CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 13-0053
Study Title:

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

NCT02422524

Version 2.0

DATE: 08 May 2024

RESTRICTED

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 13-0053**
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 subject enrolled 29MAR2018 (screened 19MAR)
Clinical Trial Completion Date:	
Date of the Analysis Plan:	08 May 2024
Version Number:	2.0

This study was performed in compliance with Good Clinical Practice.

VERSION HISTORY

SAP Version	Change	Rationale
1.0	Not Applicable	Original version.
2.0	Removed "sequential" when describing the order of group enrollments based on changes to the study design (i.e., simultaneous enrollment allowed in the moderate and severe groups). "PA-824" replaced with "Pretomanid" throughout to align with the protocol. Added language to clarify the definition of baseline in Section 6.1: "In general, the last recorded value prior to study drug administration will be considered as baseline." Section 6.2 was updated to adjust the planned timing of interim analyses to align with protocol v7.0. Updated Section 6.7, Section 10.3, added additional tables, and expanded others to account for by-site summaries and analyses following the addition of the Saint Louis site. Updated eligibility criteria listed throughout to align with protocol v7.0. Updated Table 3: Schedule of Study Procedures and Figure 2: Schematic of Study Design to align with protocol v7.0. Updated Table 5: Laboratory/Clinical Adverse Event Grading Scale to align with the protocol v7.0.	The study protocol was amended after finalization of the SAP v1.0. These SAP updates were driven by protocol changes, including the addition of a second site (Saint Louis).

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Category
AUC	Area Under the Concentration-Time Curve
$AUC_{(0\text{-last})}$	AUC to the Last Measurable Concentration
$AUC_{(0\text{-}\infty)}$	AUC Extrapolated to Infinity
BUN	Blood Urea Nitrogen
C	Celsius
CBC	Complete Blood Count
CL/F	Apparent Oral Clearance
C_{max}	Maximum Concentration
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficients of Variation
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
F	Fahrenheit
FDA	Food and Drug Administration
GM	Geometric Mean
HEENT	Head, Eyes, Ears, Nose and Throat
HDPE	High-density polyethylene
HBsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus

List of Abbreviations *(continued)*

ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to Treat
λ_z	Elimination Rate Constant
LLOQ	Lower Limit of Quantitation
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
mITT	Modified Intention to Treat
MRI	Magnetic Resonance Imaging
N	Number (typically refers to subjects)
NCA	Noncompartmental Analysis
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OTC	Over the Counter
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PR	P-R Interval on an ECG
PT	Preferred Term
QT/QTc	QT Interval of an ECG/Corrected QT Interval of an ECG
QTcF	Heart Rate-Corrected QT Interval (Fridericia's Formula)
$R^2_{adjusted}$	R-squared Adjusted
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
SOP	Standard Operating Procedures
$t_{(1/2)}$	Apparent Terminal Elimination Half-Life

List of Abbreviations *(continued)*

T_{max}	Time to Obtain Maximum Concentration (C_{max})
TB	Tuberculosis
V_d/F	Apparent Volume of Distribution During Terminal Phase
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "DMID Protocol 13-0053: A Phase 1, Single Dose, Open-label, Study Comparing the Pharmacokinetics and Safety of Pretomanid in Subjects with Mild, Moderate, and Severe Hepatic Impairment to Matched, Non-hepatically Impaired Subjects" 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 as well as all planned sample tables, listings and figures. Regarding the final analysis and final integrated Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines (1), 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).

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) causes a significant global health burden with an estimated annual worldwide incidence in 2015 of approximately 10.4 million new cases (2). Approximately 1.8 million people died from TB in 2015 (2, 3) making TB the leading infectious killer of adults worldwide. TB is also the leading infectious cause of death among people with HIV or acquired immunodeficiency syndrome (4).

TB is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (MTB). This infection primarily affects the lungs (pulmonary TB) but can affect other organs such as the kidneys, bones, and brain (5). TB is transmitted by inhalation of infective droplets containing MTB and expelled into the air by a person with active TB (5).

The mainstays of therapy against TB are antibiotic combination regimens. The recommended treatment includes a combination of rifampin, isoniazid, pyrazinamide, ethambutol or streptomycin (6 - 8). A 4-drug regimen of directly observed therapy is administered for 2 months (intensive phase) and is then followed by rifampin and isoniazid for an additional 4-7 months (7). The goal of the prolonged regimen is to ensure sterilization of tuberculosis lesions and to prevent development of drug resistance (8). If administered correctly, cure rates as high as 95% can be achieved (9).

Unfortunately, the prolonged and complicated treatment course of TB affects patient compliance (10), which has led to development of multi-drug resistant TB (MDR-TB) (7, 10) and extensively drug resistant strains (XDR-TB) (11). The WHO estimates that ~4% of new TB cases, and 20% of previously treated cases of TB have MDR-TB (4). Of those new MDR-TB cases 9% are XDR-TB (4). Therefore, there is a need to develop novel drugs, such as Pretomanid (previously known as PA-824) to be used in combination, for the treatment of TB.

In previous efficacy studies Pretomanid was shown to have bactericidal activity in a much shorter treatment time than the current recommended regimen. Table 2 shows a summary of previous phase 2 studies involving Pretomanid.

2.1. Purpose of the Analyses

Pretomanid is metabolized extensively in the liver (CYP3A4) and has a low extraction ratio. In the setting of advanced liver disease both hepatic blood flow and hepatic function can be compromised. Therefore, the pharmacokinetics of Pretomanid are likely to be altered in subjects with hepatic impairment compared to matched healthy subjects. The purpose of this protocol is to evaluate the safety and pharmacokinetics of Pretomanid in the setting of underlying liver disease defined as a Child-Pugh score of A, B, or C.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Study Objective

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

3.1.2. Primary Study Objective

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

3.2. Endpoints

3.2.1. Primary Outcome Measures

- The pharmacokinetics of a single-dose of Pretomanid will be assessed from serial blood samples collected prior to dosing (Day 1) and at multiple time points post dosing: 1 h, 2 h, 4 h, 5 h, 6 h, 8 h, 12 h, 16 h, 24 h, 36 h, 48 h, 72 h, and 96 h. The primary outcome measure will be total plasma concentration of Pretomanid. The following will be determined:
  - $AUC_{(0-\infty)}$: Area under the concentration time-curve extrapolated to infinity
  - $AUC_{(0\text{-last})}$: Area under the concentration time-curve to the last concentration above the lower limit of quantitation (LLOQ)
  - C_{max}: Maximum Pretomanid concentration
  - T_{max}: Time of maximum Pretomanid concentration
  - $t_{(1/2)}$: Apparent terminal elimination half-life
  - CL/F: Apparent oral clearance calculated from Dose/$AUC_{(0-\infty)}$
  - V_d/F: Apparent Volume of Distribution

3.2.2. Secondary Outcome Measures

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

until Day 12), safety laboratory parameters (Day of Admission, as well as Days 2, 5, and 12), and ECG data (Day of Admission and Day 12).

