pyrazinamide | 0.154 ± 0.040 | except pretomanid + pyrazinamide and standard treatment groups. | |
| | | Pretomanid + Moxifloxacin + Pyrazinamide | 0.233 ± 0.128 | | |
| | | Standard (HRZE)¥ | 0.14 ± 0.094 | | |
| Daily rate of decline in logCFU over 14 days, Mean (95% CI) | 105 | Pretomanid + Bedaquiline + Pyrazinamide + Clofazimine | 0.115 (0.039-0.189) | | [32] |
| | | Pretomanid + Bedaquiline + Pyrazinamide | 0.167 (0.075-0.257) | This regimen is a potential new TB treatment. | |
| | | Pretomanid + Bedaquiline + Clofazimine | 0.076 (0.005-0.145) | | |
| | | Bedaquiline + Pyrazinamide + Clofazimine | 0.124 (0.035-0.214) | | |
| | | Pyrazinamide | 0.036 (-0.026-0.099) | | |
| | | Clofazimine | -0.017 (-0.085-0.053) | Clofazimine has no activity alone. | |
| | | Standard (HRZE)¥ | 0.151 (0.071-0.232) | | |
| Daily rate of decline in logCFU over 56 days, Mean (95% Bayesian credibility interval) | 207 | Pretomanid (100 mg) + Moxifloxacin + Pyrazinamide | 0.133 (0.109-0.155) | | [31] |
| | | Pretomanid (200 mg) + Moxifloxacin + Pyrazinamide | 0.155 (0.133-0.178) | -Daily CFU decline significantly greater than that for standard treatment. | |
| | | Standard (HRZE)¥ | 0.112 (0.093-0.131) | | |
| | | Pretomanid (200 mg) + Moxifloxacin + Pyrazinamide | 0.117 (0.070-0.174) | -Only MDR-TB patients included.<br>-Daily reduction in CFU was comparable to that of standard treatment for patients with drug-susceptible TB. | |

CI=confidence interval; CFU=colony forming unit; HRZE=standard treatment with isoniazid, rifampin, pyrazinamide, and ethambutol; MDR-TB=multidrug-resistant tuberculosis; TB=tuberculosis.

*N includes all volunteers randomized to the different study groups. ¥, Standard (HRZE) indicates standard treatment with isoniazid, rifampin, pyrazinamide, and ethambutol.
§All pretomanid doses were once daily and all-pretomanid doses were 200 mg unless specified. Unless specified, all studies were on treatment-naïve patients with pulmonary TB.

## 2.2 Scientific Rationale

### 2.2.1 Purpose of Study

TB is a major public health problem worldwide. Treatment of drug-susceptible TB requires the use of 4 first-line anti-TB drugs for at least 6 months [4]. New drug treatments may help shorten the duration of treatment and potentially increase patient compliance, and therefore, have a direct impact on the control of TB. Furthermore, MDR and XDR-TB have made the prevalence of TB more challenging. Up to 50% of MDR-TB cases fail treatment and treatment outcome of XDR-TB is unpredictable [1], indicating that development of new anti-TB drugs is an essential component of TB control.

Pretomanid is one of a few anti-TB drugs with the following unique and attractive characteristics:

1. It has early bactericidal and sterilizing activity, with a potential to shorten the duration of treatment for drug-susceptible TB [23, 24]. It shortens the duration of treatment for MDR-TB in the context of the BPaL regimen [33],
2. It has excellent activities against both drug-sensitive and MDR-isolates of Mtb [26],
3. It has been shown to have a low incidence of AEs in multiple clinical trials [18],
4. It has narrow spectrum of activity limited primarily to Mtb with no significant activity against a broad range of Gram-positive and Gram-negative bacteria [34],
5. It has no demonstrable cross resistance to a variety of anti-TB drugs [25],
6. It is administered orally [18, 19], and
7. It neither inhibits nor is metabolized by major CYP450 enzyme isoforms except for CYP3A4 in vitro, importantly indicating a low potential for drug-drug interactions, including with presently used antiretrovirals for treatment of HIV [35, 36].

Patients with renal impairment, particularly severe renal impairment or end stage renal disease (ESRD), may have an increased risk of drug exposure and may require lower doses of certain drugs compared to patients with normal renal function [37]. According to FDA and Europe, the Middle East, and Africa (EMEA) guidelines, a PK study should be carried out during the development phase of a new drug that is likely to be used in patients with renal dysfunction and whose pharmacokinetics are likely to be significantly altered in renally impaired patients [38, 39]. Less than 1% of

unmetabolized pretomanid is excreted in the urine. [18]. Therefore, like other commonly used anti-TB drugs such as ethambutol and pyrazinamide, which are at least partly eliminated through kidneys, the PK of pretomanid must be studied in patients with CKD. CKD is a very common clinical disease with estimated prevalence of 8 to 16%, and CKD patients globally, particularly those in advanced stages, have significantly increased risk of developing TB [11-13].

Regarding pretomanid metabolites, no single metabolic pathway can be considered major. Two metabolites have been selected for quantification: M19 (4-Trifluoromethoxybenzoic acid) and M50 (hydroxy imidazole). In one mass-balance study, M19 was the largest drug-derived metabolite, representing up to 35% of the sample radioactivity at 24 hours post-dose. However, it has no activity or toxicity. In another mass-balance study, M50 was found to account for 6.3% of the parent area under the AUC and it has been identified as potentially genotoxic based on an in vitro Ames test. In 2 mouse genotoxicity studies, no genotoxicity was observed up to a 2000 mg/kg dose. In a recently completed carcinogenicity study in transgenic mice with M50 exposure 2-3 times the expected human exposure, no pretomanid-related deaths, tumors, or gross necropsy findings were seen. There is no evidence suggestive of any potential carcinogenic hazard in rat toxicity studies up to 6 months and in monkey toxicity studies up to 9 months. No metabolites have been found to represent more than 13% of the total dose in urine and feces. Therefore, based on results from previous studies and expected excretion in urine, measuring the plasma exposures of pretomanid metabolites (M50 and M19) in this patient population will be valuable.

The results from this study will help determine future dosing and frequency of administration of pretomanid that can be safely used in patients with different stages of renal impairment.

### 2.2.2 Study Population

The study population will be representative of participants with varying degrees of renal disease as defined by eGFR as well as participants who are healthy matched controls. Children will not be included as this study is designed for adult participants between the ages of 18-85 years (for detailed information see Section 5.1 Eligibility Criteria).

## 2.3 Potential Risks and Benefits

### 2.3.1 Potential Risks

The potential risks of this trial are those associated with having blood drawn, adverse reactions to pretomanid, and breach of confidentiality.

Potential adverse drug reactions include mild to moderate nausea and vomiting, mild to moderate rash, and increased transaminases. These are listed as adverse drug reactions in the pretomanid IB [18].

In pooled Phase 1 trials (i.e., pooled data from all Phase 1 studies in healthy volunteers) where pretomanid was dosed as single or multiple doses, the most frequently observed AEs were headache and nausea.

A study on the effects of pretomanid in healthy volunteers determined that increases in creatinine were noted at high repeat doses in healthy volunteers. A follow-up intensive renal function study revealed that the drug does not adversely affect GFR, renal plasma flow, or filtration fraction but appeared to decrease tubular renal secretion of creatinine. A single dose of pretomanid did not affect kidney function in healthy participants and it is not anticipated that kidney function will change from a single dose.

Testicular toxicity is considered as a potential risk based on pre-clinical studies. TB Alliance is currently conducting a study to further investigate pretomanid and testicular toxicity. A single dose of pretomanid is however, not anticipated to have an impact on testicular function in general.

After administering the pretomanid, patients will be closely observed and asked about any new symptoms before each blood draw. Clinical evaluation will be done when necessary, during the first 24 hours of hospital admission, and during follow-up visits. Life-threatening side effects, although not anticipated, will be reported immediately to the hospital emergency medical team and standard procedures will be followed. Volunteers with serious side effects identified during the follow-up visits will be transported to the Emergency Department (ED) of the local hospital where they will be examined by an ED physician and admitted to the hospital for further management if required.

To limit possible adverse reactions to study participants, volunteers who donated blood or blood products >500 mL within 30 days from screening or who plans to donate during the study or up to 14 days after dosing will be excluded from the study.

Blood Draw

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the participant lie down and elevate his/her legs. Bruising at the blood draw site may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. Rarely, drawing blood may cause infection (thrombophlebitis). The use of aseptic (sterile) technique will make infection at the site where blood will be drawn extremely unlikely.

Peripheral Catheter (if needed)

Inserting a peripheral catheter may cause pain, bleeding, hematoma, vein irritation, infiltration, extravasation, phlebitis, air embolism, and/or infection. Use of proper aseptic technique during the insertion provides protection against infection.

Pregnancy

It is unknown if the study drug poses any risks to an unborn child. As such, females of childbearing potential, i.e., women who have started menses, must agree to use an effective method of birth control for the duration of the study (Section 5.1.1). Males who are sexually active with a female of childbearing potential must agree not to father a child or donate sperm for the duration of the study.

Other Risks

*Personal Health Information (PHI)*

Participants will be asked to provide PHI. All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the participants' PHI. All study records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password-protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publications from this trial will use de-identified information. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the local Institutional Review Boards (IRBs), National Institute of Allergy and Infectious Diseases (NIAID), and FDA.

As required by US law, a description of this clinical trial will be available on https://clinicaltrials.gov/ct2/show/NCT03896750. This website will not include information that can be used to identify participants. At most, this website will include a summary of the results.

There may be other risks, discomforts, or side effects that are unknown at this time.

### 2.3.2 Potential Benefits

There is no direct benefit to participants who will receive the study product. This study is a PK study in patients with renal impairment. Patients with renal impairment have a higher risk of developing TB and participation will not prevent or reduce the risk of contracting TB. The results from this study will help determine the safe and effective dose of pretomanid for treatment of TB in patients with renal impairment. Pretomanid, in the context of the BPaL regimen, shortens the treatment of TI or NR MDR and XDR-TB to 6 months.

# 3 STUDY DESIGN, OBJECTIVES, AND ENDPOINTS OR OUTCOME MEASURES

## 3.1 Study Design Description

This is a Phase 1, open-label, single-dose, sequential group study to evaluate the PK and safety profile of pretomanid in participants with renal impairment (excluding those with ESRD needing dialysis) compared to matched participants with normal renal function.

The study will be conducted following a reduced PK study design in Part A, see Table 1 and Figure 1. Part A will enroll participants from Group 1A (i.e., 6 healthy matched controls) and Group 2 (i.e., 6 participants with severe renal impairment and ESRD, not on dialysis).

A decision to proceed to Part B will be made after the PK of pretomanid and safety of participants enrolled in Part A have been reviewed. If Part A demonstrates at least a 50% increase in pretomanid AUC in Group 2 (severe renal impairment and ESRD, not on dialysis) relative to the exposures in Group 1A (matched participants with normal renal function), then the reduced PK study will extend to the full PK study to enroll participants into Part B (i.e., to investigate mild and moderate renal impairment) and all enrollment will be initiated concurrently in Part B groups (1B, 1C, 3, and 4). Otherwise, no further study is recommended.

**Study Population**

**Part A**

**Group 1A:** 6 healthy participants (matched controls) with normal renal function: MDRD (eGFR ≥90 mL/min). Participants will be matched by race, gender, age (± 10 years, but between 18 to 85 years of age) and body mass index (BMI) (18 to 40 kg/m$^2$).

**Group 2:** 6 severe renal impairment participants: Stage 4, MDRD (eGFR 15-29 mL/min), and ESRD not on dialysis, Stage 5, MDRD (eGFR <15 mL/min).

**Part B**

**Groups 1B and 1C**: 6 healthy participants (matched controls) each, for Groups 3 and 4, respectively: MDRD (eGFR ≥90 mL/min). Participants will be matched by race, gender, age (± 10 years, but between 18 to 85 years of age) and BMI (18 to 40 kg/m$^2$).

**Group 3:** 6 mild renal impairment participants: Stage 2, MDRD (eGFR 60-89 mL/min).

**Group 4:** 6 moderate renal impairment participants: Stage 3, MDRD (eGFR 30-59 mL/min).

## 3.2 Study Objectives

### 3.2.1 Primary

- To evaluate the PK profiles of pretomanid in plasma and urine after a single oral dose of 200 mg in participants with renal impairment compared to matched healthy controls.

### 3.2.2 Secondary

- To assess the safety profile of a single oral dose of 200 mg pretomanid in renally impaired participants to matched healthy controls.
- To evaluate the PK profiles of representative pretomanid metabolites (M19 and M50) in plasma and urine.

