CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 15-0037
Study Title:
A Phase 1, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics and Safety of Pretomanid in Participants with Renal Impairment Compared to Participants with Normal Renal Function

NCT 03896750

Version 1.0

DATE: 17 February 2025

RESTRICTED

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 15-0037**
Development Phase:	Phase 1
Products:	Pretomanid
Form/Route:	Tablet/Oral
Indication Studied:	Tuberculosis
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	First participant enrolled 17APR2024
Clinical Trial Completion Date:	28 October 2024
Date of the Analysis Plan:	17 February 2025
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
1.0	17FEB2025	N/A	N/A

TABLE OF CONTENTS

Table of Contents *(continued)*

Table of Contents *(continued)*

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BCG	Bacillus Calmette-Guérin
BPM	Beats per Minute
BDQ	Bedaquiline
BPaL	Pretomanid, bedaquiline, and linezolid regimen
BUN	Blood Urea Nitrogen
BQL	Below the Quantitation Limit
C	Celsius
CI	Confidence Interval
CKD	Chronic Kidney Disease
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficients of Variation
DCF	Data Collection Form
DMID	Division of Microbiology and Infectious Diseases
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
ET	Early Termination
FDA	Federal Drug Administration
GFR	Glomerular Filtration Rate
GM	Geometric Mean
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
HgB	Hemoglobin
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention to Treat
LLOQ	Lower-Limit of Quantitation

List of Abbreviations *(continued)*

LZD	Linezolid
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
Mtb	Mycobacterium tuberculosis
N	Number (typically refers to participants)
NCA	Non-Compartmental Analysis
NCI	National Cancer Institute
NIH	National Institutes of Health
NR	Non Responsive
PI	Principal Investigator
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TI	Treatment Intolerant
U	Units
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

1 PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 1, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics and Safety of Pretomanid in Participants with Renal Impairment Compared to Participants with Normal Renal Function" (DMID Protocol 15-0037) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH.

Any deviation from this statistical plan will be described and justified in the final study report, as appropriate. The reader of this SAP is encouraged to also review the clinical protocol for details on conduct of the study and the operational aspects of clinical assessments.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

2 INTRODUCTION

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (Mtb) is an age-old disease and remains a major public health problem worldwide. It is estimated that one-third of the world's population is infected with Mtb, with about 10 million new cases of TB and 1.2 million deaths annually [**1**]. Bacillus Calmette-Guérin (also known as BCG), an attenuated strain of *Mycobacterium bovis*, is the only available TB vaccine. The efficacy of this vaccine varies from place to place and is generally low [**2**, **3**] Treatment of drug-susceptible TB requires the use of 4 first-line anti-TB drugs for at least 6 months [**4**]. New drug treatments may help shorten the duration of treatment and potentially increase patient compliance, and therefore, have a direct impact on the control of TB. Furthermore, MDR and XDR-TB have made the prevalence of TB more challenging. Up to 50% of MDR-TB cases fail treatment and treatment outcome of XDR-TB is unpredictable [**1**], indicating that development of new anti-TB drugs is an essential component of TB control.

Chronic kidney disease (CKD) is defined as a reduced glomerular filtration rate (GFR), increased urinary albumin excretion, or both, for 3 or more months and is an increasing public health issue with estimated prevalence of 8 to16% worldwide [9]. Patients with CKD and kidney transplant have a higher risk of developing TB compared with the general population presumably due to associated immunodeficiency [10 - 13]. The treatment of new drug-susceptible pulmonary TB in patients with renal impairment includes 4 first-line drugs such as INH, rifampin, ethambutol, and pyrazinamide, similar to the treatment of patients with normal renal function. However, the doses of pyrazinamide and ethambutol have to be adjusted for renal function [14]. Despite appropriate use of first-line anti-TB drugs, patients with renal impairment have worse clinical outcomes than those without renal impairment, and require close monitoring [14, 17].

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

It has early bactericidal and sterilizing activity, with a potential to shorten the duration of treatment for drug-susceptible TB [23, 24]. It shortens the duration of treatment for MDR-TB in the context of the BPaL regimen [33],

It has excellent activities against both drug-sensitive and MDR-isolates of Mtb [26],

It has been shown to have a low incidence of Adverse Events (AEs) in multiple clinical trials [18],

It has narrow spectrum of activity limited primarily to Mtb with no significant activity against a broad range of Gram-positive and Gram-negative bacteria [34],

It has no demonstrable cross resistance to a variety of anti-TB drugs [25],

It is administered orally [18, 19], and

It neither inhibits nor is metabolized by major CYP450 enzyme isoforms except for CYP3A4 in vitro, importantly indicating a low potential for drug-drug interactions, including with presently used antiretrovirals for treatment of HIV [35, 36].

Patients with renal impairment, particularly severe renal impairment or end stage renal disease (ESRD), may have an increased risk of drug exposure and may require lower doses of certain drugs compared to patients with normal renal function [37]. According to FDA and Europe, the Middle East, and Africa (EMEA) guidelines, a pharmacokinetic (PK) study should be carried out during the development phase of a new drug that is likely to be used in patients with renal dysfunction and whose pharmacokinetics are likely to be significantly altered in renally impaired patients [38, 39]. Less than 1% of unmetabolized pretomanid is excreted in the urine. [18]. Therefore, like other commonly used anti-TB drugs such as ethambutol and pyrazinamide, which are at least partly eliminated through kidneys, the PK of pretomanid must be studied in patients with CKD. CKD is a very common clinical disease with estimated prevalence of 8 to 16%, and CKD patients globally, particularly those in advanced stages, have significantly increased risk of developing TB [11--13].

2.1 Purpose of the Analyses

These analyses will assess the safety and pharmacokinetics of pretomanid in participants with varying degrees of CKD as compared to matched healthy controls and will be included in the clinical study report.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Study Objective

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

3.1.2 Secondary Study Objectives

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

3.2 Endpoints

3.2.1 Primary Outcome Measures

The pretomanid PK profiles in plasma and urine estimated by non-compartmental analysis (NCA).

3.2.1.1 Plasma PK of Pretomanid

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

C_{max}: Maximum plasma concentration

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

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

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

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

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

λ_z: First-order terminal elimination rate constant

CL/F: Apparent clearance

V_d/F: Apparent terminal phase volume of distribution

3.2.1.2 Urine PK of Pretomanid

The urine PK of a single dose of pretomanid will be assessed from urine collected up to 1 hour pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hours post-dose. The following PK parameters will be determined using urine volumes and concentrations:

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

Ae%Dose: Fraction of dose excreted into the urine

CL_R: Renal clearance

3.2.2 Secondary Outcome Measures

The secondary outcome measures will be:

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

3.3 Study Definitions and Derived Variables

Baseline will be defined as the last recorded value prior to drug administration.

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product.

A Treatment Emergent Adverse Event (TEAE) is any new or worsening AE or pre-existing condition that worsens after study drug administration.

A Serious Adverse Event (SAE) is and AE or suspected adverse reaction that, in the view of either the site principal investigator (PI) or sponsor, results in any of the following outcomes:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly/birth defect, or

- Any medical event that based upon appropriate medical judgement may jeopardize the health or safety of the patient or participant and may require medical or surgical intervention to prevent one of the other listed outcomes.

3.3.1 Pharmacokinetic Parameter Definitions

Maximum plasma concentration (C_{max}) is defined as the maximum observed concentration, occurring the time of maximal plasma concentration (T_{max}), in plasma following the first dose of pretomanid.

Time of maximum plasma concentration (T_{max}) is defined as the time at which the maximum observed plasma concentration occurs. Because non-steady-state data is collected, the entire curve is considered. If the maximum observed concentration is not unique, then the first maximum is used.

Elimination rate constant (λ_z) is defined as the first-order rate constant associated with the terminal (log-linear) portion of the curve describing the rate of elimination from plasma. Estimated by linear regression of time vs. log concentration.

The terminal elimination half-life ($t_{1/2}$) is defined as the time it takes plasma concentrations to reduce by 50% during the terminal elimination phase and will be estimated by the natural logarithm of 2 (ln(2)) divided by λz.

AUC_{last} is defined as the area under the concentration-time curve (AUC) from the time of dosing to the time of the last quantifiable concentration above the lower-limit of quantitation (LLOQ) based on observed concentrations.

C_{last} is defined as the last observed positive concentration above the LLOQ.

AUC_{∞} is defined as the AUC from the time of dosing extrapolated to time infinity based on C_{last}. It will be computed by adding AUC_{last} to an area extrapolated by C_{last} divided by λ_z, as shown below:

$$AUC_{\infty} = AUC_{last} + \frac{C_{last}}{\lambda_z}$$

$\%AUC_{ex}$ is defined as the percentage of AUC_{∞} that was extrapolated and is calculated as shown below:

$$\%AUC_{ex} = 100 \times \left(\frac{AUC_{\infty} - AUC_{last}}{AUC_{\infty}}\right)$$

Apparent oral clearance (CL/F) is defined as the apparent total body clearance and represents a volume that is cleared of the molecule of interest per hour. It will be calculated as the dose divided by the AUC_{∞}, as shown below:

$$\frac{CL}{F} = \frac{Dose}{AUC_{\infty}}$$

Apparent volume of distribution during the terminal phase (V_z/F) is defined as the theoretical volume that the total amount of the molecule of interest would occupy if uniformly distributed at the concentration observed in plasma. If the terminal phase has been adequately captured, this value should approximate the volume of distribution at steady state and is calculated as shown below:

$$\frac{V_z}{F} = \frac{Dose}{\lambda_z \times AUC_{\infty}} = \frac{CL}{\lambda_z \times F}$$

$Ae_{(0\text{-}t)}$ is defined as the total amount of drug excreted unchanged, or amount of metabolite, in urine over the time interval 0 to time t. It is calculated as the sum of all the concentrations measured in the urine samples pooled over each interval multiplied the total respective volume of each urine sample.

%AeDose is represent the percent of the dose that was excreted unchanged in urine. It is calculated as the shown below:

$$\%AeDose = \frac{Ae_{(0-t)}}{Dose}$$

The renal clearance (CL_R) is defined as the clearance attributable to the renal route. Its calculation requires both urine and non-urine (typically plasma) data to be collected from the same route and regimen in the same individuals. It can then be estimated as the amount excreted in urine divided by the observed AUC in the non-urine matrix over the equivalent time interval as the urine data was collected, as shown below:

$$CL_R = \frac{Ae_{(0-t)}}{AUC_{(0-t)}}$$

Where $Ae_{(0\text{-}t)}$ is the amount excreted in urine and $AUC_{(0\text{-}t)}$ is the AUC in the non-urine matrix.

3.3.2 Impairment Group Definitions

The estimated glomerular filtration rate (eGFR) in all groups is estimated using the Modification of Diet in Renal Disease (MDRD) equation.

Matched Healthy Controls: participants with normal renal function defined as MDRD eGFR ≥90 mL/min as estimated.

Mild Renal Impairment: participants with mild renal impairment defined as Stage 2 CKD with an MDRD eGFR of 60-89 mL/min.

Moderate Renal Impairment: participants with moderate renal impairment defined as Stage 3 CKD with an MDRD eGFR of 30-59 mL/min.

Severe Renal Impairment: participants with severe renal impairment defined as either Stage 4 CKD with an MDRD eGFR of 15-29 mL/min or Stage 5 CKD, also known as ESRD, but not on dialysis with an MDRD eGFR <15 mL/min.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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

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

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

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

4.2 Discussion of Study Design, Including the Choice of Control Groups

The study population will be representative of participants with varying degrees of renal disease as defined by MDRD eGFR as well as participants who are healthy matched controls. Children will not be included as this study is designed for adult participants between the ages of 18-85 years.

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

4.3 Selection of Study Population

Part A

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

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

Part B

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

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

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

4.3.1 Participant Inclusion Criteria

Participant Inclusion Criteria for Healthy Participants (Group 1A-1C)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.3.2 Participant Exclusion Criteria

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

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

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

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

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

    [2]*Except hormonal contraceptives*

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

    NOTE: See Table 4 in the Protocol for a list of drugs known to alter the function of CYP3A4.
16. Use of St. John's Wort within 7 days prior to admission and during the entire study.
17. Consumption of products containing grapefruit within 5 days prior to dosing until Visit 01N.
18. Donation of whole blood or blood products >500 mL within 30 days from screening and/or plans to donate during the study or up to 14 days after dosing.
19. Participation in another interventional clinical trial within 30 days prior to dosing until after the last study visit.
20. Hgb <10.0 g/dL in both men and women at the screening visit.
21. Positive Screening test for HCV, HBV, or HIV.
22. Renal transplant.
23. Presence of any condition or finding[4] which would jeopardize participant safety, impact study result validity, or diminish the participant's ability to undergo all study procedures and assessments.

    [4]*In the opinion of the investigator*
24. For men, semen donation for the duration of the study.

25. AST and ALT > ULN.
26. Bilirubin > ULN.

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

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

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

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

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

    [3]*Except hormonal contraceptives*

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

    NOTE: See Table 4 in the Protocol for a list of drugs known to alter the function of CYP3A4.
17. Use of St. John's Wort within 7 days prior to admission and during the entire study.

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

    [5]*In the opinion of the investigator*
26. For men, semen donation for the duration of the study.
27. AST and ALT > 2.5 x upper limit of normal (ULN).
28. Hyperbilirubinemia >1.5 x ULN.

4.4 Treatments

4.4.1 Treatments Administered

All participants will receive a single oral dose of pretomanid 200 mg in the form of a tablet.

4.4.2 Identity of Investigational Product(s)

Pretomanid, a nitroimidazooxazine, is a chemical entity with a molecular weight of 359 Daltons. Pretomanid is a novel TB treatment that is being investigated for use with other TB drugs to shorten and/or simplify regimens to treat either drug-susceptible or resistant disease, which may improve the current high rate of noncompliance for TB treatment. Pretomanid acts by inhibiting Mtb cell wall biosynthesis, as well as generating NO.

For this study, pretomanid 200 mg tablets are white to off-white, oval-shaped tablet debossed with M on one side and P200. The formulation of pretomanid tablets includes 200 mg of micronized pretomanid, 294.4 mg of lactose monohydrate National Formulary (NF) (Foremost FastFlo 316), 235.2 mg of microcrystalline cellulose NF (Avicel PH102), 40 mg sodium starch glycolate NF (Explotab), 8.0 mg magnesium stearate NF (Hyqual), 2.4 mg of colloidal silicon dioxide NF (Cab-O-Sil M-5P), 4 mg of sodium lauryl sulfate United States Pharmacopeia (USP), and 16 mg of povidone USP (PVP K30). There is also purified water USP that is removed during manufacture. All study product, pretomanid tablets, should be stored at 15-30°C (59-86°F) in blister-strips comprising a thermoformable-film and a lidding foil configuration.

The TB Alliance or its designee will package the study product. The study product will be labeled and supplied according to applicable regulatory requirements. Pretomanid will be provided by Global Alliance for TB Drug Development according to the terms of the Clinical Trial Agreement between the TB Alliance and NIAID.

4.4.3 Method of Assigning Participants to Impairment Groups

There is no randomization performed for this open-label study. Participants are assigned to the 3 renal impairment groups based on their MDRD eGFR, with approximately 6 participants per renal impairment group (Groups 2, 3, and 4) and approximately 18 healthy participants will be matched to 1 or more renal impairment participants (Groups 1A, 1B, and 1C).

Enrollment will be performed through the enrollment module in the electronic data capture system, maintained by the SDCC.

4.4.4 Selection of Doses in the Study

Data from the Phase 1 studies in healthy volunteers and Phase 2 studies in participants with pulmonary TB indicate that the PK profile for pretomanid following oral dosing was consistent for healthy participants and participants with pulmonary TB. In both populations, pretomanid was readily absorbed after oral administration and slowly eliminated from plasma. Pretomanid plasma concentrations increased in a dose-dependent manner after single-dose administration of up to 1000 mg in healthy participants and participants with TB, but the increase was less than dose proportional, particularly at doses above 200 mg/day. Evidence suggests that the apparent lack of dose proportionality in exposure is most likely related to decreased bioavailability with increasing dose. The clinical dose is 200 mg and it is recommended that pretomanid be administered in the fed state.

4.4.5 Selection and Timing of Dose for Each Participant

Pretomanid will be administered in the fed state in this study because there is a food effect for the drug. Following an overnight fast of at least 8 hours, participants should start the recommended meal prior to administration of pretomanid [**40**] on study day 1. Study participants should eat this meal in 30 ± 10 minutes or less; however, pretomanid should be administered 30 ± 10 minutes after start of the meal. Participants will be given one dose of 200 mg of pretomanid orally under direct supervision with 240 mL of water and a mouth check will be done at visit 01A. All participants will receive the same study product. After dosing, participants will have no food, water, or medications for 2 hours post-dose. If a participant vomits >2 hours post-dose, no redosing or exclusion is required. If a participant vomits within 2 hours of dosing, the participant will be excluded from the study with a plan to replace or rescreen and admit another time, if necessary. Since a single oral dose of pretomanid will be given, there will be no dose modifications.

4.4.6 Blinding

Not Applicable; this is an open-label study.

4.4.7 Prior and Concomitant Therapy

Medications history will include a review of all current medications and medications as specified in Table 4 of the protocol. Assessment of eligibility will include a review of all permitted and prohibited medications per the participant inclusion and exclusion criteria. In addition, the site PI or appropriate sub-investigator may identify other medications that should not be used due to a risk to participant safety or possible effects on PK parameters. Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate. Administration of any medications, therapies, or vaccines will be recorded on the appropriate Data Collection Form (DCF). Concomitant medications will include all current medications and medications taken in the 30 days prior to signing the informed consent form (ICF) through approximately 11 days after the study medication is given, early termination (ET) or unscheduled visits (if prior to 11 days after study product administration), whichever

occurs first. Medications reported are limited to those taken within 30 days prior to the study medication through approximately 11 days after the study medication. Prescription and over-the-counter drugs will be included as well as vitamins, and supplements (including herbal).

4.4.8 Treatment Compliance

All participants are to receive a single dose of study product administered under supervision in the clinic including a post-administration mouth check.

4.5 Pharmacokinetic and Safety Variables

See **Table 2** for a schedule of study procedures.

4.5.1 Pharmacokinetic Variables

The plasma PK of a single dose of pretomanid will be assessed from serial blood samples collected up to 1 hour pre-dose (Day 1) and at multiple time points post dosing: 1, 2, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours. The primary outcome measure will be total plasma concentration of pretomanid. The following PK parameters will be determined using total pretomanid and metabolites M19 and M50 concentrations:

C_{max}: Maximum plasma concentration

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

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

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

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

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

λ_z: First-order terminal elimination rate constant

CL/F: Apparent clearance

V_d/F: Apparent terminal phase volume of distribution

The urine PK of a single dose of pretomanid will be assessed from urine collected up to 1 hour pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hours post-dose. The following PK parameters will be determined using urine volumes and concentrations for pretomanid and the metabolites M19 and M50:

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

Ae%Dose: Fraction of dose excreted into the urine

CL_R: Renal clearance

4.5.2 Safety Variables

The incidence, frequency, and severity of AEs, TEAEs, and SAEs. In addition, the mean change from baseline in the following variables:

- HgB
- ALT
- AST

- BUN
- Creatinine and eGFR
- Serum potassium and magnesium
- Oral temperature
- Pulse
- Sitting blood pressure
- ECG QTcF

5 SAMPLE SIZE CONSIDERATIONS

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

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

6 GENERAL STATISTICAL CONSIDERATIONS

6.1 General Principles

There are several units of analysis in this study. For the PK analysis, the unit of analysis will be the reported pretomanid concentrations, however, PK profiles in both plasma and urine will be evaluated at the participant level. Medical history, concomitant medications, AEs, SAEs, clinical laboratory, physical examination (PE), vital signs, and ECG will be presented at the participant level, and summaries will be presented at the study and renal impairment group level.