3.3. Study Definitions and Derived Variables

Maximum plasma concentration (C_{max}) is defined as: the maximum observed drug concentration in blood plasma for a particular dose interval.

Time of maximum plasma concentration (T_{max}) is defined as: the time at which the maximum plasma concentration occurs.

Elimination rate constant (λ_z) is defined as the first-order rate constant describing rate of elimination from plasma.

The apparent terminal elimination half-life (t(1/2)) will be estimated by ln(2) divided by λ_z.

AUC(0-last) is defined as the area under the concentration-time curve (AUC) from administration (time 0) to the time of the last quantifiable concentration above the LLOQ.

AUC(0-∞) is defined as the total AUC and will be computed by adding AUC_{0-t} to an extrapolated value equal to the last measured concentration greater than limits of quantitation divided by λ_z and will be calculated using

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_{tf}}{\lambda_Z},$$

where C_{tf} is the last measurable concentration ≥ LLOQ

Apparent oral clearance (CL/F) will be calculated as the dose divided by the AUC(0-∞).

Apparent volume of distribution (V_d/F) is defined as: the theoretical volume that the total amount of administered drug would occupy to provide the same concentration as it currently is in blood plasma divided by the bioavailability.

$$V_d / F = \frac{Dose}{\lambda z \times AUC_{0-\infty}}$$

3.3.1. Impairment Group Definitions

Subjects are stratified into 4 groups based on the Child-Pugh score. The Child-Pugh score is based on five clinical measures of liver function: total bilirubin, serum albumin, prothrombin, ascites and hepatic encephalopathy. Based on their score (as determined by the site) patients are defined as mild hepatic impairment (5-6 points), moderate hepatic impairment (7-9 points), or severe hepatic impairment (10-15 points). The impairment group designations are:

- Mild Hepatic Impairment: Child-Pugh A (5-6 points)
- Moderate Hepatic Impairment: Child-Pugh B (7-9 points)
- Severe Hepatic Impairment: Child-Pugh C (10-15 points)
- Matched Controls: Non-hepatically impaired controls

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

Approximately 6 subjects will be enrolled in each of the hepatic impairment groups (Mild, Moderate and Severe), and approximately 18 non-hepatically impaired subjects will be enrolled as matched controls.

Subjects with hepatic impairment from all three groups will be enrolled starting with subjects who have mild hepatic impairment. Subjects with moderate and severe hepatic disease will be enrolled simultaneously. If enrollment into the severe hepatic impairment group is completed before that of the moderate hepatic impairment group, results from the severe cohort will be analyzed to determine the impact of severe hepatic impairment on the PK of Pretomanid and the need to continue enrollment of persons with moderate hepatic impairment will be reevaluated to determine whether the objectives of the study have been met. Non-hepatically impaired subject matches will be dosed only after the corresponding subject with hepatic impairment has completed the 36-hour blood sampling procedure. The group of up to 18 matched controls will be matched to the 18 subjects with hepatic impairment based on age (± 10 years) and body weight at screening (± 20% body weight). A control subject may be matched to more than one hepatic impairment subject if warranted, and if the subjects to which they are matched are not in the same disease severity group. Control subjects may be matched to hepatically impaired subjects at any site. Therefore, there may be less than 18 subjects with normal hepatic function (Table 1; Figure 2).

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

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

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

Non-hepatically impaired controls will be identified from the site specific registries and the community. Subjects for this study may also be identified through advertisement, letters, and other forms of communication.

4.3. Selection of Study Population

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

4.3.1. Study Inclusion Criteria

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

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

3. Acceptable laboratory values* obtained at screening (within 21 days prior to admission to the confinement/hospital unit) and at admission to the confinement/hospital unit.

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

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

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

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

   **Non-childbearing potential is defined as being post-menopausal for at least 2 years, status after bilateral oophorectomy or status after hysterectomy.*
   ***Females of childbearing potential must agree to use two acceptable methods of contraceptives: bilateral tubal ligation; barrier method (condom) by the male partner (even if vasectomized); hormonal contraceptives; intrauterine contraceptive devices; diaphragm in combination with contraceptive jelly, cream, foam, or spermicide; and abstinence from sexual intercourse with men.*

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

   **In addition to the use of a barrier method (condom) even if vasectomized, acceptable methods of birth control are restricted to a monogamous relationship with a woman who agrees to use acceptable contraception as outlined in inclusion criterion #5, and abstinence from sexual intercourse with women.*

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

8. Willingness to comply with all protocol requirements.

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

1. Subject is able to give voluntary written informed consent before any study related procedure is performed.

2. 18-70 years of age, inclusive.

3. Subject is a healthy volunteer as determined by no clinically significant findings from medical history, physical examination, vital signs, and 12-lead ECG as determined by the Site Investigator.

4. Acceptable laboratory values* obtained at screening (within 21 days prior to admission to the confinement/hospital unit) and either at or within 72 hours of admission to the confinement/hospital unit.

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

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

   **Non-childbearing potential is defined as being post-menopausal for at least 2 years, status after bilateral oophorectomy or status after hysterectomy.*
   ***Females of childbearing potential must agree to use two acceptable methods of contraceptives: bilateral tubal ligation; barrier method (condom) by the male partner (even if vasectomized); hormonal contraceptives; intrauterine contraceptive*

devices; diaphragm in combination with contraceptive jelly, cream, foam, or spermicide; and abstinence from sexual intercourse with men.

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

   **In addition to the use of a barrier method (condom) even if vasectomized, acceptable methods of birth control are restricted to a monogamous relationship with a woman who agrees to use acceptable contraception as outlined in inclusion criterion #5, and abstinence from sexual intercourse with women.*

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

4.3.2. Study Exclusion Criteria

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

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

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

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

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

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

    **except hormonal contraceptives*
    ***in the opinion of the site investigator*
    NOTE: See list of CYP450 enzyme altering drugs under the concomitant medications Section 4.4.7.

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

    **Amphetamines, barbiturates, cocaine metabolites, marijuana, opiates, phencyclidine (PCP).*
    NOTE: Results of the urine screen test can be ignored if in the opinion of the PI the results can be explained by the concomitant medications history.

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

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

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

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

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

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

3. History of fever or documented fever (oral temperature ≥100.4° F or ≥ 38.0° C) in the 48 hours prior to admission to the confinement/hospital unit.

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

   **including vitamins and herbal supplements, antacids, cough and cold medications.*
   ***in the opinion of the site investigator*
10. Use of prescription medication except hormonal contraceptives within 30 days prior to admission to the confinement/hospital unit, unless* the substance would not likely impact study result validity.