## 3.3 Study Endpoints or Outcome Measures

### 3.3.1 Primary

#### 3.3.1.1 Plasma PK of Pretomanid (see Section 10.5 for specific PK parameters)

The plasma PK of a single dose of pretomanid will be assessed from serial blood samples collected up to 1 hour pre-dose (Day 1) and at multiple time points post dosing: 1, 2, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours. The primary outcome measure will be total plasma concentration of pretomanid.

#### 3.3.1.2 Urine PK of Pretomanid (see Section 10.5 for specific PK parameters)

The urine PK of a single dose of pretomanid will be assessed from urine collected up to 1 hour pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hours post-dose. Volume of urine will be measured and recorded at each of these time intervals. Urine samples will be stored at room temperature and then frozen at -20°C within 24 hours. Urine samples will be stored in ≤100 mL aliquots at -20°C until shipped to Fisher Bioservices for storage.

The concentrations of pretomanid in plasma and urine will be measured by the validated bioanalytical methods. The pretomanid PK profiles in plasma and urine estimated through a non-compartmental analysis.

### 3.3.2 Secondary

- Safety – Number of participants reporting AEs. (Time Frame: Time of dosing [Day 1] to Day 12).
- Safety – Mean change from baseline in hemoglobin (Hgb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), creatinine (includes eGFR), serum potassium and magnesium (Time Frame: Screening [Days -28 to -7], Day 5 and Day 12).
- Safety – Mean change from baseline in oral temperature, pulse, and sitting blood pressure (Time Frame: Day 1 [pre-dose], 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, and Day 12).
- Safety – Mean change from baseline in ECG corrected QT interval by Fridericia (QTcF) (Time Frame: Screening [Days -28 to -7] and Day 5).
- The concentrations of pretomanid metabolites (M19 and M50) in plasma will be measured by validated bioanalytical methods. PK – area under the plasma concentration-time curve from time 0 to the last measurement ($AUC_{last}$), and any other parameters considered to be of interest, of representative metabolites M19 and M50 in plasma (Time Frame: Up to 96 hours post-dose).
- Excretion of representative metabolites M19 and M50 in urine. The amounts of M19 and M50 will be calculated in urine (i.e., M19 and M50 concentrations measured using validated bioanalytical methods multiplied by collected urine volume).

# 4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

## 4.1 Study Product Description

Pretomanid, a nitroimidazooxazine, is a novel TB treatment that is being investigated for use with other TB drugs to shorten and/or simplify regimens to treat either drug-susceptible or resistant disease, which may improve the current high rate of noncompliance for TB treatment. Pretomanid acts by inhibiting Mtb cell wall biosynthesis, as well as generating NO.

### 4.1.1 Formulation, Packaging, and Labeling

For this study, pretomanid 200 mg tablets are white to off-white, oval-shaped tablet debossed with M on one side and P200. The formulation of pretomanid tablets is summarized in Table 3.

**Table 3: Pretomanid Formulation**

| Ingredient | % | Weight per Unit (mg) |
|---|---|---|
| Pretomanid, Micronized | 25.0 | 200.0 |
| Lactose Monohydrate NF (Foremost FastFlo 316) | 36.8 | 294.4 |
| Microcrystalline Cellulose NF (Avicel PH102) | 29.4 | 235.2 |
| Sodium Starch Glycolate NF (Explotab) | 5.0 | 40.0 |
| Magnesium Stearate NF (Hyqual) | 1.0 | 8.0 |
| Colloidal Silicon Dioxide NF (Cab-O-Sil M-5P) | 0.3 | 2.4 |
| Sodium Lauryl Sulfate USP | 0.5 | 4.0 |
| Povidone USP (PVP K30) | 2.0 | 16.0 |
| Purified Water USP | -- | -- |
| **Total** | 100% | 800.0 mg |

NF=National Formulary; USP=United States Pharmacopeia.
Note: Water is removed during drug product manufacture.

TB Alliance or its designee will package the study product. Study product will be labeled and supplied according to applicable regulatory requirements.

### 4.1.2 Product Storage and Stability

The investigator or an approved designee (e.g., pharmacist) will ensure that the study product is stored in a locked, secure area (with access limited to authorized study personnel only) under

recommended storage conditions and in accordance with applicable regulatory requirements. Pretomanid will be stored at 15-30°C (59-86°F).

## 4.2 Acquisition/Distribution

Pretomanid will be provided by Global Alliance for TB Drug Development according to the terms of the Clinical Trial Agreement between the TB Alliance and NIAID.

Upon request by Division of Microbiology and Infectious Diseases (DMID), pretomanid will be transferred to the following address:

DMID Clinical Materials Services Contract
Fisher BioServices
20439 Seneca Meadows Parkway
Germantown, MD 20876
Phone: 240-477-1350
Fax: 240-477-1360
Email: DMID.CMS@ThermoFisher.com

All study products (i.e., pretomanid) will be shipped to the participating sites prior to the start of this study upon request and with prior approval from DMID. Should the site principal investigator (PI) require additional study product during this trial, further instructions are provided in the protocol-specific manual of procedures (MOP).

## 4.3 Dosage/Regimen, Preparation, Dispensing, and Administration of Study Intervention/Investigational Product

Pretomanid will be administered in the fed state in this study because there is a food effect for the drug. Following an overnight fast of at least 8 hours, participants should start the recommended meal prior to administration of pretomanid [40]. Study participants should eat this meal in 30 ± 10 minutes or less; however, pretomanid should be administered 30 ± 10 minutes after start of the meal. Participants will be given one dose of 200 mg of pretomanid orally under direct supervision with 240 mL of water and a mouth check will be done. All participants will receive the same study product. After dosing, participants will have no food, water, or medications for 2 hours post-dose. If a participant vomits >2 hours post-dose, no redosing or exclusion is required. If a participant vomits within 2 hours of dosing, the participant will be excluded from the study with a plan to replace or rescreen and admit another time, if necessary. When a participant vomits soon after swallowing the drug, part or all of the drug may be lost. There is no way of knowing how much of the drug is already absorbed and redosing with the full dose may affect PK results.

See the protocol-specific MOP Appendices for detailed information on the preparation, labeling, storage, and administration of study product.

## 4.4 Pre-determined Modification of Study Intervention/Investigational Product for an Individual Participant

Since a single oral dose of pretomanid will be given, there will be no dose modifications.

## 4.5 Accountability Procedures for the Study Intervention/ Investigational Product(s)

Pretomanid will be sent to the DMID Clinical Materials Services (CMS) contractor, and then supplied to the participating sites prior to the start of the study. Should the site PI require additional doses of pretomanid during the trial, further instructions are provided in the protocol-specific MOP.

After receipt of pretomanid, the site PI is responsible for study product distribution and disposition and has ultimate responsibility for drug accountability. The site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The site research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product. For this study, all study product, pretomanid tablets, should be stored at 15-30°C (59-86°F) in blister-strips comprising a thermoformable-film and a lidding foil configuration. All doses of pretomanid, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The sponsor's monitoring staff will verify the participating sites' study product accountability records and dispensing logs per the site monitoring plan.

Unused tablets should be retained within the container in which they are supplied from the CMS. Unused pretomanid tablets will be monitored and released for final disposition. Final disposition of the pretomanid will be determined by DMID and the TB Alliance and communicated to the participating sites by the DMID Clinical Project Manager.

# 5 SELECTION OF PARTICIPANTS AND STUDY ENROLLMENT AND WITHDRAWAL

The study population will be represented by participants with varying degrees of renal disease as defined by eGFR. Part A will enroll participants into Groups 1A (i.e., 6 healthy matched controls) and 2 (i.e., 6 participants with severe renal impairment and ESRD, not on dialysis).

In this study, participants with renal impairment will be mainly identified from sites' exhaustive database and through referral from local renal clinics. Non-renally impaired participants will be identified from participants who have previously participated in clinical trials and through the community.

The decision to proceed from Part A to Part B will be made jointly by representatives from DMID and TB Alliance. An independent safety review will be carried out by the Safety Monitoring Committee (SMC) and the DMID Medical Monitor. This review will inform the decision to proceed from Part A to Part B.

Part B will be conducted only if the Part A results demonstrate that participants with severe renal impairment and ESRD (not on dialysis) have different exposures to pretomanid that may impact safety or efficacy relative to the exposures of healthy participants. If no difference in PK is observed in Part A, then no further study (Part B) will be recommended.

If the decision is made to conduct Part B, 12 participants (6 participants in each group) with mild and moderate renal impairment will be enrolled in Groups 3 and 4, respectively, along with 12 healthy matched participants (Groups 1B and 1C). Participants in Part B will receive the same single 200 mg dose of pretomanid as participants in Part A.

Participant inclusion and exclusion criteria must be assessed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

No exemptions are granted for participant inclusion or exclusion criteria in DMID-sponsored studies. Questions about eligibility will be directed to the DMID Medical Officer.

## 5.1 Eligibility Criteria

### 5.1.1 Participant Inclusion Criteria

#### 5.1.1.1 Participant Inclusion Criteria for Patients with Renal Impairment (Groups 2-4)

Participants eligible to participate in this trial must meet all of the following inclusion criteria:

1. Have the ability to understand the requirements of the study and have provided written informed consent[1] before any study-related procedure is performed.

   [1]*As evidence by signature on an informed consent document approved by the IRB*

2. Agree to abide by the study restrictions.
3. Are between the ages of 18 and 85 years, inclusive, at the time of enrollment.
4. Must have mild, moderate, or severe renal impairment or ESRD, but are not on dialysis. See Table 1 for staging of renal disease.
5. Have no history of chronic tobacco/nicotine usage (i.e., >10 cigarettes per day for 3 months minimum prior to admission).
6. Have QTc interval <460 msec on ECG.
7. Have a BMI of 18 to 40 kg/m$^2$ at enrollment.
8. Women of childbearing potential[2] must use an acceptable contraception method[3] for the duration of the study.

   [2]*Not sterilized via tubal ligation, bilateral oophorectomy, bilateral salpingectomy, hysterectomy, implanted contraceptive device placement (permanent, non-surgical, non-hormonal sterilization) with documented radiological confirmation test at least 90 days after the procedure, and still menstruating or <1 year has passed since the last menses if menopausal.*

   [3]*Includes non-male sexual relationships, abstinence from sexual intercourse with a male partner, monogamous relationship with vasectomized partner who has been vasectomized for 180 days or more prior to the participant receiving study product, barrier methods such as condoms with spermicide or diaphragms/cervical caps* ***with*** *spermicide, effective intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables, or oral contraceptives ("the pill").*

9. If participant is male and capable of reproduction, agrees to avoid fathering a child for the duration of the study by using an acceptable method of birth control[4].

   [4]*In addition to the use of a barrier method (condom) unless vasectomized, acceptable methods of birth control are restricted to a monogamous relationship with a woman who agrees to use acceptable contraception as outlined in inclusion criterion #8, and/or abstinence from sexual intercourse with women.*

10. Women of childbearing potential must have a negative urine pregnancy test within 24 hours prior to receipt of study product.

#### 5.1.1.2 Participant Inclusion Criteria for Healthy Participants (Groups 1A-1C)

Healthy participants eligible to participate in this trial must meet all of the following inclusion criteria:

1. Have the ability to understand the requirements of the study and have provided written informed consent[1] before any study-related procedure is performed.

   [1]*As evidence by signature on an informed consent document approved by the IRB.*

2. Agree to abide by the study restrictions.
3. Are healthy male or non-pregnant female, between the ages of 18 and 85 years, inclusive, with normal GFR ≥90 at screening.
4. Have no history of chronic tobacco/nicotine usage (i.e., >10 cigarettes per day for 3 months minimum prior to admission).
5. Have a normal QTc interval <460 msec on ECG.
6. Have a BMI of 18 to 40 kg/m$^2$ at enrollment.
7. Women of childbearing potential[2] must use an acceptable contraception method[3] for the duration of the study.

   [2]*Not sterilized via tubal ligation, bilateral oophorectomy, bilateral salpingectomy, hysterectomy, implanted contraceptive device placement (permanent, non-surgical, non-hormonal sterilization) with documented radiological confirmation test at least 90 days after the procedure, and still menstruating or <1 year has passed since the last menses if menopausal.*

   [3]*Includes non-male sexual relationships, abstinence from sexual intercourse with a male partner, monogamous relationship with vasectomized partner who has been vasectomized for 180 days or more prior to the participant receiving study product, barrier methods such as condoms with spermicide or diaphragms/cervical caps* ***with*** *spermicide, effective intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables, or oral contraceptives ("the pill").*

8. If participant is male and capable of reproduction, agrees to avoid fathering a child for the duration of the study by using an acceptable method of birth control[4].