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), arithmetic mean, standard deviation (SD), median, minimum (min), and maximum (max). PK concentration and parameter summaries will additionally report the geometric mean (GM) and coefficient of variation (CV). Minima and maxima will be reported to the same precision as the raw values, means and medians will be presented to one extra decimal place than the raw values and standard deviations will be reported to 2 extra decimal places than the raw values.

The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. Percentages will be rounded to one decimal place (i.e. XX.X%) except for 100% which will be reported with no decimal places. In general, all data will be listed, sorted by impairment group and participant, and when appropriate by visit number and parameter within participant. In general, the last recorded value prior to study drug administration will be considered as baseline. Changes from baseline will be calculated as the follow-up visit value minus the corresponding baseline value. All summary tables will be structured with a column or row block for each impairment group in the order (Mild Renal Impairment, Moderate Renal Impairment, Severe Renal Impairment, Matched Controls) and will be annotated with the total population size relevant to that table/impairment group, including any missing observations. More details will be provided for reporting pharmacokinetic results in Section 10.

Estimates and CIs will be utilized rather than formal hypothesis tests.

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

6.2 Timing of Analyses

One interim study team and Safety Monitoring Committee (SMC) safety and PK review will occur after Part A 6 participants in Group 2 (severe renal impairment and ESRD, not on dialysis) and Group 1A their matched controls are enrolled and completed follow-up through Day 12 (Visit 02). The interim safety and PK review will present data by group, including AEs, SAEs, clinical laboratory tests, vital signs, and 12-lead ECG, and PK analysis of pretomanid. Cumulative data for all participants enrolled will be included in the safety and PK reviews. The interim safety and PK reviews will not include any statistical hypothesis testing.

The final analysis will be performed after database lock.

6.3 Analysis Populations

6.3.1 Safety Analysis Population

The safety analysis population set will include all participants who receive any amount of study product.

6.3.2 Pharmacokinetic Analysis Population

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

6.3.2.1 PK Plasma Analysis Subset

The PK plasma analysis subset will consist of all participants with sufficient plasma PK data available to estimate the plasma PK parameters listed in Section **4.5.1** . The PK plasma analysis subset may be used for post-hoc sensitivity analyses if the PK analysis population is different from the PK plasma analysis subset (i.e. when a participant has estimable plasma parameters but is excluded from the PK analysis population due to challenges with their urine PK data).

6.3.2.2 PK Urine Analysis Subset

The PK urine analysis subset will consist of all participants with sufficient urine PK data available to estimate the urine PK parameters listed in Section **4.5.1**. The PK urine analysis subset may be used for post-hoc sensitivity analyses if the PK analysis population is different from the PK urine analysis subset (i.e. when a participant has estimable urine parameters but is excluded from the PK analysis population due to challenges with their plasma PK data).

Reasons for exclusion from an analysis population will be summarized in **Table 8** by impairment group. Individual participant listing of exclusion reasons is also provided in **Listing 6**.

A tabular listing of all participants, visits, and observations excluded from the efficacy analysis will be provided in the CSR (Listing 16.2.3).

6.4 Covariates and Subgroups

The protocol does not define any formal subgroup analysis and the study is not powered to perform subgroup analyses.

6.5 Missing Data

All attempts will be made to collect all data per protocol. As missing data are expected to be minimal, no imputation or other missing data methods will be performed for missing values other than for partial or missing dates where complete dates are required to flag data as treatment emergent or concomitant with treatment. Partial or missing start and end dates for AEs and concomitant medications will be imputed such that if the missing part of the date causes ambiguity in the temporal relationship to treatment, it will be assumed to be treatment emergent or concomitant. Specifically, dates will be imputed as follows:

Partial and missing start dates

- Dates with missing day only will be imputed as the first of the month unless the month and year are the same as the month and year of the study medication administration date, in which case missing day will be imputed as the day the participant received study medication unless the end date is on or before the date of study medication administration in which case it will be imputed as the first of the month the end date was reported, or the month prior if the end date is the first of the month.
- Dates with both day and month missing will be imputed as 01JAN unless the year is the same as the year of the study medication administration, in which case the missing day and month will be imputed

as the dose day and month the participant received study medication unless the end date is on or before the date of study medication administration in which case it will be imputed as 01JAN of the year the end date was reported, or 01DEC of the year prior if the end date is the first of the year.

- Completely missing dates will be imputed as the date of study medication administration unless the end date is on or before the date of study medication administration, in which case the missing date will be imputed as 01JAN of the same year as the end date was reported, or 01DEC of the year prior if the end date is the first of the year.

Partial and missing end dates

- Dates with missing day only will be imputed as the last of the month.
- Dates with both day and month missing will be imputed as 31DEC unless the year is the same as the year of the study medication administration, in which case the missing day and month will be imputed as the day and month of the participant's last study visit.
- Completely missing dates will be imputed as the date of the participant's last study visit.
- If the status is missing or it is indicated as ongoing then the date will not be imputed unless a death date is available, in which case the missing date will be imputed as the death date.
    - If the imputed date is after the date of death, the date will be set equal to the date of death.

Original dates as reported will be displayed in listings and the imputed dates will be used for derivations only, such as study day and treatment-emergence status.

Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier and may be excluded from analysis.

6.6 Interim Analyses and Data Monitoring

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

6.7 Multicenter Studies

This study is planned to be conducted at multiple sites; however, data will be pooled across all clinical sites for analysis with the exception of demographics summaries and PK summaries that may be presented both overall and by site.

6.8 Multiple Comparisons/Multiplicity

While multiple PK parameters will be estimated in two sources, plasma and urine, no hypothesis testing will be performed. Summary statistics and confidence intervals will be used rather than formal hypothesis testing.

7 STUDY PARTICIPANTS

7.1 Disposition of Participants

Participant disposition in the study will be tabulated by renal impairment group in **Table 7**. This table will show the total number of participants screened, enrolled, that received treatment, completed all PK blood draws, terminated early, that were replaced, and included in analysis. This table will be stratified by renal impairment group and presented overall.

Table 10 will present a summary of the reasons that participants were screened but not enrolled.

The composition of analysis populations, including reasons for participant exclusion, by renal impairment group, will be presented in **Table 8**.

A flowchart showing the disposition of participants, adapted from the consort statement, will be included (**Figure 1**). This figure will depict the number of participants screened, enrolled, terminating early, and included in analysis, stratified by renal impairment group.

A listing of participant disposition including the protocol version at time of screening will also be included (**Listing 2**) as well as a listing of participants that terminated the study early and the reason for termination (**Listing 3**).

7.2 Protocol Deviations

A summary of participant-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and renal impairment group for all participants (**Table 4**), as well as similar summaries for major participant-specific protocol deviations that may affect analyses. All participant-specific protocol deviations and non-participant specific protocol deviations will be included as data listings in **Appendix 3** (**Listing 4** and **Listing 5**, respectively).

8 EFFICACY EVALUATION

This is PK study and does not include any efficacy analysis.

8.1 Primary Efficacy Analysis

Not applicable.

8.2 Secondary Efficacy Analyses

Not applicable.

8.3 Exploratory Efficacy Analyses

Not applicable.

9 SAFETY EVALUATION

All summaries and analysis of safety data will be presented for the Safety Analysis Population. Safety summaries will be presented by renal impairment group and overall.

9.1 Demographic and Other Baseline Characteristics

Listings will be sorted by renal impairment group, participant ID, parameter (if applicable), and visit (if applicable). Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. All categorical measures will be summarized by the frequency and percentages (based on the non-missing sample size) of observed levels. The denominator for the percentages may be based on the number of non-missing observations for an assessment or based on the number of participants in a population. This will be described for each table and clarified in footnotes as needed.

Summaries of age, height, weight (measured at baseline), BMI (measured at baseline), sex, ethnicity, and race will be presented by renal impairment group and overall (**Table 13**; **Table 14**) as well as by site (**Table 11** and **Table 12**). Ethnicity is categorized as Hispanic or Latino, not Hispanic and not Latino, Not Reported, or Unknown. In accordance with NIH reporting policy, participants may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the electronic Case Report Forms (eCRF) as "No" to each racial option.
Individual participant listings **Appendix 3**) will be presented for all demographics (**Listing 7**).

9.1.1 Prior and Concurrent Medical Conditions

Complete medical history will be obtained by interview of participants at the screening visit and will be reviewed and updated upon admission on Day -1, again on Day 1 prior to dosing, and again on Days 4, 5 and 12 ± 2. The medical history will also be reviewed and updated at any early termination visit. Participants will be queried regarding a history of medical disorders or procedures performed on the head, eyes, ears, nose, throat as well as blood and lymphatic, cardiovascular, endocrine and metabolic, respiratory, musculoskeletal, gastrointestinal, genital and reproductive, and hepatobiliary and pancreas systems. Participants will also be solicited for any medical history of cancer, immunodeficiency, psychiatric, drug or alcohol dependence, dermatologic, autoimmune disease, urologic, allergies, and neurologic conditions as well as any other significant medical history including conditions, diagnoses, or procedures.

All current illnesses and pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 27.0 or higher. Summaries of participants' pre-existing and newly developed medical conditions will be presented by status (i.e. pre-existing or newly developed), renal impairment group, System Organ Class (SOC) and Preferred Term (PT) as appropriate (**Table 15** through **Table 18**).

Individual participant listings will be presented for all medical conditions (**Listing 8**).

9.1.2 Prior and Concomitant Medications

Summaries of medications that were started prior to dosing and continuing at the time of dosing or initiated after dosing will be presented by WHO Drug at the Anatomical Therapeutic Chemical (ATC) Levels 2 and 3 and renal impairment group (**Table 78**). Individual participant listings will be presented for all concomitant medications (**Listing 15**).

9.2 Measurements of Treatment Compliance

Details of the date and time of the pre-dose meal beginning and ending as well as study product administration will be collected. Dates of dose administered will be presented by Site and Impairment Group (**Table 9**). Any participant enrolled but not dosed will be presented in the participant disposition table (**Table 7**).

9.3 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study participant administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes exacerbation of a pre-existing condition or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the condition under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs must be reported on the appropriate page(s) of the eCRF. All AEs will be coded using the MedDRA dictionary Version 27.0 or higher.

TEAEs are defined as any event that occurs or worsens on or after the day that study treatment initiated. AEs recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings (**Listing 9**).

The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The severity of the AE should be the maximum over the course of the AE. For AEs not listed in the NCI CTCAE, the Investigator should determine the severity of the AE according to the following criteria, as described in Section 8.1.1.1 of the protocol.

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

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

The causal relationship between the study drug and an AE will be assessed by a delegated, licensed study clinician listed on the Form FDA 1572. All AEs will be deemed related to study drug unless explicitly assessed as not related. Only two categories will be used to describe the relationship between study drug and an AE, related and not related. Any AEs for which a relationship is not provided will be assumed to be related. To assist the assessor in determining the relationship the following guidelines are provided in Section 8.1.1.1 of the protocol.

- 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

Adverse Events will be reported using the Safety Population.

9.3.1 Solicited Events and Symptoms

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

9.3.2 Unsolicited Adverse Events

An overall summary of AEs will be presented (**Table 19**) that includes the number of events and the number and percentage of participants who experienced at least one AE or TEAE, by renal impairment group. This summary will also include treatment-related TEAEs, SAEs, and TEAEs leading to early termination. AEs will be summarized using discrete summary statistics and presented at the participant level. TEAEs will also be summarized (**Table 21** through **Table 24**) by renal impairment group in a separate table at the event level by MedDRA SOC and PT. If a participant reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a participant reports multiple conditions within the same SOC, that SOC will only be reported once at the SOC summary level. SOCs will be reported in ascending alphabetical order, PTs will be listed in order of descending frequency for all participants included in the table within each SOC.

TEAEs that occur in 5% of participants in any impairment group will be presented (**Table 20**) by SOC, PT and impairment group.

A summary of TEAEs by maximum severity will be presented (**Table 25**). The number of participants within any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by renal impairment group. To count the number of participants within any TEAEs, if a participant has multiple TEAEs coded to the same PT within the same SOC, the participant will be counted once under that maximum severity.

Summaries of related TEAEs will be presented (**Table 26** through **Table 29**) by impairment group, SOC, and PT.

The denominator for all percentages will be the number of participants being summarized.

A bar chart of serious and non-serious related TEAEs by SOC will also be presented (**Figure 2** and **Figure 3**)

All AEs will be listed (**Listing 9**). All SAEs will also be listed separately (**Table 30**). Non-serious, moderate or severe adverse events will be listed (**Table 31**). Other significant adverse events will also be listed (**Table 32**).

9.4 Deaths, Serious Adverse Events, and other Significant Adverse Events

SAEs will be listed in **Table 30** and will include participant ID, renal impairment group, AE Description, Reason Reported as an SAE, Relationship to Study Treatment, Alternate Etiology if Not Related, Outcome, and Duration of Event (in days).

9.5 Pregnancies

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 85 Visit. Male participants should notify the study team if a pregnancy occurs in a partner during the study after study drug administration. If the male participant reports a pregnancy, information about the outcome of pregnancy in the female partner of male participant will be handled through contact with the male participant. Certain pregnancy outcomes (congenital anomaly or birth defect in an offspring of a participant taking study drug) will require submission as an SAE. Listings summarizing the total pregnancies, number of live births, and number of spontaneous abortions, elective abortions or still births and listing of pregnancies and outcomes will be presented (**Listing 17**, **Listing 18**, **Listing 19**, **Listing 20**, and **Listing 21**).

9.6 Clinical Laboratory Evaluations

Clinical safety laboratory adverse events will be collected prior to study product administration during the screening visit (Visit 00A), on Day 5 (Visit 01N), and on Day 12 (Visit 02). Clinical laboratory parameters to be evaluated will include hemoglobin (Hgb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), serum creatinine (including eGFR), serum potassium, and serum magnesium. At only Visit 00A human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) will also be obtained and presented in **Listing 12**. Screening laboratory assessments may be repeated once per investigator discretion.

Urine pregnancy tests will be performed locally on all women of childbearing potential by the local site laboratory at second screening (Visit 00B), on the day of hospital admission (Visit 00C), prior to administration of study product (Visit 01A), on Day 12 (Visit 02), and any Early Termination (ET). Results must be negative and known prior to administration of study product. Urine drug screen and alcohol screen will also be done at Visit 00B and 00C for all participants.

The number and percentage of participants with at least one clinical safety laboratory finding assessed as of mild or greater severity through Day 12 is presented in the overall summary of adverse events (**Table 19**).

The distribution of chemistry laboratory results by severity, time point, and renal impairment group will be presented beginning at **Table 35** and concluding at **Table 52**. The distribution of hematology results by severity, time point, and renal impairment group will be presented in **Table 68** and **Table 69**. Descriptive statistics including mean, standard deviation, median, minimum and maximum values and change from baseline by time point, for each chemistry laboratory parameter, will be summarized in **Table 53** and concluding at **Table 60**. Descriptive statistics including mean, standard deviation, median, minimum and maximum values and change from baseline by time point, for each hematology laboratory parameter, will be summarized in **Table 70**. Shift tables will be presented for each chemistry laboratory parameter beginning at **Table 61** and concluding at **Table 67**. Shift tables will be presented for each hematology laboratory parameter in **Table 71**. Change from baseline plots for continuous chemistry laboratory parameters will also be presented beginning at **Figure 4** and concluding with **Figure 19**. Change from baseline plots for continuous hematology laboratory parameters will also be presented in **Figure 20** and **Figure 21**.

Listing 10 will provide a complete listing of individual chemistry laboratory results with applicable reference ranges. **Listing 11** will provide a complete listing of individual hematology laboratory results with applicable reference ranges. **Table 33** will provide a listing of abnormal chemistry laboratory values. **Table 34** will provide a listing of abnormal hematology laboratory values.

9.7 Vital Signs and Physical Evaluations

Vital sign measurements include oral temperature, sitting pulse, sitting systolic blood pressure, and sitting diastolic blood pressure. Vital signs will be collected at the screening visit (Visit 00A), prior to administration of study product (Visit 01A), at Visit 01H (12 hours ± 10 minutes post-dose), at Visit 01J (24 hours ± 1 hour post-dose), at Visit 01L (48 hours ± 1 hour post-dose), at Visit 01M (72 hours ± 4 hours post-dose), at Visit 01N (96 hours ± 4 hours post-dose), Visit 02 (12 days ± 2 days post-dose) and any ET. Vital signs will be tabulated by visit and renal impairment group and listed (**Table 72** through **Table 76** and **Listing 13**).

A PE will be performed at the screening visit (Visit 00A). A targeted PE may be performed at all in person study visits and any ET visit if indicated based on interim medical history. The following body systems will be assessed at the screening visit and then as indicated for subsequent targeted PEs: skin, head, eyes, ears, nose and throat, thyroid, neurological system, chest and lungs, cardiovascular system, abdomen, lymph nodes, musculoskeletal system, and extremities (**Listing 14**). A summary of abnormal physical exam findings will be shown in **Table 77**. Height and weight will only be collected during screening and will be summarized in the demographics tables (**Table 12** and **Table 14**).

9.8 Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the eCRFs. A by-participant listing of concomitant medication use will be presented (**Listing 16**). The use of concomitant medications during the study will be summarized by ATC1 code, ATC2 code, and renal impairment group for the Safety population (**Table 78**).

9.9 Other Safety Measures

An ECG will be performed at the Screening Visit 00A and Visit 01N. If the result is abnormal, it may be repeated per the investigators discretion. The ECG intervals (QTcF), including change from baseline, will be summarized at the Screening Visit 00A and Visit 01N (96 hours ± 4 hours post-dose), including any repeated ECG measurements, using descriptive statistics (**Table 79**).

Individual ECG interval measurements will be provided in **Listing 15**.

10 PHARMACOKINETICS

PK analyses will be performed using NCA. PK concentrations and noncompartmental parameters will be summarized by renal impairment group. Statistics include the arithmetic mean, median, SD, GM, CV, min, and max. PK parameters of exposure (AUC_{last}, AUC_{∞}, and C_{max}) will be compared between impairment groups using ANOVA models with or without random effects. T_{max} will be compared using 90% confidence intervals calculated using the inverted rank score method. Concentrations below the quantitation limit (BQL) prior to first measurable concentration will be imputed as zero. The first BQL concentration reported in the plasma concentrations after the last measurable concentration may be imputed for the purpose of parameter estimation as the LLOQ divided by 2 only if 1) needed to estimate λ_z, 2) all other λz estimation criteria are met, and 3) if a visual predictive check of the imputed value appears to be consistent with the observed elimination trend. All other BQL samples will be treated as missing. Imputed concentration values will only be used for plasma parameter estimation by NCA and not included in concentration summaries, however, imputed BQL values will be indicated by imputation method in listings with methods clarified in the footnote and denoted in figures.

10.1 Summary of Pharmacokinetic Sampling and Sample Properties

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

The urine PK of a single dose of pretomanid will be assessed from urine collected up to 1 hour pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hours post-dose.

Samples with bioanalytical errors or quality issues reported by the laboratory will be excluded. Collection times of samples missing the actual collection time will be imputed using the nominal collection time. Such samples will be identified in the analysis report (**Listing 22**).

10.2 Pharmacokinetic Analysis

10.2.1 Concentration Summaries

Drug plasma concentrations will be listed by renal impairment group, and participant. Out of sample time window and PK analyses-excluded samples will be indicated, as will BQL values that were imputed for the purposes of parameter estimation (**Listing 22**). The listings will also indicate the nominal and actual time associated with the sample (nominal time is defined as the planned time in hours since the first dose). Potentially important bioanalytical errors and their effect on the PK analysis will be discussed.

