A Phase I, Single Dose, Open-label Study Comparing the Pharmacokinetics and Safety of Pretomanid in Subjects with Mild, Moderate, and Severe Hepatic Impairment to Matched, Non-Hepatically Impaired Subjects

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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 subjects 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 subject 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 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- 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 assurance 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 US federal regulations and ICH E6 Good Clinical Practice (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 subjects.

Site Investigator Signature:

Signed: _____ Date: _____

Name

Title

Site Investigator Signature:

Signed: _____ Date: _____

Name

Title

TABLE OF CONTENTS

STATEMENT OF ASSURANCE 2
STATEMENT OF COMPLIANCE 3
SIGNATURE PAGE 4
TABLE OF CONTENTS 5
LIST OF TABLES 11
LIST OF FIGURES 12
LIST OF ABBREVIATIONS 13
PROTOCOL SUMMARY 17
Table 1: Study Groups 20
1 KEY ROLES 21
2 BACKGROUND AND SCIENTIFIC RATIONALE 22
2.1 Background 22
2.1.1 Tuberculosis 22
2.1.1.1 Mechanism of action 23
2.1.1.2 In Vitro Microbiological Activity 23
2.1.1.3 Pharmacology and toxicology 23
2.1.1.4 Clinical Pharmacology and Biopharmaceutics 24
2.1.1.4.1 In vitro 24
2.1.1.4.2 In vivo 24
2.1.1.5 Efficacy studies 25
Table 2: Summary of 4 Pretomanid Phase 2 studies 27
Table 3: Mean log CFU for Pretomanid in the 5th Phase 2 multidrug trial (NC-003) 29
2.1.2 Summary of safety 29
2.2 Scientific Rationale 30
2.2.1 Purpose of Study 30
2.2.2 Study Population 30

2.3 Potential Risks and Benefits 31
2.3.1 Potential Risks 31
2.3.2 Known Potential Benefits 37
3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES 38
3.1 Study Design Description 38
Table 4: Study Groups 39
3.2 Study Objectives 40
3.2.1 Primary 40
3.2.2 Secondary 40
3.3 Study Endpoints or Outcome Measures 40
3.3.1 Primary 40
3.3.2 Secondary 41
4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT 42
4.1 Study Product Description 42
4.1.1 Acquisition 42
4.2 Formulation, Packaging, and Labeling 42
Table 5: Pretomanid Formulation 42
4.2.1 Product Storage and Stability 43
4.3 Acquisition/Distribution 43
4.4 Dosage/Regimen, Preparation, Dispensing and Administration of Study Intervention/Investigational Product 43
4.5 Pre-determined Modification of Study Intervention/Investigational Product for an Individual Subject 44
4.6 Accountability Procedures for the Study Intervention/Investigational Product(s) 44
4.7 Assessment of Subject Compliance with Study Intervention/Investigational Product 45
4.8 Concomitant Medications/Treatments 45
Table 6: Prohibited CYP450 Enzyme Altering Medications/Substances per Subject Exclusion Criteria 46

5 STUDY ENROLLMENT AND WITHDRAWAL 47
5.1 Eligibility Criteria 47
5.1.1 Subject Inclusion Criteria 47
5.1.2 Subject Exclusion Criteria 49
5.2 Withdrawal from the Study, Discontinuation of Study Product, or Study Termination 53
5.2.1 Reasons for Withdrawal 53
5.2.2 Handling of Withdrawals 54
5.2.3 Study Termination 55
6 STUDY SCHEDULE 56
6.1 Screening (Visit 00A) (Day -22 to Day -2) 56
6.2 Admission (Visit 00B) (Day -1) 57
6.3 Planned Study Visits 58
6.3.1 Dosing (Visit 01) (Day 1) and Confinement/Hospitalization (Visit 01A to Visit 01J) (Day 1 and Day 2) 58
6.3.2 Follow-up (Visits 02, 03, and 04) (Day 3, Day 4, and Day 5) 59
6.3.3 Final Study Visit (Visit 05) (Day 12) 60
6.3.4 Early Termination Visit 61
6.4 Unscheduled Study Visits 61
6.5 Protocol Deviations 62
7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS 63
7.1 Clinical Evaluations 63
7.1.1 Assessment of Subject Compliance with Study Intervention/Investigational Product 64
7.2 Laboratory Evaluations 64
7.2.1 Clinical Laboratory Evaluations 64
7.2.2 Special Assays or Procedures 65
7.2.2.1 ECG 65
7.2.2.2 PK Samples 66

7.2.2.3 Specimen Preparation, Handling, and Shipping 66
7.2.2.1 Instructions for Specimen Preparation, Handling, and Storage....66
7.2.2.2 Laboratory Specimen Shipping 66
8 ASSESSMENT OF SAFETY....67
8.1 Assessing and Recording Safety Parameters....67
8.1.1 Adverse Events (AEs)....67
8.1.1.1 Adverse Events Grading....67
8.1.2 Serious Adverse Events 68
8.2 Specification of Safety Parameters....69
8.3 Reporting Procedures....69
8.3.1 Reporting Serious Adverse Events 69
8.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND 70
8.3.3 Reporting of Pregnancy 71
8.4 Type and Duration of Follow-up of Subjects after Adverse Events....71
8.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings....72
8.6 Halting Rules 72
8.7 Safety Oversight (ISM plus SMC) 72
8.7.1 Independent Safety Monitor (ISM)....72
8.7.2 Safety Monitoring Committee (SMC) 73
9 HUMAN SUBJECTS PROTECTION 74
9.1 Ethical Standard....74
9.2 Institutional Review Board....74
9.3 Informed Consent Process 75
9.3.1 Exclusion of Special Populations....76
9.4 Future Use of Stored Specimens....76
9.5 Subject Confidentiality 76

9.6 Study Discontinuation 77
10 STATISTICAL CONSIDERATIONS 78
10.1 Responsibility for Analysis....78
10.2 Study Hypotheses 78
10.2.1 Primary Hypothesis....78
10.2.2 Secondary Hypotheses 78
10.3 Sample Size Considerations 78
10.4 Treatment Assignment Procedures 78
10.4.1 Randomization Procedures 78
10.4.2 Masking Procedures....79
10.5 Planned Interim Analyses 79
10.5.1 SMC Safety Review....79
10.6 Analysis Plan 80
10.6.1 Analysis Sets....80
10.6.2 Safety Analysis Set 80
10.6.3 PK Analysis Set 80
10.6.4 Primary PK Analysis....80
10.6.5 Secondary Safety Analyses....81
10.6.5.1 Adverse Events 81
10.6.5.2 Laboratory Parameters....82
10.6.5.3 Vital Signs....82
10.6.5.4 ECG Data....82
10.6.6 Demographics and Screening Summaries 83
11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS....84
12 QUALITY CONTROL AND QUALITY ASSURANCE 85
13 DATA HANDLING AND RECORD KEEPING 86
13.1 Data Management Responsibilities 86
13.2 Data Coordinating Center/Biostatistician Responsibilities 86

13.3 Data Capture Methods 87
13.4 Types of Data 87
13.5 Timing/Reports 87
13.6 Study Records Retention 87
14 CLINICAL MONITORING 88
14.1 Site Monitoring Plan 88
15 PUBLICATION POLICY 89
16 LITERATURE REFERENCES 91
17 APPENDICES 95
Appendix A. Schedule of Events 96
Appendix B. Child-Pugh System 99
Appendix C. Toxicity Tables 100

LIST OF TABLES

Table 1: Study Groups 20
Table 2: Summary of 4 Pretomanid Phase 2 studies....27
Table 3: Mean log CFU for Pretomanid in the 5th Phase 2 multidrug trial (NC-003) 29
Table 4: Study Groups 39
Table 5: Pretomanid Formulation 42
Table 6: Prohibited CYP450 Enzyme Altering Medications/Substances per Subject Exclusion Criteria 46

LIST OF FIGURES

Figure 1: Schematic of Study Design 20
Figure 2: Structure of Pretomanid (C14H12F3N3O5) 23

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC0-t	AUC from time zero to the last observable concentration
AUC0-∞	AUC extrapolated to infinity
BDQ	Bedaquiline
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CFU	Colony-Forming Unit
CFZ	Clofazimine
CL/F	Apparent Clearance
Cmax	Maximum plasma concentration
CMS	Clinical Materials Services
CNS	Central Nervous System
CROMS	Clinical Research Operations and Management Support
CSR	Clinical Study Report
CT	Computed Tomography
CV	Coefficients of Variation

DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
EBA	Early Bactericidal Activity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
EFV	Efavirenz
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HDPE	High-density polyethylene
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IDS	Investigational Drug Service
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board

ISM	Independent Safety Monitor
LPV/r	Ritonavir-Boosted Lopinavir
MDR-TB	Multi-drug resistant Tuberculosis
MedDRA®	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MOP	Manual of Procedures
MOX	Moxifloxacin
MRI	Magnetic Resonance Imaging
MTB	*Mycobacterium tuberculosis*
N	Number (typically refers to subjects)
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
OTC	Over the Counter
PCP	Phencyclidine
PI	Principal Investigator
PK	Pharmacokinetics
PR	P-R Interval on an ECG
PT	Prothrombin Time
PZA	Pyrazinamide
QA	Quality Assurance
QC	Quality Control

QRS	Q-R-S Complex on an ECG
QT/QTc	QT Interval of an ECG/Corrected QT Interval of an ECG
QTcB	Heart Rate-Corrected QT Interval (Bazett's Formula)
QTcF	Heart Rate-Corrected QT Interval (Fridericia's Formula)
RH	Relative Humidity
RIF	Rifampin
RR	R-R Interval on an ECG
SAE	Serious Adverse Event/Serious Adverse Experience
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
t1/2	Terminal elimination half life
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
Tmax	Time to maximum plasma concentration
ULN	Upper Limit of Normal
US	United States
Vd/F	Apparent Volume of distribution
VTEU	Vaccine and Treatment Evaluation Unit
WHO	World Health Organization
XDR-TB	Extensively drug resistant Tuberculosis

PROTOCOL SUMMARY

Title: A Phase 1, Single Dose, Open-label Study Comparing the Pharmacokinetics and Safety of Pretomanid in Subjects with Mild, Moderate, and Severe Hepatic Impairment to Matched, Non-hepatically Impaired Subjects

Design of the Study:

This is a Phase 1, single dose, open-label study comparing the pharmacokinetics and safety of Pretomanid in subjects with mild, moderate, and severe hepatic impairment to matched non-hepatically impaired subjects.

Mild hepatic impairment: Child-Pugh A = 5 to 6 points

Moderate hepatic impairment: Child-Pugh B = 7 to 9 points

Severe hepatic impairment: Child-Pugh C = 10 to 15 points

This study will enroll approximately 6 subjects with mild hepatic impairment (Child-Pugh A), approximately 6 subjects with moderate hepatic impairment (Child-Pugh B), approximately 6 subjects with severe hepatic impairment (Child-Pugh C), and approximately 18 matched non-hepatically impaired subjects. Non-hepatically impaired subjects in the control group will be matched to subjects with hepatic impairment based on age (± 10 years) and body weight (± 20%) as measured at screening (Visit 00A). A control subject may be matched to more than one case subject with hepatic impairment if warranted and if the subjects to which they are matched are not in the same disease severity group. Control subjects may be matched to hepatically impaired subjects at any site. In this case the control subject would participate in the study one time but be matched to more than one subject with hepatic impairment. If subjects in either the hepatic impaired or control subject groups withdraw from the

	study prior to completion of Day 5 (Visit 04) when the last PK samples are obtained, the subject may be replaced. The screening visit (00A) will occur up to 21 days prior to subject admission to the confinement/hospital unit. Subjects who meet study inclusion/exclusion criteria will then have one inpatient visit and four outpatient visits for a total of five study visits (not including the screening visit). Subjects will be admitted to the confinement/hospital unit the day before they begin the confinement/hospitalization period (Visit 00B). The subject will receive a single oral dose of 200 mg Pretomanid on the morning of Visit 01 (Day 1). Serial PK measurements will be obtained on Days 1-5 and will follow the schedule in Appendix A. Subjects will remain in the confinement/hospital unit for Visits 00B (pre-dose Admission Day) through Visit 01J (post-dose Days 1 and 2) sites may wish to keep subjects confined through Visit 2 (post-dose Day 3). Subjects may be discharged after assessments on Day 2 are complete (the 36-hour PK sampling time point) and then return for a follow-up visit on Day 3 or they may be discharged after the Day 3 (Visit 2) follow-up visit is completed depending on site preference. Subjects will return for follow-up visits on Days 4, and 5 with a final visit on Day 12 (Visits 03, 04, and 05, respectively).
Study Phase:	1
Study Population:	Approximately 18 adult males and females, 18 to 70 years of age, inclusive, with mild, moderate, or severe hepatic impairment who meet all eligibility criteria Approximately 18 matched non-hepatically impaired adult males and females, 18 to 70 years of age, inclusive, who meet all eligibility criteria
Number of Sites:	Two Sites

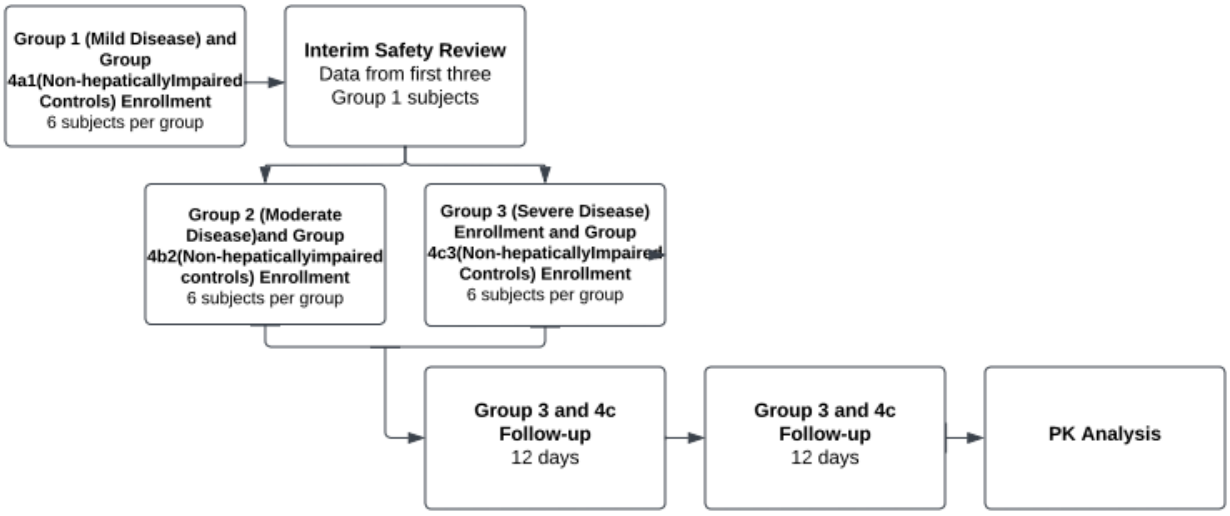
Description of Study Product or Intervention:	Single oral dose of 200 mg Pretomanid tablets manufactured by a contractor for the Global Alliance for TB Drug Development.
Study Objectives:	Primary: • To evaluate the pharmacokinetics of a single oral dose of Pretomanid in subjects with mild, moderate, and severe hepatic impairment (as assessed by Child-Pugh score), relative to matched non-hepatically impaired subjects. Secondary: • To evaluate the safety of a single oral dose of Pretomanid in subjects with mild, moderate, and severe hepatic impairment (as assessed by Child-Pugh score), relative to matched non-hepatically impaired subjects.
Subject Participation Duration:	Approximately 5 weeks (including screening)
Study Duration:	Approximately 24 months

Table 1: Study Groups

Study Group	Severity*	N
Group 1	Child-Pugh A = 5 to 6 points (Mild)	6
Group 2	Child-Pugh B = 7 to 9 points (Moderate)	6
Group 3	Child-Pugh C = 10 to 15 points (Severe)	6
Group 4	Non-hepatically impaired controls	18

* The subjects are categorized, into one of the 4 groups at screening.