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

    **except hormonal contraceptives*
    ***in the opinion of the site investigator*
    NOTE: See list of CYP450 enzyme altering drugs under the concomitant medications Section 4.4.7.
12. A positive blood screen for HIV.
13. A positive blood screen for hepatitis B surface antigen (HBsAg), or hepatitis C antibody.
14. A positive alcohol breath test (or other suitable test for alcohol) or a urine screen test for drugs of abuse* at screening and at admission to the confinement/hospital unit.

    **Amphetamines, barbiturates, benzodiazepines, cocaine metabolites, marijuana, opiates, phencyclidine (PCP).*
15. A history of alcohol abuse or dependence within the past 1 month prior to admission to the confinement/hospital unit.
16. Unwillingness to abstain from engaging in strenuous physical activity (e.g. running, bicycling, weightlifting, competitive sports) during the course of the study.
17. Consumption of grapefruit juice in the 48 hours before admission to the confinement/hospital unit, or the inability to abstain from these until completion of Day 12.

18. A QTcF interval >450 msec (males) or >450 msec (females) at screening (Visit 00A) or admission to the confinement/hospital unit (Visit 00B) or a history of prolonged QTc interval.
19. A family history* of Long QT Syndrome, premature cardiac death**, or sudden death without a preceding diagnosis of a condition*** that could be causative of sudden death.

    **parents*
    ***due to ischemic heart disease or sudden cardiac death before 55 years of age (men) or 65 years of age (women)*
    ****such as known coronary artery disease, congestive heart failure, or terminal cancer*
20. Any clinically significant ECG abnormality, in the opinion of the site investigator, at screening and at admission to the confinement/hospital unit.
21. Donation of >500 mL of blood within the 30 days prior to admission to the confinement/hospital unit.
22. Plans to donate blood during the study or up to 14 days after dosing.
23. Persons with a transjugular intrahepatic portosystemic shunt.

4.4. Treatments

4.4.1. Treatments Administered

All participants will receive a single 200 mg tablet of Pretomanid.

4.4.2. Identity of Investigational Product(s)

Pretomanid, a nitroimidazooxazine, is a novel TB treatment that is being investigated for use with other TB drugs to shorten and/or simplify regimens to treat either drug susceptible or resistant disease, which may improve the current high rate of noncompliance for TB treatment. Pretomanid acts by inhibiting *Mycobacterium tuberculosis* cell wall biosynthesis, as well as by generating reactive nitrogen species.

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

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

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

There is no randomization performed for this study. Subjects are assigned to the 3 hepatically impaired groups based on the Child-Pugh score, with approximately 6 subjects in each of the hepatic impairment groups (Groups 1, 2, and 3) and approximately 18 non-hepatically impaired subjects in Group 4.

4.4.4. Selection of Doses in the Study

The PK profile for Pretomanid following oral dosing was consistent for healthy subjects and subjects with pulmonary TB. Pretomanid was readily absorbed after oral administration and slowly eliminated in plasma. Pretomanid plasma concentrations increased in a dose-related manner after single-dose administration of up to 1000 mg in healthy subjects and subjects with TB, but the increase was less than dose proportional,

particularly at doses above 200 mg/day. There is a trend towards increased side effects with increasing dosages (8). Furthermore, efficacy studies have shown equivalent early bacterial activity at dosages ranging from 200mg to 1200mg. The doses of Pretomanid that will be evaluated in regimens in Phase 3 are 100 mg and 200 mg. Hence, the dosage of Pretomanid for this study will be 200mg daily.

4.4.5. Selection and Timing of Dose for Each Subject

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

4.4.6. Blinding

Not applicable; this is an open-label study.

4.4.7. Prior and Concomitant Therapy

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

Systemic medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. A subject will be withdrawn for use of excluded medications. Medications in this category include the prohibited medications per the Subject Exclusion Criteria (Section 4.3.2). The excluded CYP450 inducers are: Carbemazepines, Rifampicin, Alcohol (of greater than one drink per day or seven drinks per week), Phenytoin, Griseofulvin, Phenobarbital and Sulphonylureas. The excluded CYP450 inhibitors are: Sodium valproate, Isoniazid, Ketoconazole, Fluconazole, Chloramphenicol, Erythromycin, Sulfonamides, Ciprofloxacin, Metronidazole, and grapefruit juice.

4.4.8. Treatment Compliance

All subjects are to receive a single dose of study product administered in the clinic.

4.5. Pharmacokinetics and Safety Variables

See Table 3 for a schedule of study procedures.

4.5.1. Pharmacokinetics Variables

1. The pharmacokinetics of a single-dose of Pretomanid will be assessed from serial blood samples collected prior to dosing (Day 1 and at multiple time points post dosing: 1 h, 2 h, 4 h, 5 h, 6 h, 8 h, 12 h, 16 h, 24 h, 36 h, 48 h, 72 h, and 96 h. The primary outcome measure will be total plasma concentration of Pretomanid. The following will be determined:
    a. $AUC_{(0-\infty)}$: Area under the concentration time-curve extrapolated to infinity
    b. $AUC_{(0-last)}$: Area under the concentration time-curve to the last concentration above the lower limit of quantitation
    c. C_{max}: Maximum Pretomanid concentration
    d. T_{max}: Time of maximum Pretomanid concentration

e. $t_{(1/2)}$: Apparent terminal elimination half-life
f. CL/F: Apparent oral clearance calculated from Dose/$AUC_{(0-\infty)}$
g. V_d/F: Apparent Volume of Distribution

4.5.2. Safety Variables

1. The secondary outcome measures will be:

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

5. SAMPLE SIZE CONSIDERATIONS

The sample size was determined based on feasibility and FDA guidance (12). Following FDA guidance, enrollment is anticipated to include at least 6 subjects in each arm. This sample size is expected to estimate the group differences with adequate precision. Previous studies of Pretomanid have estimated coefficients of variation (CV) of <21% after 250 mg dosing (N=8) and <33% after 200 mg dosing (N=6) for single dose $AUC_{(0-\infty)}$ and C_{max} in healthy adult subjects (11). Assuming an observed two-fold difference between the group with severe hepatic impairment and matched controls with no correlation between matched pairs and a coefficient of variation of 25%, a 90% confidence interval for the fold difference between severely impaired and non-hepatically impaired group is (1.55, 2.59).

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by impairment group and subject, and when appropriate by visit number within subject. In general, the last recorded value prior to study drug administration will be considered as baseline. All summary tables will be structured with a column for each impairment group in the order (Mild Hepatic Impairment, Moderate Hepatic Impairment, Severe Hepatic 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.

6.2. Timing of Analyses

Two SMC interim safety reviews are planned.

1. After 3 subjects with mild hepatic impairment are enrolled and completed follow-up through Day 12. This review will be completed prior to opening enrollment for subjects with moderate or severe hepatic impairment. Enrollment of subjects with mild hepatic impairment and matched controls may continue during the safety review.
2. After 3 subjects with moderate or severe hepatic impairment are enrolled and complete follow-up through Day 12. Enrollment of subjects with mild hepatic impairment, moderate hepatic impairment, severe hepatic impairment, and matched controls may continue during the safety review.