Plasma drug concentrations will also be summarized by impairment group (**Table 80** through **Table 83**) and plotted.

Figure 22 through **Figure 25** (linear) and **Figure 29** through **Figure 32** (semilogarithmic) will plot all participant plasma PK profiles together by renal impairment group, as linear and semilogarithmic plots.

Linear plots of participants with renal impairment with their matched controls (**Figure 26**, **Figure 27**, and **Figure 28**).

Linear plots of plasma mean concentration curves will be shown in **Figure 33**, with error bars representing ± 1 SD.

Semi-logarithmic plots of geometric mean plasma concentration curves will be shown in **Figure 34**.

10.2.2 Pharmacokinetic Parameters

10.2.2.1 Plasma Pharmacokinetic Parameters

NCA PK parameters will be calculated using the actual post-dose time. Samples with concentrations greater than the LLOQ will be considered for the estimation of λ_z. Imputing the first BQL concentration following the last concentration greater than LLOQ to LLOQ divided by 2 will be considered on a participant-by-participant basis for participants where the λ_z acceptance criteria are not met by the observed data greater than the LLOQ. λ_z will be computed from the log-transformed concentration data. The correlation between time and concentration at the time points used to estimate λ_z should be sufficiently high (adjusted-R^2 >0.9) for λ_z. Additionally a minimum of three concentrations in the terminal elimination phase will be used for the calculation of λ_z. All concentrations used to calculate λ_z must come from samples taken at or after T_{max}. The concentrations used to calculate λ_z along with the number of concentrations used for the calculation will be included in the participant listing (**Listing 22**).

The plasma AUC will be computed using the linear-up log-down (linear-log) trapezoidal method in Phoenix WinNonlin (Certara, Radnor, PA).

All plasma PK parameters will also be summarized by renal impairment group using descriptive statistics (**Table 84** through **Table 87**). Additionally, participant-level PK parameters will be presented in the tables in the final report.

The following parameters will be estimated: C_{max}, T_{max}, AUC_{last}, AUC_{∞}, $\%AUC_{ex}$, $t_{1/2}$, λ_z, CL/F, and V_d/F.

See Section 3.3.1 for parameter definitions.

10.2.2.2 Urine Pharmacokinetic Parameters

NCA PK parameters will be calculated using the actual post-dose collection window times. Samples with concentrations greater than the LLOQ will be considered for the estimation of urine PK parameters. Phoenix WinNonlin urine NCA models 210-212 will be used to estimate all urine PK parameters. Urine concentrations and both nominal and actual collection windows will be listed in **Listing 23**.

All urine PK parameters will also be summarized by renal impairment group using descriptive statistics (**Table 88** through **Table 91** . Additionally, participant-level urine PK parameters will be presented in the tables in the final report.

The following parameters will be estimated (**Listing 24**): $Ae_{(0\text{-}t)}$, Ae%Dose, and CL_R.

See Section 3.3.1 for parameter definitions.

10.2.3 Comparison of Impairment Groups

If at least one matching participant in the healthy volunteer group is available in the renal impairment groups, the following random effects ANOVA model will be used to test for a group by site interaction and if significant (p<0.10), estimate group and site level parameters and compare impairment groups for primary PK parameters:

$$Y_{ij} = \mu + \tau_{[ij]} + \alpha_i + \gamma_k + \tau_{[ij]}\gamma_k + \varepsilon_{ij}$$

Here, *i* represents the matched block, *j* represents the participant in matched block *i*, Y_{ij} is the log-transformed PK parameter for participant *j* in block *i*, $\tau_{[ij]}$ is the impairment group effect for the group in which

participant j in block i belongs, α_i is the random group effect for matched block i, γ_k is the indicator variable for the fixed effect of study site k, and $\tau_{[ij]}\gamma_k$ is the interaction between participant impairment group and site. If no matching participants are available with PK parameters, the standard fixed effects ANOVA model without random effect α_i will be used. The following SAS code may be used to estimate the model above:

```
proc mixed data=impairment;
class match group (ref="Matched Control") site;
model logPKpar = group site group*site / solution cl alpha=0.10;
random match;
lsmeans group site group*site;
run;
```

The estimates from this model can be exponentiated to get fold differences.

If the group by site interaction is not significant then the following model will be used to estimate group level parameters:

$$Y_{ij} = \mu + \tau_{[ij]} + \alpha_i + \gamma_k + \varepsilon_{ij}$$

The following SAS code may be used to estimate the model above:

```
proc mixed data=impairment;
class match group (ref="Matched Control") site;
model logPKpar = group site / solution cl alpha=0.10;
random match;
lsmeans group;
run;
```

The estimates from this model can be exponentiated to get fold differences.

Pairwise fold differences in drug exposure will be calculated to compare each of the mild, moderate, and severe renal impairment groups with healthy controls. Fold difference and mean will be estimated by ANOVA and shown using 90% confidence intervals. An adjustment to the confidence level for multiple comparisons is not planned (**Table 92**).

T_{max} will be summarized in each impairment group using the median, and group differences will be assessed using nonparametric confidence intervals computed using the inverted rank score method (**Table 93**). Medians and confidence intervals will also be computed for each site. If the confidence intervals do not overlap between sites, then the T_{max} will also be summarized by site.

Summary box plots of PK parameters by impairment group (and site if appropriate) will also be presented (**Figure 35**, **Figure 36**, **Figure 37**, **Figure 38**, **Figure 39**, and **Figure 40**).

11 IMMUNOGENICITY

Not applicable.

12 OTHER ANALYSES

Not applicable.

13 REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the one decimal place; values greater than zero but < 1% will be presented as "<1%"; values greater than 99% but less than 100% will be reported as >99%. 100% will be reported as 100%. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures. Drug concentrations, AUCs, and C_{max} and their summary statistics will have the same number of significant digits as the drug concentrations reported by the bioanalytical laboratory. Other PK parameters will be reported to 1 decimal place.

14 TECHNICAL DETAILS

Estimation of NCA parameters will be performed in a validated version of Phoenix WinNonlin version 8.3 or later, or a similar software package. Phoenix WinNonlin, SAS version 9.4 or later or R statistical computing software 4.3.1 or higher will be used to generate all tables, figures, and listings.

15 SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

No changes in the conduct of the study or planned analysis.

16 REFERENCES

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

19. Pa-824. *Tuberculosis (Edinb)*, 2008. 88(2): p. 134-6.
20. Stover CK, et al. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. *Nature*, 2000. 405(6789): p. 962-6.
21. Manjunatha U, Boshoff HI, & Barry CE. The mechanism of action of PA-824: Novel insights from transcriptional profiling. *Commun Integr Biol*, 2009. 2(3): p. 215-8.
22. Singh R, et al. PA-824 kills nonreplicating Mycobacterium tuberculosis by intracellular NO release. *Science*, 2008. 322(5906): p. 1392-5.
23. Diacon AH, et al. Early bactericidal activity and pharmacokinetics of PA-824 in smearpositive tuberculosis patients. *Antimicrob Agents Chemother*, 2010. 54(8): p. 3402-7.
24. Tasneen R, et al. Sterilizing activity of novel TMC207- and PA-824-containing regimens in a murine model of tuberculosis. *Antimicrob Agents Chemother*, 2011. 55(12): p. 5485-92.
25. Tyagi S, et al. Bactericidal activity of the nitroimidazopyran PA-824 in a murine model of tuberculosis. *Antimicrob Agents Chemothe*r, 2005. 49(6): p. 2289-93.
26. Lenaerts AJ, et al. Preclinical testing of the nitroimidazopyran PA-824 for activity against Mycobacterium tuberculosis in a series of in vitro and in vivo models. *Antimicrob Agents Chemother*, 2005. 49(6): p. 2294-301.
27. Ahmad Z, et al. PA-824 exhibits time-dependent activity in a murine model of tuberculosis. *Antimicrob Agents Chemother*, 2011. 55(1): p. 239-45.
28. Tasneen R, et al. Contribution of Oxazolidinones to the Efficacy of Novel Regimens Containing Bedaquiline and Pretomanid in a Mouse Model of Tuberculosis. *Antimicrob Agents Chemother*, 2016. 60(1): p. 270-7.
29. Diacon AH, et al. Phase II dose-ranging trial of the early bactericidal activity of PA-824. *Antimicrob Agents Chemother*, 2012. 56(6): p. 3027-31.
30. Diacon AH, et al. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet*, 2012. 380(9846): p. 986-93.
31. Dawson R, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA- 824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *Lancet*, 2015. 385(9979): p. 1738-1747.
32. Diacon AH, et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. *Am J Respir Crit Care Med*, 2015. 191(8): p. 943-53.
33. Conradie F, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. *N Engl J Med*, 2020. 382(10): p. 893-902.
34. TB Alliance. PA-824 has a New Generic Name: Pretomanid. 2014.
35. Dooley KE, et al. Phase I safety, pharmacokinetics, and pharmacogenetics study of the antituberculosis drug PA-824 with concomitant lopinavir-ritonavir, efavirenz, or rifampin. *Antimicrob Agents Chemother*, 2014. 58(9): p. 5245-52.
36. Dogra M, et al. Comparative bioactivation of the novel anti-tuberculosis agent PA-824 in Mycobacteria and a subcellular fraction of human liver. *Br J Pharmacol*, 2011. 162(1): p. 226-36.

37. Strunk AK, et al. Single- and multiple-dose pharmacokinetics of ethambutol and rifampicin in a tuberculosis patient with acute respiratory distress syndrome undergoing extended daily dialysis and ECMO treatment. *Int J Infect Dis*, 2016. 42: p. 1-3.

38. Food and Drug Administration. Center for Drug Evaluation and Research, Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing, U.S. Department of Health and Human Services, Editor. 2020.

39. Matzke GR, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*, 2011. 80(11): p. 1122-37.

40. Food and Drug Administration. Center for Drug Evaluation and Research, Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry, U.S. Department of Health and Human Services, Editor. 2019.

41. Food and Drug Administration. Center for Drug Evaluation and Research, Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry, US Department of Health and Human Services, Editor. 2020.

42. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. 06/05/2023 [cited 2023; Available from: https://www.fda.gov/drugs/druginteractions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitorsand-inducers.

17 LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

[Global Programming Note: Only columns, legends, and any other impairment group indicators in the table, figure, and listing shells that were enrolled in the study will be included in the outputs. For example, if only the Severe Renal Impairment and Matched control groups are enrolled, columns, figure legends, or other indicators for the Mil and Moderate Renal Impairment groups may be removed.

The Severe Renal Impairment arm will be displayed in two separate columns as "Severe Renal Impairment" and "ESRD, Not on Dialysis" in tables and figures.]

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

List of Tables *(continued)*

List of Tables *(continued)*

List of Tables *(continued)*

List of Tables *(continued)*

9.1 Overall Study Design and Plan Description

Table 1: Study Design

[Implementation Note: Study design chart or schematic can be excerpted from the protocol and include here. If a schematic or flow chart is used instead of a chart, rename as Figure 1 and move to Appendix 2.]

Part A

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

Part B

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

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

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

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

9.5.1 Efficacy/Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 2: Schedule of Study Procedures

[Implementation Note: Include a graphic display of the frequency and timing of efficacy and safety measures including visit numbers. The schedule of procedures from the protocol may be excerpted and included here, as appropriate.]

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

Table 2: Schedule of Study Procedures *(continued)*

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

Table 2: Schedule of Study Procedures *(continued)*

Study Visit	00A	00B	00C	01A	01B	01C	01D	01E	01F	01G	01H	01I	01J	01K	01L	01M	01N	02[1]	03	Early Term
Study Day	**Screen -28 to -7**		**Admit -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**12 ± 2d**	**85 +7d**	
Pregnancy Assessment																			X	
Phone Call																			X	

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

1 Study visits 01M-02 may be outpatient at the site.
2 Concomitant medications will be recorded during the entire hospital stay.
3 Participants must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
4 Must be performed on all female participants of childbearing potential prior to receipt of each study product and results must be negative and known prior to receipt of study product.
5 Can be done at Visit 00C or Visit 01A if applicable. The catheter should be removed after the 36-hour time point.
6 Hemoglobin, AST, ALT, total bilirubin, BUN, serum creatinine (includes eGFR), serum potassium and magnesium will be checked.
7 The study product will be administered orally under direct supervision with a high-fat, high-calorie meal and 240 mL water. A mouth check will be done. Food, liquids, and medication will be restricted for 2 hours post doses. Study participants should eat this meal in 30 ± 10 minutes or less; however, pretomanid should be administered 30 ± 10 minutes after start of the meal.
8 Blood can be drawn up to 1 hour prior to dosing.
9 The urine PK will be assessed up to 1 hour pre-dose and at 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hours post-dosing. PK urine sample collection during the 48-72 hours and 72-96 hours may be performed at home (i.e., Day 4 and Day 5).
10 SAEs only from study drug administration to Day 85 + 7 days.
11 Alcohol testing can be done on blood or breath if breathalyzer is used for alcohol testing.
12 Participants may remain in the hospital per site decision.

9.7.1 Sample Size

Not Applicable

10.2 Protocol Deviations

Table 3: Distribution of Protocol Deviations by Category, Type, and Impairment Group

[Implementation Note: Only include the Deviation Types that are used for your study. If the table will be multi-page, move the footnote/explanation to the footer so that it repeats for each page of the table.]

Category	Deviation Type	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		Severe Renal Impairment (N=X)		Matched Controls (N=X)		All Participants (N=X)	
		No. of Ppt.	No. of Dev.	No. of Ppt.	No. of Dev.	No. of Ppt.	No. of Dev.	No. of Ppt.	No. of Dev.	No. of Ppt.	No. of Dev.
Eligibility/enrollment	Any type	x	x	x	x	x	x	x	x	x	x
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x	x	x
	Met exclusion criterion										
	ICF not signed prior to study procedures										
	Other										
Treatment administration schedule	Any type										
	Out of window visit										
	Missed visit/visit not conducted										
	Missed treatment administration										
	Delayed treatment administration										
	Other										
Follow-up visit schedule	Any type										
	Out of window visit										
	Missed visit/visit not conducted										
	Other										
Protocol procedure/assessment	Any type										
	Incorrect version of ICF signed										
	Blood not collected										

Table 3: Distribution of Protocol Deviations by Category, Type, and Impairment Group *(continued)*

Category	Deviation Type	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		Severe Renal Impairment (N=X)		Matched Controls (N=X)		All Participants (N=X)	
		No. of Ppt.	No. of Dev.	No. of Ppt.	No. of Dev.	No. of Ppt.	No. of Dev.	No. of Ppt.	No. of Dev.	No. of Ppt.	No. of Dev.
	Urine not collected										
	Stool not collected										
	Other specimen not collected										
	Too few aliquots obtained										
	Specimen result not obtained										
	Required procedure not conducted										
	Required procedure done incorrectly										
	Study product temperature excursion										
	Specimen temperature excursion										
	Other										
Treatment administration	Any type										
	Required procedure done incorrectly										
	Study product temperature excursion										
	Other										
Blinding policy/procedure	Any type										
	Treatment unblinded										
	Other										

12.2.2 Displays of Adverse Events

Please refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Please refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

14.1 Description of Study Participants

14.1.1 Disposition of Participants

Table 4: Participant Disposition by Impairment Group

[Implementation Note: The endpoint milestone listed should be the blood draw of your primary endpoint, or whatever milestone(s) is appropriate for your protocol.

This table may be presented by cohort instead of, or in addition to, treatment arm, as appropriate. If presented by cohort, then cohort-specific screening counts may be included in row 1.

Percentages are calculated using the denominators displayed in the header. These denominators are the numbers of participants who enrolled into the study for each group.]

Participant Disposition	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		…		All Participants (N=X)	
	n	%	n	%	n	%	n	%
Screened	--	--	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	xx	x	100
Received Treatment	x	xx	x	xx	x	xx	x	xx
Received All Scheduled Treatments [a]	x	xx	x	xx	x	xx	x	xx
Completed Final Blood Draw [include appropriate endpoint milestones]								
Completed Follow-up (Study Day XXX)[a]								
Completed Per Protocol[b]								

Note: N = All Enrolled Participants.
[a] Refer to Listing 16.2.1 for reasons participants discontinued or terminated early.
[b] Refer to Listing 16.2.3 for reasons participants are excluded from the Analysis populations.

Table 5: Analysis Populations by Impairment Group

[Implementation Note: The reasons listed here should match the SAP text that describes who will be excluded from analyses. Although participants may meet multiple criteria for exclusion, they should be counted under only one reason for exclusion in this table. Priority for assigning reasons for exclusions will be defined in the SAP text.]

Analysis Populations	Reason Participants Excluded	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		Severe Renal Impairment (N=X)		Matched Controls (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	%	n
Safety Population	Any Reason	x	xx	x	xx	x	xx	x	xx	x	xx
	Did not receive study product										
	[Reason 2]										
	[Reason 3]										
	[Reason 4]										
Pharmacokinetic Population	Any Reason										
	[Reason 1]										
	[Reason 2]										
PK Plasma Population	Any Reason										
PK Urine Population	Any Reason										

Table 6: Dates of First Treatment by Site and Impairment Group

[Implementation Note: If the number of sites and/or groups causes this table to be too wide (wider than the page), then break into 2 tables: one by site and one by treatment group, similar to the demographics tables.

This table is displayed by both Site and Treatment group (for multicenter studies). It is important to look at enrollment over time, especially for a study of a disease with a particular season (e.g., flu), or if there were multiple lots of a product used. Enrollment data over time is displayed by group to confirm that treatments were balanced across time, by site to show if a site enrolled in a different time period than the other sites (in a way that might affect their results.)]

Dates of Dosing	Alliance for Multispecialty Research Mild Renal Impairment (N=X)	Alliance for Multispecialty Research Moderate Renal Impairment (N=X)	…	Advanced Pharma Mild Renal Impairment (N=X)	Advanced Pharma Moderate Renal Impairment (N=X)	…	All Sites Mild Renal Impairment (N=X)	All Sites Moderate Renal Impairment (N=X)	…	All Sites All Participants (N=X)
Total (Entire period of enrollment)										
DDMMMYYYY-DDMMMYYYY [categorize based on length of enrollment period]	x	x	x	x	x	x	x	x	x	x

Note: N = Number of participants enrolled.

Table 7: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of participants failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx

[a] More than one criterion may be marked per participant.
[b] Denominator for percentages is the total number of screen failures.

14.1.2 Demographic Data by Impairment Group

Table 8: Summary of Categorical Demographic and Baseline Characteristics by Site

[Implementation Note: This table may include other categorical baseline characteristics]

Variable	Characteristic	Alliance for Multispecialty Research (N=X)		Advanced Pharma (N=X)		All Participants (N=X)	
		n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx
	Female						
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino						
	Not Reported						
	Unknown						
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx
	Asian						
	Native Hawaiian or Other Pacific Islander						
	Black or African American						
	White						
	Multi-Racial						
	Unknown						
Note: N = Number of participants enrolled.							

Table 9: Summary of Continuous Demographic and Baseline Characteristics by Site

[Implementation Note: For studies in infants or young children, may be more appropriate to summarize age by months or weeks. This table may include additional continuous baseline characteristics (e.g., height, weight, BMI).]

Variable	Statistic	Alliance for Multispecialty Research (N=X)	Advanced Pharma (N=X)	All Participants (N=X)
Age (years)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x
Height (cm)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x
Weight (kg)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x
BMI (kg/m^2)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x
Note: N = Number of participants enrolled.				