Figure 1: Schematic of Study Design



[1]Group 4a is referring to the non-hepatically impaired controls matched with Group 1

[2]Group 4b is referring to the non-hepatically impaired controls matched with Group 2

[3]Group 4c is referring to the non-hepatically impaired controls matched with Group 3

1 KEY ROLES

Lead Principal Investigator:	Julius Wilder, MD, PhD Duke University Department of Medicine
Principal Investigator:	Emmanuel Walter, MD, MPH Duke University Duke Clinical Vaccine Unit
Principle Investigator:	Getahun Abate, MD, PhD, MSc Saint Louis University School of Medicine
DMID Clinical Project Manager:	Erica Sondergaard, RN, BSN Respiratory Diseases Branch DMID/NIAID/NIH/DHHS
Statistical and Data Coordinating Center:	The Emmes Company, LLC
Institutions:	Duke University Saint Louis University

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background

2.1.1 Tuberculosis

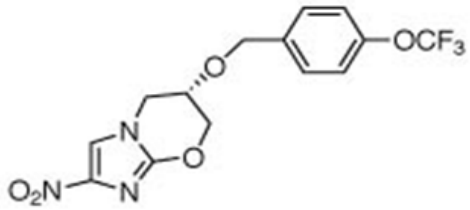
Tuberculosis (TB) causes a significant global health burden with an estimated annual worldwide incidence in 2015 of approximately 10.4 million new cases (1). Approximately 1.8 million people died from TB in 2015 (1, 2) making TB the leading infectious killer of adults worldwide. TB is also the leading infectious cause of death among people with HIV or acquired immunodeficiency syndrome (3).

TB is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (MTB). This infection primarily affects the lungs (pulmonary TB) but can affect other organs such as the kidneys, bones, and brain (4). TB is transmitted by inhalation of infective droplets containing MTB and expelled into the air by a person with active TB (4).

The mainstays of therapy against TB are antibiotic combination regimens. The recommended treatment includes a combination of rifampin, isoniazid, pyrazinamide, ethambutol or streptomycin (5-7). A 4-drug regimen of directly observed therapy is administered for 2 months (intensive phase), and is then followed by rifampin and isoniazid for an additional 4-7 months (6). The goal of the prolonged regimen is to ensure sterilization of tuberculosis lesions and to prevent development of drug resistance (7). If administered correctly, cure rates as high as 95% can be achieved (8).

Unfortunately, the prolonged and complicated treatment course of TB affects patient compliance (9), which has led to development of multi-drug resistant TB (MDR-TB) (6, 9) and extensively drug resistant strains (XDR-TB)(10). The WHO estimates that ~4% of new TB cases, and 20% of previously treated cases of TB have MDR-TB(3). Of those new MDR-TB cases 9% are XDR-TB (3). Therefore, there is a need to develop novel drugs, such as Pretomanid (previously known as PA-824) to be used in combination, for the treatment of TB.

Figure 2: Structure of Pretomanid (C14H12F3N3O5)



2.1.1.1 Mechanism of action

Pretomanid is a nitroimidazooxazine and its mechanism of action involves inhibition of the synthesis of mycobacterial cell wall proteins and lipids. A second potential source of bactericidal activity may involve generation of reactive nitrogen species including nitric oxide (11).

2.1.1.2 In Vitro Microbiological Activity

The minimum inhibitory concentration (MIC) of Pretomanid against drug-sensitive MTB isolates was similar to the MIC of isoniazid (Pretomanid MIC ≤0.015 to 0.25 µg/mL). Pretomanid also has activity against drug-resistant clinical isolates of MTB (MIC of 0.03 to 0.25 µg/mL) (7).

2.1.1.3 Pharmacology and toxicology

Numerous non-clinical single-dose studies on the PK and toxicity profile of Pretomanid have been performed. 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 (see Investigator Brochure, Section 4.4.1.1). The apparent elimination t½ of Pretomanid following a single oral dose was approximately 3 to 7 hours in rats, monkeys, and rabbits. In rats, the time to peak plasma concentration (Tmax) ranged from 3 to 8 hours. Subsequent slow elimination of Pretomanid metabolites occurs with an average of 88.1% and 67.5% of the metabolites recovered in the urine and feces for rats and monkeys, respectively.

Non-clinical studies relevant to the absorption and PK profile of Pretomanid following repeated dose administration were also performed. With repeated dosing, the exposure to Pretomanid increased as the dose level increased in the rat, rabbit, and monkey. But the increase in exposure was less than dose proportional at higher doses (see Investigator Brochure Section 4.4.1.2). Elimination kinetics were comparable to values observed after single doses, suggesting sustained Pretomanid exposure in these animal species does not result in increased clearance due to auto-induction of metabolism or other means of eliminating the drug from the body. In both pregnant rats and rabbits, maternal and fetal exposures are similar, indicating that Pretomanid readily crosses the placenta (see Investigator Brochure Section 4.4.1.2).

2.1.1.4 Clinical Pharmacology and Biopharmaceutics

2.1.1.4.1 In vitro

Human plasma protein binding for Pretomanid was evaluated and was 86.4%. The effect of Pretomanid on p-glycoprotein was determined in a screening study in MDCK II cells transfected with a vector expressing the p-glycoprotein transporter (see Investigator Brochure Section 4.4.2.1). Pretomanid did not have a significant effect on the p-glycoprotein transporter.

The potential induction and inhibition of human CYP isoforms was evaluated. *In vitro* studies showed that Pretomanid does not induce cytochrome CYP 3A4, 2C9, or 2E1. Pretomanid is a weak competitive inhibitor for CYP3A4/5, CYP2C8, 2C9 and 2C19 (see Investigator Brochure Section 4.4.3.1). An *in vitro* reaction phenotyping experiment indicated that Pretomanid is not a substrate of CYP2C9, 2C19, or 2D6. The primary pathway for Pretomanid metabolism is CYP3A4.

2.1.1.4.2 In vivo

A phase 1, open-label, single ascending dose study in healthy volunteers (N=53) of Pretomanid (50, 250, 500, 750, 1000, 1250, or 1500 mg) showed that Pretomanid was absorbed with a median Tmax of 4 to 5 hours across all treatment groups (11). Pretomanid exposure, based on Cmax or AUC values, increased in a less than dose-proportional manner with increasing doses up to 1000 mg. Dose levels above 1000 mg achieved minimal additional Pretomanid exposure for both Cmax and AUC. The overall mean apparent t½ of Pretomanid ranged from 14 to 20 hours across dose groups and elimination kinetics after single-dose administration did not exhibit

any apparent dose dependency. The mean CL/F values increased with increasing Pretomanid doses (11).

The PK of Pretomanid was further evaluated in a multiple-dose ascending study in healthy volunteers. Pretomanid (200, 600, 1,000 or 1,400 mg) was administered once daily for 7 days to healthy subjects (N=24) (11). Similar to the single ascending dose study, mean Tmax was 4-5 hours in each dose group (11). The apparent elimination half-life did not significantly change with multiple doses or dose increases (11). Pretomanid achieved steady state plasma concentrations after 5 to 6 days, and daily dosing for 5 to 7 days was associated with a mean accumulation ratio of 2 for both Cmax and AUC in the 200 mg and 600 mg groups (11). Similar to the single ascending dose study, the mean apparent t½ after 7 days of dosing was approximately 16 hours in the 200- and 600-mg dose groups. Dose levels above 600 mg achieved minimal additional Pretomanid absorption with respect to both Cmax and AUC (11).

The potential for metabolic-based drug-drug interactions mediated via CYP3A was evaluated using midazolam. Healthy subjects (N=14) received a single oral dose of midazolam 2 mg, followed by a 2-day washout interval. All subjects then received 400 mg Pretomanid, administered orally after an overnight fast once daily for 14 days. The Cmax and AUC values for midazolam after co-administration with Pretomanid were approximately 85% of those observed after treatment with midazolam alone. Furthermore, the Tmax and t½ values for midazolam and its metabolite 1-hydroxy-midazolam were not different in the presence or absence of Pretomanid. Hence, dosing with Pretomanid at 400 mg/day for 14 days (to steady state) had minimal effect on the PK of midazolam. These results suggest a low risk for drug-drug interactions with Pretomanid in vivo.

A Phase 1 PK study to evaluate drug-drug interactions between Pretomanid (200 mg daily) and efavirenz (EFV), ritonavir-boosted lopinavir (LPV/r), and rifampin (RIF), showed no changes in EFV exposures and PK parameters and moderate changes in LPV/r exposure (<20%). Co-administration with RIF showed a >50% decrease in Pretomanid exposure (see investigator brochure).

2.1.1.5 Efficacy studies

Pretomanid has been evaluated in 5 (single and multi-dose) Phase-2 studies. The Phase-2 studies characterized the bactericidal activity, safety, and PK in subjects with newly diagnosed pulmonary TB. Phase 3 efficacy and safety trials are planned or underway for Pretomanid given orally at a dose of 100 or 200 mg/day in combination with other anti-TB drugs.

The early bacterial activity (EBA_{CFU} (0-14)) of Pretomanid over 14 days in adult subjects with newly diagnosed, smear-positive, pulmonary TB was evaluated in three Phase 2, randomized, blinded, parallel-group studies. The EBA_{CFU} (0-14) is the rate of decline of the log CFU count over 14 days, i.e., – (log (CFU_{Day14}) – log (CFU_{Day0})/14 (note the negative sign; a higher positive number means a greater rate of decline). In each of the Phase 2 studies, treatment was administered once daily for 14 days either alone or in combination with other anti-TB drugs. Each study included a group of subjects who were randomly assigned to receive Rifafour e-275 (single combination pill of rifampicin, isoniazid, pyrazinamide, and ethambutol) as a control. The subjects were hospitalized throughout the 2-week treatment period and sputum collections were done at specified time points for assessment of CFU count.

The first study evaluated oral doses of 200, 600, 1000, and 1200 mg/day in 60 subjects (15 per dose category) (7). The primary endpoint was the mean rate of change in log CFU of MTB in sputum. The mean EBA_{CFU} (0-14) of TB for Pretomanid was equivalent at all four dosages (0.098 +/- SD 0.072) (Table 2). Since maximum efficacy was unexpectedly achieved at the lowest dosage tested, the activity of lower dosages was explored.

The second phase 2 single dose study evaluated lower oral dosages of Pretomanid at 50, 100, 150, and 200 mg/day in 60 subjects (12). The primary efficacy endpoint was the mean rate of decline in log CFU of TB in sputum. The mean EBA_{CFU} (0-14) was 50 mg (0.063 ± 0.058), 100 mg (0.091 ± 0.073), (150 mg 0.078 ± 0.074), and 200 mg (0.112 ± 0.070) (12) (Table 2). The study was not powered for testing the difference between arms, but there was a trend toward significance, indicating a lower early bacterial activity at the 50 mg dose (12).

A third phase 2 clinical trial was designed to select multi-drug combination therapies involving Pretomanid (200 mg) and included the following combination regimens (Pretomanid + bedaquiline, Pretomanid + pyrazinamide, and Pretomanid + pyrazinamide + moxifloxacin) (13). Other regimens in the study included bedaquiline alone, bedaquiline + pyrazinamide, and Rifafour e-275. The primary endpoint was the mean rate of decline in log CFU of TB in sputum. The combination of Pretomanid + moxifloxacin + pyrazinamide (0.233, SD 0.128) had a significantly higher EBA_{CFU} (0-14) than bedaquiline (0.07, SD.0068), bedaquiline + pyrazinamide (0.131, SD 0.102), bedaquiline + Pretomanid (0.114, SD 0.050) (13), Pretomanid + pyrazinamide (0.154, SD 0.040), and the standard TB treatment regimen (0.140, SD 0.094) (13) (Table 2).

A fourth Phase 2 study evaluated the efficacy of Pretomanid (100 and 200 mg) as add-on therapy to multi-drug regimens with moxifloxacin and pyrazinamide to treat patients with MTB and MDR-TB (NC-002, see investigator brochure). The primary end point was the rate of decline of

log CFU over the course of 56 days, BA_{CFU} (0-56), defined analogously to EBA_{CFU} (0-14). The MOX + Pretomanid 200 mg + PZA group had the highest mean BA_{CFU} (0-56) relative to control (Rifafour). The second highest BA_{CFU} (0-56) was found in the MOX + Pretomanid 100mg + PZA group (Table 2). There were 9 patients with MDR-TB who were treated with MOX + Pretomanid 200 mg + PZA and the mean log CFU reduction in this group compared favorably with the Rifafour control group.

The fifth Phase 2 study (NC-003, see investigator brochure) evaluated the efficacy of Pretomanid as part of a drug regimen including bedaquiline (BDQ), pyrazinamide (PZA), and clofazimine (CFZ) (Table 3). The primary efficacy variable was the EBA_{CFU} (0-14). There were 7 treatment groups in this study (Table 3). Treatment group BDQ + PA + PZA had the highest mean EBA over 14 days of treatment.

Table 2: Summary of 4 Pretomanid Phase 2 studies

Year	N	Pretomanid Regimen	Dosage	Primary Outcome	Mean daily fall in CFU
2010	60	Once Daily	200, 600, 1000, and 1200 mg/day	Mean rate of decline in log CFU of TB over 14 days	0.098 (+/-0.072) was equivalent for all four dosages
2012	60	Once Daily	50, 100, 150, and 200 mg/day	Mean rate of decline in log CFU of TB over 14 days	50mg 0.063 ± 0.058 100mg 0.091 ± 0.073 150mg 0.078 ± 0.074 200mg 0.112 ± 0.070
2012	81	Once Daily	1. Pretomanid + bedaquiline 2. Pretomanid + pyrazinamide 3. Pretomanid + pyrazinamide + moxifloxacin (all Pretomanid doses were 200 mg/day)	Mean rate of decline in log CFU of TB over 56 days	Pretomanid + moxifloxacin + pyrazinamide (0.233) was significantly higher than bedaquiline (0.061), bedaquiline + pyrazinamide (0.131), and comparable with that of standard treatment

Year	N	Pretomanid Regimen	Dosage	Primary Outcome	Mean daily fall in CFU
2014	207	Once Daily	1. Pretomanid 200 mg + pyrazinamide + moxifloxacin 2. Pretomanid 100 mg + pyrazinamide + moxifloxacin 3. Pretomanid 200 mg + pyrazinamide + moxifloxacin (Tx MDR-TB)	Mean rate of decline in log CFU of TB over 14 days	1. Pretomanid 200 mg + pyrazinamide + moxifloxacin (0.155) 2. Pretomanid 100 mg + pyrazinamide + moxifloxacin (0.133) 3. Pretomanid 200 mg + pyrazinamide + moxifloxacin (Tx MDR-TB) (0.117)

Table 3: Mean log CFU for Pretomanid in the 5th Phase 2 multidrug trial (NC-003)

Treatment Group	Mean rate of decline in log CFU of TB over 14 Days [CI]
BDQ + PA + PZA + CFZ (N=14)	0.111 [0.037-0.184]
BDQ + PA + PZA (N=12)	0.167 [0.078-0.256]
BDQ + PA + CFZ (N=15)	0.076 [0.007-0.147]
BDQ + PZA + CFZ (N=14)	0.119 [0.031-0.211]
PZA (N=15)	0.037 [-0.025-0.100]
CFZ (N=15)	-0.017 [-0.086-0.055]
Rifafour e-275 (N=15)	0.151 [0.070-0.231]

2.1.2 Summary of safety

Approximately 1000 subjects across 15 clinical trials (Phase-1 and Phase-2) have been exposed to Pretomanid. These studies indicate the drug is well tolerated. The most common side effect noted in Phase-1 clinical studies was headache (11). The most common side effects in Phase-2 studies were gastrointestinal (GI) including stomach discomfort, nausea, vomiting, flatulence, and diarrhea (11).