   [4]*In addition to the use of a barrier method (condom) unless vasectomized, acceptable methods of birth control are restricted to a monogamous relationship with a woman who agrees to use acceptable contraception as outlined in inclusion criterion #7, and/or abstinence from sexual intercourse with women.*

9. Women of childbearing potential must have a negative urine pregnancy test within 24 hours prior to receipt of study product.

### 5.1.2 Participant Exclusion Criteria

#### 5.1.2.1 Participant Exclusion Criteria for Patients with Renal Impairment (Groups 2-4)

Participants eligible to participate in this trial must not meet any of the following exclusion criteria:

1. History of known active TB.

2. History of peptic ulcer disease.
3. Known hypersensitivity to pretomanid or any of the excipients.
4. History of any clinically significant uncontrolled cardiac abnormality (as deemed by the PI).
5. Any clinically significant ECG abnormality at screening[1].

   [1]*Note: the following can be considered not clinically significant:*

   - *Heart rate ≤50 beats per minute (bpm) (sinus bradycardia with heart rate between 45 and 49, inclusive, is acceptable only in younger athletic participants, as determined by the PI)*
   - *Mild first-degree atrioventricular (A-V) block (P-R interval >0.23 seconds)*
   - *Right or left axis deviation*
   - *Incomplete right bundle branch block*
   - *Isolated left anterior fascicular block (left anterior hemiblock) in younger athletic participants*
6. History of, or screening results show a QTc interval ≥460 msec.
7. Family history of Long-QT Syndrome or sudden death when a cause of death is unknown.
8. Inability to swallow tablets.
9. History of fever or documented fever (oral temperature ≥100.4°F) in the 48 hours prior to admission to the hospital.
10. Resting pulse rate <50 or >110 bpm at Screening.
11. At Screening, blood pressure ≥20 mm Hg systolic or >10 mm Hg diastolic above baseline[2] (sitting).

    [2]*Baseline is most recent blood pressure in the last 3 months.*

12. Current hyperkalemia or hypomagnesemia.
13. Positive result of urine drug screen or alcohol screen prior to hospital admission except for approved prescriptions that are not opiates and benzodiazepines.
14. Significant history of drug and/or food allergies (as deemed by the PI).
15. For women, participant is pregnant (positive test for urine Human Chorionic Gonadotropin [HCG]) at screening or Admission, breastfeeding, or planning to conceive for the duration of the study.
16. Any contraindication to the use of nitroimidazoles, or prior treatment with pretomanid or delamanid.
17. Treatment with strong or moderate CYP3A4 inducers or inhibitors[3] within 14 days before admission and during the study[4].

[3]*Except hormonal contraceptives*

[4]*In the opinion of the site investigator*

*NOTE: See Table 4 for a list of drugs known to alter the function of CYP3A4 (Section 7.1.1).*

18. Use of St. John's Wort within 7 days prior to admission and during the entire study.
19. Consumption of products containing grapefruit within 5 days prior to dosing until Visit 01N.
20. Donation of whole blood or blood products >500 mL within 30 days from screening and/or plans to donate during the study or up to 14 days after dosing.
21. Participation in another interventional clinical trial within 30 days prior to dosing until after the last study visit.
22. Hgb <8.0 g/dL in both men and women at the screening visit.
23. Positive Screening test for hepatitis C virus (HCV), hepatitis B virus (HBV), or HIV.
24. Renal transplant.
25. Scheduled for hemodialysis or peritoneal dialysis.
26. Presence of any condition or finding[5] which would jeopardize participant safety, impact study result validity, or diminish the participant's ability to undergo all study procedures and assessments.

[5]*In the opinion of the investigator*

27. For men, semen donation for the duration of the study.
28. AST and ALT > 2.5 x upper limit of normal (ULN).
29. Hyperbilirubinemia >1.5 x ULN.

#### 5.1.2.2 Participant Exclusion Criteria for Healthy Participants (Groups 1A-1C)

Participants eligible to participate in this trial must not meet any of the following exclusion criteria:

1. History of known active TB.
2. History of peptic ulcer disease.
3. Known hypersensitivity to pretomanid or any of the excipients.
4. History of any clinically significant uncontrolled cardiac abnormality (as deemed by the PI).
5. Any clinically significant ECG abnormality at screening.[1]

[1]*Note: the following can be considered not clinically significant:*

- *Heart rate ≤50 bpm (sinus bradycardia with heart rate between 45 and 49, inclusive, is acceptable only in younger athletic participants)*
- *Mild first-degree A-V block (P-R interval >0.23 seconds)*
- *Right or left axis deviation*
- *Incomplete right bundle branch block*
- *Isolated left anterior fascicular block (left anterior hemiblock) in younger athletic participants*

6. Family history of Long-QT Syndrome or sudden death when a cause of death is unknown.
7. Inability to swallow tablets.
8. History of fever or documented fever (oral temperature ≥100.4°F) in the 48 hours prior to admission to the hospital.
9. At Screening blood pressure >140/90 mm Hg or <90/65 mm Hg (sitting).
10. History of, or screening results show a QTc interval ≥460 msec.
11. Positive result of urine drug screen or alcohol screen prior to hospital admission except for approved prescriptions that are not opiates and benzodiazepines.
12. Significant history of drug and/or food allergies (as deemed by the PI).
13. Women of childbearing potential with a positive urine pregnancy test within 24 hours prior to receipt of study product.
14. Any contraindication to the use of nitroimidazoles, or prior treatment with pretomanid or delamanid.
15. Treatment with strong or moderate CYP3A4 inducers or inhibitors[2] within 14 days before admission and during the study[3].

    [2]*Except hormonal contraceptives*

    [3]*In the opinion of the site PI*

    *NOTE: See Table 4 for a list of drugs known to alter the function of CYP3A4 (Section 7.1.1).*

16. Use of St. John's Wort within 7 days prior to admission and during the entire study.
17. Consumption of products containing grapefruit within 5 days prior to dosing until Visit 01N.
18. Donation of whole blood or blood products >500 mL within 30 days from screening and/or plans to donate during the study or up to 14 days after dosing.
19. Participation in another interventional clinical trial within 30 days prior to dosing until after the last study visit.
20. Hgb <10.0 g/dL in both men and women at the screening visit.

21. Positive Screening test for HCV, HBV, or HIV.
22. Renal transplant.
23. Presence of any condition or finding[4] which would jeopardize participant safety, impact study result validity, or diminish the participant's ability to undergo all study procedures and assessments.

    [4]*In the opinion of the investigator*

24. For men, semen donation for the duration of the study.
25. AST and ALT > ULN.
26. Bilirubin > ULN

## 5.2 Withdrawal from the Study or Study Termination

### 5.2.1 Withdrawal from the Study

Participants may voluntarily withdraw their consent for trial participation at any time and for any reason, without penalty.

A participant may withdraw or be withdrawn from this trial for any of the following reasons:

- Medical disease or condition, or any new clinical finding for which continued participation, in the opinion of the site PI or appropriate sub-investigator, would compromise the safety of the participant, or would interfere with the participant's successful completion of this trial, or would interfere with the evaluation of data.
- Participant no longer meets eligibility criteria (see Section 5.1).
- As deemed necessary by the site PI or appropriate sub-investigator for noncompliance or other reasons.
- Withdrawal of consent.
- Lost to follow-up (defined as 3 unsuccessful attempts to contact the participant; the methods and dates contact was attempted will be documented).
- Termination of this trial.

A participant who is withdrawn or voluntarily withdraws from the study for any reason, whether related to the study drug or not, after having received the study drug, will be considered an early termination subject. The PI or sub-investigator will make every effort to ensure that early termination

participants who have received the study drug complete the early termination assessments and safety follow-up assessments.

### 5.2.2 Participant Replacement

Participants who sign the informed consent form (ICF) and receive study product, and subsequently withdraw before the first 24-hour time point will be replaced. All other participants who sign the ICF and receive study product, and subsequently withdraw or are withdrawn or terminated from this study or are lost to follow-up will not be replaced. If participants withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the ICF but before receipt of study product, additional participants may be enrolled for replacement. Participants may be rescreened once. Participants who miss a PK blood draw due to lack of venous access will be replaced. If the healthy matched replaced participant does not match the renally impaired participant, the healthy matched participant will be replaced. If a participant vomits within 2 hours of dosing, the participant will be excluded from the study with a plan to replace or rescreen and admit another time, if necessary.

### 5.2.3 Study Termination

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study participants and assure appropriate therapy or follow-up for the participants, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB/ Independent Ethics Committee (IEC).

# 6 STUDY PROCEDURES

Complete study schedule details listed by type of visit are described below. Refer also to APPENDIX A: Schedule of Study Procedures and Evaluations.

## 6.1 Screening

### 6.1.1 Visit 00A, Screening Clinic Visit (Day -28 to -7)

- Participants will be provided with a description of this trial (purpose and study procedures) and asked to read and sign the ICF. The ICF will be signed prior to performing any study procedures.
- Eligibility criteria will be reviewed with the participant.
- Demographic variables (age, gender, race and ethnicity) and screening characteristics (height and weight) will be collected.
- Complete medical history will be obtained by interview of the participant to ensure eligibility.
- All concomitant medications taken within 30 days prior to signing the ICF will be reported on the appropriate Data Collection Form (DCF).
- Oral temperature, sitting blood pressure, and sitting pulse will be obtained. Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A complete physical examination will be performed on all participants by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- A 12-lead ECG will be performed.
- Height and weight will be obtained for BMI calculations.
- Approximately 10 mL of venous blood will be collected for safety laboratory assessments including Hgb, BUN, serum creatinine (includes eGFR), ALT, AST, total bilirubin, serum potassium, and serum magnesium.
- Approximately 12 mL of venous blood will be collected for HCV, hepatitis B surface antigen (HBsAg), and HIV testing.
- Advise to refrain from alcohol use for at least 72 hours before admission.

### 6.1.2 Visit 00B, 2nd Screening Clinic Visit (Day -28 to -7)

- Participant's willingness to participate will be reconfirmed and documented in the participant's study source document records prior to performing any further study procedures.

- A urine pregnancy test will be performed on all women of childbearing potential and must be negative to ensure eligibility.
- Urine screen for drugs.
- Approximately 6 mL of venous blood will be collected to screen for alcohol or breath collection if breathalyzer is used for alcohol testing
- Remind to refrain from use of alcohol for 72 hours prior to hospital admission.

### 6.1.3 Visit 00C, Hospital Admission, Day -1

- Participants will be admitted to the hospital 12-24 hours before administration of study product.
- Participant's willingness to participate will be reconfirmed and documented in the participant's study source document records prior to performing any further study procedures.
- Eligibility criteria will be reviewed with the participant.
- Interim medical history, including an assessment for new medical conditions and stability of chronic diseases, will be obtained by interview of participants and any changes since the first visit (Visit 00A) will be noted.
- All concomitant medications will be reviewed with participants prior to the administration of study medication. Any new concomitant medications taken since the screening visit will be reviewed with participants and assessed for continued eligibility.
- A urine pregnancy test will be performed on all women of childbearing potential and must be negative to ensure eligibility.
- Urine screen for drugs.
- Approximately 6 mL of venous blood will be collected to screen for alcohol or breath collection if a breathalyzer is used for alcohol testing.
- Alcohol and urine drug screening will be performed, and results will be checked when available. Participants with positive results will be discharged unless the participants are on approved prescriptions. However, opiates and benzodiazepines, which are CYP3A4 substrates, will not be allowed even if prescribed. Participants who are discharged because of a positive alcohol or urine drug screen will not be rescreened for enrollment.
- If applicable, a peripheral intravenous catheter will be placed at this Visit or Visit 01A for participants with negative alcohol and drug screening except for participants who are on approved prescriptions. However, opiates and benzodiazepines, which are CYP3A4 substrates, will not be allowed even if prescribed.
- Participants will be reminded that they must fast overnight (i.e., at least 8 hours). Participants will be required to bring in from home all their medications they take at home.