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

Interim safety reviews will not include any statistical hypothesis testing.

The final analysis will be performed after database lock.

6.3. Analysis Populations

Summaries and analysis of safety data will be presented for the Safety Population. Summaries and analysis of pharmacokinetics data will be presented for the Pharmacokinetics Population. A tabular listing of all subjects, visits, and observations excluded from the analysis populations will be provided in the CSR (Table 7; Listing 1; and Listing 4).

6.3.1. Safety Population

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

6.3.2. Pharmacokinetics Population

The PK analysis set will consist of participants in the safety population who have evaluable plasma PK samples for the estimation of C_{max} or $AUC_{(0-\infty)}$. Subjects may also be excluded from analysis for reasons such

as wrong dose or eating before a dose. What constitutes a reason for exclusion will be assessed on a case-by-case basis by DMID and the VTEU PI.

6.4. Covariates and Subgroups

This study is not powered for formal subgroup analyses and none will be explored.

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 will be performed for missing values. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier.

6.6. Interim Analyses and Data Monitoring

See Section 6.2.

6.7. Multicenter Studies

This study will take place at two VTEU sites, Duke University and St. Louis University. Data will be pooled across both clinical sites except for demographics which will be summarized by site and the comparison of PK parameters will be presented according to site and impairment group (if applicable, as described in Section 10.3).

6.8. Multiple Comparisons/Multiplicity

This study was designed to test the hypothesis that Pretomanid PK parameters following drug exposure will differ between patients with hepatic impairment and non-hepatically impaired controls. This results in three comparisons, however no adjustment for multiple comparisons is planned.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Table 8 will present a summary of the reasons that subjects were screened but not enrolled.

The composition of analysis populations, including reasons for subject exclusion, by impairment group, is presented in Table 7.

The disposition of subjects in the study will be tabulated by impairment group (Table 6). The table shows the total number of subjects screened, enrolled, who received treatment, completed all hourly assessments, and the number who completed the Day 12 follow-up.

A flowchart showing the disposition of study subjects, adapted from the Consort Statement (12) will be included (Figure 1). This figure will present the number of subjects screened, enrolled, terminated early, and analyzed, by impairment group.

A listing of subjects who are terminated from study follow-up and the reason will be included in Listing 1.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and impairment group for all subjects (Table 4). All subject-specific protocol deviations and non-subject specific protocol deviations will be included in Appendix 3 as data listings (Listing 2 and Listing 3, respectively).

8. EFFICACY EVALUATION

This study is primarily a pharmacokinetics study and does not include an efficacy evaluation.

9. SAFETY EVALUATION

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

Listings will be sorted by impairment group, subject 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 subjects in a population. This will be described for each table.

9.1. Demographic and Other Baseline Characteristics

Summaries of age, height, weight (measured at screening), sex, ethnicity, and race will be presented by impairment group and overall (Table 11; Table 12) as well as by site (Table 9 and Table 10). Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual subject listings (Appendix 3) will be presented for all demographics (Listing 5).

9.1.1. Prior and Concurrent Medical Conditions

Complete medical history will be obtained by interview of subjects at the screening visit and will be reviewed and/or updated on Day 1 prior to dosage. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited.

All current illnesses and pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 21.0 or higher. Summaries of subjects' pre-existing medical conditions will be presented by impairment group (Table 13).

Individual subject listings will be presented for all medical conditions (Listing 6).

9.1.2. Prior and Concomitant Medications

Summaries of medications that were started prior to dosing and continuing at the time of dosing will be presented by WHO Drug Terms 2 and 3 and impairment group (Table 140).

Individual subject listings will be presented for all concomitant medications (Listing 14).

9.2. Measurements of Treatment Compliance

Any subjects who were enrolled but not dosed will be presented by impairment group as part of the subject disposition table (Table 6).

9.3. Adverse Events

When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the total population size. All adverse events reported will be included in the summaries and analyses. Adverse event grading scales are presented in Table 5.

An overall summary of adverse events is presented in Table 14.

9.3.1. Unsolicited Adverse Events

The proportion of subjects reporting at least one unsolicited adverse event will be summarized by MedDRA system organ class and preferred term for each impairment group. Denominators for percentages are the number of subjects who received Pretomanid being summarized.

Adverse events by subject will be presented in Listing 7.

The following summaries for unsolicited adverse events will be presented by MedDRA system organ class, preferred term, and impairment group:

- Subject incidence and total frequency of adverse events over time by dose with 95% CI (Days 1-5, Days > 5) (Table 15; Table 16; Table 17; and Table 18);
- Summary of severity and relationship to study product (Table 19);
- Subject listing of non-serious adverse events of moderate or greater severity (Table 21);
- Bar chart of serious and non-serious related adverse events by severity and MedDRA system organ class (Figure 3 and Figure 4).

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

The following listings will be presented including Subject ID, Adverse Event Description, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days):

- Deaths and Serious Adverse Events (Table 20).

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 12 Visit. Male subjects should notify the study team if a pregnancy occurs in a partner within 3 months after study drug administration. If the male subject reports a pregnancy, information about complications during pregnancy, labor and delivery, or congenital birth defects will be collected from the male subject's female partner using a site-specific Pregnant Partner Information and Authorization form. Certain pregnancy outcomes (congenital anomaly or birth defect in an offspring of a subject taking study drug) will require submission as an SAE. A listing of pregnancies will be presented (Listing 15; Listing 16; Listing 17; Listing 18; and Listing 19).

9.6. Clinical Laboratory Evaluations

Clinical safety laboratory adverse events will be collected at the time of dosage, at 36 hours post dose (Day 2), Day 5 and Day 12. Chemistry parameters to be evaluated include: total bilirubin, serum albumin, potassium, magnesium, calcium, serum creatinine, blood urea nitrogen (BUN), alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). For patients with severe hepatic impairment an ammonia level will be drawn at screening and will be used as a baseline reading for safety purposes, not as a study entry criterion. Hematology parameters to be evaluated included: hematocrit, hemoglobin, red blood cell count, white blood cell count, automated differential (absolute neutrophils, absolute eosinophils, absolute basophils, absolute lymphocytes, absolute monocytes), and platelet count. The coagulation parameter international normalized ratio (INR) is to be evaluated. Urinalysis parameters to be evaluated by dipstick include: protein, glucose and blood. If any of the urinalysis parameters are positive by dipstick then the sample will be analyzed by reflex microscopy and the results for protein, glucose and blood will be summarized. Grading scales for safety laboratory parameters are presented in Table 5.

The number and percentage of subjects with at least one clinical safety laboratory of mild or greater severity through Day 12 is presented in the overall summary of adverse events (Table 14).