Phase-1 and Phase-2 studies have shown Pretomanid to have a minimal impact on the liver. Three subjects exposed to Pretomanid in one study (NC-001, see investigator brochure) developed elevation of ALT in the setting of taking a Pretomanid (200 mg daily) containing regimen (Pretomanid + bedaquiline, Pretomanid + pyrazinamide, and Pretomanid + pyrazinamide + moxifloxacin groups). These subjects were withdrawn from treatment due to this elevation in ALT levels. Of note, the rate of discontinuation for this adverse event in this study was similar to that for bedaquiline-containing regimens in other studies (13). Furthermore, none of the subjects had associated symptoms and the elevated transaminases resolved upon discontinuation of treatment (13). Among the other completed Phase 1 and 2 studies, there were only two treatment emergent adverse events (TEAEs) of changes in hepatic enzymes. One TEAE of hepatic enzymes involved increased AST/ALT for a subject taking 200 mg/day. The other involved a subject in the 1200 mg/day group. Neither TEAE was assessed as severe, and neither

resulted in discontinuation of treatment (11). New information concerning reported fulminant hepatic failure and resulting deaths in persons taking Pretomanid are described in Section 2.3.1 below.

2.2 Scientific Rationale

Pretomanid is metabolized extensively in the liver (CYP3A4) and has a low extraction ratio. In the setting of advanced liver disease both hepatic blood flow and hepatic function can be compromised. Therefore, the pharmacokinetics of Pretomanid are likely to be altered in subjects with hepatic impairment compared to matched healthy subjects. We hypothesize that the metabolism of Pretomanid will be impacted by the presence of advanced liver disease. The purpose of this protocol is to evaluate the safety and pharmacokinetics of Pretomanid in the setting of underlying liver disease defined as a Child-Pugh score of A, B, or C. The severity of liver disease is based on five clinical features: 1) total bilirubin level, 2) serum albumin, 3) prothrombin time (measured as the INR), 4) the degree of ascites, and 5) the grade of hepatic encephalopathy. The total point score is then used to determine the subject's Child-Pugh class.

The route of administration of Pretomanid for this study will be oral and the dose will be 200 mg. A single oral dose of Pretomanid will be taken once. The PK profile for Pretomanid following oral dosing was consistent for healthy subjects and subjects with pulmonary TB. Pretomanid was readily absorbed after oral administration and slowly eliminated in plasma. Pretomanid plasma concentrations increased in a dose-related manner after single-dose administration of up to 1000 mg in healthy subjects and subjects with TB, but the increase was less than dose proportional, particularly at doses above 200 mg/day. There is a trend towards increased side effects with increasing dosages (7). Furthermore, efficacy studies have shown equivalent early bacterial activity at dosages ranging from 200 mg to 1200 mg. The doses of Pretomanid that will be evaluated in regimens in Phase 3 are 100 mg and 200 mg. Hence, the dosage of Pretomanid for this study will be 200 mg daily.

2.2.1 Purpose of Study

For the primary objective, the hypothesis is that Pretomanid PK parameters following drug exposure will differ between patients with hepatic impairment and non-hepatically impaired controls.

2.2.2 Study Population

The study population will be representative of subjects with varying degrees of liver disease as defined by Child-Pugh scores. The Child-Pugh scores used for eligibility in the study will be

calculated at screening only. The Child-Pugh score is based on five clinical measures of liver function: total bilirubin, serum albumin, prothrombin, ascites, and hepatic encephalopathy. Based on their score patients are defined as mild (5-6 points), moderate (7-9 points), or severe (10-15 points). Approximately 36 subjects between the ages of 18 and 70 years will be enrolled over an estimated 9-month period. A subject is considered enrolled in this study once they have signed a study consent form, met all eligibility criteria, and have been admitted to the confinement/hospital unit on Admission Visit (Day -1).

Subjects with hepatic impairment for this study will be mainly identified at Duke University Health System Hospitals and Clinics and the Durham Veterans Administration Hospital as well as St Louis University. Non-hepatically impaired controls will be identified from the site-specific recruitment registries and the community. Subjects for this study may also be identified through advertisement, letters, and other forms of communication.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The potential risks of this study are those associated with having blood drawn, adverse reactions to the Pretomanid medication, and breach of confidentiality. Drawing blood may cause transient discomfort and fainting. Fainting is usually brief and managed by having the subject lie down. Bruising at the blood draw site may occur but can be prevented or lessened by applying pressure to the draw site for several minutes. Drawing blood may also cause infection. The use of sterile technique will make infection at the site where blood will be drawn extremely unlikely.

Among 10 completed Phase 1 clinical trials, there were no reported deaths or serious TEAEs. One subject was withdrawn from study due to a TEAE. The subject who required withdrawal was assigned to a Pretomanid 1000 mg group and developed a severe generalized rash on day 9 of therapy. She was treated with diphenhydramine, prednisone, and hydroxyzine and the rash resolved within 11 days. A second subject who likely had a pre-existing condition developed a significant TEAE characterized by proteinuria. She never developed symptoms and her proteinuria resolved following her completion of the study. A renal biopsy later revealed the diagnosis of focal segmental glomerulosclerosis (11).

In the single-dose, dose range-finding study in healthy subjects, the overall percentage of subjects reporting TEAEs was similar for Pretomanid and placebo, and there was no apparent increase in frequency of TEAEs across the Pretomanid dose range of 50 to 1500 mg/day. In the repeated-dose, dose ranging study the overall percentage of subjects with TEAEs was higher for Pretomanid (50%) than for placebo (33%) and appeared to increase with increasing dose (17%

for 200 mg/day, 50% for 600 mg/day, and 83% for 1000 mg/day). In the renal safety study, the frequency of AEs was higher for Pretomanid 1000 mg (90%) than Pretomanid 800 mg (52%) and placebo (38%). Higher dosages appeared to be associated with increased frequency of TEAEs.

Headache was the most common TEAE reported in healthy subjects. Across the completed Phase 1 studies, a total of 42 healthy subjects were treated with the 200-mg dose of Pretomanid (the highest dose proposed for future clinical development). Of these 42 subjects, 24% (10/42) reported headache. The most common side effects reported in Phase 2 studies (13/167 subjects, 7.8%) were gastrointestinal, including abdominal discomfort, nausea, vomiting, flatulence and diarrhea.

The possible effect of Pretomanid on the QT interval was examined in a "thorough QT/QTc study," (DMID 10-0058, see investigators brochure). In that study, the upper limit of the 90% confidence limit showed a decrease in heart rate as well as increases in the QT interval corrected for heart rate (using Bazett [QTcB] or Fridericia [QTcF] formulas), PR interval, and QRS interval. The increases in the PR and QRS interval were small and not considered clinically significant. The mean decrease in ECG-recorded heart rate averaged approximately 6 bpm for the 200 mg Pretomanid dose given as a single agent.

Adverse events in subjects with pulmonary TB were evaluated in Phase 2 studies and one death was reported. Across these Phase 2 studies, serious TEAEs were reported in 3.6% (13/360) of subjects exposed to Pretomanid and 9.2% (33/360) of subjects exposed to Pretomanid were withdrawn from treatment due to a TEAE (see Investigator Brochure Section 5.3.1.2). None of the nine serious TEAEs were related to study drug. Four of the subjects with serious TEAEs were treated with Pretomanid 200 mg, either alone or as part of a multi-drug combination regimen. For two subjects, the serious TEAE occurred more than 30 days after the last dose of Pretomanid (pneumonia and worsening pulmonary TB). The remaining serious TEAEs occurred while the subjects were receiving study treatment and included hemoptysis, pneumothorax, and neurocysticercosis. These three serious TEAEs led to discontinuation of study drug. The death that occurred was in Study NC-002. This study evaluated Pretomanid (at 100 mg and 200 mg dosages) as part of a multidrug regimen with moxifloxacin and pyrazinamide to treat patients with MTB and MDR-TB (NC-002, see investigator brochure). A 37-year-old female received the Moxifloxacin 400 mg + Pretomanid 100 mg + Pyrazinamide 1500 mg regimen for only 1 day and was withdrawn from the study because of elevated liver enzymes found present before dosing. Thirty-four days after administration of study drug she developed chest pain and difficulty breathing, cough, fever, weakness, vomiting, loss of appetite, and syncope and died. Death was not believed to be related to study drug (NC002, see investigator brochure).

Adverse events leading to discontinuation of treatment included elevation of ALT and electrocardiogram (ECG) changes. For three subjects, all from the same study, the TEAE leading to discontinuation was increased ALT. The elevated transaminases were detected at a scheduled laboratory evaluation and in all three subjects the increased ALT was asymptomatic and ALT value returned towards baseline levels upon discontinuation of study treatment. The maximum increase ranged from 4.0 to 5.5 x the Upper Limit of Normal (ULN). There were no reported significant changes in bilirubin or alkaline phosphatase. Elevation of ALT requiring withdrawal was also seen among two additional subjects in this study (one in bedaquiline alone group and one in bedaquiline + pyrazinamide group) (13). Data thus far suggests that Pretomanid is not associated with significant hepatic toxicity when given as a single agent for up to 14 days. However, when administered within a regimen with other drugs (for example MOX and PZA) known to be associated with hepatic toxicity, increases in aminotransferase levels have been observed in a few subjects requiring withdrawal from clinical trials.

There were three deaths within an ongoing Phase 3 study evaluating the safety and efficacy of bedaquiline plus linezolid plus Pretomanid in subjects with pulmonary infection of either XDR-TB or treatment intolerant/non-responsive MDR-TB (The Nix-TB Study). Approximately half of the subjects were HIV co-infected, and all had documented XDR-TB. The causes of death have varied based on autopsies and clinical data. Two deaths were related to severe pulmonary tuberculosis, disseminated tuberculosis, acute severe worsening of pulmonary tuberculosis and multi-organ TB. These deaths were both considered by the investigator and sponsor as not related to the study drug regimen. A third death occurred as a result of gastrointestinal bleeding. This was reported by the investigator as possibly related to the investigational drug regimen, although the sponsor considered the event unlikely to be related to the study drug regimen.

In a separate Phase 3 study evaluating the efficacy, safety, and tolerability of the combination of Pretomanid combined with moxifloxacin and pyrazinamide (STAND trial), there were three deaths. All subjects died with associated liver injury. Review of the deaths by an independent safety board concluded that these deaths were related to Drug Induced Liver Injury (DILI). In all 3 cases the onset of DILI symptoms was early during the course of TB treatment (22, 24 and 21 days respectively) suggesting that the etiology was likely an immuno-allergic pattern of DILI. In all 3 cases there was rapid clinical deterioration and 2 had coagulopathy (in the other case, INR was not tested). Two cases were HIV-infected, and one was HIV negative. In all 3 cases there was a delay to stopping study medication after DILI symptom onset. This incidence of fatal DILI (1.4%) among participants receiving study drug in combination with moxifloxacin and pyrazinamide is considerably higher than observed with conventional TB treatment. The risk of DILI with traditional TB drugs is approximately 1% and fulminant hepatitis approximately 0.1%. Although a direct causal relationship between Pretomanid and the deaths in this study could not

be definitively established or ruled out, these events raised the possibility that subjects taking Pretomanid for at least three weeks duration might be at risk for liver injury and should be monitored for evidence of hepatotoxicity, including routine monitoring of serum transaminase levels. The risk of liver injury appears raised when Pretomanid is combined with other agents known for hepatic toxicity.

Given the deaths that occurred on the STAND trial, the Food and Drug Administration (FDA) performed a review of the study findings and safety of Pretomanid. Following its own internal review, the FDA authorized continuation of clinical trials evaluating Pretomanid's safety and efficacy and suggested recommendations for the Pretomanid clinical development program. These included 1) close monitoring of liver enzymes; 2) study personnel education regarding signs/symptoms of liver toxicity; 3) close medical monitoring of liver related laboratory tests; 4) study drug holding rules in the event that liver toxicity is observed; and 5) close AE/laboratory data monitoring. The design of this protocol meets FDA recommendations. In addition, this study is designed as a single dose study which should reduce the risk of liver toxicity substantially.

The increases in the QTc interval seen with Pretomanid were relatively small at doses of <200 mg and there was a suggestion that with higher doses, this effect was saturated. The prolongation of the QTc interval was rarely clinically significant. No Pretomanid-treated subject across the Phase 2 studies had a QTcF interval of 500 msec or greater, and few subjects had an increase from baseline in the QTcF interval of >60 msec. Cardiac-related TEAEs were reported for 19 of the 360 subjects (5%) exposed to Pretomanid across the completed Phase 2 studies, and for none of the 289 subjects treated with Pretomanid in the Phase 1 studies. One of these events was considered to be serious.

Two subjects exposed to Pretomanid in Phase 2 studies were discontinued due to cardiac-related TEAEs (Wolff-Parkinson-White syndrome and prolonged ECG QTc). The subject withdrawn due to QTc prolongation was asymptomatic and the event resolved upon discontinuation of treatment. The subject with Wolff-Parkinson-White syndrome was lost to follow-up. Results of ECG evaluations in the completed Phase 2 studies in subjects with pulmonary TB suggest that once-daily oral administration of Pretomanid is associated with increases in the QTc (at dosages of 50, 100, 150, 200, 600, 1000, and 1200 mg), PR (at dosages of 50, 200, 600, and 1000 mg), and QRS intervals (at dosages of 50, 100, 600, and 1200 mg/day), as well as with a decrease in heart rate. One subject in one of the comparator groups also had ECG findings. Rifafour e-275 was associated with mean decreases in the QTcF interval, QRS interval and PR interval with a mean increase in heart rate. There were no reported TEAEs of bradycardia across the Phase 1 or Phase 2 studies with Pretomanid.

Skin and subcutaneous disorder TEAEs were among the most common events reported following Pretomanid dosing in the completed Phase 1 and 2 studies. Among Phase 1 studies, 12.2% of subjects reported a skin or subcutaneous disorder. Among the Phase 2 studies, 12.6% reported a skin/subcutaneous disorder. The most common skin related TEAEs reported following Pretomanid exposure were pruritus and rash. The overall percentage of subjects in Phase 1 and Phase 2 studies with rash was 1.3% and 2.4% respectively. The percentage of subjects exposed to Pretomanid who had pruritus in Phase 1 and Phase 2 studies was 2.5% and 2.4% respectively. Across all completed clinical studies, most of the skin related TEAEs were assessed as mild in intensity, and only one was assessed as severe. A severe generalized rash occurred in a subject following 8 days of dosing 1000 mg/day Pretomanid and resulted in the discontinuation of the subject from the study. Although treatment with Pretomanid does appear to be associated with skin related TEAEs, such as pruritus or rash, these events tend to be mild in intensity and resolve without sequelae.