## 6.2 Dosing (Day 1) and In-house Confinement/ PK Collection

### 6.2.1 Visit 01A, Administration of Study Product

- Eligibility criteria will be reviewed.
- Interim medical history, including an assessment for new medical conditions and stability of chronic diseases, will be obtained by interview of participants and any changes since the previous visit (Visit 00C) will be noted.
- Alcohol and urine drug screening results from Day -1 will be checked for participants whose alcohol and drug screening results were not available on time and who are not discharged on Day -1. Participants with positive results will be discharged unless the participants are on approved prescriptions. However, opiates and benzodiazepines, which are CYP3A4 substrates, will not be allowed even if prescribed. Participants who are discharged because of a positive alcohol or urine drug screen will not be rescreened for enrollment.
- Vital signs, including oral temperature, sitting pulse, and sitting blood pressure, will be obtained to ensure eligibility of participants with negative alcohol and urine drug screening results.
- If applicable, a peripheral intravenous catheter will be placed if not already placed on Visit 00C.
- A targeted physical examination may be performed prior to administration of study product, if indicated based on review of complete medical history and any updates obtained by interview of participants since the screening visit, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect and measure urine volume for PK up to 1 hour pre-dose and again after the dose has been administered; urine will be collected in collection beakers at 1 hour pre-dose and at intervals 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hours post-dose. Urine volume will be measured and recorded for each of these time intervals. Urine will be stored at room temperature and then frozen at -20°C within 24 hours. Urine will be in ≤100 mL aliquots and stored at -20°C until shipped to Fisher Bioservices for storage. Fisher Bioservices will ship samples to bioanalytical laboratory for concentration measurements.
- A urine pregnancy test will be performed prior to administration of the study product on all women of childbearing potential. Results must be negative and known prior to receipt of the study product.
- Approximately 4 mL of venous blood will be collected for PK prior to administration of study product (up to 1 hour pre-dose).
- Participants should start the recommended meal (high-fat and high-calorie, https://www.fda.gov/media/121313/download) 30 minutes prior to administration of

pretomanid. Study participants should eat this meal in 30 ± 10 minutes or less; however, pretomanid should be administered 30 ± 10 minutes after start of the meal.

- Participants will receive one dose of 200 mg pretomanid orally with 240 mL water under direct supervision and a mouth check will be done. If a participant meets eligibility criteria and is admitted, but is not dosed, the participant may be re-evaluated for participation in the study.
- Liquids, food, and medicine will not be allowed until at least 2 hours after dosing.
- All AEs/Serious Adverse Events (SAEs) will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.2 Visit 01B, Day 1, Time 1 Hour ± 10 Minutes Post-dose; Hospital Stay

- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AEs/Serious Adverse Events (SAEs) will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.3 Visit 01C, Day 1, Time 2 Hours ± 10 Minutes Post-dose; Hospital Stay

- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AEs/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.4 Visit 01D, Day 1, Time 4 Hours ± 10 Minutes Post-dose; Hospital Stay

- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AE/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.5 Visit 01E, Day 1, Time 5 Hour ± 10 Minutes Post-dose; Hospital Stay

- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AEs/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.6 Visit 01F, Day 1, Time 6 Hours ± 10 Minutes Post-dose; Hospital Stay

- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AEs/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.7 Visit 01G, Day 1, Time 8 Hour ± 10 Minutes Post-dose; Hospital Stay

- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AE/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.8 Visit 01H, Day 1, Time 12 Hours ± 10 Minutes Post-dose; Hospital Stay

- Vital signs, including oral temperature, sitting blood pressure, and sitting pulse will be obtained. Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AEs/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.9 Visit 01I, Day 1, Time 16 Hour ± 10 Minutes Post-dose; Hospital Stay

- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AE/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.10 Visit 01J, Day 2, Time 24 Hour ± 1 Hour Post-dose; Hospital Stay

- Vital signs, including oral temperature, sitting blood pressure, and sitting pulse will be obtained. Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AEs/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.11 Visit 01K, Day 2, Time 36 Hour ± 1 Hour Post-dose; Hospital Stay

- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AEs/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.2.12 Visit 01L, Day 3, Time 48 Hours ± 1 Hour Post-dose, Hospital Stay

- A targeted physical examination may be performed if indicated based on new symptoms after administration of study product, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Vital signs, including oral temperature, sitting blood pressure, and sitting pulse will be obtained. Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- Collect all urine for PK, measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.

- Approximately 4 mL of venous blood will be collected for PK.
- If applicable, the intravenous catheter will be removed by a nurse or physician.
- Provide urine PK collection instructions and containers. Instruct the participant to collect urine for 2 more days at home and keep urine container at room temperature with the cap on.
- Discharge after review by physician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator. Note: Participants may remain in the hospital per site decision.
- All AEs/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

## 6.3 Follow-Up

### 6.3.1 Visit 01M, Day 4, Time 72 Hours ± 4 Hours Post-dose, Clinic Visit or Continued Hospital Stay, per Site Decision

- Interim medical history, including an assessment for new medical conditions and stability of chronic diseases, will be obtained by interview of participants and any changes since the previous visit will be noted.
- A targeted physical examination may be performed if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Vital signs, including oral temperature, sitting blood pressure, and sitting pulse will be obtained. Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- Receive home urine collected jug from subject. Measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Provide urine PK collection container and remind the participant to collect urine at home and keep urine container at room temperature with cap on for PK.
- Approximately 4 mL of venous blood will be collected for PK.
- All AE/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

### 6.3.2 Visit 01N, Day 5, Time 96 Hours ± 4 Hours Post-dose, Clinic Visit or Continued Hospital Stay, per Site Decision

- Interim medical history, including an assessment for new medical conditions and stability of chronic diseases, will be obtained by interview of participants and any changes since the previous visit will be noted.
- A targeted physical examination may be performed if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.
- Vital signs, including oral temperature, sitting blood pressure, and sitting pulse will be obtained. Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A 12-Lead ECG will be performed.
- Receive home urine collected jug from subject. Measure and record urine PK volume, aliquot, label and freeze per Section 7.2.2.1.
- Approximately 4 mL of venous blood will be collected for PK.
- All AE/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.
- Approximately 10 mL of venous blood will be collected for safety laboratory assessments including Hgb, BUN, serum creatinine (includes eGFR), ALT, AST, total bilirubin, serum potassium, and serum magnesium.
- If hospitalization was continued, discharge after review by physician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

### 6.3.3 Visit 02, Day 12 ± 2 Days Post-dose, Clinic Visit

- Interim medical history, including an assessment for new medical conditions and stability of chronic diseases, will be obtained by interview of participants and any changes since the previous visit will be noted.
- A targeted physical examination may be performed on all participants by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- All concomitant medications will be recorded on the appropriate DCF.

- Vital signs, including oral temperature, sitting blood pressure, and sitting pulse will be obtained. Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- A urine pregnancy test will be performed on all women of childbearing potential.
- All AE/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.
- Approximately 10 mL of venous blood will be collected for safety laboratory assessments including Hgb, BUN, serum creatinine (includes eGFR), ALT, AST, total bilirubin, serum potassium, and serum magnesium.

## 6.4 Final Visit, Visit 03, Day 85+7 Days Post-dose, Phone Visit

- The participant will be asked if they or their partner became pregnant. If the participant became pregnant, the Pregnancy Report and Follow-Up forms will be completed. If the participant's partner became pregnant, details about the pregnancy should be reported to the sponsor to document the outcome of the pregnancy. All SAEs will be recorded on the appropriate DCF/DMID SAE Report Form.

## 6.5 Early Termination Visit (if needed)

The following activities will be performed at the early termination (ET) visit on participants who withdraw, or are withdrawn or terminated from this trial:

- Obtain interim medical history, including an assessment of new symptoms and conditions from the patient, and note any changes since the previous visit.
- A targeted review of systems. For participants with renal impairment, this targeted review of systems will also focus on renal disease and will include questions pertaining to changes in the frequency and volume of urine, requirement for dialysis, and mental status.
- Targeted physical examination, if needed.
- All concomitant medications will be recorded on the appropriate DCF.
- Assess for AEs/SAEs.
- Urine pregnancy test for females of childbearing potential.
- Vital signs including oral temperature, sitting blood pressure, and sitting pulse will be obtained.
- Approximately 10 mL of venous blood will be collected for safety laboratory assessments including Hgb, BUN, serum creatinine (includes eGFR), ALT, AST, total bilirubin, serum potassium, and serum magnesium.

## 6.6 Unscheduled Visit (if needed)

Unscheduled visits will be allowed for the following reasons:

- Management of AEs and SAEs.
- Performance of repeat or additional laboratory tests for clinically abnormal test values.
- For a repeat urine pregnancy test if the participant suspects pregnancy.
- Anytime the investigator believes that it is clinically appropriate for patient safety.

## 6.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, or protocol-specific MOP requirements. The noncompliance may be either on the part of the participant, the site PI, or the site personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviations, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the Statistical Data Coordinating Center (SDCC) protocol deviation reporting procedures.

All deviations, as defined above, must be addressed in study participant DCFs. A completed copy of the DMID Protocol Deviation Form must be maintained in the regulatory file, as well as the participant's chart. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI and personnel are responsible for knowing and adhering to their IRB requirements.

# 7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

## 7.1 Clinical Evaluations

Complete medical history will be obtained by interview of participants during the screening visit. Participants will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidneys, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited.

During the hospital stay, any new symptoms after study product administration will be collected. After hospital discharge, an interim medical history will be obtained by interview of participants noting any changes since the previous visit or contact.

Medications history (concomitant medications) will include a review of all current medications and medications as specified in Section 7.1.1. Assessment of eligibility will include a review of all permitted and prohibited medications per the participant inclusion and exclusion criteria (see Sections 5.1.1 and 5.1.2). In addition, the site PI or appropriate sub-investigator may identify other medications that should not be used due to a risk to participant safety or possible effects on PK parameters.

At the first visit (Visit 00A) a physical examination will be performed on all participants to include the following organs and organ systems: skin, head, eyes, ears, nose and throat, thyroid, neurological system, chest and lungs, cardiovascular system, abdomen, lymph nodes, musculoskeletal system, and extremities by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator. At Visit 01A, all follow-up visits, and ET visit after administration of study product, a targeted physical examination may be performed, if indicated based on the participant's interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator. At the ET visit, for participants with renal impairment, a targeted review of systems focused on renal disease will include questions pertaining to changes in frequency and volume of urine, requirement for dialysis, and mental status.

Vital sign measurements must include the participant's sitting pulse, sitting blood pressure (mm Hg), and oral body temperature (ºF) at the screening Visit 00A, 01A, 12, 24, 48, 72, and 96 hours and Day 12 or at ET after study product administration. Height and weight will be obtained at screening Visit 00A only. If a physiologic parameter, e.g., vital signs, is outside of the protocol-specified range (for control participants) or outside the patient's baseline (for renally impaired participants), then the measurement may be repeated once if, in the judgment of the investigator, the abnormality is the

result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety, or "white coat syndrome"). The participant's baseline is the latest vital sign recorded in their electronic health record (EHR) in the last 3 months before screening. For participants with CKD but no vital signs recorded in their EHR, the protocol-specified range used for control participants will be used. Once participants are dosed, the vital signs measured at Visit 01A will be considered their baseline. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by a malfunction, or an inappropriate measuring device (i.e., inappropriate-sized blood pressure cuff). If there is an abnormal blood pressure measurement, the participant should lay down for 10 minutes and then the measurement should be repeated while the participant is awake and resting supine. For analyzing secondary safety endpoints in rescreened participants (if any) and that include a comparison to screening baseline values should have the rescreening values as baseline.

In addition, a 12-lead ECG will be performed at Screening Visit 00A and Visit 01N. If at Visit 01N the ECG is abnormal, it can be repeated.

At subsequent visits, assessment for AEs and SAEs will occur and the participant will be interviewed about interim AEs/SAEs and medical history.

Participants will be admitted for multiple blood draws following oral administration of study product. Any AEs/SAEs will be recorded on the appropriate DCF/DMID SAE Report Form prior to discharge from the hospital.

### 7.1.1 Assessment of Concomitant Medications/Treatments Other Than Study Product

Administration of any medications, therapies, or vaccines will be recorded on the appropriate DCF. Concomitant medications will include all current medications and medications taken in the 30 days prior to signing the ICF through approximately 11 days after the study medication is given, ET or unscheduled visits (if prior to 11 days after study product administration), whichever occurs first. Medications reported are limited to those taken within 30 days prior to the study medication through approximately 11 days after the study medication. Prescription and over-the-counter drugs will be included as well as vitamins, and supplements (including herbal).