Table 10: Summary of Categorical Demographic and Baseline Characteristics by Impairment Group, All Enrolled Participants

[Implementation Note: This table may include other categorical baseline characteristics and may be generated for multiple analysis populations in addition to all enrolled participants. The N's should match the number of participants in the analysis population.]

		Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		…		All Participants (N=X)	
Variable	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sex	Male	x	xx	x	xx	x	xx	x	xx
	Female								
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx	x	xx
	Hispanic or Latino								
	Not Reported								
	Unknown								
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	x	xx
	Asian								
	Native Hawaiian or Other Pacific Islander								
	Black or African American								
	White								
	Multi-Racial								
	Unknown								
Note: N = Number of enrolled participants.									

Table 11: Summary of Continuous Demographic and Baseline Characteristics by Impairment Group, All Enrolled Participants

[Implementation Note: For studies in infants or young children, may be more appropriate to summarize age by months or weeks. This table may include other continuous baseline characteristics.]

Variable	Statistic	Mild Renal Impairment (N=X)	Moderate Renal Impairment (N=X)	…	All Participants (N=X)
Age (years)	Mean	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx
	Median	x	x	x	x
	Minimum	x	x	x	x
	Maximum	x	x	x	x
Height (cm)	Mean	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx
	Median	xx	xx	xx	xx
	Minimum	x	x	x	x
	Maximum	x	x	x	x
Weight (kg)	Mean	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx
	Median	xx	xx	xx	xx
	Minimum	x	x	x	x
	Maximum	x	x	x	x
BMI (kg/m^2)	Mean	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx
	Median	xx	xx	xx	xx
	Minimum	x	x	x	x
	Maximum	x	x	x	x
Note: N = Number of enrolled participants.					

14.1.3 Prior and Concurrent Medical Conditions

Table 12: Summary of Participants with Pre-Existing Medical Conditions by MedDRA System Organ Class and Impairment Group

MedDRA System Organ Class	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		…		All Participants (N=X)	
	n	%	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx	x	xx
[SOC 1]								
[SOC 2]								

Note: N = Number of participants enrolled. n = Number of participants reporting medical history within the specified SOC. A participant is only counted once per SOC.

Table 13: Summary of Participants with Pre-Existing Medical Conditions by MedDRA Preferred Term and Impairment Group

MedDRA Preferred Term	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		…		All Participants (N=X)	
	n	%	n	%	n	%	n	%
Any PT	x	xx	x	xx	x	xx	x	xx
[PT 1]								
[PT 2]								

Note: N = Number of participants enrolled. n = Number of participants reporting medical history within the specified PT. A participant is only counted once per PT.

Table 14: Summary of Participants with Newly Developed Medical Conditions by MedDRA System Organ Class and Impairment Group

MedDRA System Organ Class	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		…		All Participants (N=X)	
	n	%	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx	x	xx
[SOC 1]								
[SOC 2]								

Note: N = Number of participants enrolled. n = Number of participants reporting medical history within the specified SOC. A participant is only counted once per SOC.

Table 15: Summary of Participants with Newly Developed Medical Conditions by MedDRA Preferred Term and Impairment Group

MedDRA Preferred Term	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		…		All Participants (N=X)	
	n	%	n	%	n	%	n	%
Any PT	x	xx	x	xx	x	xx	x	xx
[PT 1]								
[PT 2]								

Note: N = Number of participants enrolled. n = Number of participants reporting medical history within the specified PT. A participant is only counted once per PT.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 16: Overall Summary of Adverse Events

	Mild Renal Impairment (N = x)		Moderate Renal Impairment (N = x)		…		All Participants (N = x)	
Participants[a] with	n	%	n	%	n	%	n	%
At least one lab finding of mild or worse severity through Day 12	x	x	x	x	x	x	x	x
At least one unsolicited adverse event	x	x	x	x	x	x	x	x
At least one unsolicited treatment emergent adverse event	x	x	x	x	x	x	x	x
At least one related unsolicited treatment emergent adverse event	x	x	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x	x	x
Not yet assessed								
At least one severe (Grade 3) unsolicited treatment emergent adverse event	x	x	x	x	x	x	x	x
Related	x	x	x	x	x	x	x	x
Unrelated	x	x	x	x	x	x	x	x
At least one treatment emergent serious adverse event[b]	x	x	x	x	x	x	x	x
At least one related treatment emergent serious adverse event	x	x	x	x	x	x	x	x
At least one treatment emergent adverse event leading to early termination[c]	x	x	x	x	x	x	x	x

N = Number of participants in the Safety Population
[a] Participants are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in the Listing of Serious Adverse Events table.
[c] As reported on the Adverse Event eCRF.

Table 17: Treatment Emergent Adverse Events Occurring in 5% of Participants in Any Impairment Group by MedDRA System Organ Class and Preferred Term, and Impairment Group - Safety Population

[Implementation Note: this table is used to complete the "Other Adverse Event Template" for clinicaltrials.gov reporting (See slide 6 in https://prsinfo.clinicaltrials.gov/trainTrainer/Adverse-Events-Module.pdf). Threshold value may be 0% to 5% (default 5). This table should include a row for All PT/SOC and for any PT/SOC reported by ≥[threshold]% participants in any group. Note, this table summarize SAEs and non-serious events separately. This includes all adverse events collected (e.g., solicited, unsolicited, AESI, laboratory adverse events, etc.), regardless of relationship to study product, so this summary should combine data collected across multiple eCRFs/domains.]

Preferred Term	MedDRA System Organ Class	Mild Renal Impairment (N=X)			Moderate Renal Impairment (N=X)			…			All Participants (N=X)		
		n	%	Events	n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events													
All	All	x	x	x	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x	x	x	x
Etc.	Etc.												
Other (Non-serious) Adverse Events													
All	All	x	x	x	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x	x	x	x
Etc.	Etc.												

N = number of participants in the Safety Population (number of participants at risk).
n= number of participants reporting event.
Events= total frequency of events reported.

14.3.1.1 Solicited Adverse Events

Not Applicable.

14.3.1.2 Unsolicited Adverse Events

Table 18: Summary of Unsolicited Treatment Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Impairment Group – Mild Renal Impairment

[Implementation Note: All of the Unsolicited Adverse Event summary tables include serious and non-serious AEs. Update the Groups and Doses as appropriate for your study. Intervals should correspond to AE collection period during the study, for example in a vaccine study Day x-y may correspond to the solicited event collection period (often, Days 1-7), while Days y-z is the remainder of the unsolicited AE collection period (often, through Day 21 or Day 28) or up until the subsequent dose; Treatment or device study may not include such intervals.]

[Repeat for each Treatment Group (each table numbered separately) or include all treatment groups on one table using merged rows as in the alternate presentation included for Table 23]

MedDRA System Organ Class	MedDRA Preferred Term	Days 1-4 Post Dose (N=X)			Days 5-12 Post Dose (N=X)			Day 85 Post Dose (N=X)			Any Time Post Dose (N=X)		
		n	%	Events	n	%	Events	n	%	Events	n	%	Events
Any SOC	Any PT	x	xx	x	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												
Note: N = number of participants in the Safety Population. This table presents number and percentage of participants. A participant is only counted once per PT.													

Tables with similar format to Table 18:

Table 19: Summary of Unsolicited Treatment Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Impairment Group – Moderate Renal Impairment

Table 20: Summary of Unsolicited Treatment Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Impairment Group – Severe Renal Impairment

Table 21: Summary of Unsolicited Treatment Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Impairment Group – Matched Controls

Table 22: Unsolicited Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Impairment Group

MedDRA System Organ Class	Preferred Term	Severity	Mild Renal Impairment (N = X)						Moderate Renal Impairment (N = X)						…						All Participants (N = X)					
			Related		Not Related		Total		Related		Not Related		Total		Related		Not Related		Total		Related		Not Related		Total	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Life Threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	PT 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Life Threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	PT 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Life Threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Note: N = Number of participants in the Safety Population.

Table 23: Related Unsolicited Treatment Emergent Adverse Events Within 85 Days Post Dosing by MedDRA System Organ Class and Preferred Term, and Impairment Group

Mild Renal Impairment (N=X)

[Implementation Note: Repeat for each Treatment Group (with each table numbered separately) or include all treatment groups on one table using merged rows as in the alternate presentation included for Table 23]

[Implementation Note: Day x-y interval should correspond to period of collection for solicited symptoms, if applicable.]

		Day 1-4 Post Dose			Day 5-12 Post Dose			Within 85 Days Post Dose		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**
Any SOC	Any PT	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any PT									
	[PT 1]									
	[PT 2]									
[SOC 2]	Any PT									
	[PT 1]									
	[PT 2]									
Note: N = Number of participants in the Safety Population. This table presents number and percentage of participants. For each time point, a participant is only counted once per PT.										

Tables with similar format to Table 23:

Table 24: Related Unsolicited Treatment Emergent Adverse Events Within 85 Days Post Dosing by MedDRA System Organ Class and Preferred Term, and Impairment Group

Moderate Renal Impairment (N=X)

Table 25: Related Unsolicited Treatment Emergent Adverse Events Within 85 Days Post Dosing by MedDRA System Organ Class and Preferred Term, and Impairment Group

Severe Renal Impairment (N=X)

Table 26: Related Unsolicited Treatment Emergent Adverse Events Within 85 Days Post Dosing by MedDRA System Organ Class and Preferred Term, and Impairment Group

Matched Controls (N=X)

14.3.2 Listing of Deaths, Other Serious and Significant Treatment Emergent Adverse Events

Table 27: Listing of Serious Adverse Events

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. If the event is ongoing (no stop date), indicate "ongoing" for the "Duration". If more than one reason is selected for the reason reported as an SAE, list all reasons in the column, separated by a comma. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. If there are no comments for an event, populate 'Comments' row with 'None'. Add columns for MedDRA HLT or LLT depending on halting criteria or other study needs. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Participant ID, Associated with Dose No., and No. of Days Post Associated Dose.]

Adverse Event	No. of Days Post Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Participant ID: Impairment Group: , AE Number:										
Comments:										
Participant ID: Impairment Group: , AE Number:										
Comments:										

Table 28: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

[Implementation Note: This listing is included in the tables document, as it is included in the body of the CSR. If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. If there are no comments for an event, populate 'Comments' row with 'None'. Add columns for MedDRA HLT or LLT depending on halting criteria or other study needs. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Participant ID, Associated with Dose No., and No. of Days Post Associated Dose.]

Adverse Event	No. of Days Post Dose (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Participant ID: Impairment Group: , AE Number:								
Comments:								
Participant ID: Impairment Group: , AE Number:								
Comments:								

Table 29: Listing of Other Significant Adverse Events

[Implementation Note: This listing is included in the tables document, as it is included in the body of the CSR. If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. If there are no comments for an event, populate 'Comments' row with 'None'. Add columns for MedDRA HLT or LLT depending on halting criteria or other study needs. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Participant ID, Number of Doses Received at Time of Event, and Date of Product Administration]

Adverse Event	No. of Days Post Dose	Duration of Event	Severity	MedDRA System Organ Class	Relationship	Outcome
Participant ID: Impairment Group: , AE Number:						
Comments:						
Participant ID: Impairment Group: , AE Number:						
Comments:						

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(not included in SAP, but this is a placeholder for the CSR)

14.3.4 Abnormal Laboratory Value Listings (by Participant)

Table 30: Listing of Abnormal Laboratory Results - Chemistry

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing should include all hematology results for any participant that had at least one abnormal chemistry laboratory result. A complete listing of all laboratory results is included in the listings document. In the Laboratory Parameter column, indicate the units after the parameter, e.g., Hemoglobin (g/dL). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 16.2 (mild). In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.]

Participant ID	Impairment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Participant Discontinued Due to Result?

Table 31: Listing of Abnormal Laboratory Results - Hematology

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing should include all hematology results for any participant that had at least one abnormal hematology laboratory result. A complete listing of all laboratory results is included in the listings document. In the Laboratory Parameter column, indicate the units after the parameter, e.g., Hemoglobin (g/dL). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 16.2 (mild). In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.]

Participant ID	Impairment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Participant Discontinued Due to Result?

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 32: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Any Chemistry Parameter

[Implementation Note: Generate one table for "Any Chemistry Parameter" and one table for each chemistry parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity.]

Any Chemistry Parameter Time Point	Impairment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 1	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 5	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 12	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													

Table 32: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Any Chemistry Parameter *(continued)*

Any Chemistry Parameter Time Point	Impairment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N = Number of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Table 33: Chemistry Laboratory Results by Range, Maximum Severity, Time Point, and Impairment Group –Potassium

[Repeat for each chemistry laboratory parameter, number each table separately]

Time Point	Impairment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Life Threatening/ Grade 4 (Low)		Life Threatening/ Grade 4 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					
Day 1	Mild Renal Impairment																					
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					
Day 5	Mild Renal Impairment																					
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					

Table 33: Chemistry Laboratory Results by Range, Maximum Severity, Time Point, and Impairment Group –Potassium *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Life Threatening/ Grade 4 (Low)		Life Threatening/ Grade 4 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 12	Mild Renal Impairment																					
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					
Max Severity Post Baseline	Mild Renal Impairment																					
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N= Number of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Table 34: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Blood Urea Nitrogen

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 1	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 5	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 12	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Max Severity Post Baseline	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N= Number of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Table 35: Chemistry Laboratory Results by Range, Maximum Severity, Time Point, and Impairment Group – Creatinine

Time Point	Impairment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Life Threatening/ Grade 4 (Low)		Life Threatening/ Grade 4 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					
Day 1	Mild Renal Impairment																					
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					
Day 5	Mild Renal Impairment																					
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					

Table 35: Chemistry Laboratory Results by Range, Maximum Severity, Time Point, and Impairment Group – Creatinine *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Life Threatening/ Grade 4 (Low)		Life Threatening/ Grade 4 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 12	Mild Renal Impairment																					
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					
Max Severity Post Baseline	Mild Renal Impairment																					
	Moderate Renal Impairment																					
	Severe Renal Impairment																					
	Matched Controls																					

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N= Number of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Table 36: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – eGFR

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 1	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 5	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 12	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Max Severity Post Baseline	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N= Number of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Tables with a similar format to Table 36:

Table 37: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Magnesium

Table 38: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Alanine Aminotransferase

Table 39: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Aspartate Aminotransferase

Table 40: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Total Bilirubin

Table 41: Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Any Chemistry Parameter

[Implementation Note: Generate one table for "Any Chemistry Parameter" and one table for each parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity. Number each table separately]

Time Point	Impairment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4	
			n	%	n	%	n	%	n	%
Day 1	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Day 5	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Day 12	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Max Severity Post Baseline	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N= Number of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Table 42: Abnormal Chemistry Laboratory Results Related to Study Treatment by Range, Maximum Severity, Time Point, and Impairment Group – Potassium

[Repeat for each chemistry laboratory parameter; number each table separately]

Time Point	Impairment Group	N	Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Life Threatening/ Grade 4 (Low)		Life Threatening/ Grade 4 (High)	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 1	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment																	
	Severe Renal Impairment																	
	Matched Controls																	
Day 5	Mild Renal Impairment																	
	Moderate Renal Impairment																	
	Severe Renal Impairment																	
	Matched Controls																	
Day 12	Mild Renal Impairment																	
	Moderate Renal Impairment																	
	Severe Renal Impairment																	
	Matched Controls																	
Max Severity Post Baseline	Mild Renal Impairment																	
	Moderate Renal Impairment																	
	Severe Renal Impairment																	
	Matched Controls																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N= of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Table 43: Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Blood Urea Nitrogen

Time Point	Impairment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4	
			n	%	n	%	n	%	n	%
Day 1	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Day 5	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Day 12	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Max Severity Post Baseline	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N= Number of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Table 44: Abnormal Chemistry Laboratory Results Related to Study Treatment by Range, Maximum Severity, Time Point, and Impairment Group –Creatinine

Time Point	Impairment Group	N	Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Life Threatening/ Grade 4 (Low)		Life Threatening/ Grade 4 (High)	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 1	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment																	
	Severe Renal Impairment																	
	Matched Controls																	
Day 5	Mild Renal Impairment																	
	Moderate Renal Impairment																	
	Severe Renal Impairment																	
	Matched Controls																	
Day 12	Mild Renal Impairment																	
	Moderate Renal Impairment																	
	Severe Renal Impairment																	
	Matched Controls																	
Max Severity Post Baseline	Mild Renal Impairment																	
	Moderate Renal Impairment																	
	Severe Renal Impairment																	
	Matched Controls																	

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N= of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Table 45: Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – eGFR

Time Point	Impairment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4	
			n	%	n	%	n	%	n	%
Day 1	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Day 5	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Day 12	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Max Severity Post Baseline	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N= Number of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Tables with a similar format to Table 45:

Table 46: Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Magnesium

Table 47: **Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Alanine Aminotransferase**

Table 48: Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Aspartate Aminotransferase

Table 49: Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Total Bilirubin

Table 50: Chemistry Laboratory Summary Statistics and Change from Baseline by Time Point, and Impairment Group –Potassium

[Implementation Note: Generate one table for each chemistry parameter. For calculated fields (Mean, SD, Median), decimal place should be the format in which the data were collected + 1 extra place. For Min, Max, decimal place should be in the same format in which the data were collected.]

[Repeat for each Chemistry Laboratory Parameter, number each table separately]

		Measurement					Change from Baseline				
Time Point	**Impairment Group**	**N**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**	**N**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**
Baseline	Mild Renal Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x	-	-	-	-	-
	Moderate Renal Impairment						-	-	-	-	-
	Severe Renal Impairment						-	-	-	-	-
	Matched Controls						-	-	-	-	-
Day 1	Mild Renal Impairment										
	Moderate Renal Impairment										
	Severe Renal Impairment										
	Matched Controls										
Day 5	Mild Renal Impairment										
	Moderate Renal Impairment										
	Severe Renal Impairment										
	Matched Controls										
Day 12	Mild Renal Impairment										
	Moderate Renal Impairment										
	Severe Renal Impairment										
	Matched Controls										

Note: N = Number of participants with lab results at the specified time point. Baseline = last recorded value prior to drug administration.

Tables with similar format to Table 50:

Table 51: Chemistry Laboratory Summary Statistics and Change from Baseline by Time Point, and Impairment Group – Blood Urea Nitrogen

Table 52: Chemistry Laboratory Summary Statistics and Change from Baseline by Time Point, and Impairment Group – Creatinine

Table 53: Chemistry Laboratory Summary Statistics and Change from Baseline by Time Point, and Impairment Group – eGFR

Table 54: Chemistry Laboratory Summary Statistics and Change from Baseline by Time Point, and Impairment Group – Magnesium

Table 55: Chemistry Laboratory Summary Statistics and Change from Baseline by Time Point, and Impairment Group – Alanine Aminotransferase

Table 56: Chemistry Laboratory Summary Statistics and Change from Baseline by Time Point, and Impairment Group – Aspartate Aminotransferase

Table 57: Chemistry Laboratory Summary Statistics and Change from Baseline by Time Point, and Impairment Group – Total Bilirubin

Table 58: Chemistry Laboratory Toxicity Grade, Maximum Post-Baseline Severity Compared to Baseline Severity by Impairment Group – Potassium

Impairment Group	Baseline Severity	Maximum Post-Baseline Severity									
		None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4	
		n	%	n	%	n	%	n	%	n	%
Mild Renal Impairment (N=X)	None	x	x	x	x	x	x	x	x	x	x
	Mild/ Grade 1	x	x	x	x	x	x	x	x	x	x
	Moderate/ Grade 2	x	x	x	x	x	x	x	x	x	x
	Severe/ Grade 3	x	x	x	x	x	x	x	x	x	x
	Life Threatening/Grade 4	x	x	x	x	x	x	x	x	x	x
Moderate Renal Impairment (N=X)	None										
	Mild/ Grade 1										
	Moderate/ Grade 2										
	Severe/ Grade 3										
	Life Threatening/Grade 4										
Severe Renal Impairment (N=X)	None										
	Mild/ Grade 1										
	Moderate/ Grade 2										
	Severe/ Grade 3										
	Life Threatening/Grade 4										
Matched Controls (N=X)	None										
	Mild/ Grade 1										
	Moderate/ Grade 2										
	Severe/ Grade 3										
	Life Threatening/Grade 4										

Notes: N = Number of participants in the Safety Population with the laboratory result assessed at baseline and at least once post-baseline. Baseline = The last result obtained before drug administration. The maximum post-baseline severity indicates the maximum severity experienced by each participant at any time point post-baseline, including unscheduled assessments.