In the single and multiple ascending dose studies, Pretomanid had a dose dependent effect on serum creatinine. In the single ascending dose study, 11 subjects (28%) treated with Pretomanid experienced a shift in serum creatinine from within the normal range at baseline to above the normal range at 36 hours; no placebo subjects exhibited this shift (11). Abnormal serum creatinine values in these subjects ranged from 1.22 to 1.45 mg/dL (normal range: 0.69 -1.20 mg/dL) (11). By the end of the washout period (Day 7), serum creatinine levels had returned to baseline values (11). In the multiple ascending dose study, the maximum absolute postdose serum creatinine value was 1.60 mg/dL and the maximum change from baseline was 0.38 mg/dL, both observed on Day 5 at supra-therapeutic doses (1000 mg/day). Serum creatinine values did not exceed 1.3 mg/dL in the 200-mg group or 1.4 mg/dL in the 600-mg group (11). Serum creatinine levels returned to normal levels during the 7-day washout period in all subjects (11). Given the findings in these studies, a Phase 1 renal safety study was performed. This randomized, double-blind, placebo-controlled, ascending multiple-dose study (800 or 1000 mg/day) showed a dose dependent increase in serum creatinine. There was also one renal related TEAE. This involved a subject who developed proteinuria in association with hypoalbuminuria who was eventually diagnosed with focal segmental glomerulosclerosis believed to have been present prior to exposure to Pretomanid (11). Pharmacokinetic data from the renal safety study suggests that serum creatinine changes occurred due to inhibition of renal tubular creatinine secretion. This is considered a benign effect that has been described for several marketed drugs (14).

The initial 3-month nonclinical toxicology studies in rats and monkeys reported the development of cataracts during both treatment and recovery in rats dosed with Pretomanid 300 mg/kg/day and during the 3-month recovery period in monkeys in the Pretomanid 450/300-mg/kg/day

group. Four clinical studies have been conducted, each of which included prospectively planned ophthalmologic evaluations (slit-lamp examinations, visual acuity testing) pre-dose and at 3- or 6-months after the final dose of study treatment (Studies CL-010, CL-006, CL-009, and NC-001). Mild lenticular opacities were noted upon visual acuity testing in 2 of the 152 subjects exposed to Pretomanid across these four studies; both subjects were asymptomatic. The ophthalmological data accumulated thus far indicates that Pretomanid does not appear to pose a cataractogenic potential in humans. There may be other risks that are currently unforeseeable.

Although rat and rabbit embryonic development studies indicate no effects of Pretomanid on fetal development, testicular atrophy in rats was observed in 3-month and 6-month repeat-dose toxicology studies and a Segment I fertility study. In this fertility study, testicular atrophy was associated with infertility; an approximate 30% reduction in fertility was also observed at a lower dose not associated with testicular atrophy. A detailed study in sexually mature male monkeys demonstrated no effects on testicular histology or function in adult cynomolgus monkeys after 3 months' dosing. Male subjects in the 8-week study of NC-002 had evaluations of the male hormones testosterone, LH and FSH at baseline and at the end of the eight weeks of treatment. No median changes were noted that raised concern that the regimen caused any testicular toxicity.

An analysis of male reproductive tract hormones to assess testicular function and the hypothalamic-pituitary-gonadal axis has been completed using data from two Phase 2 trials (NC-002 and NC-005) with 8 weeks of Pretomanid dosing and one ongoing Phase 3 trial (NC-006) with 17-26 weeks of Pretomanid dosing. This interim analysis for NC-006 included approximately 20-50/time point/group for the drug sensitive (DS) groups and 5-13/time point/group for the multidrug resistant group.

An independent expert in reproductive toxicology reported that at baseline the male trial subjects had reproductive tract hormones levels consistent with primary hypogonadism associated with their illness, and that this improved with the treatments administered over the course of the trials. The expert concluded that based on the hormone evaluations to date, there is no evidence that Pretomanid is a testicular toxicant in men at the doses and exposure times evaluated. If Pretomanid were a testicular toxicant, the subject's hormones would be expected to change to reflect damage to the testis. Such toxicity-related changes would include a decline in inhibin B levels, a hormone produced by Sertoli cells, the sustentacular cells of the seminiferous epithelium, and an associated compensatory increase in follicle stimulating hormone (FSH) levels. These toxicity-related hormone changes would be expected to be associated with Pretomanid treatment, to occur in a dose dependent manner, and to be exacerbated by increasing time of exposure. This pattern of response was not observed. In addition, if Pretomanid were

causing testicular injury, testosterone levels might be expected to fall slightly with a compensatory increase in luteinizing hormone (LH) levels in a dose- and time-dependent manner. In fact, testosterone levels increased in all groups receiving Pretomanid, and LH levels remain unchanged (NC-002 and NC-006).

The potential for Pretomanid to have an effect on the testes will remain under evaluation.

2.3.2 Known Potential Benefits

There is no known benefit to subjects in this study who will receive Pretomanid besides the potential to treat future TB patients. This novel medication may provide a less complicated regimen for treating TB that has activity against drug resistant strains. Furthermore, the substantial low potential for metabolic based drug-drug interactions makes this a viable candidate for treating TB in subjects infected with HIV as well without adjusting the dose of either anti-retroviral therapy or Pretomanid.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

3.1 Study Design Description

This is a Phase 1, single dose (200 mg), open-label, study comparing the pharmacokinetics and safety of Pretomanid in subjects with mild, moderate, and severe hepatic impairment relative to matched non-hepatically impaired subjects.

This study will enroll approximately 6 subjects with mild hepatic impairment (Child-Pugh A), approximately 6 subjects with moderate hepatic impairment (Child-Pugh B), approximately 6 subjects with severe hepatic impairment (Child-Pugh C), and approximately 18 matched non-hepatically impaired subjects. Subjects with moderate hepatic (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) will be enrolled simultaneously following enrollment of subjects with mild impairment. An interim safety analysis of data for the first 3 hepatic impairment subjects' data will be performed in between the mild hepatic impairment group and the moderate and severe hepatic groups (Child-Pugh B and Child-Pugh C). A second interim safety analysis will be performed after the first 3 subjects are enrolled in the moderate or severe hepatic groups. If enrollment into the severe hepatic impairment group (Child-Pugh C) is completed before that of the moderate hepatic impairment group (Child-Pugh B), results from the Child-Pugh C cohort will be analyzed to determine the impact of severe hepatic impairment on the PK of Pretomanid and the need to continue enrollment of persons with moderate hepatic impairment (Child-Pugh B) will be reevaluated to determine whether the objectives of the study have been met.

Non-hepatically impaired subjects in the control group will be matched to hepatically impaired subjects by age (± 10 years) and screening body weight (± 20%) consistent with previous studies on hepatic impairment with matched controls (15-17). A control subject may be matched to more than one hepatic impairment subject if warranted (e.g., lack of sufficient enrollment of non-hepatically impaired subjects) and if the subjects to which they are matched are not in the same disease severity group. In this case the control subject would participate in the study one time but be matched to more than one subject with hepatic impairment. If subjects in either the hepatically impaired or non-hepatically impaired control groups withdraw from the study prior to completion of Day 5 (Visit 04) when the last PK samples are obtained, the subject may be replaced. At screening, the subjects will be categorized, into one of the following 4 groups as described in Table 4.

Table 4: Study Groups

Study Group	Severity	N
Group 1	Child-Pugh A = 5 to 6 points (Mild)	6
Group 2	Child-Pugh B = 7 to 9 points (Moderate)	6
Group 3	Child-Pugh C = 10 to 15 points (Severe)	6
Group 4	Non-hepatically impaired controls	18

A detailed schedule of assessments is shown in Appendix A. The study will consist of the following:

- Screening period (Day -22 to Day -2) will occur between 1 and 21 days before admission to the confinement/hospital unit clinic (Day -1).
- Study product will be administered on Study Day 1.
- An approximately 36-hour – 60 hour confinement/hospitalization period that includes intensive PK sampling from Study Day 1 through Study Day 2 (36-hour sample) or Day 3 depending on site preference.
- Visits on Study Days (3), 4, and 5 for medical/surgical history and concomitant medications review, safety laboratory testing (Study Day 5), assessment of vital signs, PK sampling, and SAE/AE assessment, and on Study Day 12 for final study procedures (review of medical/surgical history and concomitant medications, assessment of vital signs, testing for coagulation and pregnancy, urinalysis, physical exam, ECG, safety laboratory testing and SAE/AE assessment).

3.2 Study Objectives

3.2.1 Primary

- To evaluate the pharmacokinetics of a single oral dose of Pretomanid in subjects with mild, moderate, and severe hepatic impairment (as assessed by Child-Pugh score), relative to matched non-hepatically impaired subjects.

3.2.2 Secondary

- To evaluate the safety of a single oral dose of Pretomanid in subjects with mild, moderate, and severe hepatic impairment (as assessed by Child-Pugh score), relative to matched non-hepatically impaired subjects.

3.3 Study Endpoints or Outcome Measures

3.3.1 Primary

- The pharmacokinetics of a single dose of Pretomanid will be assessed from serial blood samples collected prior to dosing (Day 1) and at multiple time points post dosing: 1h, 2h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 36h, 48h, 72h, and 96h. The primary outcome measure will be total plasma concentration of Pretomanid. The following will be determined:

    - AUC(0-∞): Area under the concentration time-curve extrapolated to infinity
    - AUC(0-last): Area under the concentration time-curve to the last concentration above the lower limit of quantitation
    - Cmax: Maximum Pretomanid concentration
    - Tmax: Time of maximum Pretomanid concentration
    - t(1/2): Apparent terminal elimination half-life
    - CL/F: Apparent oral clearance calculated from Dose/AUC(0-∞)
    - Vd/F: Apparent Volume of Distribution

3.3.2 Secondary

- The secondary outcome measures will be:
    - Incidence and severity of serious adverse events reported at any time from the time of study treatment through the end of the study.
    - Incidence and severity of related adverse events at any time from the time of study treatment through Day 12.
    - Summary of physical examination findings (height at baseline, and weight at serial time points from Day of Admission until Day 12), vital signs (serial time points from Day of Admission until Day 12), safety laboratory parameters (Day of Admission, as well as Days 2, 5, and 12), and ECG data (Day of Admission and Day 12).

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 *Mycobacterium tuberculosis* cell wall biosynthesis, as well as by generating reactive nitrogen species.

4.1.1 Acquisition

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

4.2 Formulation, Packaging, and Labeling

For this study, Pretomanid 200 mg tablets are white to off-white, odorless and oval in appearance. The formulation of Pretomanid tablets is summarized in Table 5. Study drug will be packaged in high-density polyethylene (HDPE) bottles, each containing 50 tablets, and in blister-strips comprised of a thermoformable-film and a lidding foil configuration, each strip containing 7 individual tablets. Sites will receive study product in either packaging depending on supply. Study product in either form of packaging should be stored at 15-30°C (59-86°F).

Table 5: 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

*Water is removed during drug product manufacture.

DMID or its designee will package the study drug. Study drug will be labeled and supplied according to applicable regulatory requirements.

4.2.1 Product Storage and Stability

The investigator or an approved representative (e.g., pharmacist) will ensure that the study drug is stored in a locked, secured area (with access limited to authorized study personnel) only under recommended storage conditions and in accordance with applicable regulatory requirements. The Pretomanid tablets will be stored at 15-30°C (59-86°F).

The drug is stable at 25°C at 60% relative humidity (RH) for at least two years and for 6 months at 40°C and 75% RH.

4.3 Acquisition/Distribution

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

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

A single 200 mg tablet will be administered orally on the morning of Visit 01, Day 1 with 240 mL of water following an overnight fast. All participants will receive the same study product.

4.5 Pre-determined Modification of Study Intervention/Investigational Product for an Individual Subject

There will be no dose modifications.

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

The Pretomanid will be sent to the DMID Clinical Materials Services (CMS), Fisher Bioservices, and then will be supplied to the participating VTEU site prior to the start of the study. Should the site principal investigator require additional doses of Pretomanid during the trial, further instructions are provided in the protocol-specific MOP.

After receipt of the Pretomanid, the site principal investigator is responsible for its distribution and disposition and has ultimate responsibility for drug accountability. The site principal investigator may delegate to the site research pharmacist responsibility for study product accountability. The participating VTEU site's 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 the research pharmacy. 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 VTEU site's study product accountability records and dispensing logs per the site monitoring plan. The research pharmacists at each site will maintain an up-to-date inventory of study product. Prior to administration, the research pharmacist will transfer a single dose of study product for a subject to confinement/hospital unit staff using the MOP-specific timeframe, and a record of the transfer will be made. Any unused product will be returned to Any unused tablets at the research site's pharmacy should be retained within the container in which they were supplied from the CMS. Unused Pretomanid tablets will be retained until 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 VTEU sites by the DMID Clinical Project Manager.

4.7 Assessment of Subject Compliance with Study Intervention/Investigational Product

Subject compliance is not anticipated to be an issue. Direct observation of study drug administration will be performed by confinement/hospital unit personnel per their standard procedures. If a subject vomits within two hours of dosing, they will not be redosed, they will not have further study samples taken for PK analysis, and they will be discontinued from the study. This subject could either be replaced or be reconsidered for the study after two weeks following completion of re-screening activities specified in the protocol. If a subject vomits >2 hours of dosing, they will not be redosed, but will continue with study assessments including collection of PK samples.

4.8 Concomitant Medications/Treatments

Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications recorded will include all current medications and medications taken within 30 days prior to signing the informed consent and during the study period. Medications reported in the electronic case report form (eCRF) are limited to those taken within 30 days prior to the study drug administration through day 12 of the study. Prescription and over-the-counter drugs will be included as well as herbals, vitamins, and supplements.

Systemic medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. A subject will be withdrawn for use of excluded medications. Medications in this category include the prohibited medications per the Subject Exclusion Criteria (see Section 5.2) and are summarized in Table 6.

Table 6: Prohibited CYP450 Enzyme Altering Medications/Substances per Subject Exclusion Criteria

CYP450 Inducers	CYP450 Inhibitors
Carbemazepines	Sodium valproate
Rifampicin	Isoniazid
Alcohol (chronic)*	Ketoconazole
Phenytoin	Fluconazole
Griseofulvin	Chloramphenicol
Phenobarbital	Erythromycin
Sulphonylureas	Sulfonamides
	Ciprofloxacin
	Metronidazole
	Grapefruit juice

*Chronic alcohol use for this study is the consistent consumption of greater than one drink per day or seven drinks per week.

5 STUDY ENROLLMENT AND WITHDRAWAL

The study population will be representative of subjects with varying degrees of liver disease as defined by Child-Pugh scores. The Child-Pugh scores used for eligibility in the study will be calculated at screening only. The Child-Pugh score is based on five clinical measures of liver function: total bilirubin, serum albumin, prothrombin, ascites and hepatic encephalopathy. Based on their score patients are defined as mild (5-6 points), moderate (7-9 points), or severe (10-15 points). Approximately 36 subjects between the ages of 18 and 70 years will be enrolled over an estimated 9-month period. A subject is considered enrolled in this study once they have signed a study consent form, met all eligibility criteria, and have been admitted to the confinement/hospital unit on Admission Visit (Day -1).

Subjects with hepatic impairment for this study will be mainly identified at Duke University Health System Hospitals and Clinics and the Durham Veterans Administration Hospital as well as St Louis University. Non-hepatically impaired controls will be identified from the site-specific recruitment registries and the community. Subjects for this study may also be identified through advertisement, letters, and other forms of communication.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses.

No exemptions are granted on Subject Inclusion/Exclusion Criteria in DMID-sponsored studies. Questions about eligibility will be directed toward the DMID Medical Officer.

5.1 Eligibility Criteria

5.1.1 Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria in order to participate in the study:

Inclusion Criteria for Patients with Hepatic Impairment (Groups 1-3)

1) Subject is able to give voluntary written informed consent before any study related procedure is performed.
2) 18-70 years of age, inclusive.
3) Acceptable laboratory values* obtained at screening (within 21 days prior to admission to the confinement/hospital unit) and either at or within 72 hours of admission to the confinement/hospital unit.

**Chemistry, complete blood count, AST, ALT, total bilirubin, alkaline phosphatase, albumin, and urinalysis deemed not clinically significant by the investigator.*

4) Hepatic impairment classified as Child-Pugh class A (mild), B (moderate), or C (severe) criteria at screening for Groups 1, 2, or 3, respectively, and documented evidence of hepatic cirrhosis*.