The distribution of chemistry results by severity, time point, and impairment group will be presented beginning at Table 26 and concluding at Table 47. The distribution of hematology results by severity, time point, and impairment group will be presented beginning at Table 58 and concluding at Table 79. The distribution of urine dipstick results by timepoint and impairment group will be shown in Table 90. The distribution of urinalysis results by severity, time point, and impairment group will be presented in Table 91; Table 92; Table 93; Table 94; Table 95; Table 96; Table 97; and Table 98. The distribution of coagulation results by severity, time point, and impairment group will be presented in Table 102 and Table 103. Descriptive statistics including mean, standard deviation, median, minimum and maximum values by time point, for each laboratory parameter, will be summarized in Table 48 and concluding at Table 57 (chemistry); Table 80 and concluding at Table 89 (hematology); Table 99 (Urinalysis); and Table 104 (Coagulation). Table 100; and Table 101 will show distribution of categorical urinalysis results. Shift tables will be presented for each laboratory parameter beginning at Table 105 and concluding at Table 128. Change from baseline plots for continuous laboratory parameters will also be presented beginning at Figure 5 and concluding with Figure 25.

Listing 8; Listing 9; Listing 10; and Listing 11 will provide complete listings of individual clinical laboratory results with applicable reference ranges. Table 22; Table 23; Table 24;and Table 25 will provide listings of abnormal laboratory values.

9.7. Vital Signs and Physical Evaluations

Vital sign measurements included oral temperature, pulse, systolic blood pressure, and diastolic blood pressure. Vital signs will be summarized at admission (Day -1), Day 1 pre-dose (Baseline), 1-hour post-dose, 2 hours post-dose, 4 hours post-dose, 5 hours post-dose, 6 hours post-dose, 8 hours post-dose, 12 hours post-dose, 16 hours post-dose, 24 hours post-dose, 36 hours post-dose, Day 3, Day 4, Day 5 and Day 12. Vital signs will be tabulated by visit and impairment group (Table 129 through Table 137; and Listing 12).

Physical Examinations performed at admission and Day 12. The following body systems will be assessed: Abdomen, Cardiovascular/heart Extremities, General Appearance, HEENT, Lymph nodes, Musculoskeletal, Neck, Neurological, Pulmonary/Chest, and Skin (Listing 13). A summary of abnormal physical exam findings

will be shown in Table 138. Weight will be summarized at admission (Day -1), Day 1 pre-dose (Baseline), 1-hour post-dose, 2 hours post-dose, 4 hours post-dose, 5 hours post-dose, 6 hours post-dose, 8 hours post-dose, 12 hours post-dose, 16 hours post-dose, 24 hours post-dose, 36 hours post-dose, Day 3, Day 4, Day 5 and Day 12. Weight will be tabulated by visit and impairment group (Table 139).

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 CRFs. A by-subject listing of concomitant medication use will be presented (Listing 14). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and impairment group for the Safety population (Table 140).

9.9. Other Safety Measures

ECG intervals (RR, QRS, QT, QTcF, PR and ventricular rate) will be summarized at the day of admission and Day 12 using descriptive statistics (Table 141; Table 142; Table 143; Table 144; Table 145; and Table 146). The proportion of subjects with bradycardia, tachycardia, conduction system disease (e.g., prolongation of the PR Interval, bundle branch block, fascicular block), arrhythmia (e.g., atrial fibrillation, atrial flutter, premature atrial/ventricular contractions, ventricular tachycardia), and Brugada pattern will be summarized by hepatic impairment group (Table 147). Individual overall interpretation and comments will be provided in Listing 20. Individual ECG interval measurements will be provided in Listing 21.

10. PHARMACOKINETICS

Pharmacokinetic (PK) analyses will be performed using noncompartmental analysis (NCA). PK concentrations and noncompartmental parameters will be summarized by impairment group. Statistics include the arithmetic mean, geometric mean (GM), standard deviation (SD), coefficient of variation (CV), minimum (min), maximum (max), and median. PK parameters ($AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, 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.

10.1. Summary of Pharmacokinetic Sampling and Sample Properties

Samples with bioanalytical errors 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 impairment group, and subject, out of sample time window, and PK analyses-excluded samples indicated (Listing 22). The listings will also indicate the nominal and actual time associated with the sample (nominal time is defined as the 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 148; Table 149; Table 150; and Table 151) and plotted.

- Figure 26; Figure 27; Figure 28; and Figure 29 (linear) and Figure 33; Figure 34; Figure 35; and Figure 36 (semilogarithmic) will plot all subject plasma PK profiles together by impairment group, as linear and semilogarithmic plots.
- Linear plots of subjects with hepatic impairment with their matched control (Figure 30; Figure 31; and Figure 32).
- Linear plots of plasma mean concentration curves will be shown in Figure 37, with error bars representing +/- 1 standard deviation.
- Semi-logarithmic plots of geometric mean plasma concentration curves will be shown in Figure 38.

10.2.2. Pharmacokinetic Parameters

NCA PK parameters will be calculated using actual post-dose time. Samples with concentrations greater than the LLOQ will be considered for the estimation of λ_z. This slope will be computed from log-transformed concentration data. The correlation between time and concentration in the time points used to estimate λ_z should be sufficiently high ($R^2_{adjusted}$>0.9 for λ_z. to be estimated reliably. At least three samples will be used for the calculation of λ_z. The range of selected time points should include all timepoints post 12 hours inclusive if appropriate.

Samples used to calculate λ_z along with the number of samples used for the calculation will be included in subject listings (Listing 22).

The AUC will be computed using the linear-up log-down (linear-log) trapezoidal method in WinNonlin (Pharsight Corporation, Cary, NC).

All PK parameters will also be summarized by impairment group using descriptive statistics (Table 152; Table 153; Table 154; and Table 155). Additionally, subject-level PK parameters will be presented by participant in the table in the final report.

The following parameters will be estimated: C_{max}, T_{max}, $t_{(1/2)}$, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}\infty)}$, CL/F and V_d/F. See Section 3.3 for parameter definitions.

10.3. Comparison of Impairment Groups

If at least one matching participant in the healthy volunteer group is available in the 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 subject 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 impairment groups with non-hepatically impaired 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 156).

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 157). 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 prepared (Figure 39; Figure 40; Figure 41; Figure 42; Figure 43; and Figure 44).