**Table 4: Prohibited Strong and Moderate CYP450 Enzyme Inducer or Inhibitor Medications/Substances per Participant Exclusion Criteria**

| CYP3A (including 3A4) inhibitors and inducers | | | |
|---|---|---|---|
| **Strong inhibitors** | **Moderate inhibitors** | **Strong inducers** | **Moderate inducers** |
| • Adagrasib<br>• Atazanavir<br>• Ceritinib<br>• Clarithromycin<br>• Cobicistat and cobicistat-containing coformulations<br>• Darunavir<br>• Idelalisib<br>• Indinavir<br>• Itraconazole<br>• Ketoconazole<br>• Levoketoconazole<br>• Lonafarnib<br>• Lopinavir<br>• Mifepristone[d]<br>• Nefazodone<br>• Nelfinavir<br>• Nirmatrelvir-ritonavir<br>• Ombitasvir-paritaprevir-ritonavir<br>• Ombitasvir-paritaprevir-ritonavir plus dasabuvir<br>• Posaconazole<br>• Ritonavir and ritonavir-containing coformulations<br>• Saquinavir<br>• Tucatinib<br>• Voriconazole | • Amiodarone[a]<br>• Aprepitant<br>• Berotralstat<br>• Cimetidine[a]<br>• Conivaptan<br>• Crizotinib<br>• Cyclosporine[a]<br>• Diltiazem<br>• Duvelisib<br>• Dronedarone<br>• Erythromycin<br>• Fedratinib<br>• Fluconazole<br>• Fosamprenavir<br>• Fosaprepitant[a]<br>• Fosnetupitant-palonosetron<br>• Grapefruit juice<br>• Imatinib<br>• Isavuconazole (isavuconazonium sulfate)<br>• Lefamulin<br>• Letermovir<br>• Netupitant<br>• Nilotinib<br>• Ribociclib<br>• Schisandra<br>• Verapamil | • Apalutamide<br>• Carbamazepine<br>• Enzalutamide<br>• Fosphenytoin<br>• Lumacaftor<br>• Lumacaftor-ivacaftor<br>• Mitotane<br>• Phenobarbital<br>• Phenytoin<br>• Primidone<br>• Rifampin (rifampicin) | • Bexarotene<br>• Bosentan<br>• Cenobamate<br>• Dabrafenib<br>• Dexamethasone[b]<br>• Dipyrone<br>• Efavirenz<br>• Elagolix, estradiol, and norethindrone therapy pack[c]<br>• Eslicarbazepine<br>• Etravirine<br>• Lorlatinib<br>• Mitapivat<br>• Modafinil<br>• Nafcillin<br>• Pexidartinib<br>• Rifabutin<br>• Rifapentine<br>• Sotorasib<br>• St. John's wort |

CYP=cytochrome P450; FDA=Food and Drug Administration; US=United States (of America)
From https://www.uptodate.com/contents/image?imageKey=CARD%2F76992
For drug interaction purposes, inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
These classifications are based upon US FDA guidance [41, 42]. Other sources may use a different classification system resulting in some agents being classified differently.
Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (e.g., target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.

Refer to UpToDate topics on specific agents and indications for further details.

[a] Classified as a weak inhibitor of CYP3A4 according to FDA system [41].

[b] Classified as a weak inducer of CYP3A4 according to FDA system [41].

[c] The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When Elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

[d] Mifepristone is a significant inhibitor of CYP3A4 when used chronically (e.g., for hyperglycemia in patients with Cushing syndrome); not in single-dose use.

## 7.2 Laboratory Evaluations

### 7.2.1 Clinical Laboratory Evaluations

Clinical laboratory parameters to be evaluated prior to the study product administration on screening visit (Visit 00A), on Day 5 (Visit 01N) and on Day 12 (Visit 02) will include Hgb, ALT, AST, total bilirubin, BUN, serum creatinine (includes eGFR), serum potassium and serum magnesium. HIV, HBsAg, and HCV will be obtained at Visit 00A only. Screening laboratory assessments may be repeated once per investigator discretion.

Urine pregnancy tests will be performed locally on all women of childbearing potential by the site laboratory at screening (Visit 00B), on the day of hospital admission (Visit 00C), prior to administration of study product (Visit 01A), at Visit 02, and ET. Results must be negative and known prior to administration of study product. Urine drug screen and alcohol screen will also be done on Visit 00B and 00C.

### 7.2.2 Research Assays

All PK samples collected in the study will be analyzed using validated bioanalytical methods for pretomanid, and the metabolites, M19 and M50 in plasma and urine.

Blood samples will be collected (dipotassium ethylenediaminetetraacetic acid [$K_2$ EDTA] tubes) in this study to characterize the PK of pretomanid in non-renally impaired controls and in participants with renal impairment (see PK sampling points in APPENDIX A: Schedule of Study Procedures and Evaluations.

The exact date and time of collection of all PK blood and urine samples will be recorded. The pre-dose blood sample will be collected up to 1 hour prior to dosing. For the post-dose PK blood samples collected through the first 16 hours after dosing, collection times must be ± 10 minutes from the nominal time. For post-dose collections at 24, 36, and 48 hours, collection times must be within ± 1 hour from the nominal time. Post-dose collections at within 72 and 96 hours must be within ± 4 hours from the nominal time.

Dates should be recorded in an unambiguous format (e.g., DDMMMYYYY), and time should be recorded to the nearest minute (e.g., HH:MM using the 24-hour clock). Blood samples drawn outside

of the defined window should not be considered protocol deviations. Blood samples that are not drawn should be recorded and reported as protocol deviations.

#### 7.2.2.1 Laboratory Specimen Preparation, Handling, and Shipping

Instructions for specimen preparation, handling, and storage are included in the central (clinical) laboratory manual and protocol-specific MOP as appropriate.

Briefly, whole blood will be collected into commercially available anticoagulant ($K_2$ EDTA)-treated tubes. Cells including platelets will be removed from plasma by centrifugation for 15 minutes at 2,000 x g using a refrigerated centrifuge. The resulting supernatant is designated plasma. Following centrifugation, the plasma will be transferred into a clean polypropylene tube using sterile pipettes. The plasma samples will be apportioned into 0.5 mL aliquots immediately while the samples are maintained at 2–8°C. The aliquots will be stored at –20°C or colder.

The urine PK of a single dose of pretomanid will be assessed from urine collected at up to 1 hour pre-dose, 0-4, 4-8, 8-12, 12 24, 24 48, 48-72, and 72-96 hours post-dose. Urine volume will be measured and recorded for each of these time intervals. Urine will be stored at room temperature and then frozen at -20°C within 24 hours. Urine will be in ≤100 mL aliquots and stored at -20°C until shipped to Fisher Bioservices. The rest of the urine will be stored until the study is completed.

#### 7.2.2.2 Laboratory Specimen Shipment

Specimen shipment will occur at intervals during the course of this trial following all applicable International Air Transport Association (IATA) requirements and according to the specifics for storage temperature and documentation as detailed in the protocol-specific MOP as appropriate.
Plasma and urine PK samples will be shipped on dry ice to Fisher Bioservices prior to sending to the bioanalytical laboratory measuring concentrations of pretomanid and its metabolites (M19 and M50).

Instructions for specimen shipment are included in the protocol-specific MOP, as appropriate.

# 8 ASSESSMENT OF SAFETY

## 8.1 Assessing and Recording Safety Parameters

Safety will be assessed by the frequency and severity of the following:

1. SAEs (Section 8.1.2) occurring from the time of the study product administration through Visit 03, Day 85+7 days.

2. Adverse Events occurring from the time of the first study product administration (Visit 01A) through Visit 02, Day 12 ± 2 days.

3. Clinical safety laboratory AEs occurring from the time of the first study product administration (Visit 01A) through Visit 02 Day 12 ± 2 days. Parameters to be evaluated include a Hgb, AST, ALT, total bilirubin, BUN, serum creatinine, eGFR, and serum potassium and magnesium.

All AEs/SAEs will be followed until resolution.

### 8.1.1 Adverse Events

**Adverse Event (AE):** The International Council for Harmonisation (ICH) E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product regardless of its causal relationship to the study treatment. The FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study participants presenting for medical care, or upon review by a study monitor.

All AEs, systemic (participative and quantitative) reactions from Day 1 to the end of the study, will be captured on the appropriate (source documentation and eCRF) (Section 8.3). Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator), date of resolution, seriousness, and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship to the study product. AEs will be followed through resolution or until stable.

Any medical condition(s) that is/are present at the time that the participant is screened will be considered as baseline and not reported as an AE but must be reported in the medical history

(APPENDIX A: Schedule of Study Procedures and Evaluations). However, if the severity of any pre-existing medical condition increases, it will be recorded as an AE (Section 8.3).

#### 8.1.1.1 Adverse Events Grading

All AEs, including laboratory and clinical symptoms, will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50), and assessed for relationship to study product. AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate DCF and eCRF.

**Severity of Event:**

- Mild (Grade 1): Asymptomatic or mild symptoms, Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities.
- Severe (Grade 3): Severe or medically significant but not immediately life threatening, interrupt the participant's daily activities; and may require intervention and hospitalization. Severe events are usually incapacitating.
- Life-threatening (Grade 4): Life-threatening consequences; urgent intervention indicated.

AEs characterized as intermittent require documentation of onset and duration of each episode.

**Relationship to Study Product:** The assessment of the AE's relationship to study product will be performed by a delegated, licensed study clinician listed on the Form FDA 1572. The assessment will be part of the documentation process. Whether the AE is related or not is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. In a clinical trial, the study product must always be suspect. To help assess the relationship, the following guidelines will be used:

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

### 8.1.2 Serious Adverse Events

**Serious Adverse Event (SAE):** An AE or suspected adverse reaction is considered "serious" if, in the view of either the site PI or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening AE*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

*An AE is considered "life-threatening" if, in the view of either the site PI or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the health or safety of the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product).
- Recorded on the appropriate DCF and eCRF, and on the DMID SAE Report Form.
- Followed through resolution.
- Reviewed and evaluated by the DMID, SMC (periodic review unless related), and the IRB per reporting requirements.

At any time after the protocol follow-up period or completion of this study, if the site PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

## 8.2 Specification of Safety Parameters

There are no solicited events to be captured for this study.

## 8.3 Reporting Procedures

Non-serious AEs will be documented and reported from the time of receipt of study product through approximately 11 days after receipt of study product.

SAEs will be documented and reported through approximately 3 months after receipt of study product.

AEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

### 8.3.1 Reporting SAEs

SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

**Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on a PDF-fillable SAE form to the DMID Pharmacovigilance Group at the following address:**

**DMID Pharmacovigilance Group**
**Clinical Research Operations and Management Support (CROMS)**
**6500 Rock Spring Dr. Suite 650**
**Bethesda, MD 20817, US**
**SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)**
**SAE FAX: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)**
**SAE Email Address: PVG@dmidcroms.com**

In addition to the SAE form, selected SAE data fields must also be entered into the SDCC system (for example Advantage eClinical). Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The site will send a copy of the SAE report(s) to the DMID Pharmacovigilance Group. The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study participant safety and protocol conduct.

At any time after completion of this trial, if the site PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

### 8.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the investigator, DMID, the IND sponsor will report any suspected adverse reaction that is both serious and unexpected. DMID will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the AE. DMID will notify the FDA and all participating site investigators (i.e., all investigators to whom the sponsor is providing drug under its IND[s] or under any PI's IND[s]) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in US 21 CFR Part 312.32. DMID will also notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Upon request from the FDA, DMID will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All serious events designated as "not related" to study product(s), will be reported to FDA at least annually in a summary format.

### 8.3.3 Reporting of Pregnancy

Pregnancies occurring in female study participants will be reported via Advantage eClinical® on the Pregnancy Report form. With the participant's permission all protocol-required venous blood samples will be obtained and the participant will continue to be followed for safety for the duration of this trial. Efforts will be made to follow all pregnancies reported during the course of this trial to pregnancy outcome pending the participant's permission.

Male participants will be asked if their female partner has become pregnant during the study and any pregnancy will be reported. The outcome of pregnancy in the female partner of male participant will be handled through contact with the male participant.

## 8.4 Type and Duration of Follow-up of Participants After Adverse Events

AEs/SAEs will be collected, assessed, and followed through resolution from the time of study product administration through approximately 3 months after receipt of study product.

Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the appropriate DCF.

## 8.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

The site PI or appropriate sub-investigator is responsible for recording all AE/SAEs that are observed or reported during this trial, regardless of the relationship to study product. AE/SAEs, abnormal laboratory test values, or abnormal clinical findings will be collected, assessed, documented, reported, and followed appropriately, using a local laboratory as necessary. Participants with elevated aminotransferase and/or bilirubin will be asked about recent seizures and mental health status change. In determining eligibility, refer to Section 5.1 and the protocol-specific MOP.