**by biopsy, nuclear scan, CT, MRI, ultrasound, or other clinically acceptable methods*

5) If female, not of childbearing potential* or agrees to avoid becoming pregnant by using acceptable contraception** during the duration of the study.

**Non-childbearing potential is defined as being post-menopausal for at least 2 years, status after bilateral oophorectomy or status after hysterectomy.*

***Females of childbearing potential must agree to use two acceptable methods of contraceptives: bilateral tubal ligation; barrier method (condom) by the male partner (even if vasectomized); hormonal contraceptives; intrauterine contraceptive devices; diaphragm in combination with contraceptive jelly, cream, foam, or spermicide; and abstinence from sexual intercourse with men.*

6) If subject is male and capable of reproduction, agrees to avoid fathering a child for three months after dosing by using an acceptable method of birth control*.

**In addition to the use of a barrier method (condom) even if 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 #5, and abstinence from sexual intercourse with women.*

7) If the subject is female, a negative serum pregnancy test at screening and a negative urine pregnancy test at admission to the confinement/hospital unit.

8) Willingness to comply with all protocol requirements.

Inclusion Criteria for Non-Hepatically Impaired Controls (Group 4)

1) Subject is able to give voluntary written informed consent before any study related procedure is performed.
2) 18-70 years of age, inclusive.

3) Subject is a healthy volunteer as determined by no clinically significant findings from medical history, physical examination, vital signs, and 12-lead ECG as determined by the Site Investigator.
4) Acceptable laboratory values* obtained at screening (within 21 days prior to admission to the confinement/hospital unit) and either at or within 72 hours of admission to the confinement/hospital unit.

**Chemistry, complete blood count, AST, ALT, total bilirubin, alkaline phosphatase, albumin, and urinalysis within the reference range for the test laboratory, unless deemed not clinically significant by the investigator.*

5) If female, not of childbearing potential* or agrees to avoid becoming pregnant by using acceptable contraception** during the duration of the study.

**Non-childbearing potential is defined as being post-menopausal for at least 2 years, status after bilateral oophorectomy or status after hysterectomy.*

***Females of childbearing potential must agree to use two acceptable methods of contraceptives: bilateral tubal ligation; barrier method (condom) by the male partner (even if vasectomized); hormonal contraceptives; intrauterine contraceptive devices; diaphragm in combination with contraceptive jelly, cream, foam, or spermicide; and abstinence from sexual intercourse with men.*

6) If subject is male and capable of reproduction, agrees to avoid fathering a child for three months after dosing by using an acceptable method of birth control*.

**In addition to the use of a barrier method (condom) even if 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 #5, and abstinence from sexual intercourse with women.*

7) If the subject is female, a negative serum pregnancy test at screening and a negative urine pregnancy test at admission to the confinement/hospital unit.
8) Willingness to comply with all protocol requirements.

5.1.2 Subject Exclusion Criteria

Subjects meeting any of these exclusion criteria during screening (Visit 00A) will be excluded from study participation:

Exclusion Criteria for Patients with Hepatic Impairment (Groups 1-3)

1) Hypokalemia (< 3.5mEq/L), severe hypomagnesemia (< 1.1 mg/dL) or severe hypocalcemia (< 7.5 mg/dL).
2) AST or ALT > 10 times the upper limit of normal.
3) Creatinine clearance <60 ml/min.
4) Inability to swallow tablets.
5) Presence of any condition or finding* which would jeopardize subject safety, impact study result validity, or diminish the subject's ability to undergo all study procedures and assessments**.

   **in the opinion of the site investigator*
   ***e.g., inability to draw PK samples*

6) History of fever or documented fever (oral temperature ≥100.4° F or ≥ 38.0° C) in the 48 hours prior to admission to the confinement/hospital unit.
7) Currently breastfeeding.
8) History of chronic tobacco/nicotine use (>10 cigarettes per day for 3 months minimum prior to admission).
9) History of clinically significant allergy or severe side effects with nitroimidazoles (e.g., Metronidazole and related substances and azole antifungals or aromatase inhibitors).
10) Receipt of an investigational drug, vaccine or biologic in a clinical trial within 30 days prior to screening.
11) Use of any over the counter (OTC) medication* within 7 days prior to admission to the confinement/hospital unit, unless** the substance would not likely impact the validity of the study results.

    **including vitamins and herbal supplements, cough and cold medications.*
    ***in the opinion of the site investigator*

12) Treatment with CYP450 enzyme altering drugs* within 7 days prior to admission to the confinement/hospital unit, unless** the substance would not likely impact the validity of the study results.

    **except hormonal contraceptives*
    ***in the opinion of the site investigator*

    NOTE: See list of CYP450 enzyme altering drugs under the concomitant medications section Table 6.

13) A positive blood screen for HIV.
14) A positive alcohol breath test (or other suitable test for alcohol) or a urine screen test for drugs of abuse* at screening and at admission to the confinement/hospital unit.

**Amphetamines, barbiturates, cocaine metabolites, marijuana, opiates, phencyclidine (PCP).*

NOTE: Results of the urine screen test can be ignored if in the opinion of the PI the results can be explained by the concomitant medications history.

15) Unwillingness to abstain from engaging in strenuous physical activity (e.g., running, bicycling, weightlifting, competitive sports) during the course of the study.
16) Consumption of grapefruit juice in the 48 hours before admission to the confinement/hospital unit, or the inability to abstain from these until completion of Day 12.
17) A QTcF interval >450 msec (males) or >450 msec (females) at screening (Visit 00A) or admission to the confinement/hospital unit (Visit 00B) or a history of prolonged QTc interval.
18) A family history* of Long QT Syndrome, premature cardiac death**, or sudden death without a preceding diagnosis of a condition*** that could be causative of sudden death.

**parents*
***due to ischemic heart disease or sudden cardiac death before 55 years of age (men) or 65 years of age (women)*
****such as known coronary artery disease, congestive heart failure, or terminal cancer*

19) Any clinically significant ECG abnormality, in the opinion of the site investigator, at screening and at admission to the confinement/hospital unit.
20) Donation of >500 mL blood within the 30 days prior to admission to the confinement/hospital unit.
21) Plans to donate blood during the study or up to 14 days after dosing.
22) Persons with a transjugular intrahepatic portosystemic shunt

Exclusion Criteria for Non-Hepatically Impaired Controls (Group 4)

1) Inability to swallow tablets.
2) Presence of any condition or finding* which would jeopardize subject safety, impact study result validity, or diminish the subject's ability to undergo all study procedures and assessments**.

**in the opinion of the site investigator*
***e.g., inability to collect PK samples*

3) History of fever or documented fever (oral temperature ≥100.4° F or ≥ 38.0° C) in the 48 hours prior to admission to the confinement/hospital unit.
4) Currently breastfeeding.
5) History of chronic tobacco/nicotine use (>10 cigarettes per day for 3 months minimum prior to admission to the confinement/hospital unit).
6) History of seizures (other than febrile seizures during childhood) or known or suspected CNS disorders that may predispose to seizures.
7) History of clinically significant allergy or severe side effects with nitroimidazoles (e.g., Metronidazole and related substances and azole antifungals or aromatase inhibitors).
8) Receipt of an investigational drug, vaccine or biologic in a clinical trial within 30 days prior to screening.
9) Use of any over the counter (OTC) medication* within 7 days prior to admission to the confinement/hospital unit, unless** the substance would not likely impact the validity of the study results.

**including vitamins and herbal supplements, antacids, cough and cold medications.*
***in the opinion of the site investigator*

10) Use of prescription medication except hormonal contraceptives within 30 days prior to admission to the confinement/hospital unit, unless* the substance would not likely impact study result validity.

**in the opinion of the site investigator*

11) Treatment with CYP450 enzyme altering drugs* within 7 days prior to admission to the confinement/hospital unit, unless** the substance would not likely impact the validity of the study results.

**except hormonal contraceptives*
***in the opinion of the site investigator*
NOTE: See list of CYP450 enzyme altering drugs under the concomitant medications section.

12) A positive blood screen for HIV.
13) A positive blood screen for hepatitis B surface antigen (HBsAg), or hepatitis C antibody.

14) A positive alcohol breath test (or other suitable test for alcohol) or a urine screen test for drugs of abuse* at screening and at admission to the confinement/hospital unit.

**Amphetamines, barbiturates, benzodiazepines, cocaine metabolites, marijuana, opiates, phencyclidine (PCP).*

15) A history of alcohol abuse or dependence within the past 1 month prior to admission to the confinement/hospital unit.
16) Unwillingness to abstain from engaging in strenuous physical activity (e.g., running, bicycling, weightlifting, competitive sports) during the course of the study.
17) Consumption of grapefruit juice in the 48 hours before admission to the confinement/hospital unit, or the inability to abstain from these until completion of Day 12.
18) A QTcF interval >450 msec (males) or >450 msec (females) at screening (Visit 00A) or admission to the confinement/hospital unit (Visit 00B) or a history of prolonged QTc interval.
19) A family history* of Long QT Syndrome, premature cardiac death**, or sudden death without a preceding diagnosis of a condition*** that could be causative of sudden death.

**parents*
***due to ischemic heart disease or sudden cardiac death before 55 years of age (men) or 65 years of age (women)*
****such as known coronary artery disease, congestive heart failure, or terminal cancer*

20) Any clinically significant ECG abnormality, in the opinion of the site investigator, at screening and at admission to the confinement/hospital unit.
21) Donation of >500 mL of blood within the 30 days prior to admission to the confinement/hospital unit.
22) Plans to donate blood during the study or up to 14 days after dosing.
23) Persons with a transjugular intrahepatic portosystemic shunt.

5.2 Withdrawal from the Study, Discontinuation of Study Product, or Study Termination

5.2.1 Reasons for Withdrawal

Subjects may voluntarily withdraw their consent at any time and for any reason, without penalty.

A subject may withdraw or may be withdrawn from the study for any of the following reasons:

- Medical disease or condition, or any new clinical findings for which continued participation, in the opinion of the site principal investigator or appropriate sub-investigator, would compromise the safety of the subject, or would interfere with the subject's successful completion of the study, or would interfere with the evaluation of responses.
- Subject no longer meets eligibility criteria.
- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
- Subject's withdrawal of consent.
- Subject lost to follow-up.
- Termination of the study.
- New information becomes available that makes further participation unsafe.

5.2.2 Handling of Withdrawals

The primary reason for withdrawal from the study will be recorded on the Study Status data collection form. Subjects will be encouraged to complete the Early Termination Visit. The Early Termination Visit procedures are listed in Section 6.3.4.

Although subjects are free to withdraw at any time or may be withdrawn by the site principal investigator or appropriate sub-investigator at any time, subjects who only receive Pretomanid will be encouraged to remain in this study for safety follow-up assessments.

Every attempt will be made to follow all adverse events, including unsolicited non-serious adverse events, serious adverse events, and new onset chronic medical conditions, ongoing at the time of early withdrawal through resolution as per applicable collection times defined for the specific type of adverse event.

In the case of subjects who fail to appear for a safety follow-up assessment, extensive effort (i.e., three documented contact attempts via phone calls, e-mails, etc., made on separate occasions and followed by a certified letter if possible) will be made to locate or recall them, or at least to determine their health status. These efforts will be documented in the subject's records.

Subjects may be replaced if they vomit study drug within two hours of dosing, if they withdraw, are withdrawn or terminated from this study or are lost to follow-up prior to completion of Day 5 (Visit 04) when the last PK samples are obtained.

5.2.3 Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by the IRB or regulatory agencies.

6 STUDY SCHEDULE

6.1 Screening (Visit 00A) (Day -22 to Day -2)

The screening visit (00A) will occur up to 21 days prior to subject enrollment to assess eligibility of study subjects. A subject is considered enrolled in this study once they have signed a study consent form, met all eligibility criteria and have been admitted to the confinement/hospital unit on Admission Visit (Day -1). The investigator or designees must provide the subject with the written informed consent form, allowing the subject to review and understand the informed consent, ask questions, and receive answers prior to signing the consent form. Screening procedures are not required to be performed on a single visit. However, all procedures should be completed within the 21-day window.

The following procedures are to occur within the screening period:

- Obtain signed and dated written informed consent. Informed consent must be obtained before any other procedures are performed.
- Review inclusion and exclusion criteria.
- Review complete medical and surgical history. All medical and surgical history occurring within the past 5 years must be noted, including drug, alcohol and tobacco use.
- Collect demographic data and current disease characteristics including age, gender, race, ethnicity, Child-Pugh class.
- Complete physical examination.
- Record medication history including the name and total daily dose of medication over the past 30 days, including vitamins, over the counter, and prescription drugs. Per exclusion criteria, determine if concomitant medications could exclude subject from study.
- Record a resting (5-minute rest period) 12-lead ECG.
- Record vital sign measurements (sitting blood pressure, sitting heart rate, height/weight, and oral body temperature).
- Draw a fasting (2 hours) blood sample for clinical chemistry tests.
- Draw blood samples for the following:
  - Serum pregnancy test for females of childbearing potential.
  - Hematology tests.
  - Coagulation Parameter: INR.
  - HIV antibodies.
  - Hepatitis B surface antigen and hepatitis C antibody.

- Alcohol breath test or other suitable test for alcohol (e.g., blood alcohol test).
- Calculate Child-Pugh score (Appendix B) using historical information.
- Collect urine samples for urinalysis and drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, cannabinoids, and phencyclidine (PCP)).
- The investigator must review all laboratory results and screening criteria before a subject initiates the Study Day 1 Visit.
- Subjects who do not qualify for the study based on the results of the screening procedures do not need to return for any subsequent visit.

Documentation of the subject's fulfillment of the entry criteria, for all subjects considered for the study and subsequently included or excluded, is to be completed. Documentation of screening failure details may be recorded using eligibility screening forms or a subject screen failure log.

A subject may be re-screened if there is a transient disease status (e.g., subject complained of a "cold or fever" and met a temporary delaying enrollment criterion of acute illness or fever). No subject may be screened **more than twice due to a screening failure result as defined above.** Please contact the DMID Medical Officer for clarification or questions regarding screening failures.

6.2 Admission (Visit 00B) (Day -1)

Subjects will be admitted to the confinement/hospital unit on Day -1 (Visit 00B). The following procedures are to occur on the Admission Day:

- Review inclusion and exclusion criteria.
- Obtain interim medical/surgical history, including an assessment for new medical conditions and symptoms by interview of subjects and note any changes since the previous clinic visit.
- Complete physical examination.
- Record concomitant medications including name and total daily dose of all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Per exclusion criteria, determine if concomitant medications could exclude subject from study.
- Record a resting (5-minute rest period) 12-lead ECG. May be performed within 72 hours of admission to the confinement unit.
- Record vital sign measurements (sitting blood pressure, sitting heart rate, weight, and oral body temperature).
- Urine pregnancy test for females of childbearing potential.

- Draw a fasting (2 hour) blood sample for clinical chemistry tests. May be performed within 72 hours of admission to the confinement unit.
- Draw blood samples for the following (these can be drawn with fasting draw for chemistry tests) May be performed within 72 hours of admission to the confinement unit.
  - Hematology tests.
  - Coagulation parameter: INR.
- Alcohol breath test or other suitable test for alcohol (e.g., blood alcohol test).
- Collect urine sample for urinalysis and drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, cannabinoids, and phencyclidine (PCP).

If screening laboratory tests are performed within 72 hours of admission to the confinement/hospital unit, the tests do not have to be repeated with the exception of the urine pregnancy test for females of childbearing potential and the urine drug screen for all subjects, which will be repeated. If a subject meets eligibility criteria and is admitted, but is not dosed, the subject could be re-evaluated for participation in the study. If subject is re-evaluated within 3 months of serologic testing, serology testing (HIV, HCV, HBsAg) will not be repeated. The subject's history will be reviewed to ensure they do not have any new risk factors since the last serological testing that would predispose them to hepatitis or HIV.