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 nearest whole number; values greater than zero but < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as >99%. 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 WinNonlin version 6.3 or later, or a similar software package. WinNonlin, SAS version 9.3 or later or R statistical computing software 3.4.2 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

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17. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

LIST OF TABLES *(continued)*

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9.1 Overall Study Design and Plan Description

Table 1: Study Design

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

Table 2: Summary of 4 Pretomanid Phase 2 studies

Year	N	Pretomanid Regimen	Dosage	Primary Outcome	Mean daily fall in CFU
2010	60	Once Daily	200, 600, 1000,and 1200 mg/day	Mean rate of decline in log CFU of TB over 14 days	0.098 (+/-0.072) was equivalent for all four dosages
2012	60	Once Daily	50, 100, 150, and 200 mg/day	Mean rate of decline in log CFU of TB over 14 days	50mg 0.063 ± 0.058 100mg 0.091 ± 0.073 150mg 0.078 ± 0.074 200mg 0.112 ± 0.070
2012	81	Once Daily	Pretomanid + bedaquiline Pretomanid + pyrazinamide Pretomanid + pyrazinamide + moxifloxacin (all Pretomanid dosages were 200mg/day)	Mean rate of decline in log CFU of TB over 56 days	Pretomanid+ moxifloxacin+pyrazinamide (0.233) was significantly higher than bedaquiline (0.061), bedaquiline+pyrazinamide (0.131), and comparable with that of standard treatment
2014	207	Once Daily	Pretomanid 200mg + pyrazinamide + moxifloxacin Pretomanid 100mg + pyrazinamide + moxifloxacin Pretomanid 200mg + pyrazinamide + moxifloxacin (Tx MDR-TB)	Mean rate of decline in log CFU of TB over 14 days	Pretomanid 200mg + pyrazinamide + moxifloxacin (0.155) Pretomanid 100mg + pyrazinamide + moxifloxacin (0.133) Pretomanid 200mg + pyrazinamide + moxifloxacin (Tx MDR-TB) (0.117)

9.5.1 Efficacy/Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 3: Schedule of Study Procedures

Study Visit	**00A**	**00B**	**01**	**01A**	**01B**	**01C**	**01D**	**01E**	**01F**	**01G**	**01H**	**01I**	**01J**	**02**	**03**	**04**	**05**	**Early Term**
Study Day	**Screen** -22 to -2	**Admission -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**12**	
Time (Window)			**0** (-10 min)	**1 hr** (+/- 10 min)	**2 hr** (+/- 10 min)	**4 hr** (+/- 10 min)	**5 hr** (+/- 10 min)	**6 hr** (+/- 10 min)	**8 hr** (+/- 10 min)	**12 hrs** (+/- 10 min)	**16 hr** (+/- 10 min)	**24 hrs** (+/- 1 hr)	**36 hrs** (+/- 1 hr)	**48 hrs** (+/- 4 hrs)	**72 hrs** (+/- 4 hrs)	**96 hrs** (+/- 4 hrs)		
Informed Consent	X																	
Review Inclusion/ Exclusion Criteria	X	X																
Demographics[1]	X																	
Medical/Surgical History[2]	X	X												X	X	X	X	X
Physical Examination[3]	X	X															X	X
Targeted Review of Body Systems[12]														X	X	X	X	X
Concomitant Medication	X	X												X	X	X	X	X
12-Lead ECG (Resting)	X	X[1]															X	
Vital Signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Laboratory Testing (Hematology, Chemistry)[9,11]	X[4]	X[13]											X[10]			X	X	
Coagulation[9]	X[4]	X[13]											X[10]			X	X	
Urinalysis[9]	X[4]	X[13]											X[10]			X	X	
Pregnancy Test[9]	X[4]	X[13]															X	X
Drug and Alcohol Screen [5,8]	X[4]	X																
Blood for HIV, HCV, HBsAg testing[8]	X[4]																	
Blood for PK Sampling[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Discharge from the confinement/hospital unit[14]													X	X				

Table 3: Schedule of Study Procedures *(continued)*

Study Visit	**00A**	**00B**	**01**	**01A**	**01B**	**01C**	**01D**	**01E**	**01F**	**01G**	**01H**	**01I**	**01J**	**02**	**03**	**04**	**05**	**Early Term**
Study Day	**Screen** -22 to -2	**Admission -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**12**	
Time (Window)			**0** (-10 min)	**1 hr** (+/- 10 min)	**2 hr** (+/- 10 min)	**4 hr** (+/- 10 min)	**5 hr** (+/- 10 min)	**6 hr** (+/- 10 min)	**8 hr** (+/- 10 min)	**12 hrs** (+/- 10 min)	**16 hr** (+/- 10 min)	**24 hrs** (+/- 1 hr)	**36 hrs** (+/- 1 hr)	**48 hrs** (+/- 4 hrs)	**72 hrs** (+/- 4 hrs)	**96 hrs** (+/- 4 hrs)		
Study Product Administration[7b]			**X**															
AE Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total blood drawn	27.5mL	11.5mL	6mL	6mL	6mL	6mL	6mL	6mL	6mL	6mL	6mL	6mL	17.5mL	6mL	6mL	17.5mL	14.5mL	0mL

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

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

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

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

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

6 Vital sign measurements must include the subject's sitting heart rate, sitting blood pressure (mm Hg), height (screening only), and oral body temperature (ºC). Vital signs will be obtained at screening, and on Days -1 to 12 at the following time points:, admission day, prior to dosing, and 30 minutes after dosing, 1, 2, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96 hours and Day 12. Weight will be collected at screening, admission day, prior to dosing, 36, 48, 72, 96 hours and Day 12 time points.

7 Blood samples for pharmacokinetic assessments of Pretomanid will be obtained on Days 1 to 5 at the following time points: pre-dose and 1, 2, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post-dose.
   a. The following collection windows are allowed for the PK blood sample time points:
      i. Pre-dose: -10 minutes
      ii. Dosing through 16 hours post-dose inclusive: ± 10 minutes
      iii. 24 and 36 hours post-dose: ± 1 hour
      iv. 48, 72, and 96 hours: ± 4 hours
   b. Subjects will receive the single oral dose of Pretomanid 200 mg taken with 240 mL of water after overnight fast.
   c. The following parameters will be used for PK assessments: AUC0-inf, AUC0-t, Cmax, tmax, half-life and CL/F.

8 Screening labs include: blood screen for hepatitis B surface antigen (HBsAg) and hepatitis C antibody, alcohol breath test or other suitable test for alcohol (e.g., blood alcohol test), urine screen test for drugs of abuse [amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, cannabinoids, phencyclidine (PCP)] and a blood screen for HIV.

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

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

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

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

13 Baseline admissions labs and resting 12-Lead ECG recording may be done within 72 hours of admission or at the time of admission depending on ability to obtain lab results at the site.