Tables with similar format to Table 58:

Table 59: Chemistry Laboratory Toxicity Grade, Maximum Post-Baseline Severity Compared to Baseline Severity by Impairment Group – Blood Urea Nitrogen

Table 60: Chemistry Laboratory Toxicity Grade, Maximum Post-Baseline Severity Compared to Baseline Severity by Impairment Group – Creatinine

Table 61: Chemistry Laboratory Toxicity Grade, Maximum Post-Baseline Severity Compared to Baseline Severity by Impairment Group – eGFR

Table 62: Chemistry Laboratory Toxicity Grade, Maximum Post-Baseline Severity Compared to Baseline Severity by Impairment Group – Alanine Aminotransferase

Table 63: Chemistry Laboratory Toxicity Grade, Maximum Post-Baseline Severity Compared to Baseline Severity by Impairment Group – Aspartate Aminotransferase

Table 64: Chemistry Laboratory Toxicity Grade, Maximum Post-Baseline Severity Compared to Baseline Severity by Impairment Group – Total Bilirubin

14.3.5.2 Hematology Results

Table 65: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Hemoglobin

[Implementation Note: Generate one table for "Any Hematology Parameter" and one table for each hematology parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity.]

Any Hematology Parameter Time Point	Impairment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 1	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 5	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 12	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													

Table 65: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Hemoglobin *(continued)*

Any Hematology Parameter Time Point	Impairment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N = Number of participants in the Safety Population. Baseline = The last result obtained before drug administration.

Table 66: Hematology Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Hemoglobin

[Repeat for each hematology laboratory parameter; number each table separately]

Time Point	Impairment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4	
			n	%	n	%	n	%	n	%
Day 1	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Day 5	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Day 12	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									
Max Severity Post Baseline	Mild Renal Impairment									
	Moderate Renal Impairment									
	Severe Renal Impairment									
	Matched Controls									

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N = Number of participants in the Safety Population. Baseline = The last result obtained before drug administration.

Table 67: Hematology Laboratory Summary Statistics and Change from Baseline by Time Point, and Impairment Group – Hemoglobin

[Implementation Note: Generate one table for each hematology parameter. For calculated fields (Mean, SD, Median), decimal place should be the format in which the data were collected + 1 extra place. For Min, Max, decimal place should be in the same format in which the data were collected.]

[Repeat for each Hematology Laboratory Parameter and a table for each Parameter's Change from Baseline, number each table separately]

		Measurement					Change from Baseline				
Time Point	**Impairment Group**	**N**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**	**N**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**
Baseline	Mild Renal Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x	-	-	-	-	-
	Moderate Renal Impairment						-	-	-	-	-
	Severe Renal Impairment						-	-	-	-	-
	Matched Controls						-	-	-	-	-
Day 1	Mild Renal Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Moderate Renal Impairment										
	Severe Renal Impairment										
	Matched Controls										
Day 5	Mild Renal Impairment										
	Moderate Renal Impairment										
	Severe Renal Impairment										
	Matched Controls										
Day 12	Mild Renal Impairment										
	Moderate Renal Impairment										
	Severe Renal Impairment										
	Matched Controls										
Note: N = Number of participants with lab results at the specified time point. Baseline = last recorded value prior to drug administration.											

Table 68: Hematology Laboratory Toxicity Grade, Maximum Post-Baseline Severity Compared to Baseline Severity by Impairment Group – Hemoglobin

Impairment Group	Baseline Severity	Maximum Post-Baseline Severity									
		None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life Threatening/ Grade 4	
		n	%	n	%	n	%	n	%	n	%
Mild Renal Impairment (N=X)	None	x	x	x	x	x	x	x	x	x	x
	Mild/ Grade 1	x	x	x	x	x	x	x	x	x	x
	Moderate/ Grade 2	x	x	x	x	x	x	x	x	x	x
	Severe/ Grade 3	x	x	x	x	x	x	x	x	x	x
	Life Threatening/Grade 4	x	x	x	x	x	x	x	x	x	x
Moderate Renal Impairment (N=X)	None										
	Mild/ Grade 1										
	Moderate/ Grade 2										
	Severe/ Grade 3										
	Life Threatening/Grade 4										
Severe Renal Impairment (N=X)	None										
	Mild/ Grade 1										
	Moderate/ Grade 2										
	Severe/ Grade 3										
	Life Threatening/Grade 4										
Matched Controls (N=X)	None										
	Mild/ Grade 1										
	Moderate/ Grade 2										
	Severe/ Grade 3										
	Life Threatening/Grade 4										

Notes: N = Number of participants in the Safety Population with the laboratory result assessed at baseline and at least once post-baseline. Baseline = The last result obtained before drug administration. The maximum post-baseline severity indicates the maximum severity experienced by each participant at any time point post-baseline, including unscheduled assessments.

14.3.6 Displays of Vital Signs

Table 69: Vital Signs by Assessment, Maximum Severity, Time Point, and Impairment Group – Any Assessment

[Implementation Note: Generate one table for "Any Assessment" and one table for each assessment. If an assessment has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the first sample table below. If not, then just include one column per severity, as shown in the second sample table. "Any Assessment" will just summarize one column per severity.]

Time Point	Impairment Group	N	None		Mild		Moderate		Severe		Life Threatening		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 1 (12 hours post-dose)	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 2 (24 hours post-dose)	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 3 (48 hours post-dose)	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													

Table 69: Vital Signs by Assessment, Maximum Severity, Time Point, and Impairment Group – Any Assessment *(continued)*

Time Point	Impairment Group	N	None		Mild		Moderate		Severe		Life Threatening		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 5	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 7	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Day 12	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													
Max Severity Post Baseline	Mild Renal Impairment													
	Moderate Renal Impairment													
	Severe Renal Impairment													
	Matched Controls													

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N = Number of participants in the Safety Population. Baseline = last recorded value prior to drug administration.

Table 70: Vital Signs by Assessment, Maximum Severity, Time Point, and Impairment Group –Assessment Systolic Blood Pressure

[Repeat for each Vital Sign Assessment; number each table separately]

Time Point	Impairment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Life Threatening	Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%		n	%
Baseline	Mild Renal Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx		x	xx
	Moderate Renal Impairment																		
	Severe Renal Impairment																		
	Matched Controls																		
Day y	Mild Renal Impairment																		
	Moderate Renal Impairment																		
	Severe Renal Impairment																		
	Matched Controls																		
Day z	Mild Renal Impairment																		
	Moderate Renal Impairment																		
	Severe Renal Impairment																		
	Matched Controls																		

Table 70: Vital Signs by Assessment, Maximum Severity, Time Point, and Impairment Group –Assessment Systolic Blood Pressure *(continued)*

Time Point	Impairment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Life Threatening	Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%		n	%
Max Severity Post Baseline	Mild Renal Impairment																		
	Moderate Renal Impairment																		
	Severe Renal Impairment																		
	Matched Controls																		
Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N = of participants in the Safety Population. Baseline = last recorded value prior to drug administration.																			

Tables with similar format to Table 70:

Table 71: Vital Signs by Assessment, Maximum Severity, Time Point, and Impairment Group –Assessment Diastolic Blood Pressure

Table 72: Vital Signs by Assessment, Maximum Severity, Time Point, and Impairment Group –Assessment Pulse

Table 73: Vital Signs by Assessment, Maximum Severity, Time Point, and Impairment Group –Assessment Oral Temperature

Table 74: Vital Signs Mean Change by Time Point, and Impairment Group –Assessment Systolic Blood Pressure

[Repeat for each Vital Sign Assessment; number each table separately]

Time Point	Impairment Group	N	Mean	Standard Deviation	Mean Change from Baseline	Standard Deviation of Mean Change from Baseline
Baseline	Mild Renal Impairment					
	Moderate Renal Impairment					
	Severe Renal Impairment					
	Matched Controls					
12 Hours	Mild Renal Impairment					
	Moderate Renal Impairment					
	Severe Renal Impairment					
	Matched Controls					
24 Hours	Mild Renal Impairment					
	Moderate Renal Impairment					
	Severe Renal Impairment					
	Matched Controls					
48 Hours	Mild Renal Impairment					
	Moderate Renal Impairment					
	Severe Renal Impairment					
	Matched Controls					
72 Hours	Mild Renal Impairment					
	Moderate Renal Impairment					
	Severe Renal Impairment					
	Matched Controls					
96 Hours	Mild Renal Impairment					
	Moderate Renal Impairment					
	Severe Renal Impairment					
	Matched Controls					

Table 74: Vital Signs Mean Change by Time Point, and Impairment Group –Assessment Systolic Blood Pressure *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Mean Change from Baseline	Standard Deviation of Mean Change from Baseline
Day 12	Mild Renal Impairment					
	Moderate Renal Impairment					
	Severe Renal Impairment					
	Matched Controls					

Tables with similar format to Table 74:

Table 75: Vital Signs Mean Change by Time Point, and Impairment Group –Assessment Diastolic Blood Pressure

Table 76: Vital Signs Mean Change by Time Point, and Impairment Group –Assessment Pulse

Table 77: Vital Signs Mean Change by Time Point, and Impairment Group –Assessment Oral Temperature

Table 78: Summary of Abnormal Physical Exam Findings by Impairment Group

Time Point	Body System	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		Severe Renal Impairment (N=X)		Matched Controls (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%
Baseline	Any Body System	x	xx	x	xx	x	xx	x	xx	x	xx
	Skin										
	HEENT										
	Thyroid										
	Neurological										
	Chest/Lungs										
	Cardiovascular										
	Abdomen										
	Lymph Nodes										
	Musculoskeletal										
	Extremities										
Day 1	Any Body System	x	xx	x	xx	x	xx	x	xx	x	xx
	Skin										
	HEENT										
	Thyroid										
	Neurological										
	Chest/Lungs										
	Cardiovascular										
	Abdomen										
	Lymph Nodes										
	Musculoskeletal										
	Extremities										
Day 2	Any Body System	x	xx	x	xx	x	xx	x	xx	x	xx
	Skin										
	HEENT										
	Thyroid										
	Neurological										
	Chest/Lungs										
	Cardiovascular										
	Abdomen										
	Lymph Nodes										
	Musculoskeletal										
	Extremities										
Day 3	Any Body System	x	xx	x	xx	x	xx	x	xx	x	xx
	Skin										
	HEENT										
	Thyroid										
	Neurological										
	Chest/Lungs										
	Cardiovascular										
	Abdomen										
	Lymph Nodes										
	Musculoskeletal										
	Extremities										

Table 78: Summary of Abnormal Physical Exam Findings by Impairment Group *(continued)*

Time Point	Body System	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		Severe Renal Impairment (N=X)		Matched Controls (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%
Day 4	Any Body System	x	xx	x	xx	x	xx	x	xx	x	xx
	Skin										
	HEENT										
	Thyroid										
	Neurological										
	Chest/Lungs										
	Cardiovascular										
	Abdomen										
	Lymph Nodes										
	Musculoskeletal										
	Extremities										
Day 5	Any Body System	x	xx	x	xx	x	xx	x	xx	x	xx
	Skin										
	HEENT										
	Thyroid										
	Neurological										
	Chest/Lungs										
	Cardiovascular										
	Abdomen										
	Lymph Nodes										
	Musculoskeletal										
	Extremities										
Day 12	Any Body System	x	xx	x	xx	x	xx	x	xx	x	xx
	Skin										
	HEENT										
	Thyroid										
	Neurological										
	Chest/Lungs										
	Cardiovascular										
	Abdomen										
	Lymph Nodes										
	Musculoskeletal										
	Extremities										

14.4 Summary of Concomitant Medications

Table 79: Number and Percentage of Participants with Prior and Concurrent Medications by WHO Drug Classification and Impairment Group

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Mild Renal Impairment (N=X)		Moderate Renal Impairment (N=X)		…		All Participants (N=X)	
		n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]								
	[ATC 2 - 1]								
	[ATC 2 - 2]								
	[ATC 2 - 3]								
[ATC Level 1 – 2]	[ATC 2 - 1]								
	[ATC 2 - 2]								
	[ATC 2 - 3]								

N = Number of participants in the Safety Population. n=Number of participants reporting taking at least one medication in the specific WHO Drug Class.

14.5 Other Safety Measures

Table 80: ECG Measurement and Change from Pre-Dose Baseline QTcF by Time Point

Parameter	Timepoint	N	Measurement				Change from Baseline				
			Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max	90% CI
QTcF Interval (msec)	Baseline	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-	-
	Day 5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)

Notes: N = Number of participants in the Safety Population with the ECG measurement assessed at the respective timepoint. Baseline = The most recent measurement prior to drug administration.

14.6 Pharmacokinetics Results

Table 81: Individual and Summary Statistics for Plasma Concentrations by Nominal Time (hours) – Mild Renal Impairment Group

	Pre-Dose	1	2	4	5	6	8	12	16	24	36	48	72	96
001														
002														
003														
N														
N Not Evaluable														
Number < LLOQ[a]														
Mean														
SD														
Min														
Median														
Max														
Notes: [a] LLOQ = 10 ng/mL														

Tables with similar format to Table 77:

Table 82: Individual and Summary Statistics for Plasma Concentrations by Nominal Time (hours) – Moderate Renal Impairment Group

Table 83: Individual and Summary Statistics for Plasma Concentrations by Nominal Time (hours) – Severe Renal Impairment Group

Table 84: Individual and Summary Statistics for Plasma Concentrations by Nominal Time (hours) – Matched Controls

Table 85: Individual and Summary Statistics for Noncompartmental Plasma PK Parameters – Mild Renal Impairment

Participant ID	C_{max} (µg/mL)	T_{max} (hr)	AUC_{last} (µg*h/mL)	AUC_{∞} (µg*h/mL)	$\%AUC_{ex}$ (µg*h/mL)	$t_{1/2}$ (hr)	λ_z	CL/F (L)	V_d/F (L)
001									
002									
003									
N									
Mean									
SD									
Min									
Max									
CV %									
GM									

Tables with similar format to Table 85:

Table 86: Individual and Summary Statistics for Noncompartmental Plasma PK Parameters – Moderate Renal Impairment

Table 87: Individual and Summary Statistics for Noncompartmental Plasma PK Parameters – Severe Renal Impairment

Table 88: Individual and Summary Statistics for Noncompartmental Plasma PK Parameters – Matched Controls

Table 89: Individual and Summary Statistics for Noncompartmental Urine PK Parameters – Mild Renal Impairment

Participant ID	$Ae_{(0-t)}$ µg	Ae%Dose	CL_R (L/h)
001			
002			
003			
N			
Mean			
SD			
Min			
Max			
CV %			
GM			

Tables with similar format to Table 89:

Table 90: Individual and Summary Statistics for Noncompartmental Urine PK Parameters – Moderate Renal Impairment

Table 91: Individual and Summary Statistics for Noncompartmental Urine PK Parameters – Severe Renal Impairment

Table 92: Individual and Summary Statistics for Noncompartmental Urine PK Parameters – Matched Controls

Table 93: Estimated Impairment Group Fold Change for Noncompartmental PK Parameters

[Implementation Note: The site column will only be included if the group by site interaction is significant at a p-value < 0.10 level.]

Site	Impairment Group	Statistic	AUC_{last} (µg*h/mL)	AUC_{∞} (µg*h/mL)	C_{max} (µg/mL)
All Sites	Mild	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Fold Change			
	Moderate	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Fold Change			
	Severe	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Fold Change			
	Matched Controls	Mean			
		90% CI of Mean			
Alliance for Multispeciality Research	Mild	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Fold Change			
	Moderate	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Fold Change			
	Severe	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Fold Change			
	Matched Controls	Mean			

Table 93: Estimated Impairment Group Fold Change for Noncompartmental PK Parameters *(continued)*

		90% CI of Mean			
Advanced Pharma	Mild	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Fold Change			
	Moderate	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Fold Change			
	Severe	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Fold Change			
	Matched Controls	Mean			
		90% CI of Mean			
Notes: [a] Comparison is to matched controls.					

Table 94: Estimated Impairment Group Shift for Noncompartmental PK Parameters

[Implementation Note: Site column will only be included if confidence intervals between sites do not overlap.]