6.3 Planned Study Visits

6.3.1 Dosing (Visit 01) (Day 1) and Confinement/Hospitalization (Visit 01A to Visit 01J) (Day 1 and Day 2)

Prior to dosing on Day 1, subjects will have pharmacokinetic samples collected (10 minutes pre-dose) and vital signs (sitting blood pressure, sitting heart rate, weight, and oral body temperature) obtained (30 minutes pre-dose). Subjects will then be administered a single oral 200 mg tablet of Pretomanid the morning of Visit Day 1 with 240 mL of water following an overnight fast, and the AE and SAE assessment period will begin. Vital signs (sitting blood pressure, sitting heart rate, and oral body temperature) will also be obtained 30 minutes after dose administration. Events that occur between the time of consent and administration of study drug will be recorded in the medical history. Subjects will be confined in the confinement/hospital unit overnight. Subjects will be discharged after assessments on Day 2 are completed (the 36-hour PK sampling time point).

After dosing, subjects will be assessed at 1, 2, 4, 5, 6, 8, 12-, 16-, 24- and 36-hours post-dose. For each assessment, the PK sample will be collected, AEs and SAEs will be assessed, and vital

signs (sitting blood pressure, sitting heart rate, and oral body temperature) will be recorded. A supine blood pressure will be obtained if the sitting blood pressure is abnormal. Weight will be collected at the 36-hour sampling time point. Instruct the subjects to volunteer any information regarding AEs/SAEs at any time during the study or query the subjects with an open question regarding any AEs/SAEs they may be experiencing (for example, "How do you feel?"), and document the findings.

Approximately 36 to 48 hours after the dose, depending on site preference, subjects will be discharged.

At 36 hours:

- Draw a fasting (2 hours) blood sample for clinical chemistry tests. This laboratory can be performed prior to the 36-hour post-dose draw to ensure fasting.
- Draw blood samples for the following (these can be drawn with fasting draw for chemistry tests):
    - Hematology tests
    - Coagulation parameter: INR
    - Collect urine samples for urinalysis.

Depending on site preference, participants may be discharged from the confinement/hospital unit.

6.3.2 Follow-up (Visits 02, 03, and 04) (Day 3, Day 4, and Day 5)

Subjects discharged at Day 2 will return for a follow-up visit on Day 3 (Visit 02). Subjects remaining in the confinement/hospital unit at Day 2 will complete all Day 3 (Visit 02) procedures as outlined for all subjects. After completion of Day 3 procedures those participants may be discharged from the hospital/confinement unit.

All subjects will return for follow-up visits on Days 4 (Visit 03) and 5 (Visit 04).

The following procedures are to occur on Days 3 (Visit 02), 4 (Visit 03) and 5 (Visit 04):

- Obtain interim medical/surgical history, including an assessment for new medical conditions and symptoms by interview of subjects and note any changes since the previous clinic visit.
- A targeted review of body systems will be obtained at these visits focused on liver disease and will include questions pertaining to development of ascites, jaundice, pruritis,

gastrointestinal bleeding, and encephalopathy. If the subject answers yes to any of these questions, a targeted physical exam will be performed.
- Record concomitant medications including name and total daily dose of all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Per exclusion criteria, determine if concomitant medications could exclude subject from study.
- Record vital sign measurements (sitting blood pressure, sitting heart rate, weight, and oral body temperature).
- Obtain blood sample for PK analysis.
- Information regarding AEs/SAEs will be assessed and recorded on the appropriate data collection form.
- Day 5 (in addition to the assessments listed above):

    - Draw a fasting (2 hours) blood sample for clinical chemistry tests
    - Draw blood samples for the following (these can be drawn with fasting draw for chemistry tests):

        - Hematology tests.
        - Coagulation parameter: INR.
    - Collect urine samples for urinalysis.

6.3.3 Final Study Visit (Visit 05) (Day 12)

The final study visit will occur 11 days after Pretomanid administration. The following procedures are to occur on Day 12:

- Complete physical examination.
- Obtain interim medical/surgical history, including an assessment for new medical conditions and symptoms by interview of subjects and note any changes since the previous clinic visit.
- A targeted review of systems will be obtained at these visits focused on liver disease and will include questions pertaining to development of ascites, jaundice, pruritus, gastrointestinal bleeding, and encephalopathy.
- Record concomitant medications including name and total daily dose of all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Per exclusion criteria, determine if concomitant medications could exclude subject from study
- Record a resting (5-minute rest period) 12-lead ECG.

- Record vital sign measurements (sitting blood pressure, sitting heart rate, weight and oral body temperature).
- Draw a fasting (2 hours) blood sample for clinical chemistry tests.
- Draw blood samples for the following:

    - Serum pregnancy test for females of childbearing potential.
    - Hematology tests.
    - Coagulation Parameter: INR.

- Collect urine samples for urinalysis.
- Information regarding AEs/SAEs will be assessed and recorded on the appropriate data collection form.

6.3.4 Early Termination Visit

The following assessments will be performed at the early termination visit for subjects who withdraw, or are withdrawn or terminated from this study:

- Obtain interim medical/surgical history, including an assessment for new medical conditions and symptoms by interview of subjects and note any changes since the previous clinic visit.
- Complete physical examination
- A targeted review of systems will be obtained at these visits focused on liver disease and will include questions pertaining to development of ascites, jaundice, pruritis, gastrointestinal bleeding, and encephalopathy.
- All concomitant medications will be recorded on the appropriate data collection form.
- Information regarding AEs/SAEs will be assessed and recorded on the appropriate data collection form.
- Urine or serum pregnancy test.

6.4 Unscheduled Study Visits

Unscheduled visits are allowed for the following reasons:

- Management of an AE or SAE.
- Performance of additional laboratory tests for clinically abnormal test values (e.g., confirming elevated levels of liver enzymes).

- Any time the investigator feels that it is clinically appropriate for subject safety.
- Urine or serum pregnancy test.
- PK sampling.

Unscheduled visits will be labeled and documented by the number of the visit the subject just completed, followed by the letter "S" to denote the first unscheduled visit (e.g., 01AS, 02S), the letter "T" to denote second unscheduled visit, etc.

6.5 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the site principal investigator, or other study personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Non-compliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site principal investigator and other study personnel to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID, via the SDCC's IDES.

All protocol deviations, as defined above, must be addressed in study subject or non-subject specific data collection forms. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site principal investigator and other study 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 subjects during the screening visit. Subjects 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, kidney, urologic system, nervous system, blood, lymph glands, 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.

Medication history (concomitant medications) will include a review of all current medications and medications as specified in Section 4.8.

A physical examination will be performed by a licensed clinician listed on the Form FDA 1572, to include MD, NP and PA. The comprehensive physical examination must include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; neurological; chest and lungs; cardiovascular; abdomen (liver and spleen); lymph nodes; musculoskeletal, and extremities. Assessments of any specific signs or symptoms reported by the subject must also be performed and documented along with any other findings of note. Findings from the screening must be characterized as either normal or abnormal, and if abnormal, a description of the abnormality must be provided. Following the screening visit physical examination, changes must be classified as new, worsened, or improved from those at screening.

Vital sign measurements must include the subject's sitting heart rate, sitting blood pressure (mm Hg), height (at screening only), weight (at screening, admission day, prior to dosing, 36-hour, 48-hour, 72-hour, 96-hour and Day 12 time points) and oral body temperature (ºC). If a physiologic parameter, e.g., vital signs, is outside of the protocol-specified range, 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"). A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized blood pressure cuff). If there is an abnormal blood pressure measurement, the subject should lay down for 10 minutes and then the measurement should be repeated while the subject is awake and resting supine.

In addition, a resting 12-lead ECG will be performed at screening, admission, and the final visit.

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

7.1.1 Assessment of Subject Compliance with Study Intervention/Investigational Product

Subject compliance is not anticipated to be an issue. Direct observation of study drug administration will be performed by confinement/hospital unit personnel per their standard procedures. If a subject vomits within two hours of dosing, they will not be redosed, they will not have further study samples taken for PK analysis, and they will be discontinued from the study. This subject could either be replaced or be reconsidered for the study after two weeks following completion of re-screening activities specified in the protocol. If a subject vomits >2 hours of dosing, they will not be redosed, but will continue with study assessments including collection of PK samples.

7.2 Laboratory Evaluations

7.2.1 Clinical Laboratory Evaluations

Clinical laboratory evaluations will include the following safety and screening labs:

- Blood Screen of hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibodies
- Urine screen test for drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, cannabinoids, and phencyclidine (PCP)
- Chemistry parameters (2 hour fasting): total bilirubin, serum albumin, potassium, magnesium, calcium, serum creatinine, BUN, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and CBC with differential. For patients with severe hepatic impairment (Child-Pugh C) an ammonia level will be drawn at screening and will be used as a baseline reading for safety purposes, not as a study entry criterion.
- Hematology parameters: hematocrit, hemoglobin, red blood cell count, white blood cell count, automated differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes), and platelet count.
- Coagulation parameter: INR

- Urinalysis: A macroscopic urine test (dip) will be performed at the confinement/hospital unit. If the macroscopic urine test is abnormal, a microscopic Urinalysis including color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrites, and leukocyte esterase will be performed.
- Women of childbearing potential must complete a serum pregnancy test in the screening period and on Day 12. A urine pregnancy test will be performed on the day of admission. A negative result is required for continued participation in the study.
- Alcohol breath test or other suitable test for alcohol (e.g., blood alcohol test)

The total blood volume collected for this study will be approximately 160.5 mL including:

- Visit 00A (Screening): Chemistry, hematology, serology (HIV, HCV, and HBsAg), coagulation, and pregnancy tests for a total of approximately 27.5 mL.
- Visit 00B (Admission or within 72 hours of Admission): Chemistry, hematology, and coagulation for a total of approximately 11.5 mL.
- Visits 01-01I (Day 1): PK samples - 6 mL blood/sample x 10 samples for a total of approximately 60 mL.
- Visit 01J (36 hours after dosing): Chemistry, hematology, PK sample, and coagulation tests for a total of approximately 17.5 mL.
- Visit 02 (Day 3) and Visit 03 (Day 4): PK samples - 6 mL blood/sample x 2 samples for a total of approximately 12 mL.
- Visit 04 (Day 5 Visit): Chemistry, hematology, PK sample, and coagulation tests for a total of approximately 17.5 mL.
- Visit 05 (Day 12 Visit): Chemistry, hematology, coagulation, and pregnancy tests for a total of approximately 14.5 mL.
- To avoid multiple needle sticks (venipunctures), after the first blood draw, a venous catheter will remain in place until discharge from the confinement/hospital unit.

7.2.2 Special Assays or Procedures

7.2.2.1 ECG

A standard 12-lead ECG must be recorded in the screening period, on the day of admission, and Study Day 12 after the subject has been resting for at least five minutes. The heart rate from the ECG machine should not be used as part of the vital sign measurements.

7.2.2.2 PK Samples

Blood samples will be collected (K2 EDTA tubes) in this study to characterize the pharmacokinetics of Pretomanid in non-hepatically impaired controls and subjects with hepatic impairment (see PK sampling points in Appendix A, Schedule of Events).

The exact date and time of all pharmacokinetic blood samples should be recorded. The pre-dose blood sample should be collected within 10 minutes 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 collections at 24 and 36 hours after dosing, collection times must be +/- 1 hour, and at 48, 72, and 96 hours after dosing, they must be +/-4 hours.

Dates should be recorded in an unambiguous format (e.g., DD MMM YYYY), and time should be recorded to the nearest minute (e.g., HH:MM using the 24-hour clock). Blood samples not drawn or drawn out of the defined window should be recorded and reported as protocol deviations.

7.2.2.3 Specimen Preparation, Handling, and Shipping

7.2.2.1 Instructions for Specimen Preparation, Handling, and Storage

Instructions related to handling of safety laboratory samples and pharmacokinetic samples are provided in study documents (e.g., laboratory manual, MOP).

7.2.2.2 Laboratory Specimen Shipping

Clinical laboratory assessments will be performed at Duke and SLU. PK samples will be shipped on dry ice to Fisher BioServices prior to sending to the bioanalytical laboratory.

Fisher BioServices

20439 Seneca Meadows Parkway

Germantown, MD 20876

Telephone: 240-477-1350

Email: DMID.CMS@ThermoFisher.com

Fax: 240-477-1360

The frequency and conditions of shipment will be described in the MOP.

8 ASSESSMENT OF SAFETY

8.1 Assessing and Recording Safety Parameters

8.1.1 Adverse Events (AEs)

An adverse event is defined as any untoward medical occurrence in a subject regardless of its causal relationship to study treatment. An adverse event can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study-drug related. Included in this definition are any newly occurring events or previous condition that has increased in severity or frequency since the administration of study drug.

All adverse events that are observed or reported by the subject during the study (from the time of the first dose of study drug until the Study Day 12 Visit) must be reported, regardless of their relationship to study drug or their clinical significance.

8.1.1.1 Adverse Events Grading

Severity of Event:

AEs will be assessed by the investigator using a protocol-defined grading system (toxicity table included as an appendix). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

Relationship to Study Product: The assessment of the AE's relationship to study product will be done by the licensed study physician indicated on the Form FDA 1572 and 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. The relationship to study product will be assessed for AEs using the terms related or not related:

- 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

A serious adverse event (SAE) is any adverse event occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect in an offspring of a subject taking study drug
- Is an important medical event.

The term “life-threatening” refers to an event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above, however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an adverse event; however, for females, information will be collected for any pregnancies which occur during study drug administration until the Study Day 12 Visit. Male subjects should notify the study team if a pregnancy occurs in a partner within 3 months after study drug administration. If the male subject reports a pregnancy, information about complications during pregnancy, labor and delivery, or congenital birth defects will be

collected from the male subject's female partner using a site-specific Pregnant Partner Information and Authorization form. Certain pregnancy outcomes (congenital anomaly or birth defect in an offspring of a subject taking study drug) will require submission as an SAE. (See Section 8.3.1)

The investigator is responsible for reporting to the Sponsor or designee all adverse events and SAEs that are observed or reported by the subject during the study (from Day 1 until the Study Day 12 Visit), regardless of their relationship to study drug or their clinical significance. All SAEs reported or observed during the study must be followed until return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic. The Sponsor or designee may contact the investigator to obtain additional information on any SAE which has not resolved at the time the subject completes the study.

8.2 Specification of Safety Parameters

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

8.3 Reporting Procedures

AE and SAE reporting is to occur at Visits 01 through 05.

Any medical condition that is present at screening or admission will be considered as pre-existing reported on the Medical History form and will not be reported as an AE. If the severity or frequency of any pre-existing medical condition increases during the study period, then it will be recorded as an AE.

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 Serious Adverse Events

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

DMID Pharmacovigilance Group

Clinical Research Operations and Management Support (CROMS)

6500 Rock Spring Drive, Suite 650

Bethesda, MD 20817, USA

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: PVG@dmidcroms.com

In addition to the SAE form, selected SAE data fields must also be entered into AdvantageEDC. 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 Independent Safety Monitor (ISM) when they are provided 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 subject safety and protocol conduct.

At any time after completion of the study, if the site principal investigator or appropriate sub investigator becomes aware of an SAE that is suspected to be related to study product, the site principal investigator 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 site principal investigator or appropriate sub-investigator, DMID, the Investigational New Drug (IND) sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. DMID will notify FDA and all participating site principal investigators (i.e., all principal investigators to whom the Sponsor is providing drug under its IND(s) or under any principal investigator'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 21 CFR Part 312.32. DMID will also notify 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 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 the FDA at least annually in a summary format.