14 Discharge from confinement/hospital unit either after Visit 01J or Visit 2 depending upon site preference.

10.2 Protocol Deviations

Table 4: Distribution of Protocol Deviations by Category, Type, and Impairment Group

Category	Deviation Type	Mild Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type										
	Did not meet inclusion criterion	x	x	x	x					x	x
	Met exclusion criterion										
	ICF not signed prior to study procedures										
	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										
	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										

Table 4: Distribution of Protocol Deviations by Category, Type, and Treatment Group *(continued)*

Category	Deviation Type	Mild Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Treatment administration	Any type										
	Required procedure done incorrectly										
	Study product temperature excursion										
	Other										
Note: N= All Enrolled Subjects											

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 5: Laboratory/Clinical Adverse Event Grading Scale

Category	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Comments
VITAL SIGNS				
Fever (°C) **	38.0 – 38.4	38.5 – 38.9	≥ 39.0	** Oral temperature; no recent hot or cold beverages or smoking. A protocol should select either °C or °F for inclusion.
(°F) **	100.4 – 101.1	101.2 – 102.0	≥ 102.1	
Tachycardia – beats per minute	101 – 115	116 – 130	> 130 or ventricular dysrhythmias	
Bradycardia – beats per minute	50 – 54 or 45-50 bpm if pre-dose visit rate < 60 bpm	45 – 49 or 40-44 if pre-dose visit rate < 60bpm	< 45 or <40bpm if pre-dose visit rate <60bpm	
Hypertension (systolic) – mm Hg	141 – 150	151 – 160	> 160	Assume supine position for 10 min at rest in non-sleeping subjects; for adverse events, need three measurements on the same arm with concordant results.
Hypertension (diastolic) – mm Hg	91 – 95	96 – 100	> 100	
Hypotension (systolic) –mm Hg	85 – 89	80 – 84	< 80	
Tachypnea – breaths per minute	23 – 25	26 – 30	> 30	
CARDIOVASCULAR				
Arrhythmia	Asymptomatic, transient signs, no Rx required	Recurrent/ persistent; symptomatic; Rx required	Unstable dysrhythmia; hospitalization and treatment required	
Hemorrhage, Blood Loss	Estimated blood loss ≤ 100 mL	Estimated blood loss > 100 mL, no transfusion required	Transfusion required	
QT/QTc prolongation	Male: 441-470 msec Female: 451-470 msec	Male: 471-500 msec Female: 471-500 msec:	> 500 msec OR > 60 msec change from admission visit	

Table 5: Laboratory/Clinical Event Grading Scale *(continued)*

Category	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Comments
RESPIRATORY				
Cough	Transient- no treatment	Persistent cough;	Interferes with daily activities	
Bronchospasm, Acute	Transient; no treatment; 71% - 80% FEV1 of peak flow	Requires treatment; normalizes with bronchodilator; FEV1 60% - 70% (of peak flow)	No normalization with bronchodilator; FEV1 < 60% of peak flow	
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment	
GASTROINTESTINAL				
Nausea	No interference with activity	Some interference with activity	Prevents daily activities	
Vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity or requires IV hydration	
Diarrhea	2 – 3 loose or watery stools or < 400 gms/24 hours	4 – 5 loose or watery stools or 400 – 800 gms/24 hours	6 or more loose or watery stools or > 800gms/24 hours or requires IV hydration	
LABORATORY ADVERSE EVENTS				
Blood, Serum, or Plasma *				
Potassium – Hypokalemia mmol/L	3.1 – <LLN	2.7 – 3.0	<2.7	
Potassium – Hyperkalemia mmol/L	>ULN – 5.6	>5.6 – 6.5	>6.5	
Glucose – Hypoglycemia Fasting – mg/dL [#]	61 – <LLN	55 – <61	<55	
Glucose – Hyperglycemia Fasting – mg/dL [#]	>ULN – 120	>120 – 130	>130	
Blood Urea Nitrogen mg/dL	>ULN – 29	30 – 35	>35	
Creatinine – mg/dL	>ULN – 1.7	1.8 – 2.0	>2.0	
Calcium – hypocalcemia mg/dL	8.0 – <LLN	7.5 – 7.9	<7.5	

Table 5: Laboratory/Clinical Event Grading Scale *(continued)*

Category	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Comments
Calcium – hypercalcemia mg/dL	>ULN – 11.0	11.1 – 11.5	>11.5	
Magnesium – hypomagnesemia mg/dL	1.3 – <LLN	1.0 – <1.3	<1.0	
Albumin – Hypoalbuminemia g/dL	2.8 – <LLN	2.5 – 2.7	<2.5	
Alkaline phosphatase – U/L(Age 18 years)	>ULN – 240	241 – 360	>360	
AST U/L	>ULN – 105	106 – 175	>175	
ALT U/L	>ULN – 105	106 – 175	>175	
Bilirubin (serum total) mg/dL	>ULN – 2.0	2.1 – 2.5	>2.5	
Hemoglobin - g/dL	10.5 – <LLN	9.5 – 10.4	< 9.5	
Hematocrit - %	32.3 – <LLN	28.0 – 32.2	< 28.0	
RBC Decrease (Female) X10^12/L	3.61 – <LLN	3.14 – 3.60	< 3.14	
RBC Decrease (Male) X10E6/uL X10^12/L	3.89 – <LLN	3.28 – 3.88	< 3.28	
WBC Increase X10^9/L	>ULN – 15.0	15.1 – 20.0	> 20.0	
WBC Decrease X10^9/L	2.5 – <LLN	1.5 – 2.4	< 1.5	
Lymphocytes Decrease - X10^9/L	0.5 – <LLN	0.3 – 0.4	<0.3	
Neutrophils Decrease - X10^9/L	1.0 – <LLN	0.5 – 1.0	< 0.5	
Monocytes Increased X10^9/L	>ULN – 2.5	2.6 – 3.0	>3.0	
Eosinophils Increased X10^9/L	>ULN – 0.75	0.76-1.50	>1.50	
Basophils Increased X10^9/L	>ULN – 0.40	0.41 – 0.80	>0. 80	
Platelets Decreased - X10^9/L	120 – <LLN	100 – 119	<100	
INR	>ULN – 1.3	1.4 – 1.6	>1.6	
Urine *				
Protein	1+	2+	> 2+	
Glucose	Trace – 1+	2+	> 2+	
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	3 – 10	11 – 50	> 50 and/or gross blood	

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters.

* Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

[#] Laboratory Parameter will not be used as halting criteria.

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 6: Subject Disposition by Impairment Group

Subject Disposition	Mild Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N=X)	
	n	%	n	%					n	%
Screened	--	--	--	--					x	--
Enrolled	x	100	x	100					x	100
Received Treatment	x	xx	x	xx					x	xx
Completed all hourly assessments	x	xx	x	xx					x	xx
Completed Follow-up (Study Day 12)[a, b]										

[a] Refer to Listing 16.2.1 for reasons subjects discontinued or terminated early.

[b] Completed all daily assessments following discharge through study day 12.