Clinical and safety laboratory results will be graded for severity according to the CTCAE Version 5.0, November 2017 (see Section 8.1.1.1).

## 8.6 Halting Rules

### 8.6.1 Study Halting Criteria

The study will be immediately suspended, and no additional doses administered if any of the following occurs:

- Any death occurring during the study that was not the result of trauma or accident.
- Two or more participants experience an SAE, related to the study product.
- Three or more participants in each part of the trial (A or B) develop a severe, Grade 3 or higher, AE, systemic or laboratory, in the same MedDRA Low Level Term (LLT), assessed as related to the study product.

If any halting criterion is met, the study will be suspended, and a SMC *ad hoc* meeting will convene. The study will not be re-started until the SMC meets and provides its recommendation to DMID, the study sponsor.

## 8.7 Safety Oversight

### 8.7.1 Safety Monitoring Committee (SMC)

This study will utilize a SMC, which is an independent group of experts that advises DMID. The primary responsibility of the SMC is to monitor participant safety. The SMC is external to DMID and is composed of at least 3 voting members. The SMC will consist of members with appropriate Phase 1 study expertise to contribute to the interpretation of the data from this trial. Its activities will be delineated in a SMC charter that will describe the membership, responsibilities, and the scope and frequency of data reviews. The SMC will operate on a conflict-free basis independently of the study team. The DMID or the SMC may convene *ad hoc* meetings of the SMC according to protocol criteria or if there are concerns that arise during the study.

The SMC will review the safety data at the following milestones:

- Organizational meeting (prior to start of the study).
- After 6 participants in Group 2 (severe renal impairment and ESRD, not on dialysis) and their matching controls are enrolled and complete follow-up through Day 12 (Visit 02). This review will be completed prior to determining if Part B will be conducted and opening enrollment for Groups 3 and 4 and their matched healthy control participants.
- An *ad hoc* SMC meeting will be convened when a halting rule is met, or at the request of the investigator and/or DMID if there are safety concerns during the course of the study.
- Final Data Review Meeting: Approximately 6 to 8 months after final clinical database lock to review the cumulative unblinded safety data for this trial. The data will be provided in a standard summary format. The SMC may be asked to provide recommendations in response to questions posed by DMID.
- The DMID Medical Monitor is empowered to stop study enrollment if AEs that meet the halting criteria are reported or if any serious safety concerns arise. The DMID Medical Monitor will be responsible for reviewing SAEs in real time. The SMC will review SAEs on a regular basis and *ad hoc* during the study.

# 9 HUMAN PARTICIPANT PROTECTION

## 9.1 Institutional Review Board

The site PI will obtain IRB approval for this protocol to be conducted at his/her research site(s) and send supporting documentation to the DMID before initiating recruitment of participants. The investigator will submit applicable information to the IRB on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6 Good Clinical Practice (GCP), and as applicable, 21 CFR 56 (IRB) and 21 CFR 50 (Protection of Human Participants), other federal, state, and local regulations. The IRB must be registered with the Office for Human Research Protections (OHRP) as applicable to the research. DMID must receive the documentation that verifies IRB approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the participants, prior to recruitment and enrollment of participants.

Any amendments to the protocol or consent materials will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the enrollment and follow-up of participants and may cease if annual review is no longer required by applicable regulations. The investigator will notify the IRB of deviations from the protocol and reportable SAEs, as applicable to the IRB policy.

Each institution engaged in this research will hold a current Federal Wide Assurance (FWA) issued by the OHRP for federally funded research.

The IRB/IEC will determine that adequate provisions are made for soliciting the permission of each participant.

## 9.2 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained from the participant and documented. Participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written ICF. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

An investigator or designee will describe the protocol to potential participants face-to-face. The key information about the purpose of the study, the procedures, and experimental aspects of the study, risks and discomforts, any expected benefits to the participant, and alternative treatment will be presented first to the participant.

Participants will also receive an explanation that the trial involves research, and a detailed summary of the proposed study procedures and study interventions/products. This will include aspects of the trial that are experimental, the probability for random assignment to treatment groups, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the participant or to the unborn child, if the participant is or may become pregnant, that are currently unforeseeable), the expected duration of the participant's participation in the trial, alternative procedures that may be available and the important potential benefits and risks of these available alternative procedures.

Participants will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. Participants will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Participants will be informed of the anticipated financial expenses, if any, to the participant for participating in the trial, as well as any anticipated prorated payments, if any, to the participant for participating in the trial. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project.

Information will also include the foreseeable circumstances and/or reasons under which the participant's participation in the trial may be terminated. The participants will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the participant is otherwise entitled.

The extent of the confidentiality of the participants' records will be defined, and participants will be informed that applicable data protection legislation will be followed. Participants will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations, and that, by signing a written ICF, the participant is authorizing such access.

Participants will be informed that records identifying the participant will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the participant's identity will remain confidential. Participants will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Participants will be allowed sufficient time to consider participation in this research trial and have the opportunity to discuss this trial with their family, friends, or legally authorized representative, or think about it prior to agreeing to participate.

ICFs will be IRB-approved, and participants will be asked to read and review the consent form. Participants must sign the ICF prior to starting any study procedures being done specifically for this trial.

Once signed, a copy of the ICF will be given to the participant(s) for their records. The participant(s) may withdraw consent at any time throughout the course of the trial. The rights and welfare of the participant(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Study personnel may employ recruitment efforts prior to obtaining study consent if a patient-specific screening consent is on record or if the IRB has agreed that chart review is allowed without a fully executed screening consent. In cases where there is not a patient-specific screening consent on record, site staff may pre-screen via chart review and refer potential participants to the Research staff. Research staff would obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

New information will be communicated by the site PI to participants who consent to participate in this trial in accordance with IRB requirements. The ICF will be updated, and participants will be re-consented per IRB requirements, if necessary. Participants will be given a copy of all ICFs that they sign.

## 9.3 Special Populations

This trial will be inclusive of participants age 18-85 years of age who meet the participant inclusion criteria (see Section 5.1.1) and do not meet any of the participant exclusion criteria (see Section 5.1.2), regardless of religion, sex, or ethnic background. CKD is mostly seen in adults, and participants enrolled in the control arms must meet certain criteria to match the CKD participants. Therefore, no one under the age of 18 years will be enrolled in this study. Should the outcome of this trial be deemed acceptable, additional trials may be initiated, including those in other populations.

## 9.4 Participant Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, participant's clinical information, and all other information generated during participation in the study.

No information concerning the study, or the data generated from the study, will be released to any unauthorized third party without prior written approval of the DMID and the participant. Participant confidentiality will be maintained when study results are published or discussed at conferences.

The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. All records will be kept locked, and all computer entry and networking programs will be carried out with coded

numbers only and with password-protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

## 9.5 Certificate of Confidentiality

As this research is funded by the National Institutes of Health (NIH), it is covered by NIH policy which effectively issues the research a Certificate of Confidentiality. By this policy, researchers cannot be forced to disclose or provide, in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains.

The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally funded projects, like this trial, or for information that must be released to meet the requirements of the Federal FDA.

A Certificate of Confidentiality does not prevent the participant from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not cover matters that must be legally reported, including child and elder abuse, sexual abuse, wanting to harm themselves or others, and certain infectious diseases that meet the criteria for reporting. In these cases, researchers may report information that would identify a participant without the participant's consent.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, or for the purposes of other research that the release complies with the applicable Federal regulations governing the protection of human participants in research.

## 9.6 Costs, Participant Compensation, and Research Related Injuries

There is no cost to participants for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the participant, participant's insurance or third party. Participants may be compensated for their participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and participant to IRB approval.

If it is determined by the site PI that an injury occurred to a participant as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the participant. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site. No financial

compensation will be provided to the participant by the NIAID, NIH to the participant, or by the participating site for any injury suffered due to participation in this trial.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Study Hypotheses

FDA guidance document suggests using a reduced PK design for drugs that are predominantly metabolized or secreted in the bile [38]. In a reduced PK study design, the trial compares PK in patients with normal renal function and to patients with severe renal impairment and patients with ESRD not yet on dialysis. If the reduced PK study shows at least a 50% increase in AUC in patients with severe renal impairment and patients with ESRD not yet on dialysis relative to the matched healthy controls, a "full" renal impairment study in patients with all intermediate levels of renal function impairment should be conducted [38]. Otherwise, no further study is recommended.

In the current study, Part A is considered the reduced PK study in which the geometric mean ratio of AUC ($AUC_{last}$ and area under the plasma concentration-time curve from time zero to infinity [$AUC_{\infty}$]) will be determined comparing Group 2 participants (Severe renal impairment and ESRD, not on dialysis) to matched Group 1A participants (healthy participants with normal GFR). The ratio of geometric mean AUCs and 90% confidence interval (CI) of the parent compound will be considered in determining whether to continue with a full renal impairment study (enrollment of subsequent cohorts in Part B). Interim PK data of the parent compound will be reviewed by some members of the study team from DMID and TB Alliance before decision is made to proceed to Part B. For further details, please refer to the PK Manual.

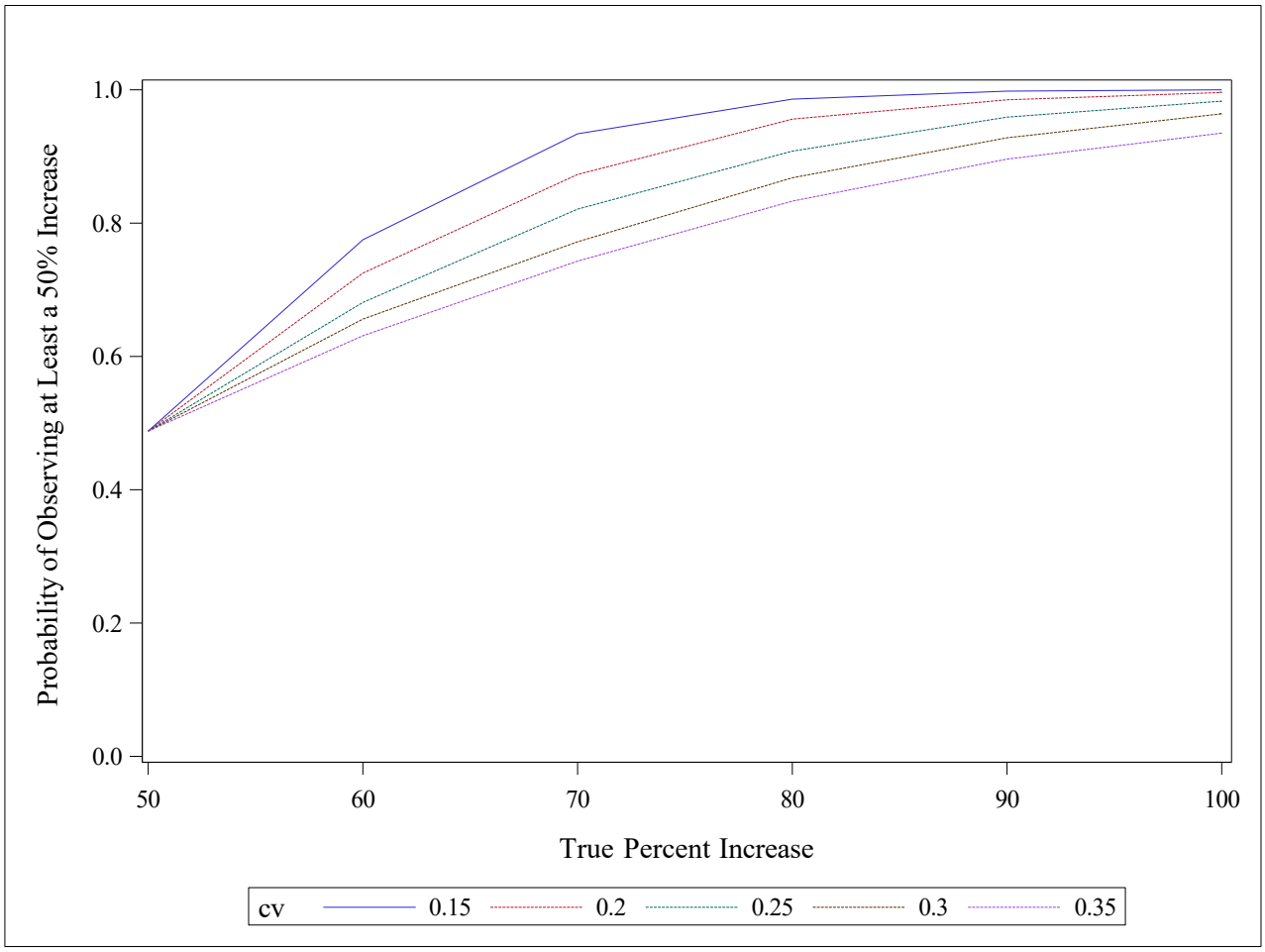
In Part B, the primary intent will be to estimate PK parameters of the parent compound and metabolites and model the relationship between measures of renal function and the PK parameters to determine whether dosage adjustment is required for patients with impaired renal function. Estimates and CIs will be utilized rather than formal hypothesis tests.