Site	Impairment Group	Statistic	T_{max} (h)
All Sites	Mild	Median	
		90% CI of Median[a]	
		Shift[b]	
		90% CI of Shift[a]	
	Moderate	Median	
		90% CI of Median[a]	
		Shift[b]	
		90% CI of Shift[a]	
	Severe	Median	
		90% CI of Median[a]	
		Shift[b]	
		90% CI of Shift[a]	
	Matched Controls	Median	
		90% CI of Median[a]	
Alliance for Multispeciality Research	Mild	Median	
		90% CI of Median[a]	
		Shift[b]	
		90% CI of Shift[a]	
	Moderate	Median	
		90% CI of Median[a]	
		Shift[b]	
		90% CI of Shift[a]	
	Severe	Median	
		90% CI of Median[a]	
		Shift[b]	
		90% CI of Shift[a]	
	Matched Controls	Median	
		90% CI of Median[a]	
Advanced Pharma	Mild	Median	
		90% CI of Median[a]	
		Shift[b]	
		90% CI of Shift[a]	

Table 94: Estimated Impairment Group Shift for Noncompartmental PK Parameters *(continued)*

	Moderate	Median	
		90% CI of Median[a]	
		Shift[b]	
		90% CI of Shift[a]	
	Severe	Median	
		90% CI of Median[a]	
		Shift[b]	
		90% CI of Shift[a]	
	Matched Controls	Median	
		90% CI of Median[a]	

Notes:
[a]Confidence limits will be estimated using the inverted rank score method.
[b]Comparison is to matched controls.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

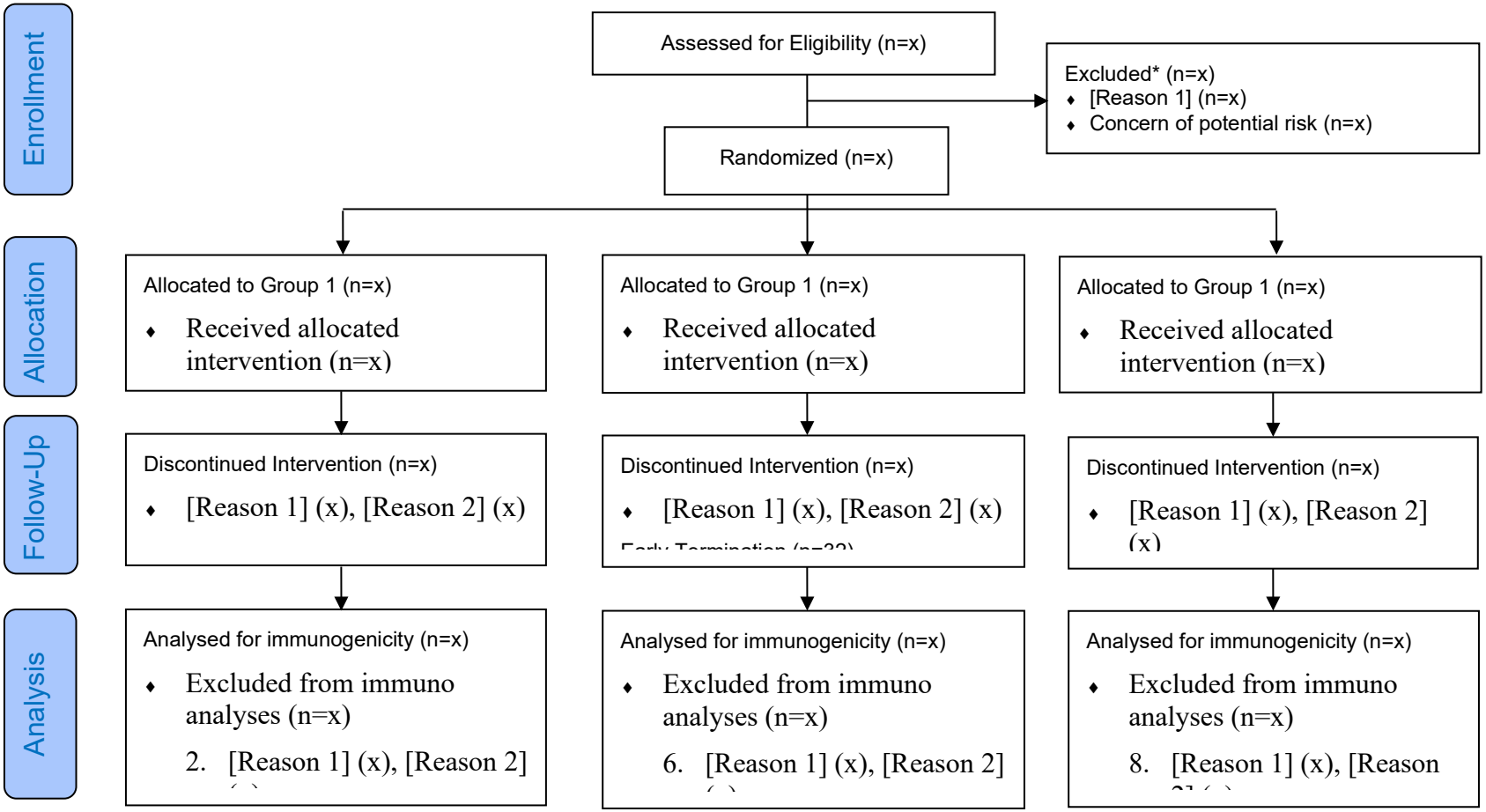
Figures *(continued)*

Figures *(continued)*

10.1 Disposition of Participants

Figure 1: CONSORT Flow Diagram

[Implementation Note: In the SAP, include a blank diagram with the possible reasons why participants may be excluded from analyses. The reasons for exclusion should be in line with the SAP text. If possible, indicate the analysis population in the CONSORT diagram. Order the reasons for exclusion by descending 'N'or 'n'].



14.3.1.2 Unsolicited Adverse Events

Figure 2: Frequency of Related Treatment Emergent Adverse Events by MedDRA System Organ Class and Severity

[Implementation Note: A sample figure is shown below. Separate panels will be displayed for each impairment group and matched controls and labeled "Mild Renal Impairment (N=X)" "Moderate Renal Impairment (N=X)" "Severe Renal Impairment (N=X)" "Matched Controls (N=X)". The y-axis will be labeled "System Organ Class" and the x-axis will be labeled "Number of Events".]

[Repeat for each Treatment Group, number each figure separately]

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events deemed related to study product. The SOCs should be sorted in descending frequency; e.g., for this figure, "Infections and infestations" should be listed first.]

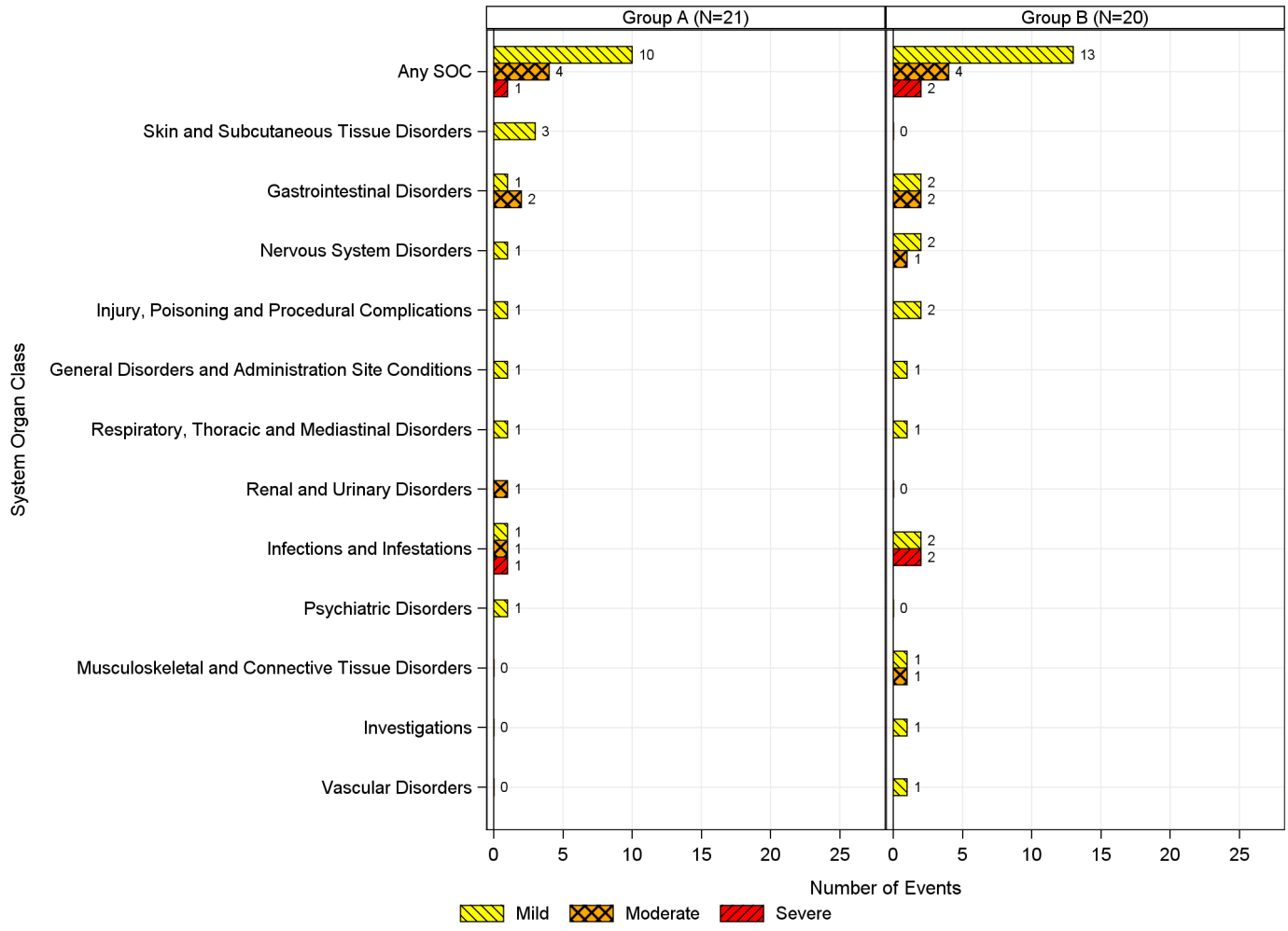
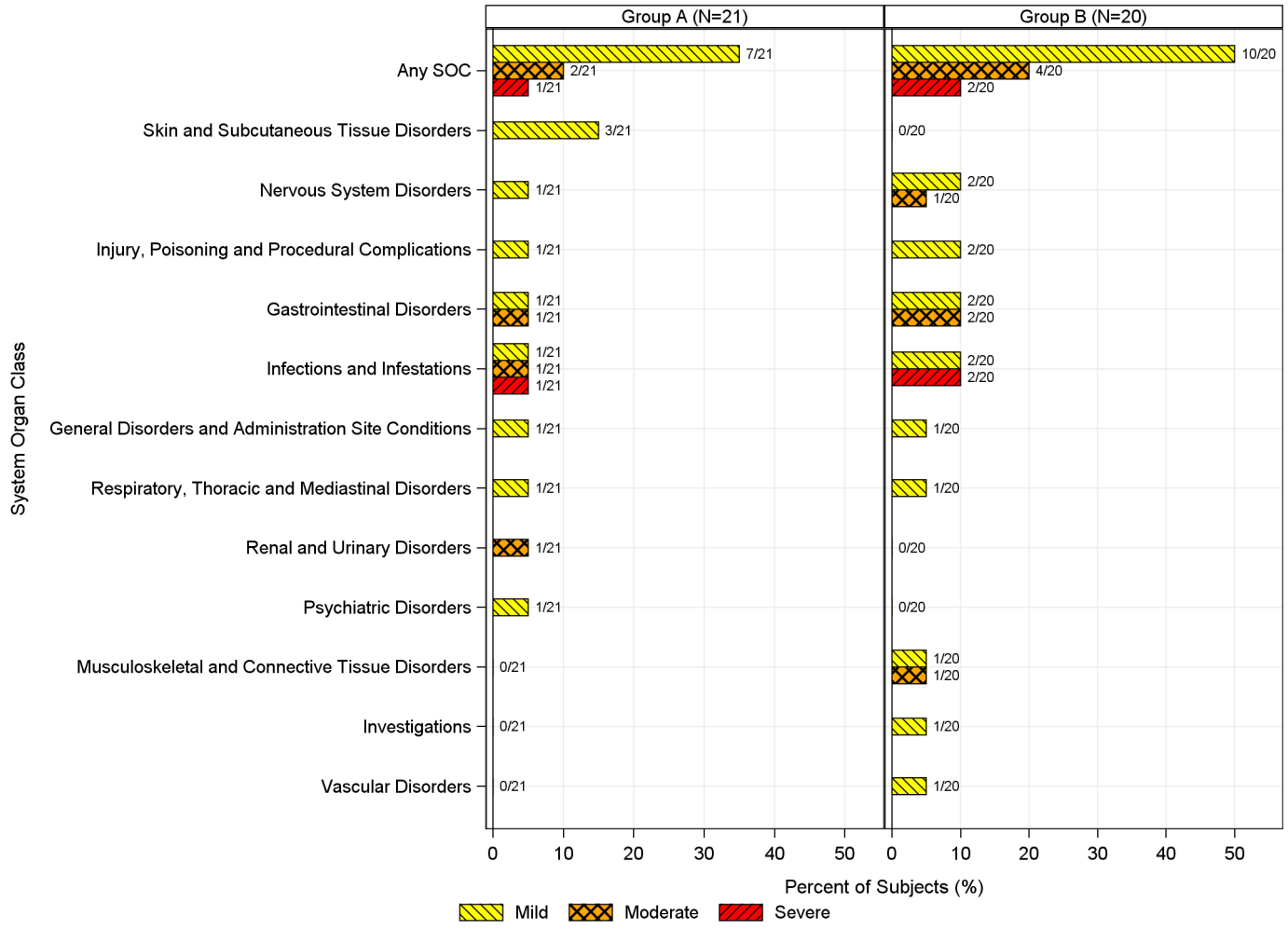


Figure 3: Incidence of Related Treatment Emergent Adverse Events by MedDRA System Organ Class and Maximum Severity

[Implementation Note: A sample figure is shown below. Separate panels will be displayed for each impairment group and matched controls and labeled "Mild Renal Impairment (N=X)" "Moderate Renal Impairment (N=X)" "Severe Renal Impairment (N=X)" "Matched Controls (N=X)". The y-axis will be labeled "System Organ Class" and the x-axis will be labeled "Percent of Participants (%)".]

[Repeat for each Treatment Group, number each figure separately]

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events deemed related to study product. The SOCs should be sorted in descending incidence; e.g., for this figure, "Infections and infestations" should be listed first.]

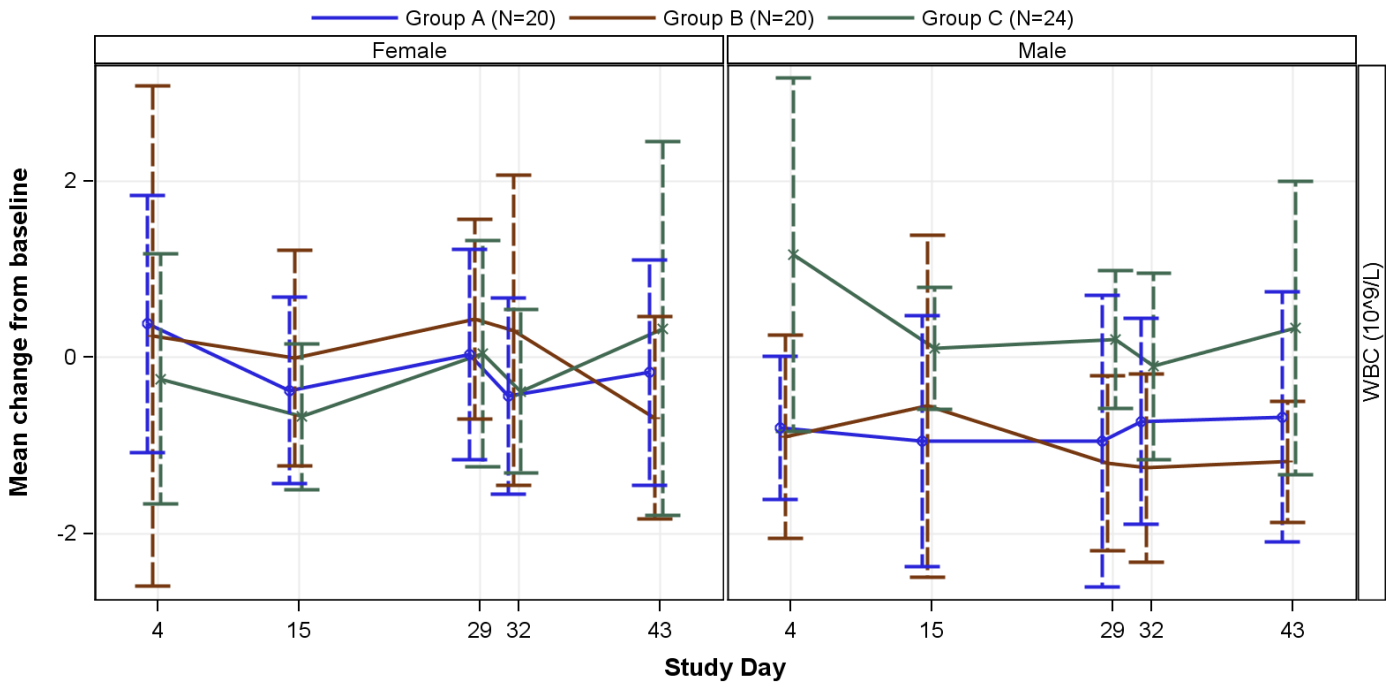


14.3.5 Displays of Laboratory Results

Figure 4: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Impairment Group – Potassium

[Implementation Note: A sample figure is shown below. This figure will not be paneled by sex, and will include the following groups: "Mild Renal Impairment (N=X)" "Moderate Renal Impairment (N=X)" "Severe Renal Impairment (N=X)" "Matched Controls (N=X)".

[Repeat for each Treatment Group, number each figure separately]



Figures with similar format to Figure 4:

Figure 5: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Impairment Group – Blood Urea Nitrogen

Figure 6: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Impairment Group – Creatinine

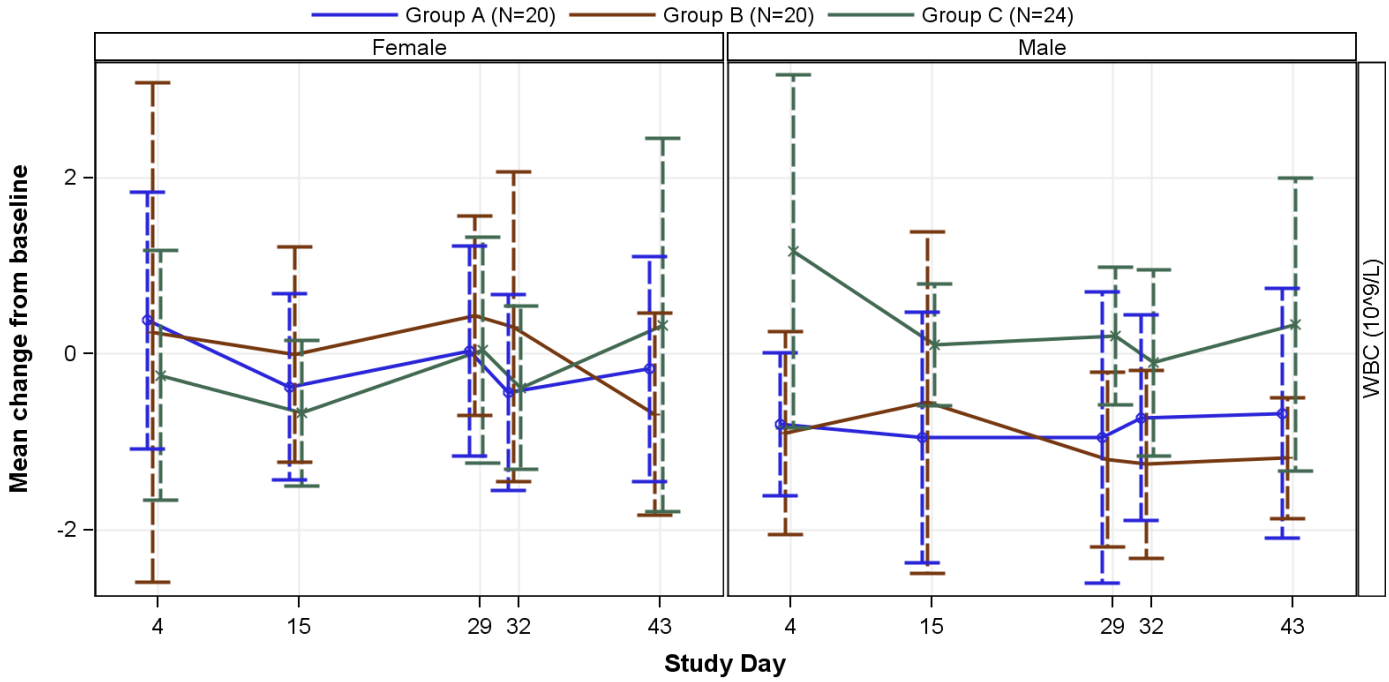
Figure 7: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Impairment Group – eGFR

Figure 8: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Chemistry Laboratory Parameter, and Impairment Group – Magnesium

Figure 9: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Impairment Group – Alanine Aminotransferase

Figure 12: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Impairment Group – Potassium

[Implementation Note: A sample figure is shown below. This figure will include the following groups: "Mild Renal Impairment (N=X)" "Moderate Renal Impairment (N=X)" "Severe Renal Impairment (N=X)" "Matched Controls (N=X)".