8.3.3 Reporting of Pregnancy

Pregnancies occurring in study subjects will be reported via AdvantageEDC on the Pregnancy Report form. Efforts will be made to follow all pregnancies reported during the course of the study to pregnancy outcome pending the subject's permission. For females, pregnancies will be reported from the time of study drug administration until after the study is completed (Study Day 12). Male subjects should contact the study team to report a pregnancy in a partner up to 3 months after study drug administration. If the male subject reports a pregnancy, information about complications during pregnancy, labor and delivery, or congenital birth defects will be collected from the male subject's female partner using a site-specific Pregnant Partner Information and Authorization form.

8.4 Type and Duration of Follow-up of Subjects after Adverse Events

AEs will be collected, assessed, and followed through the resolution from the time of receipt of study drug through study Day 12.

SAEs will be followed from the time of the time of receipt of study drug through resolution even if this extends beyond the study-reporting period (approximately 12 days after study drug administration). 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 data collection form.

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

The site principal investigator or appropriate sub-investigator is responsible for reporting all AE/SAEs that are observed or reported during the study, regardless of the relationship to study product. AE/SAEs, abnormal clinical laboratory test values, or abnormal clinical findings will be documented, reported, and followed appropriately.

8.6 Halting Rules

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

1. *Any death occurring during the study that was not the result of trauma or accident.*
2. *2 or more hepatically impaired subjects experience a serious adverse event (other than death), related to study product.*
3. *2 or more non-hepatically impaired subjects experience a serious adverse event (other than death), related to study product.*
4. *3 or more subjects develop a severe (Grade 3) abnormality in the same laboratory parameter, regardless of relatedness to study product. Exception to this would be:*
    a. *Grade 3 CK elevation without systemic complaints*
    b. *If there are obvious and acceptable physiological explanations for a Grade 3 abnormality (e.g., Grade 3 hematuria in a menstruating female).*

In this case, the study will be suspended pending review and discussion of all appropriate study data by the Investigator, Sponsor or DMID Medical Monitor, the Independent Safety Monitor, and the Safety Monitoring Committee. The study will not be re-started until all parties have agreed to the course of action to be taken, the IRB and Food and Drug Administration (FDA) have been notified, and IRB approval is obtained.

8.7 Safety Oversight (ISM plus SMC)

8.7.1 Independent Safety Monitor (ISM)

The ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. The ISM will review SAEs in real time and

other AEs as needed and provide an independent assessment to DMID. Each participating VTEU site will have an ISM with experience in infectious diseases or internal medicine, in close proximity to the VTEU site, and have the authority to readily access study participant records.

8.7.2 Safety Monitoring Committee (SMC)

The SMC will meet at several time points during the study (see Section 10.5.1) to monitor subject safety. The SMC will consist of independent evaluators who will have no relationship with the conduct of the trial. The SMC will operate under the rules of a DMID-approved charter that will be approved at the organizational meeting of the SMC. Within the Charter each data element that the SMC needs to assess will be clearly defined and may include safety and ECG outcomes. The SMC will provide recommendation regarding enrollment following enrollment of the mild hepatic impairment group (Child-Pugh A) and after enrollment of the first three subjects in the moderate or severe hepatic impairment groups (Child-Pugh B or Child-Pugh C). The study unblinded statistician may provide independent analyses to the SMC as needed. The SMC will advise DMID of its findings. In the event of study halt, the SMC will be consulted to review the data and provide a recommendation related to the continued dosing of the subjects.

9 HUMAN SUBJECTS PROTECTION

9.1 Ethical Standard

The site principal investigator will ensure that this trial is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable. The site principal investigator's Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

9.2 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 subjects. 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 GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Subjects), other federal, state, and local regulations. The IRB must be registered with the Office of Human Research Protection (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 subjects, prior to recruitment and enrollment of subjects.

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 subjects 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 subject.

9.3 Informed Consent Process

The site principal investigator will choose subjects in accordance with the eligibility criteria detailed in Section 5. Before any study procedures are performed, subjects must sign an informed consent form and subjects must provide consent as appropriate for age that complies with the requirements of 21 CFR Part 50 and 45 CFR 46 and the local IRB.

Informed consent is a process that is initiated prior to the individuals agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, including pre-screening of subjects for eligibility, subjects will receive a comprehensive explanation of the proposed study procedures and study interventions/products, including the nature and risks of this trial, alternate therapies, any known AEs, the investigational status of the components, and the other elements that are part of obtaining proper informed consent. Subjects will also receive a detailed explanation of the proposed use and disclosure of their protected health information, including specifically their serum samples. Subjects will be allowed sufficient time to consider participation in the trial, after having the nature and risks of the trial explained to them and have the opportunity to discuss the trial with their family, friends or legally authorized representative or think about it prior to agreeing to participate.

Informed consent forms describing in detail the study interventions/products, study procedures, risks and possible benefits are given to the subjects. The informed consent form must not include any exculpatory statements. Informed consent forms will be IRB-approved, and the subject will be asked to read and review the appropriate document. Upon reviewing the appropriate document, the site principal investigator (or designee) will explain the research study to the subject and answer any questions that may arise. Subjects must sign the informed consent form, and written documentation of the informed consent process is required prior to starting any study procedures/interventions being done specifically for the trial, including administering study product.

DMID will provide the site principal investigator, in writing, any new information that significantly impacts the subjects' risk of receiving the investigational product. This new information will be communicated by the site principal investigator to subjects who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be re-consented, if necessary.

Study personnel may employ IRB-approved recruitment efforts prior to obtaining the subject's consent; however, before any study procedures are performed to determine protocol eligibility an

informed consent form must be signed. Subjects will be given a copy of all informed consent forms that they sign.

By signing the informed consent form, the subject agrees to complete all evaluations required by the trial, unless the subject withdraws voluntarily, or is withdrawn or terminated from the trial for any reason.

The rights and welfare of the subjects will be protected by emphasizing to the subject that the quality of their medical care will not be adversely affected if they decline to participate in or withdraw from this trial.

New information will be communicated by the site principal investigator to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be re-consented per IRB requirements, if necessary. Subjects will be given a copy of all informed consent forms that they sign.

9.3.1 Exclusion of Special Populations

This trial will be inclusive of all adult persons who meet the Subject Inclusion/Exclusion Criteria, regardless of religion, sex, or ethnic background. No persons under the age of 18 will be enrolled in this study.

9.4 Future Use of Stored Specimens

Samples will not be banked for future use.

9.5 Subject Confidentiality

Subjects will have code numbers and will not be identified by name. Subject confidentiality is strictly held in trust by the participating site principal investigators, their study personnel, the Sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All information provided by the Sponsor and all data and information generated by the participating VTEU site as part of the trial (other than a subject's medical records) will be kept confidential by the site principal investigator and other study personnel to the extent permitted by

law. This information and data will not be used by the site principal investigator or other study personnel for any purpose other than conducting the trial. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the site principal investigator or other study personnel; (2) information which is necessary to disclose in confidence to an IRB solely for the evaluation of the trial; (3) information which is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in Section 15. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

The study monitor, applicable regulatory authorities, such as the FDA, or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the site principal investigator. This includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The participating VTEU site will permit access to such records.

9.6 Study Discontinuation

If the study is discontinued, enrolled subjects will continue to be followed for safety assessments. No further doses of Pretomanid will be administered.

10 STATISTICAL CONSIDERATIONS

10.1 Responsibility for Analysis

The statistical analysis of the data obtained from this study will be the responsibility of the SDCC. A separate statistical analysis plan will be written and finalized prior to the clinical database lock.

10.2 Study Hypotheses

10.2.1 Primary Hypothesis

For the primary objective, the hypothesis is that Pretomanid PK parameters following drug exposure will differ between patients with hepatic impairment and non-hepatically impaired controls.

10.2.2 Secondary Hypotheses

No formal hypothesis will be tested for the secondary safety analyses.

10.3 Sample Size Considerations

The sample size was determined based on feasibility and FDA guidance (18). Following FDA guidance, enrollment is anticipated to include at least 6 subjects in each arm. This sample size is expected to estimate the group differences with adequate precision. Previous studies of Pretomanid have estimated coefficients of variation (CV) of <21% after 250 mg dosing (N=8) and <33% after 200 mg dosing (N=6) for single dose AUC(0-∞) and Cmax in healthy adult subjects (10). Assuming an observed two-fold difference between the group with severe hepatic impairment and matched controls with no correlation between matched pairs and a coefficient of variation of 25%, a 90% confidence interval for the fold difference between severely impaired and non-hepatically impaired group is (1.55, 2.59).

10.4 Treatment Assignment Procedures

10.4.1 Randomization Procedures

There is no randomization performed for this study. Subjects are assigned to the 4 study groups based on the Child-Pugh score, with approximately 6 subjects in each of the hepatic impairment

groups (Groups 1, 2, and 3) and approximately 18 non-hepatically impaired subjects in Group 4. The group designations are:

Group 1: Child-Pugh A (Mild)

Group 2: Child-Pugh B (Moderate)

Group 3: Child-Pugh C (Severe)

Group 4: Non-hepatically impaired controls

Subjects with hepatic impairment will be enrolled starting with subjects who have mild disease. Subjects with moderate and severe hepatic disease will be enrolled simultaneously. If enrollment into the severe hepatic impairment group (Child-Pugh C) is completed before that of the moderate hepatic impairment group (Child-Pugh B), results from the Child-Pugh C cohort will be analyzed to determine the impact of severe hepatic impairment on the PK of Pretomanid and the need to continue enrollment of persons with moderate hepatic impairment (Child-Pugh B) will be reevaluated to determine whether the objectives of the study have been met. Non-hepatically impaired subject matches will be dosed only after the corresponding subject with hepatic impairment has completed the 36-hour blood sampling procedure. The group of up to 18 subjects with normal hepatic function will be matched to the 18 subjects with hepatic impairment based on age (± 10 years) and body weight at screening (± 20% body weight). A control subject may be matched to more than one hepatic impairment subject if warranted, and if the subjects to which they are matched are not in the same disease severity group. Therefore, there may be less than 18 subjects with normal hepatic function.

10.4.2 Masking Procedures

Not applicable; this is an open-label study.

10.5 Planned Interim Analyses

10.5.1 SMC Safety Review

Two SMC interim safety reviews are planned.

1. After 3 subjects in Group 1 (Child-Pugh A (Mild)) are enrolled and complete follow-up through Day 12 (Visit 05). This review will be completed prior to opening enrollment for Group 2 (Child-Pugh B (Moderate) and Group 3 (Child-Pugh C (Severe)). Enrollment in Group 1 and Group 4 may continue during the safety review.

2. After 3 subjects in Group 2 (Child-Pugh B (Moderate)) or Group 3 (Child-Pugh C (Severe)) are enrolled and complete follow-up through Day 12 (Visit 05). Enrollment of Group 2, Group 3, and Group 4 may continue during the safety review.

Each interim safety review will present data by cohort, including AEs, SAEs, clinical laboratory tests, vital signs, PK analysis and 12-lead ECG. Cumulative data for all subjects enrolled will be included in the safety reviews.

Interim safety reviews will not include any statistical hypothesis testing.

10.6 Analysis Plan

10.6.1 Analysis Sets

The following analysis sets are defined for the analysis and reporting of data.

10.6.2 Safety Analysis Set

The safety analysis set will include all participants who receive study product.

10.6.3 PK Analysis Set

The PK analysis set will consist of participants in the safety population who have evaluable plasma PK samples for the estimation of Cmax or AUC (0-∞). This set will be used to assess the PK endpoints. Any subjects or data values excluded from this analysis set will be identified, along with their reason for exclusion, in the CSR.

10.6.4 Primary PK Analysis

All PK parameters will be estimated through a non-compartmental analysis using a validated installation of WinNonlin version 6.3 or later. The recorded true time points will be used for PK calculation. Estimated total plasma PK parameters will include the following:

- AUC(0-∞): Area under the concentration time-curve extrapolated to infinity
- AUC(0-last): Area under the concentration time-curve to the last concentration above the lower limit of quantitation
- Cmax: Maximum concentration
- Tmax: Time of maximum concentration
- t(1/2): Apparent terminal elimination half-life
- CL/F: Apparent oral clearance calculated from Dose/AUC(0-∞)

- Vd/F: Apparent Volume of Distribution

Details of the statistical analysis will be included in the statistical analysis plan and may not be limited to the following: Hepatic impairment group means of drug exposure will be estimated through analysis of variance (ANOVA) models with impairment group as a fixed effected for the log-transformed estimated parameters. If the PK analysis set contains a matched control for each participant in all impairment groups, correlation between these matched pairs will be incorporated into the ANOVA model. Pairwise fold differences in drug exposure will be calculated to compare each of the mild, moderate, and severe impairment groups with non-hepatically impaired controls. Fold differences will be estimated using 90% confidence intervals. Tmax will be summarized in each group using the median and range, and group differences will be assessed using nonparametric confidence intervals.

Linear and semilogarithmic concentration-time profiles will also be plotted by impairment and non-hepatically impaired groups. Calculated PK parameters will be summarized using standard summary statistics (such as mean, median, standard deviation, coefficient of variation, or range) by impairment and non-hepatically impaired groups.

10.6.5 Secondary Safety Analyses

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

10.6.5.1 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities® (MedDRA). All AEs that occur after the receipt of study product will be summarized using frequency counts and percentages. Summaries will be presented by hepatic impairment and non-hepatically impaired groups MedDRA level hierarchy (system organ class and preferred term) as follows:

- Overall (i.e., regardless of severity or relationship to treatment)
- By severity grade (mild, moderate, or severe)
- By relationship to study product

Unless otherwise specified, at each level of subject summarization in reporting the incidence of the AEs, a subject will be counted once if the subject 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.

Serious AEs (SAEs) will also be summarized by hepatic impairment group and non-hepatically impaired group and relationship.

10.6.5.2 Laboratory Parameters

Descriptive summary statistics for laboratory data at admission, Day 2, Day 5, Day 12, and change from admission for each post-treatment day will be presented by hepatic impairment and non-hepatically impaired groups. For change from admission summaries, subjects with an undefined change from admission, because of missing data, will be excluded. Shift tables, showing individual subject changes from admission to Days 2, 5, and 12 will be presented for each laboratory parameter, by hepatic impairment and non-hepatically impaired groups, using the normal ranges from the central laboratory. Subjects with clinically significant outliers will be identified in listings. Of note, if screening laboratory tests are performed within 72 hours of admission to the confinement/hospital unit, the tests do not have to be repeated with the exception of the urine pregnancy test for females of childbearing potential and the urine drug screen for all subjects, which will be repeated.

10.6.5.3 Vital Signs

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

10.6.5.4 ECG Data

ECG intervals (RR, QRS, QT, and PR) will be summarized at the day of admission and Day 12 using descriptive statistics.

In addition, the proportion of subjects with bradycardia, tachycardia, conduction system disease (e.g., prolongation of the PR Interval, bundle branch block, fascicular block), arrhythmia (e.g., atrial fibrillation, atrial flutter, premature atrial/ventricular contractions, ventricular tachycardia), and Brugada pattern will be summarized by hepatic impairment group.

10.6.6 Demographics and Screening Summaries

Demographic variables (age, gender, race, and ethnicity) and screening characteristics (height, weight) will be summarized by hepatic impairment and non-hepatically 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, 25th and 75th quartiles, minimum and maximum values. For categorical data, frequency counts and percentages will be reported. Of note, weight is measured at specified subsequent visits and therefore will be summarized for all available post-dose visits, in addition to screening.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The participating VTEU site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. The participating VTEU 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 study records for the purposes of quality assurance reviews, audits, monitoring and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the participating VTEU site is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all trial-related source data/data collection forms, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The SDCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

13 DATA HANDLING AND RECORD KEEPING

The site principal investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported.