No formal hypothesis tests are planned for safety analyses, but safety data will be collected and analyzed.

## 10.2 Sample Size Considerations

A sample size of 6 per group is standard for renal impairment PK studies. Prior studies of pretomanid (PA-824) with similar dosing (200 to 250 mg) have estimated coefficients of variation (CV) of 16% to 33% for the AUC after a single dose in healthy adult participants. Assuming a 20% CV for the AUC of both groups, the probability of observing at least a 50% increase in the geometric mean ratio of AUCs given a true 100% increase is >99%. Figure 3 shows the probability of observing at least a 50% increase in the geometric mean ratio for other potential scenarios. The probability of the lower bound of the 90% CI for the geometric mean ratio of AUCs being at least 1.5 in this scenario is approximately 70%.

**Figure 3: Probability of Observing at Least 50% Increase by Varying CV and True Percent Increase**




CV=coefficients of variation

The sample size per arm in Part B was chosen based on feasibility and appropriateness for a PK study in renal impaired participants to estimate group differences in PK parameters with adequate precision. Assuming an observed 2-fold difference between each renal impairment group and matched controls with no correlation between matched pairs and a coefficient of variation of 20%, a 90% CI for the fold difference between groups is (1.70, 2.35).

## 10.3 Treatment Assignment Procedures

### 10.3.1 Randomization Procedures

There will be no randomization performed for this study. Participants will be assigned to study groups based on eGFR.

### 10.3.2 Masking Procedures

Not applicable. This is an open-label study.

## 10.4 Planned Interim Analyses

### 10.4.1 Interim Safety and PK Review

A study team and SMC safety and PK review will occur after Part A 6 participants in Group 2 (severe renal impairment and ESRD, not on dialysis) and Group 1A their matched controls are enrolled and completed follow-up through Day 12 (Visit 02). This review will decide if Part B will be conducted and whether enrollment for Group 3 (eGFR 60-89), and Group 4 (eGFR 30-59) will occur. The interim safety and PK review will present data by group, including AEs, SAEs, clinical laboratory tests, vital signs, and 12-lead ECG, and PK analysis of pretomanid. Cumulative data for all participants enrolled will be included in the safety and PK reviews.

## 10.5 Final Analysis Plan

### 10.5.1 Analysis Populations

The following sections define the analysis populations for the analysis and reporting of data.

#### 10.5.1.1 Safety Analysis Population

The safety analysis population will include all participants who received study product.

#### 10.5.1.2 PK Analysis Population

The PK analysis population will consist of participants who received pretomanid and provided sufficient bioanalytical assessment results to calculate reliable estimates of the PK parameters. Any participants or data values excluded from PK analyses will be identified, along with their reason for exclusion, in the clinical study report.

### 10.5.2 Analysis of Primary Endpoint (PK for Pretomanid)

All PK parameters will be estimated through a non-compartmental analysis using a validated installation of Phoenix WinNonlin (Certara, Princeton, NJ) version 8.0 or later. The recorded true time points will be used for PK calculation. Estimated total plasma PK parameters are listed below.

**Plasma PK of Pretomanid**

The plasma PK of a single dose of pretomanid will be assessed from serial blood samples collected up to 1 hour pre-dose (Day 1) and at multiple time points post dosing: 1, 2, 4, 5, 6, 8, 12, 16, 24, 36,

48, 72, and 96 hours. The primary outcome measure will be total plasma concentration of pretomanid. The following PK parameters will be determined using total pretomanid concentrations:

$C_{max}$: Maximum plasma concentration

$T_{max}$ : Time to peak (maximum) plasma concentration

$AUC_{last}$: Area under the plasma concentration-time curve from time zero to time of last measurable concentration

$AUC_{\infty}$: Area under the plasma concentration-time curve from time zero to infinity

$\%AUC_{ex}$: Percentage of $AUC_{\infty}$ obtained by extrapolation

$t_{1/2}$ : Terminal-phase elimination half-life

$\lambda_z$: Apparent first-order terminal elimination rate constant

CL/F: Apparent clearance

$V_d$/F: Apparent volume of distribution

**Urine PK of Pretomanid**

The urine PK of a single dose of pretomanid will be assessed from urine collected up to 1 hour pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hours post-dose. Volume of urine will be measured and recorded at each of these time intervals. Urine samples will be stored at room temperature and then frozen at -20°C within 24 hours. Urine will be stored in ≤100 mL aliquots at -20°C until shipped to Fisher Bioservices for storage.

$Ae_{(0-t)}$: Cumulative amount excreted into the urine from time 0 to the time t

Ae%Dose: Fraction of dose excreted into the urine

$CL_R$: Renal clearance

Details of the statistical analysis will be included in the statistical analysis plan.

### 10.5.3 Analysis of Secondary Endpoint (Safety)

All safety analyses will be presented using the safety analysis set. No formal hypothesis testing will be conducted.

#### 10.5.3.1 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities® (MedDRA). All AEs that occur after the receipt of study product will be summarized using the number of events as well as the number and percent of participants experiencing the event. Summaries will be presented by renally impaired and non-renally impaired groups and MedDRA level hierarchy (system organ class [SOC] and preferred term) as follows:

- Overall (i.e., regardless of severity or relationship to treatment)

- By severity grade (mild, moderate, severe, or life-threatening)
- By relationship to study product

Unless otherwise specified, at each level of participant summarization in reporting incidence of AEs, a participant will be counted only once even if the participant reported one or more events. If more than one occurrence of an event is reported, the event of the worst severity or the worst-case relationship assessment will be summarized.

The number of SAEs is expected to be small, as such these events will be reported in detailed listings showing the event description, MedDRA preferred term and SOC, event date, severity, relatedness, and outcome for each event.

#### 10.5.3.2 Laboratory Parameters

Descriptive summary statistics for laboratory data at admission, Day 12, and change from baseline will be presented by renal impairment and non-renally impaired control groups. For change from baseline summaries, participants with an undefined change from admission, because of missing data, will be excluded. Graphs, showing individual participant changes from admission to Day 12 will be presented for each laboratory parameter, by renal impairment and non-renally impaired groups. Participants with clinically significant outliers will be identified in listings.

#### 10.5.3.3 Vital Signs

Descriptive summary statistics of vital signs at Day 1 pre-dose and each post-dose time point (both absolute and change) will be summarized by renal impairment group and non-renally impaired control group. For change from pre-dose summaries, participants with an undefined change from pre-dose, because of missing data, will be excluded.

#### 10.5.3.4 ECG Data

ECG intervals (QTcF), including change from baseline, will be summarized at the Screening Visit 00A and Visit 01N using descriptive statistics.

#### 10.5.3.5 Demographics and Screening Summaries

Demographic variables (age, gender, race, and ethnicity) and screening characteristics (height, weight) will be summarized by renally impaired and non-renally impaired groups. The comparability of the groups for relevant demographic and screening characteristics will be assessed by descriptive statistics and/or graphs. No statistical hypothesis tests will be performed. For continuous data, summaries will include the number of observations, mean, standard deviation, median, $25^{th}$ and $75^{th}$ quartiles, minimum and maximum values. For categorical data, frequency counts and percentages will be reported. Of note, weight will be measured at specified subsequent visits and therefore will be summarized for all available post-dose visits, in addition to screening.

### 10.5.4 Analysis of Secondary Endpoint (PK for M19 and M50)

$AUC_{last,}$ and any other parameters considered to be of interest, of the pretomanid representative metabolites M19 and M50 in plasma will be estimated.

Excretion in urine of metabolites M19 and M50 will be estimated.

# 11 ELECTRONIC CASE REPORT FORMS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical trial records for the purposes of quality assurance reviews, audits, evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents.

Source data are 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 data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Study data will be collected on paper DCFs and entered into the eCRF, or data will be entered into the eCRF from electronic source documents. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

# 12 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, each participating site is responsible for conducting routine quality assurance and quality control (QC) activities to internally monitor study progress and protocol compliance. The site PI will provide direct access to all study-related sites, source data/DCFs, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site PI will ensure all study personnel are appropriately trained and training documentation is current and maintained on site.

The SDCC will implement QC procedures beginning with the data entry system and generate data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating sites for clarification and resolution.

# 13 DATA HANDLING AND RECORD KEEPING

## 13.1 Data Management Responsibilities

The investigator is responsible to keep a complete medical history and ensure the accuracy, completeness, legibility, and timeliness of the data reported. Section 11 details source data collection formats. Site staff will be trained on the use of the data system and error correction procedures. The site will include on the Delegation of Authority log personnel trained and authorized to enter original source data.

The sponsor and/or its designee will provide guidance to the site PI and other study personnel on making corrections to any DCFs and eCRFs.

## 13.2 Data Coordinating Center/Biostatistician Responsibilities

Data collection is the responsibility of the study personnel at each participating clinical site under the supervision of the site PI. During this trial, the site PI must maintain complete and accurate documentation for the study.

The Data Coordinating Center (DCC) for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

## 13.3 Data Capture Methods

Clinical data (including, but not limited to, AEs/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values) will be collected on DCFs by study personnel then entered into the corresponding eCRFs via a 21 CFR 11-compliant Internet Data Entry System provided by the SDCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

## 13.4 Types of Data

Data for this trial will include safety and outcome measures (e.g., clinical and PK data).

## 13.5 Study Records Retention

Study records and reports including, but not limited to, DCFs, source documents, ICFs, laboratory test results, and study product disposition records will be retained for a minimum of 2 years after a marketing application is approved for the study product for which it is being investigated; or, if no application is to be filed or if the application is not approved for the study product, until 2 years after the investigation is discontinued and FDA has been notified. These documents will be retained for a

longer period, however, if required by local regulations. ICFs for future use will be maintained as long as the sample/specimen exists.

No records will be destroyed without written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. The participating sites must contact DMID for authorization prior to the destruction of any study records.

# 14 CLINICAL MONITORING

Site monitoring is conducted to ensure that the human participants' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP, and applicable sponsor standard operating procedures. DMID, the sponsoring agency, or its designee will conduct site monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, ICFs, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site PIs to discuss any problems and actions to be taken and document visit findings and discussions.

# 15 PUBLICATION POLICY

This trial will be conducted in accordance with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/) upon acceptance for publication.

*Refer to:*

- NIH Public Access Policy, http://publicaccess.nih.gov/
- NIH Office of Extramural Research (OER) Grants and Funding, http://grants.nih.gov/grants/oer.htm

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first participant. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClincialTrials.gov.

For this trial the responsible party is DMID which will register the trial and post results.

The responsible party plans not to request certification of delayed posting.