Figures with similar format to Figure 12:

Figure 13: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Impairment Group – Blood Urea Nitrogen

Figure 14: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Impairment Group – Creatinine

Figure 15: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Impairment Group – eGFR

Figure 16: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Chemistry Laboratory Parameter, Sex, and Impairment Group – Magnesium

Figure 17: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Impairment Group – Alanine Aminotransferase

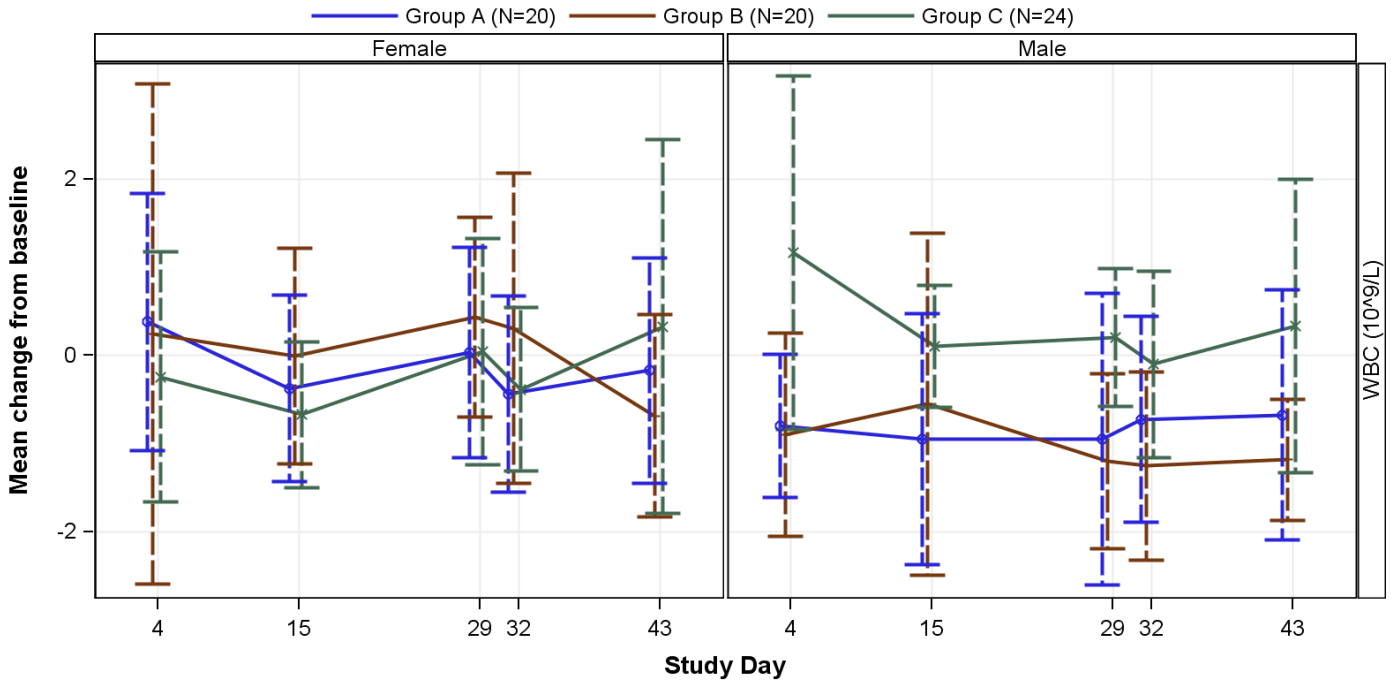
Figure 18: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Impairment Group – Aspartate Aminotransferase

Figure 19: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Impairment Group – Total Bilirubin

Figure 20: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Impairment Group –Hemoglobin

[Implementation Note: A sample figure is shown below. This figure will not be paneled by sex, and will include the following groups: "Mild Renal Impairment (N=X)" "Moderate Renal Impairment (N=X)" "Severe Renal Impairment (N=X)" "Matched Controls (N=X)".

[Repeat for each Treatment Group, number each figure separately]



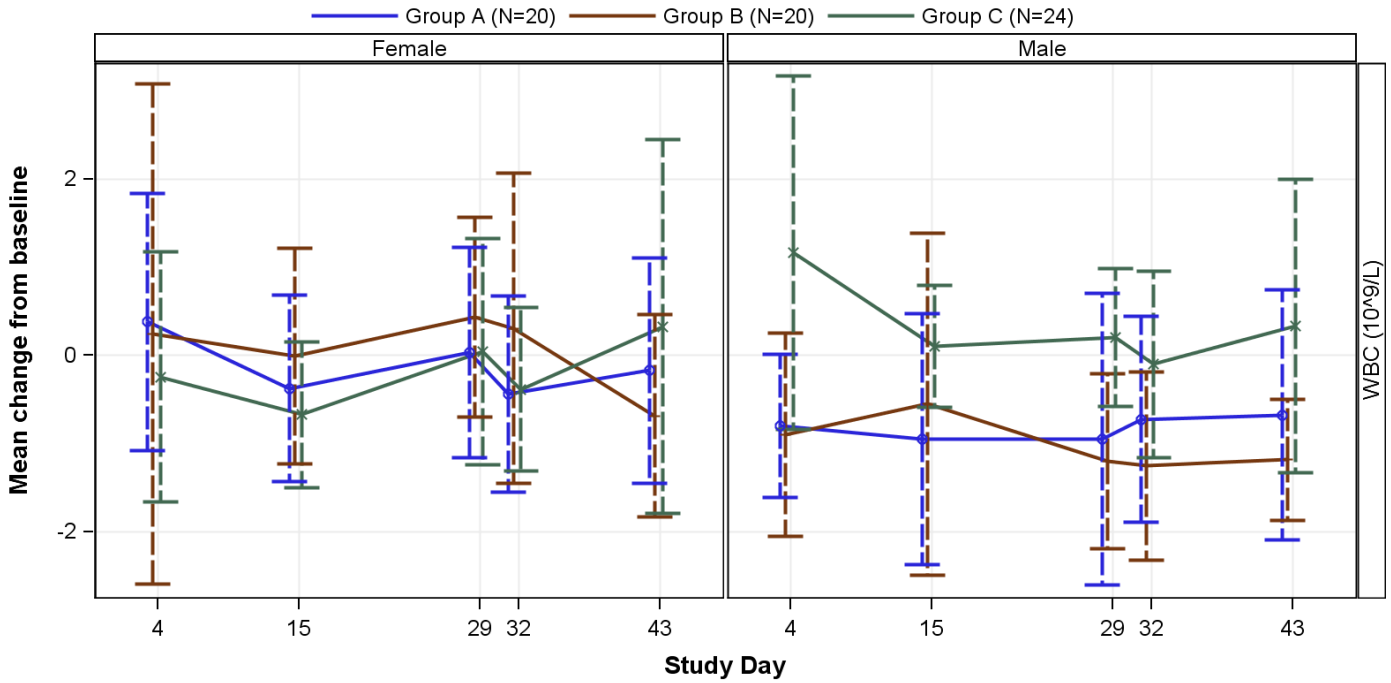
Figures with similar format to Figure 20:

Figure 21: Electrocardiogram Results by Scheduled Visits: Mean Changes from Baseline by Parameter, and Impairment Group – Corrected QT interval by Fridericia

Figure 22: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Impairment Group – Hemoglobin

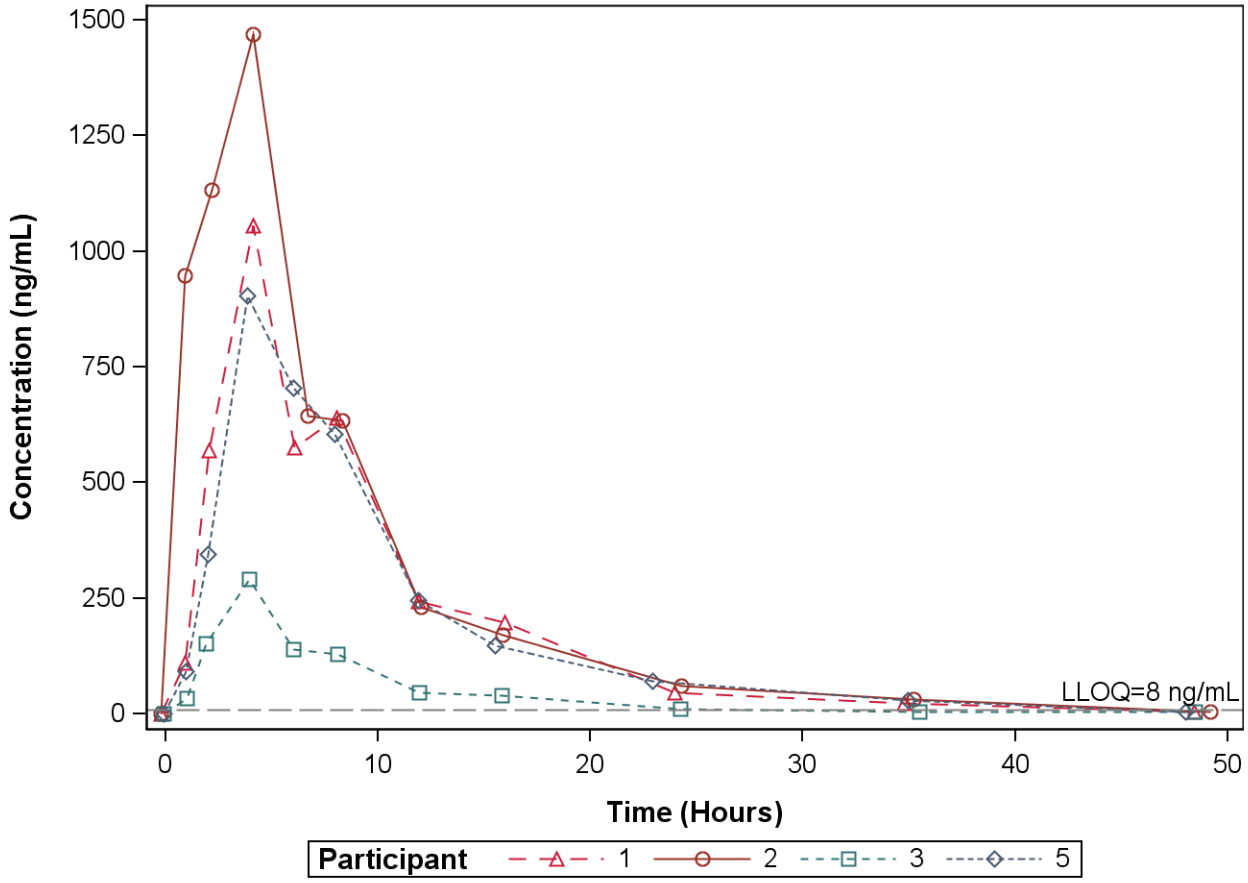
[Implementation Note: A sample figure is shown below. This figure will include the following groups: "Mild Renal Impairment (N=X)" "Moderate Renal Impairment (N=X)" "Severe Renal Impairment (N=X)" "Matched Controls (N=X)".

[Repeat for each Treatment Group, number each figure separately]



14.6 Pharmacokinetics

Figure 23: Linear Plot of Pretomanid Concentration Profiles by Nominal Time – Mild Renal Impairment Group



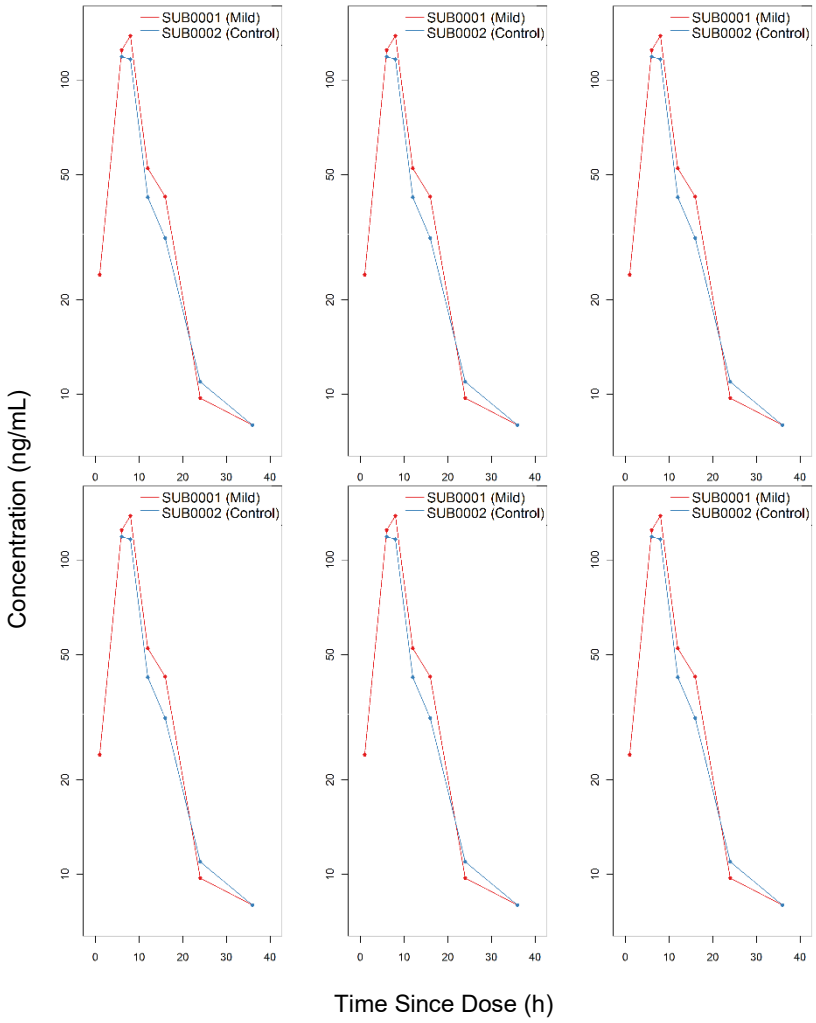
Figures with similar format to Figure 23:

Figure 24: Linear Plot of Pretomanid Concentration Profiles by Nominal Time – Moderate Renal Impairment Group

Figure 25: Linear Plot of Pretomanid Concentration Profiles by Nominal Time – Severe Renal Impairment Group

Figure 26: Linear Plot of Pretomanid Concentration Profiles by Nominal Time – Matched Controls

Figure 27: Linear Plot of Pretomanid Concentration Profiles by Nominal Time for Participants with Mild Renal Impairment and Their Matched Controls

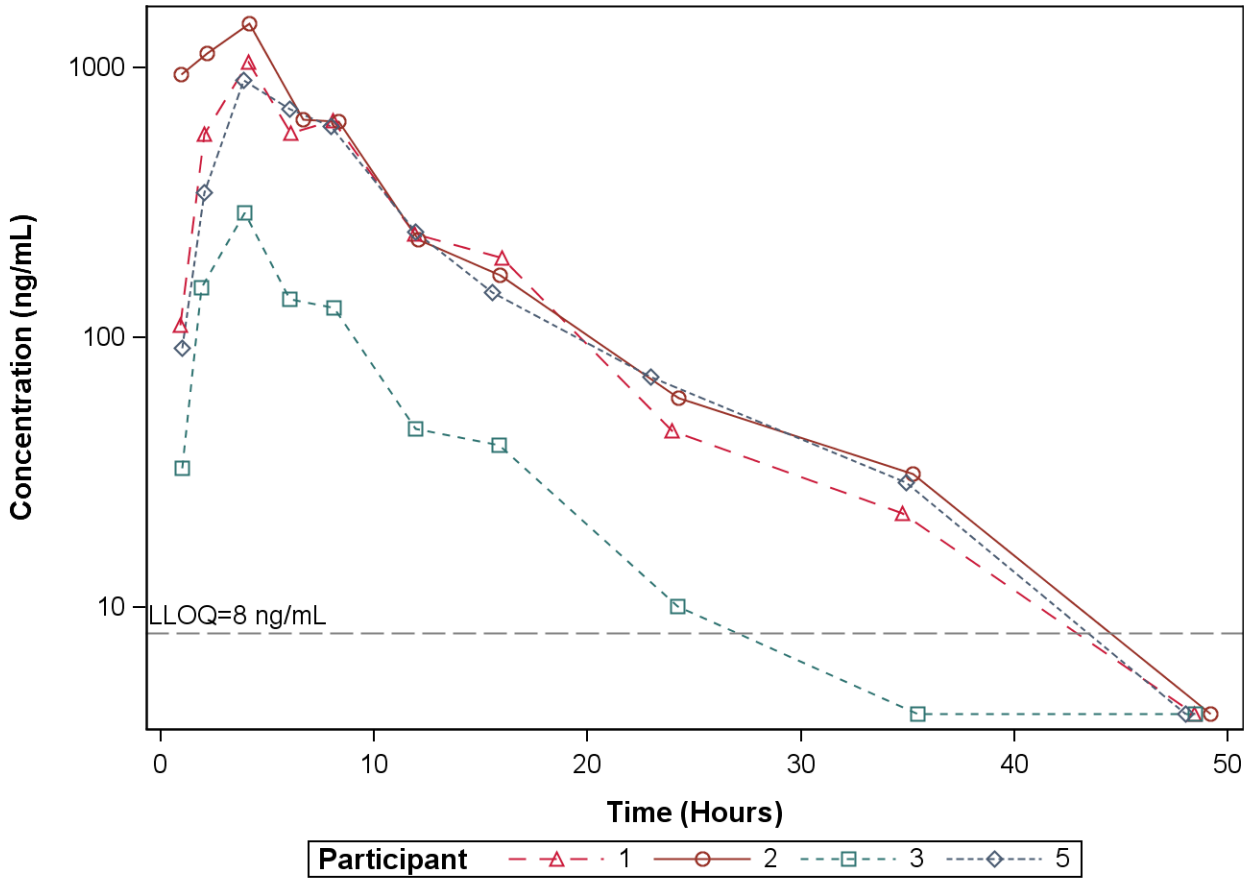


Figures with similar format to Figure 27:

Figure 28: Linear Plot of Pretomanid Concentration Profiles by Nominal Time for Participants with Moderate Renal Impairment and Their Matched Controls

Figure 29: Linear Plot of Pretomanid Concentration Profiles by Nominal Time for Participants with Severe Renal Impairment and Their Matched Controls

Figure 30: Semilogarithmic Plot of Pretomanid Concentration Profiles by Nominal Time – Mild Renal Impairment



Figures with similar format to Figure 30:

Figure 31: Semilogarithmic Plot of Pretomanid Concentration Profiles by Nominal Time – Moderate Renal Impairment

Figure 32: Semilogarithmic Plot of Pretomanid Concentration Profiles by Nominal Time – Severe Renal Impairment

Figure 33: Semilogarithmic Plot of Pretomanid Concentration Profiles by Nominal Time – Matched Controls

Figure 34: Linear Plots of Mean Pretomanid Plasma Concentration by Nominal Time

[Implementation Note: A sample figure is shown below. This figure will include the following groups: "Mild Renal Impairment (N=X)" "Moderate Renal Impairment (N=X)" "Severe Renal Impairment (N=X)" "Matched Controls (N=X)".