The SDCC will provide data collection forms to be used by the site as source documents. All data collection forms should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a change or correction, cross out the original entry with a single line and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the eCRF derived from the data collection forms should be consistent with the data collection forms or the discrepancies should be explained. The Sponsor and/or its designee will provide guidance to site principal investigators and other study personnel on making corrections to the data collection forms and eCRF.

13.1 Data Management Responsibilities

All data collection forms, and laboratory reports must be reviewed by the clinical team and data entry personnel, who will ensure that they are accurate and complete. Adverse events must be recorded on the appropriate data collection form, assessed for severity and relationship, and reviewed by the site principal investigator or appropriate sub-investigator.

Data collection is the responsibility of the study personnel at the participating VTEU site under the supervision of the respective site principal investigator. During the study, the site principal investigator must maintain complete and accurate documentation for the study.

The SDCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

13.2 Data Coordinating Center/Biostatistician Responsibilities

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

The data coordinating center 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, AE/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values) and PK data will be entered into a 21 CFR 11-compliant Internet Data Entry System (IDES) 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. Clinical data will be entered directly from the data collection forms completed by the study personnel.

13.4 Types of Data

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

13.5 Timing/Reports

A final report will be prepared following the availability of the cumulative safety and PK data at the completion of the study. Interim statistical reports may be generated as deemed necessary and appropriate by DMID. Safety summary reports may be generated for the SMC.

13.6 Study Records Retention

Study records and reports, including but not limited to eCRFs, source documents, informed consent/assent forms), laboratory test results, and medication inventory records, shall be retained for at least six years after the study is completed, but no less than 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified. The site must contact DMID for authorization prior to the destruction of any study records.

14 CLINICAL MONITORING

14.1 Site Monitoring Plan

Site monitoring is conducted to ensure that the human subject 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 the study 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, informed consent/assent forms, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to the study site, study personnel, and all study documentation according to the DMID-approved monitoring plan. Study monitors will meet with site principal investigators to discuss any problems and actions to be taken and document visit findings and discussions.

15 PUBLICATION POLICY

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, http://publicaccess.nih.gov/
- NIH OER Grants and Funding, http://grants.nih.gov/grants/oer.htm

Following completion of the study, the lead principal investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov* (http://clinicaltrials.gov/), which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy. As this is a Phase I study, it is exempt from this policy.

It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration, before considering the results of the trial for publication.

For trials in which DMID is not the IND/IDE Sponsor, or there is no IND/IDE, and DMID does not provide data management services, it is the responsibility of the investigator to register the trial and post results in compliance with Public Law 110-85, the Food and Drug Administration

Amendments Act of 2007 (FDAAA). However, this is an IND study, and DMID is the IND sponsor.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases

*Journal Citation: De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004; 351:1250-1

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17 APPENDICES

Appendix A. Schedule of Events

Study Visit	00A	00B	01	01A	01B	01C	01D	01E	01F	01G	01H	01I	01J	02	03	04	05	Early Term
Study Day	**Screen** -22 to -2	**Admission -1**	1	1	1	1	1	1	1	1	1	2	2	3	4	5	12	
Time (Window)			**0** (-10 min)	**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 hrs** (+/-10 min)	**16 hr** (+/-10 min)	**24 hrs** (+/-1 hr)	**36 hrs** (+/-1 hr)	**48 hrs** (+/-4 hrs)	**72 hrs** (+/-4 hrs)	**96 hrs** (+/-4 hrs)		
Informed Consent	X																	
Review Inclusion/ Exclusion Criteria	X	X																
Demographics [1]	X																	
Medical/Surgical History[2]	X	X												X	X	X	X	X
Physical Examination[3]	X	X															X	X
Targeted Review of Body Systems[12]														X	X	X	X	X
Concomitant Medication	X	X												X	X	X	X	X
12-Lead ECG (Resting)	X	X [1]															X	
Vital Signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Laboratory Testing (Hematology, Chemistry)[9,11]	X[4]	X [13]											X[10]			X	X	
Coagulation[9]	X[4]	X [13]											X[10]			X	X	
Urinalysis[9]	X[4]	X [13]											X[10]			X	X	
Pregnancy Test[9]	X[4]	X [13]															X	X
Drug and Alcohol Screen [5,8]	X[4]	X																
Blood for HIV, HCV, HBsAg testing[8]	X[4]																	
Blood for PK Sampling[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		

1

Study Visit	00A	00B	01	01A	01B	01C	01D	01E	01F	01G	01H	01I	01J	02	03	04	05	Early Term
Study Day	**Screen** -22 to -2	**Admission -1**	1	1	1	1	1	1	1	1	1	2	2	3	4	5	12	
Time (Window)			**0** (-10 min)	**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 hrs** (+/-10 min)	**16 hr** (+/-10 min)	**24 hrs** (+/-1 hr)	**36 hrs** (+/-1 hr)	**48 hrs** (+/-4 hrs)	**72 hrs** (+/-4 hrs)	**96 hrs** (+/-4 hrs)		
Discharge from the confinement/hospital unit [14]													X	X				
Study Product Administration[7b]			X															
AE Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total blood drawn	27.5mL	11.5mL	6mL	6mL	6mL	6mL	6mL	6mL	6mL	6mL	6mL	6mL	17.5mL	6mL	6mL	17.5mL	14.5mL	0mL

1 Child-Pugh Score calculated for hepatically-impaired subjects at screening

2 Complete medical/surgical history taken at screening and interim medical/surgical history as sequent indicated visits.

3 Physical examination must include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; neurological; chest and lungs; cardiovascular; abdomen (liver and spleen); lymph nodes; musculoskeletal, and extremities. At early termination visit, a physical examination will be performed.

4 If screening laboratory tests are performed within 72 hours of admission to the confinement/hospital unit, the tests do not have to be repeated with the exception of the urine pregnancy test for females of child bearing potential and the urine drug screen for all subjects, which will be repeated.

5 Alcohol screen includes alcohol breath test or other suitable test for alcohol (e.g., blood alcohol test).

7 Blood samples for pharmacokinetic assessments of Pretomanid will be obtained on Days 1 to 5 at the following time points: pre-dose and 1, 2, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post-dose.

a. The following collection windows are allowed for the PK blood sample time points:
   i. Pre-dose: -10 minutes
   ii. Dosing through 16 hours post-dose inclusive: ± 10 minutes
   iii. 24 and 36 hours post-dose: ± 1 hour
   iv. 48, 72, and 96 hours: ± 4 hours

b. Subjects will receive the single oral dose of Pretomanid 200 mg taken with 240 mL of water after overnight fast.

c. The following parameters will be used for PK assessments: AUC0-inf,

9 Safety labs (also performed at screening and 2 hour fasting) include: total bilirubin, serum albumin, electrolytes including potassium, magnesium, and calcium levels, serum creatinine, BUN, alkaline phosphatase, AST, ALT, INR (PT prolongation), CBC w/differential, urinalysis, and pregnancy testing. Pregnancy testing at screening and Day 12 will be serum, and testing at admission will be a urine test.

10 Chemistry (2 hour fasting), hematology, coagulation and urinalysis to be done prior to discharge.

11 For patients with severe hepatic impairment (Child-Pugh C) an ammonia level will be drawn at screening and will be used as a baseline reading for safety purposes, not as a study entry criterion.

12 A targeted review of body systems will be obtained at these visits focused on liver disease and will include questions pertaining to development of ascites, jaundice, pruritis, gastrointestinal bleeding, and encephalopathy. If the

6 Vital sign measurements must include the subject's sitting heart rate, sitting blood pressure (mm Hg), height (screening only), and oral body temperature (ºC). Vital signs will be obtained at screening, and on Days -1 to 12 at the following time points:, admission day, prior to dosing, and 30 minutes after dosing, 1, 2, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96 hours and Day 12. Weight will be collected at screening, admission day, prior to dosing, 36, 48, 72, 96 hours and Day 12 time points.	AUC0-t, Cmax, tmax, half-life and CL/F. 8 Screening labs include: blood screen for hepatitis B surface antigen (HBsAg) and hepatitis C antibody, alcohol breath test or other suitable test for alcohol (e.g., blood alcohol test),urine screen test for drugs of abuse [amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, cannabinoids, phencyclidine (PCP)] and a blood screen for HIV.	subject answers yes to any of these questions, a targeted physical exam will be performed 13 Baseline admissions labs and resting 12-Lead ECG recording may be done within 72 hours of admission or at the time of admission depending on ability to obtain lab results at the site. 14 Discharge from confinement/hospital unit either after Visit 01J or Visit 2 depending upon site preference

Appendix B. Child-Pugh System

Encephalopathy grade*	None or 0	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	< 2	2 - 3	> 3
Serum albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
Prothrombin Time Prolongation (seconds over control)	< 4	4 - 6	> 6
or [INR]	(INR < 1.7)	(INR 1.7 - 2.3)	(INR > 2.3)
Points scored for observed finding	**1**	**2**	**3**

*Encephalopathy must be attributable to liver disease and graded according to present or historical data. If a subject with hepatic impairment is taking a pharmaceutical agent to control symptoms of liver disease (e.g., lactulose to reduce ammonia) the principal investigator may assign a score that is representative of the subject's status without pharmaceutical intervention. This action will be clearly documented in the source documents and approved by the Sponsor's medical monitor.

Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram (EEG)

Grade 1: restless, sleep-disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves on EEG

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves on EEG

Grade 3: somnolent, stuporous, place-disorientated, hyperactive reflexes, rigidity slower waves on EEG

Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity on EEG.

Group	Cumulative Score	Child-Pugh Class	Description
1	5-6 points	A	Mild hepatic impairment
2	7-9 points	B	Moderate hepatic impairment
3	10-15 points	C	Severe hepatic impairment

References:

1. Child CG, Turcotte JG. Surgery and portal hypertension. In: The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders 1964:50-64.

2. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973 Aug;60(8):646-9.

Appendix C. Toxicity Tables

ABBREVIATIONS:

Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

- **GRADE 1: Mild** Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
- **GRADE 2: Moderate** Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- **GRADE 3: Severe** Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

Clinical Adverse Events

VITAL SIGNS	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	
Fever (°C) **	38.0 – 38.4	38.5 – 38.9	≥ 39.0	** Oral temperature; no recent hot or cold beverages or smoking. A protocol should select either °C or °F for inclusion.
(°F) **	100.4 – 101.1	101.2 – 102.0	≥ 102.1	
Tachycardia - beats per minute	101 – 115	116 – 130	> 130 or ventricular dysrhythmias	
Bradycardia - beats per minute	50 – 54 or 45-50 bpm if pre-dose visit rate < 60 bpm	45 – 49 or 40-44 if pre-dose visit rate < 60bpm	< 45 or <40 bpm if pre-dose visit rate <60 bpm	
Hypertension (systolic)- mm Hg	141-150	151-160	> 160	Assume supine position for 10 min at rest in non-sleeping subjects; for

				adverse events, need three measurements on the same arm with concordant results.
Hypertension (diastolic) - mm Hg	91-95	96-100	> 100	
Hypotension (systolic) - mm Hg	85-89	80-84	< 80	
Tachypnea – breaths per minute	23-25	26-30	> 30	

CARDIOVASCULAR	Grade 1	Grade 2	Grade 3
Arrhythmia	Asymptomatic, transient signs, no Rx required	Recurrent/ persistent; symptomatic; Rx required	Unstable dysrhythmia; hospitalization and treatment required
Hemorrhage, Blood Loss	Estimated blood loss ≤ 100 mL	Estimated blood loss > 100 mL, no transfusion required	Transfusion required
QT/QTc prolongation	Male: 441-470 msec Female: 451-470 msec	Male: 471-500 msec Female: 471-500 msec:	> 500 msec OR > 60 msec change from admission visit

RESPIRATORY	Grade 1	Grade 2	Grade 3
Cough	Transient- no treatment	Persistent cough;	Interferes with daily activities
Bronchospasm, Acute	Transient; no treatment; 71% - 80% FEV1 of peak flow	Requires treatment; normalizes with bronchodilator; FEV1 60% - 70% (of peak flow)	No normalization with bronchodilator; FEV1 < 60% of peak flow
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment

GASTROINTESTINAL	Grade 1	Grade 2	Grade 3
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity or requires IV hydration
Diarrhea	2 - 3 loose or watery stools or < 400 gms/24 hours	4 - 5 loose or watery stools or 400 - 800 gms/24 hours	6 or more loose or watery stools or > 800gms/24 hours or requires IV hydration

Laboratory Adverse Events			
Blood, Serum, or Plasma *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Potassium – Hypokalemia mmol/L	3.1 – <LLN	2.7 – 3.0	<2.7
Potassium – Hyperkalemia mmol/L	>ULN – 5.6	6. – 6.5	>6.5
Glucose – Hypoglycemia Fasting- mg/dL [#]	61 – <LLN	55 – <61	<55
Glucose – Hyperglycemia Fasting – mg/dL [#]	>ULN – 120	>120 – 130	>130
Blood Urea Nitrogen mg/dL	>ULN – 29	30 – 35	>35
Creatinine – mg/dL	>ULN – 1.7	1.8 – 2.0	>2.0
Calcium – hypocalcemia mg/dL	8.0 – <LLN	7.5 – 7.9	<7.5
Calcium – hypercalcemia mg/dL	>ULN – 11.0	11.1 – 11.5	>11.5
Magnesium – hypomagnesemia mg/dL	1.3 – <LLN	1.0 – <1.2	<1.0

Laboratory Adverse Events			
Blood, Serum, or Plasma *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Albumin – Hypoalbuminemia g/dL	2.8 – <LLN	2.5 – 2.7	<2.5
Alkaline phosphatase – U/L(Age 18 years)	>ULN – 240	241 – 360	>360
AST U/L	>ULN – 105	106 – 175	>175
ALT U/L	>ULN – 105	106 – 175	>175
Bilirubin (serum total) mg/dL	>ULN - 2.0	2.1 - 2.5	>2.5
Hemoglobin - g/dL	10.5 – <LLN	9.5 – 10.4	< 9.5
Hematocrit %	32.3 – <LLN	28.0 – 32.2	< 28.0
RBC Decrease (Female) X10^12/L	3.61 – <LLN	3.14 – 3.60	< 3.14
RBC Decrease (Male) X10E6/uL X10^12/L	3.89 – <LLN	3.28 – 3.88	< 3.28
WBC Increase X10^9/L	>ULN– 15.0	15.1 – 20.0	> 20.0
WBC Decrease X10^9/L	2.5 – <LLN	1.5 – 2.4	< 1.5

Laboratory Adverse Events			
Blood, Serum, or Plasma *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Lymphocytes Decrease - X10^9/L	0.5 – <LLN	0.3 – 0.4	<0.3
Neutrophils Decrease - X10^9/L	1.0 – <LLN	0.5 – 1.0	< 0.5
Monocytes Increased X10^9/L	>ULN-2.5	2.6-3.0	>3.0
Eosinophils Increased X10^9/L	>ULN-0.75	0.76-1.50	>1.50
Basophils Increased X10^9/L	>ULN - 0.40	0.41-0.80	>0. 80
Platelets Decreased - X10^9/L	120 – <LLN	100 – 119	<100
INR	>ULN – 1.3	1.4 - 1.6	>1.6

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Protein	1+	2+	>2+
Glucose	Trace - 1+	2+	>2+

Blood (microscopic) - red blood cells per high power field (rbc/hpf)	3 - 10	11 - 50	>50 and/or gross blood
* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters.			
* Institutional normal reference ranges should be provided to demonstrate that they are appropriate.			
# Laboratory Parameter will not be used as halting criteria.			