*Refer to:*

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42CFR11
- NIH NOT-OD-16-149

# 16 LITERATURE REFERENCES

1. World Health Organization, *Global Tuberculosis report.* 2020.
2. Rodrigues, L.C., V.K. Diwan, and J.G. Wheeler, *Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis.* Int J Epidemiol, 1993. **22**(6): p. 1154-8.
3. Colditz, G.A., et al., *Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature.* JAMA, 1994. **271**(9): p. 698-702.
4. ATS, C., IDSA, *Treatment of tuberculosis.* MMWR Recommendations and Reports 2003. **52 (RR-11)**: p. 1-77.
5. *Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society.* MMWR Recomm Rep, 2000. **49**(RR-6): p. 1-51.
6. Center for Disease, C.P., *Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection.* MMWR Morb Mortal Wkly Rep, 2011. **60**(48): p. 1650-3.
7. Organization, W.H., *Global Tuberculosis Report 2014.* 2014.
8. Pietersen, E., et al., *Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study.* Lancet, 2014. **383**(9924): p. 1230-9.
9. Jha, V., et al., *Chronic kidney disease: global dimension and perspectives.* Lancet, 2013. **382**(9888): p. 260-72.
10. Kurts, C., et al., *The immune system and kidney disease: basic concepts and clinical implications.* Nat Rev Immunol, 2013. **13**(10): p. 738-53.
11. Romanowski, K., et al., *Tuberculosis and chronic kidney disease: an emerging global syndemic.* Kidney Int, 2016. **90**(1): p. 34-40.
12. Zuo, L., M. Wang, and A. Chinese Association of Blood Purification Management of Chinese Hospital, *Current burden and probable increasing incidence of ESRD in China.* Clin Nephrol, 2010. **74 Suppl 1**: p. S20-2.
13. Carrero, J.J. and P. Stenvinkel, *Inflammation in end-stage renal disease--what have we learned in 10 years?* Semin Dial, 2010. **23**(5): p. 498-509.
14. Nahid, P., et al., *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis.* Clin Infect Dis, 2016. **63**(7): p. e147-e195.
15. Alsultan, A. and C.A. Peloquin, *Therapeutic drug monitoring in the treatment of tuberculosis: an update.* Drugs, 2014. **74**(8): p. 839-54.
16. Launay-Vacher, V., H. Izzedine, and G. Deray, *Pharmacokinetic considerations in the treatment of tuberculosis in patients with renal failure.* Clin Pharmacokinet, 2005. **44**(3): p. 221-35.
17. Baghaei, P., et al., *Impact of chronic renal failure on anti-tuberculosis treatment outcomes.* Int J Tuberc Lung Dis, 2014. **18**(3): p. 352-6.
18. Global Alliance for TB Drug Development, *Investigator's Brochure: PA-824 (Pretomanid), v22.* 31 January 2023.
19. *Pa-824.* Tuberculosis (Edinb), 2008. **88**(2): p. 134-6.
20. Stover, C.K., et al., *A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis.* Nature, 2000. **405**(6789): p. 962-6.
21. Manjunatha, U., H.I. Boshoff, and C.E. Barry, *The mechanism of action of PA-824: Novel insights from transcriptional profiling.* Commun Integr Biol, 2009. **2**(3): p. 215-8.

22. Singh, R., et al., *PA-824 kills nonreplicating Mycobacterium tuberculosis by intracellular NO release.* Science, 2008. **322**(5906): p. 1392-5.
23. Diacon, A.H., et al., *Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients.* Antimicrob Agents Chemother, 2010. **54**(8): p. 3402-7.
24. Tasneen, R., et al., *Sterilizing activity of novel TMC207- and PA-824-containing regimens in a murine model of tuberculosis.* Antimicrob Agents Chemother, 2011. **55**(12): p. 5485-92.
25. Tyagi, S., et al., *Bactericidal activity of the nitroimidazopyran PA-824 in a murine model of tuberculosis.* Antimicrob Agents Chemother, 2005. **49**(6): p. 2289-93.
26. Lenaerts, A.J., et al., *Preclinical testing of the nitroimidazopyran PA-824 for activity against Mycobacterium tuberculosis in a series of in vitro and in vivo models.* Antimicrob Agents Chemother, 2005. **49**(6): p. 2294-301.
27. Ahmad, Z., et al., *PA-824 exhibits time-dependent activity in a murine model of tuberculosis.* Antimicrob Agents Chemother, 2011. **55**(1): p. 239-45.
28. Tasneen, R., et al., *Contribution of Oxazolidinones to the Efficacy of Novel Regimens Containing Bedaquiline and Pretomanid in a Mouse Model of Tuberculosis.* Antimicrob Agents Chemother, 2016. **60**(1): p. 270-7.
29. Diacon, A.H., et al., *Phase II dose-ranging trial of the early bactericidal activity of PA-824.* Antimicrob Agents Chemother, 2012. **56**(6): p. 3027-31.
30. Diacon, A.H., et al., *14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial.* Lancet, 2012. **380**(9846): p. 986-93.
31. Dawson, R., et al., *Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis.* Lancet, 2015. **385**(9979): p. 1738-1747.
32. Diacon, A.H., et al., *Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline.* Am J Respir Crit Care Med, 2015. **191**(8): p. 943-53.
33. Conradie, F., et al., *Treatment of Highly Drug-Resistant Pulmonary Tuberculosis.* N Engl J Med, 2020. **382**(10): p. 893-902.
34. TB Alliance, *PA-824 has a New Generic Name: Pretomanid.* 2014.
35. Dooley, K.E., et al., *Phase I safety, pharmacokinetics, and pharmacogenetics study of the antituberculosis drug PA-824 with concomitant lopinavir-ritonavir, efavirenz, or rifampin.* Antimicrob Agents Chemother, 2014. **58**(9): p. 5245-52.
36. Dogra, M., et al., *Comparative bioactivation of the novel anti-tuberculosis agent PA-824 in Mycobacteria and a subcellular fraction of human liver.* Br J Pharmacol, 2011. **162**(1): p. 226-36.
37. Strunk, A.K., et al., *Single- and multiple-dose pharmacokinetics of ethambutol and rifampicin in a tuberculosis patient with acute respiratory distress syndrome undergoing extended daily dialysis and ECMO treatment.* Int J Infect Dis, 2016. **42**: p. 1-3.
38. Center for Drug Evaluation and Research, *Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing*, U.S. Department of Health and Human Services, Editor. 2020, Food and Drug Administration
39. Matzke, G.R., et al., *Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO).* Kidney Int, 2011. **80**(11): p. 1122-37.

40. Center for Drug Evaluation and Research, *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry*, U.S. Department of Health and Human Services, Editor. 2019, Food and Drug Administration,.
41. Center for Drug Evaluation and Research, *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry*, US Department of Health and Human Services, Editor. 2020, Food and Drug Administration,.
42. FDA. *Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers*. 06/05/2023 [cited 2023; Available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

# 17 APPENDICES

# APPENDIX A: Schedule of Study Procedures and Evaluations

| Study Visit | 00A | 00B | 00C | 01A | 01B | 01C | 01D | 01E | 01F | 01G | 01H | 01I | 01J | 01K | 01L | 01M | 01N | 02[1] | 03 | Early Term |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Screen -28 to -7** | | **Admit -1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **2** | **3** | **4** | **5** | **12 ± 2d** | **85 +7d** | |
| **PK Time Window** | | | | Up to 1 hour Pre-dose[8] | 1 hr ( ± 10 min) | 2 hr ( ± 10 min) | 4 hr ( ± 10 min) | 5 hr ( ± 10 min) | 6 hr ( ± 10 min) | 8 hr ( ± 10 min) | 12 hr ( ± 10 min) | 16 hr ( ± 10 min) | 24 hrs ( ± 1hr) | 36 hrs ( ± 1hr) | 48 hrs ( ± 1hr) | 72 hrs ( ± 4hrs) | 96 hr ( ± 4hrs) | | | |
| **Obtain Written Informed Consent** | X | | | | | | | | | | | | | | | | | | | |
| **Verify Eligibility** | X | | X | X | | | | | | | | | | | | | | | | |
| **Reconfirm participant's willingness to participate** | | X | X | | | | | | | | | | | | | | | | | |
| **Medical History** | X | | X | X | | | | | | | | | | | | X | X | X | | X |
| **Concomitant Medications** | X | | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X | X | X | | X |
| **12-Lead ECG** | X | | | | | | | | | | | | | | | | X | | | |
| **Vital Signs (Oral Temp, Sitting Pulse and BP)[3]** | X | | | X | | | | | | | X | | X | | X | X | X | X | | X |
| **Physical Examination** | X | | | | | | | | | | | | | | | | | | | |
| **Targeted PE if needed** | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| **Height and Weight** | X | | | | | | | | | | | | | | | | | | | |
| **Urine Pregnancy Test[4]** | | X | X | X | | | | | | | | | | | | | | X | | X |
| **Placement of Peripheral Catheter (if applicable)** | | | X[5] | X[5] | | | | | | | | | | | | | | | | |
| **HIV, HBsAg, HCV** | X | | | | | | | | | | | | | | | | | | | |
| **Safety and Basic Lab Testing[6]** | X | | | | | | | | | | | | | | | | X | X | | X |

| Study Visit | 00A | 00B | 00C | 01A | 01B | 01C | 01D | 01E | 01F | 01G | 01H | 01I | 01J | 01K | 01L | 01M | 01N | 02[1] | 03 | Early Term |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Screen -28 to -7** | | **Admit -1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **2** | **3** | **4** | **5** | **12 ± 2d** | **85 +7d** | |
| **PK Time Window** | | | | Up to 1 hour Pre-dose[8] | 1 hr ( ± 10 min) | 2 hr ( ± 10 min) | 4 hr ( ± 10 min) | 5 hr ( ± 10 min) | 6 hr ( ± 10 min) | 8 hr ( ± 10 min) | 12 hr ( ± 10 min) | 16 hr ( ± 10 min) | 24 hrs ( ± 1hr) | 36 hrs ( ± 1hr) | 48 hrs ( ± 1hr) | 72 hrs ( ± 4hrs) | 96 hr ( ± 4hrs) | | | |
| **Urine Drug Screen and Alcohol screening** | | X | X | | | | | | | | | | | | | | | | | |
| **In-house Confinement** | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| **Study Product Administration[7]** | | | | X | | | | | | | | | | | | | | | | |
| **Blood for PK** | | | | X[8] | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| **Urine collection for PK and volume measurement[9]** | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| **Discharge from Hospital[12]** | | | | | | | | | | | | | | | X | | | | | |
| **Remove Intravenous Catheter (if applicable)** | | | | | | | | | | | | | | | X | | | | | |
| **Targeted Review of Systems for Renal Participants** | | | | | | | | | | | | | | | | | | | | X |
| **AE/SAE Assessment** | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[10] | X |
| **Pregnancy Assessment** | | | | | | | | | | | | | | | | | | | X | |
| **Phone Call** | | | | | | | | | | | | | | | | | | | X | |

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PE=physical examination; PK=pharmacokinetic; SAE=serious adverse event

1 Study visits 01M-02 may be outpatient at the site.

2 Concomitant medications will be recorded during the entire hospital stay.

3 Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.

4 Must be performed on all female participants of childbearing potential prior to receipt of each study product and results must be negative and known prior to receipt of study product.

5 Can be done at Visit 00C or Visit 01A if applicable. The catheter should be removed after the 36-hour time point.

[6] Hemoglobin, AST, ALT, total bilirubin, BUN, serum creatinine (includes eGFR), serum potassium and magnesium will be checked.

[7] The study product will be administered orally under direct supervision with a high-fat, high-calorie meal and 240 mL water. A mouth check will be done. Food, liquids, and medication will be restricted for 2 hours post doses. Study participants should eat this meal in 30 ± 10 minutes or less; however, pretomanid should be administered 30 ± 10 minutes after start of the meal.

[8] Blood can be drawn up to 1 hour prior to dosing.

[9] The urine PK will be assessed up to 1 hour pre-dose and at 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hours post-dosing. PK urine sample collection during the 48-72 hours and 72-96 hours may be performed at home (i.e., Day 4 and Day 5).

[10] SAEs only from study drug administration to Day 85 + 7 days.

[11] Alcohol testing can be done on blood or breath if breathalyzer is used for alcohol testing.

[12] Participants may remain in the hospital per site decision.

# APPENDIX B: Venipuncture Volumes (mL)

| Study Visit | 00A | 00B | 00C | 01A | 01B | 01C | 01D | 01E | 01F | 01G | 01H | 01I | 01J | 01K | 01L | 01M | 01N | 02 | 03 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Screen -28 to -7** | | **Admit -1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **2** | **3** | **4** | **5** | **12 ± 2d** | **85+7 d** |
| **PK Time Window** | | | | Up to 1 hour Pre-dose | 1 hr ( ± 10 min) | 2 hr ( ± 10 min) | 4 hr ( ± 10 min) | 5 hr ( ± 10 min) | 6 hr ( ± 10 min) | 8 hr ( ± 10 min) | 12 hr ( ± 10 min) | 16 hr ( ± 10 min) | 24 hrs ( ± 1 hr) | 36 hrs ( ± 1 hr) | 48 hrs ( ± 1 hrs) | 72 hrs ( ± 4 hrs) | 96 hrs ( ± 4 hrs) | | |
| **HIV, HBsAg, HCV** | 12 | | | | | | | | | | | | | | | | | | |
| **Blood for Safety** | 10 | | | | | | | | | | | | | | | | 10 | 10 | |
| **Blood to Screen for Alcohol[1]** | | 6 | 6 | | | | | | | | | | | | | | | | |
| **Blood for PK** | | | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | | |
| **Total** | 22 | 6 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 10 | 0 |
| **Cumulative Total (Cumulative total plus next total)** | 22 | 28 | 34 | 38 | 42 | 46 | 50 | 54 | 58 | 62 | 66 | 70 | 74 | 78 | 82 | 86 | 90 | 100 | 100 |

HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic

[1] Alcohol testing can be done on blood or breath if breathalyzer is used for alcohol testing.