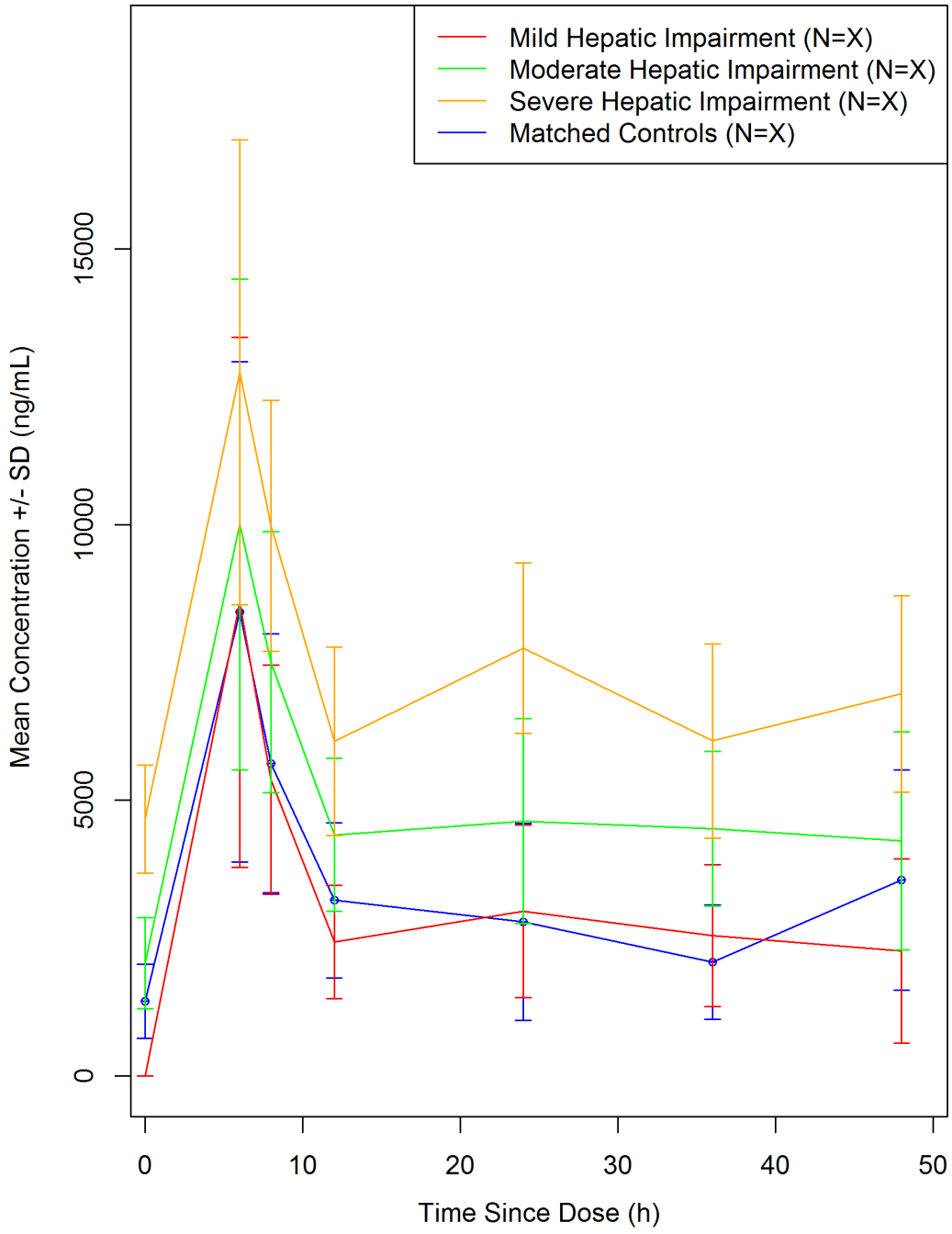


Figure 35: Semilogarithmic Plots of Geometric Mean Pretomanid Plasma Concentration by Nominal Time

[Implementation Note: A sample figure is shown below. This figure will include the following groups: "Mild Renal Impairment (N=X)" "Moderate Renal Impairment (N=X)" "Severe Renal Impairment (N=X)" "Matched Controls (N=X)".

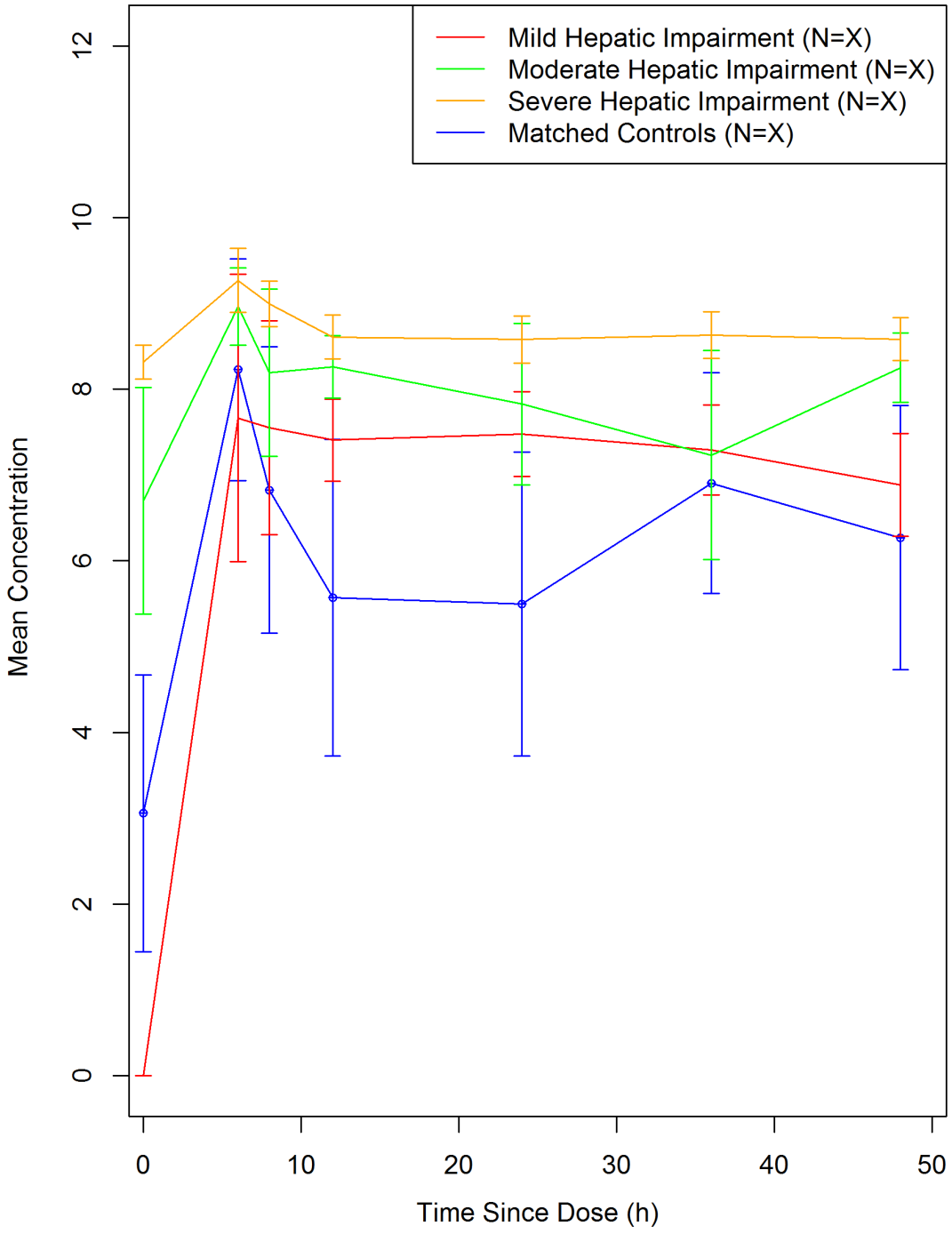
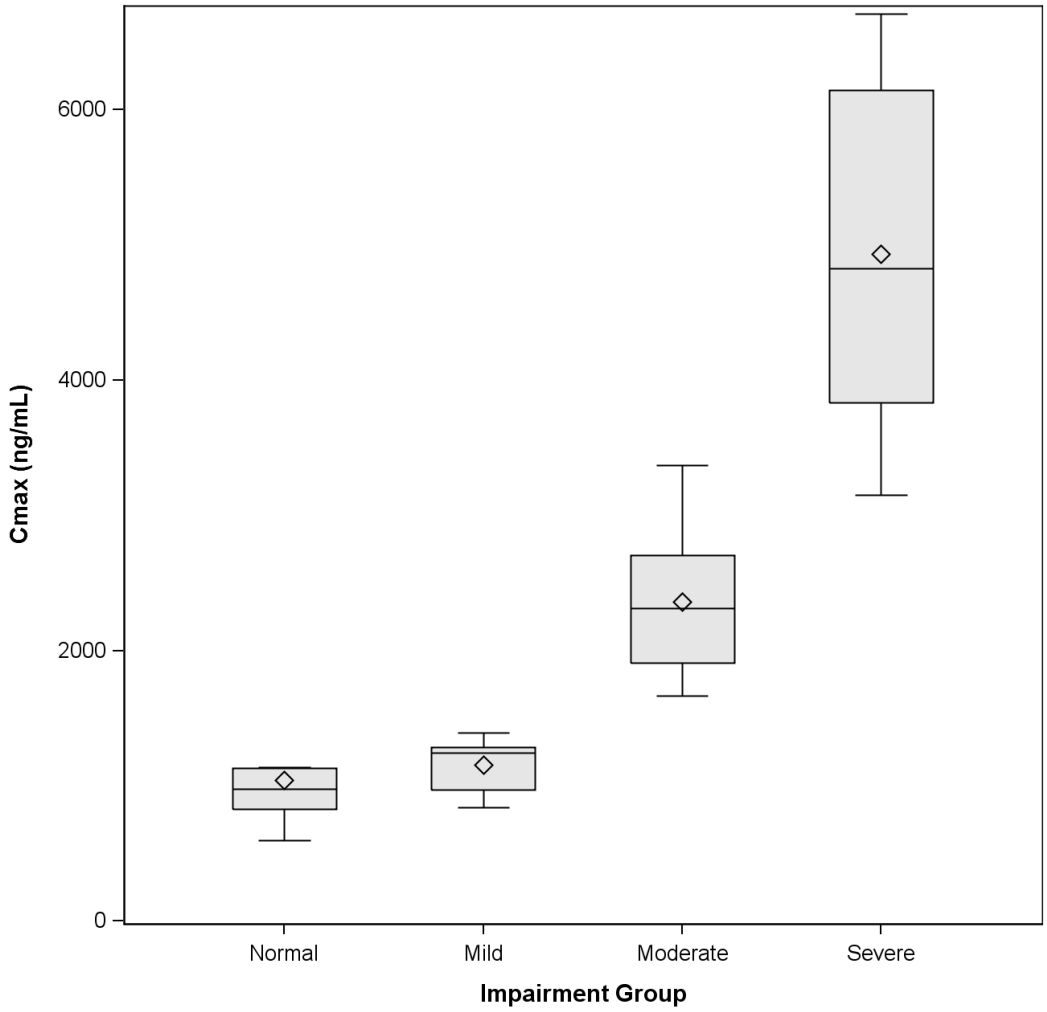


Figure 36: Impairment Group Summary for Noncompartmental PK Parameters – C_{max}

[Implementation Note: Each boxplot may include panels by site if appropriate as described in Section 10.2.3.]



Figures with similar format to Figure 36:

Figure 37: Impairment Group Summary for Noncompartmental PK Parameters – T_{max}

Figure 38: Impairment Group Summary for Noncompartmental PK Parameters – AUC_{∞}

Figure 39: Impairment Group Summary for Noncompartmental PK Parameters – AUC_{last}

Figure 40: Impairment Group Summary for Noncompartmental PK Parameters – CL/F

Figure 41: Impairment Group Summary for Noncompartmental PK Parameters – V_d/F

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: **16.1.6: Listing of Participants Receiving Investigational Product**

(not included in SAP, but this is a placeholder for the CSR)

16.2 Database Listings by Participant

16.2.1 Discontinued Participants

Listing 2: 16.2.1.1: Participant Disposition

Participant ID	Screening Date	Protocol Version at Time of Screening	Did participant Complete Study?	Study Completion or Early Termination Date	Last Visit Completed	Screen Fail?

Listing 3: 16.2.1.2: Early Terminations or Discontinued Participants

[Implementation Note: Category will be either "Early Termination" or "Treatment Discontinuation." In the "Reason" column, concatenate any "specify" fields, including AE number and DV number. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, alphabetically by Category (in the case a participant both terminates early and discontinues treatment).]

Impairment Group	Participant ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 4: **16.2.2.1: Participant-Specific Protocol Deviations**

[Implementation Note: In the "Deviation" column, concatenate any and all "specify" fields (including visit number, etc.). If "Reason for Deviation" is "Other," concatenate "specify" field, separate by a colon, e.g., "Other: Participant refusal." In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, DV Number.]

Impairment Group	Participant ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Participant Termination?	Deviation Affected Product Stability?	Deviation Resolution	Deviation Classification	Comments

Listing 5: 16.2.2.2: Non-Participant-Specific Protocol Deviations

[Implementation Note: In the "Deviation" column, concatenate any and all "specify" fields (including visit number, etc.). If "Reason for Deviation" is "Other," concatenate "specify" field, separate by a colon, e.g., "Other: Participant refusal." Sort order: Site, Start Date.]

Site	Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Participant Termination ?	Deviation Affected Product Stability ?	Deviation Category	Deviation Resolution	Deviation Classification (Major/Minor)	Comments

16.2.3 Participants Excluded from the Efficacy Analysis

Listing 6: 16.2.3: Participants Excluded from Analysis Populations

[Implementation Note: This data in this listing should be congruent with the "Analysis Populations by Treatment Group" table. The reasons included here should match the SAP text that describes who will be excluded from analyses. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: Treatment Group, Participant ID.]

Impairment Group	Participant ID	Analyses in which Participant is Included	Analyses from which Participant is Excluded	Results Available?	Reason Participant Excluded
		[e.g., Safety, ITT, PP]	[e.g., Safety, ITT, PP, Day x]		
Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.					

16.2.4 Demographic Data

Listing 7 : 16.2.4.1: Demographic Data

[Implementation Note: If a participant is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)."

For studies in infants and young children, may be more appropriate to use weeks or months for age at enrollment. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: Treatment Group, Participant ID.]

Impairment Group	Participant ID	Sex	Age at Enrollment (years)	Ethnicity	Race

Listing 8: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

[Implementation Note: "Condition Start Day" and "Condition End Day" are relative to enrollment (which is Day 1, day before enrollment is Day -1). Rather than use exact study days, categorize as follows:

- 5 years prior to enrollment
- 1-5 years prior to enrollment
- 1-12 months prior to enrollment
- Within 1 month of enrollment
- During study
- If ongoing, display "Ongoing" in the "Condition End Day" column
- Within 1 month of enrollment
- During study
- If ongoing, display "Ongoing" in the "Condition End Day" column

It may be appropriate to add another category, based on exclusion criteria that restrict conditions within a particular time period (e.g., within 3 years prior to enrollment). In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, MH Number.]

Impairment Group	Participant ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

16.2.5 Compliance and/or Drug Concentration Data (if available)

Not Applicable.

16.2.6 Individual Efficacy/Immunogenicity Response Data

Not Applicable.

16.2.7 Adverse Events

Listing 9: 16.2.7.3: Unsolicited Adverse Events

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. This listing includes all unsolicited adverse events. If there are no comments for an event, populate 'Comments' row with 'None'. Add columns for MedDRA HLT or LLT depending on halting criteria or other study needs. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, Associated with Dose No., No. of Days Post Associated Dose. If the table will be multi-page, move the footnote/explanation to the footer so that it repeats for each page of the table.]

Adverse Event	No. of Days Post Dose (Duration)	Severity	SAE?	Relationship to Study Treatment	In Not Related, Alternative Etiology	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Impairment Group: , Participant ID: , AE Number:									
Comments:									
Impairment Group: , Participant ID: , AE Number:									
Comments:									
Note: For additional details about SAEs, see Table: xx.									

16.2.8 Individual Laboratory Measurements

Listing 10 : 16.2.8.1: Clinical Laboratory Results – Chemistry

[Implementation Note: These listings (for hematology, chemistry, and urinalysis) include all laboratory results, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., 16.2 (Mild). The "extra" fields that are completed for abnormal results are not included in this listing; they are included in the listing of abnormal laboratory results that is included in the table shells document. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, and Planned Time Point.]

Impairment Group	Participant ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

Listing 11 : 16.2.8.2: Clinical Laboratory Results – Hematology

Impairment Group	Participant ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

Listing 12: 16.2.8.3: Screening Laboratory Results – Serology

Impairment Group	Participant ID	Timepoint	Actual Study Day	HBsAg	HCV Antibodies	HIV Antibodies

16.2.9 Vital Signs and Physical Exam Findings

Listing 13 : 16.2.9.1: Vital Signs

[Implementation Note: This listing includes all vital sign assessments, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal assessments, e.g., 100.7 (Mild). In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, Planned Time Point.]

Impairment Group	Participant ID	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Weight (kg)	Height (cm)

Listing 14 : 16.2.9.2: Physical Exam Findings

[Implementation Note: This listing includes all physical exam findings, scheduled and unscheduled. If a participant does not have any findings upon examination, they will not be included in this listing. If reported as an AE, display "Yes" with the AE Number in parentheses, e.g., "Yes (7)". In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: Treatment Group, Participant ID, Planned Time Point.]

Impairment Group	Participant ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

Listing 15: 16.2.9.3: Echocardiogram Results

Impairment Group	Participant ID	Date of Procedure	Procedure Type	Result

16.2.10 Concomitant Medications

Listing 16 : 16.2.10: Concomitant Medications

[Implementation Note: "Medication Start Day" and "Medication End Day" are relative to enrollment (which is Day 1, day before enrollment is Day -1). For medication start dates that are > 30 days prior to enrollment, rather than use exact study days, categorize as follows:

- 5 years prior to enrollment
- 1-5 years prior to enrollment
- 1-12 months prior to enrollment

If ongoing, display "Ongoing" in the "Medication End Day" column. If taken for an AE or MH, display "Yes" with the AE or MH Number in parentheses, e.g., "Yes (7)". In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, and CM Number.]

Impairment Group	Participant ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)

16.2.11 Pregnancy Reports

Listing 17 : 16.2.11.1: Pregnancy Reports – Maternal Information

[Implementation Note: Only include the "Pregnancy Number" column if a participant has more than 1 pregnancy. Date of Conception will be calculated based on estimated delivery date. BMI will be calculated based on pre-pregnancy height and weight. Mother's weight gain will be calculated based on pre-pregnancy weight and end of pregnancy weight. If a major congenital anomaly with previous pregnancy, display "Yes" and the text from the "specify" field, separated by a colon. If any substance use is reported, include a listing of substance use. If autopsy revealed an alternate etiology, display "Yes" and the text from the "specify" field, separated by a colon. If abnormality in product of conception, display "Yes" and the text from the "specify" field, separated by a colon. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, Pregnancy Number.]

Impairment Group	Participant ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.											

Listing 18 : 16.2.11.2: Pregnancy Reports – Gravida and Para

			Live Births												
Participant ID	Pregnancy Number	Gravida	Extremely PB[a]	Very Early PB[a]	Early PB[a]	Late PB[a]	Early TB[b]	Full TB[b]	Late TB[b]	Post TB[b]	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?
Note: Gravida includes the current pregnancy, para events do not.															

[a] Preterm Birth
[b] Term Birth

Listing 19 : 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

Participant ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?
Note: Congenital Anomalies are included in the Adverse Event listing.												

Listing 20 : 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

Participant ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 21 : 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Participant ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion

APPENDIX 4. NCA TEMPLATE

See separate document, if applicable.

Listing 22: Participant Level Plasma Drug Concentrations

Impairment Group	Participant ID	Nominal Time[a] (hr)	Actual Time[a] (hr)	Drug Concentration (ng/mL)	Sample Within Time Window	Used in λ_z Calculations	Excluded from NCA	Reason for Exclusion from NCA

Listing 23: Participant Level Urine Drug Concentrations

Impairment Group	Participant ID	Nominal Collection Window Start Time[a] (hr)	Nominal Collection Window End Time[a] (hr)	Actual Collection Window Start Time[a] (hr)	Actual Collection Window End Time[a] (hr)	Drug Concentration (ng/mL)	Sample Within Time Window	Excluded from NCA	Reason for Exclusion from NCA

Listing 24: Participant Level Urine PK Parameters

Impairment Group	Participant ID	$Ae_{(0-t)}$ µg	Ae%Dose	CL_R (L/h)