Note: N=All Enrolled Subjects

Table 7: Analysis Populations by Impairment Group

Analysis Populations	Reason Subjects Excluded	Mild Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	%	n
Safety Population	Any Reason	x	xx	x	xx					x	xx
	Did not receive study product										
Pharmacokinetics Population	Any Reason										
	Insufficient number of samples for estimation of PK parameters										
	Did not meet all inclusion criteria or met exclusion criteria										

Note: N= Number of subjects enrolled

Table 8: Ineligibility Summary of Screen Failures

Subjects with Hepatic Impairment/ Non-Hepatically Impaired Controls	**Inclusion/ Exclusion Category**	**Inclusion/Exclusion Criterion**	**n**[a]	**%**[b]
All Subjects	**Inclusion and Exclusion**	**Number of subjects failing any eligibility criterion**	x	100
Subjects with Hepatic Impairment	**Inclusion and Exclusion**	**Number of subjects failing any eligibility criterion**	**x**	**100**
	Inclusion	**Any inclusion criterion**	x	xx
		Subject is able to give voluntary written informed consent before any study related procedure is performed	x	xx
		18-70 years of age, inclusive	x	xx
		…. (continued)	x	xx
	Exclusion	**Any exclusion criterion**	**x**	**xx**
		Hypokalemia (< 3.5mEq/L), severe hypomagnesemia (< 1.1 mg/dL) or severe hypocalcemia (< 7.5 mg/dL)	x	xx
		AST or ALT > 10 times the upper limit of normal	x	xx
		…. (continued)	x	xx
	Eligible but Not Enrolled	**Any Reason**	**x**	**xx**
		Time Commitment	x	xx
		Concern of Potential Risks	x	xx
		Number of Procedures/Blood Draws	x	xx
		Unable to Contact Subjects	x	xx
		Other	x	xx
Non-Hepatically Impaired Controls	**Inclusion and Exclusion**	**Number of subjects failing any eligibility criterion**	**x**	**100**
	Inclusion	**Any inclusion criterion**	**x**	**xx**
		Subject is able to give voluntary written informed consent before any study related procedure is performed	x	xx
		18-70 years of age, inclusive	x	xx
		… (continued)	x	xx
	Exclusion	**Any exclusion criterion**	**x**	**Xx**
		Inability to swallow tablets	x	Xx
		Presence of any condition or finding which would jeopardize subject safety, impact study result validity, or diminish the subject's ability to undergo all study procedures and assessments	x	Xx
		… (continued)	x	Xx

Table 8: Ineligibility Summary of Screen Failures *(continued)*

Subjects with Hepatic Impairment/ Non-Hepatically Impaired Controls	**Inclusion/ Exclusion Category**	**Inclusion/Exclusion Criterion**	**n**[a]	**%**[b]
	Eligible but Not Enrolled	**Any Reason**	x	xx
		Time Commitment	x	xx
Non-Hepatically Impaired Controls *(continued)*	**Eligible but Not Enrolled (*continued*)**	Concern of Potential Risks	x	xx
		Number of Procedures/Blood Draws	x	xx
		Unable to Contact Subjects	x	xx
		Other	x	xx

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

14.1.2 Demographic Data by Impairment Group

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

		Duke (N=X)		Saint Louis (N=X)		All Subjects (N=X)	
Variable	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**
Sex	Male	x	xx	x	xx	x	xx
	Female	x	xx	x	xx	x	xx
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino	x	xx	x	xx	x	xx
	Not Reported	x	xx	x	xx	x	xx
	Unknown	x	xx	x	xx	x	xx
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx
	Asian	x	xx	x	xx	x	xx
	Native Hawaiian or Other Pacific Islander	x	xx	x	xx	x	xx
	Black or African American	x	xx	x	xx	x	xx
	White	x	xx	x	xx	x	xx
	Multi-Racial	x	xx	x	xx	x	xx
	Unknown	x	xx	x	xx	x	xx

Note: N= All Enrolled Subjects

Table 10: Summary of Continuous Demographic and Baseline Characteristics by Site

Variable	**Statistic**	**Duke (N=X)**	**Saint Louis (N=X)**	**All Subjects (N=X)**
Age (years)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	25th Quartile	x	x	x
	75th Quartile	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Weight* (kg)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	25th Quartile	x	x	x
	75th Quartile	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Height (cm)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	25th Quartile	x	x	x
	75th Quartile	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
BMI (kg/m^2)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	25th Quartile	x	x	x
	75th Quartile	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x

Note: N=All Enrolled Subjects
*Weight measured at screening

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Impairment Group

		Mild Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N=X)	
Variable	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sex	Male	x	xx	x	xx	x	xx	x	xx	x	xx
	Female										
Ethnicity	Not Hispanic or Latino	x	xx	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	x	xx
	Asian										
	Native Hawaiian or Other Pacific Islander										
	Black or African American										
	White										
	Multi-Racial										
	Unknown										

Note: N= All Enrolled Subjects

Table 12: Summary of Continuous Demographic and Baseline Characteristics by Impairment Group

Variable	Statistic	Mild Hepatic Impairment (N=X)	Moderate Hepatic Impairment (N=X)	Severe Hepatic Impairment (N=X)	Matched Controls (N=X)	All Subjects (N=X)
Age (years)	Mean	xx	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx	xx
	Median	x	x	x	x	x
	25th Quartile	x	x	x	x	x
	75th Quartile	x	x	x	x	x
	Minimum	x	x	x	x	x
	Maximum	x	x	x	x	x
Weight* (kg)	Mean	xx	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx	xx
	Median	x	x	x	x	x
	25th Quartile	x	x	x	x	x
	75th Quartile	x	x	x	x	x
	Minimum	x	x	x	x	x
	Maximum	x	x	x	x	x
Height (cm)	Mean	xx	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx	xx
	Median	x	x	x	x	x
	25th Quartile	x	x	x	x	x
	75th Quartile	x	x	x	x	x
	Minimum	x	x	x	x	x
	Maximum	x	x	x	x	x
BMI (kg/m^2)	Mean	xx	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx	xx
	Median	x	x	x	x	x
	25th Quartile	x	x	x	x	x
	75th Quartile	x	x	x	x	x
	Minimum	x	x	x	x	x
	Maximum	x	x	x	x	x

Note: N=All Enrolled Subjects
*Weight measured at screening

14.1.3 Prior and Concurrent Medical Conditions

Table 13: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Impairment Group

	Mild Hepatic Impairment (N=X)		**Moderate Hepatic Impairment (N=X)**		**Severe Hepatic Impairment (N=X)**		**Matched Controls (N=X)**		**All Subjects (N=X)**	
MedDRA System Organ Class	**n**	**%**	**n**	**%**					**n**	**%**
Any SOC	x	xx	x	xx					x	xx
[SOC 1]										
[SOC 2]										

Note: N= Number of subjects in the Safety Population
n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

14.2 Efficacy/Immunogenicity Data

Not Applicable.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 14: Overall Summary of Adverse Events

	Mild Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N = X)	
Subjects[a] with	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
At least one unsolicited adverse event	x	x	x	x	x	x	x	x	x	x
At least one clinical safety laboratory of mild or greater severity through Day 12	x	x	x	x	x	x	x	x	x	x
At least one related unsolicited adverse event	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
Not yet assessed	x	x	x	x	x	x	x	x	x	x
At least one severe (Grade 3) unsolicited adverse event	x	x	x	x	x	x	x	x	x	x
Related	x	x	x	x	x	x	x	x	x	x
Unrelated	x	x	x	x	x	x	x	x	x	x

Table 14: Overall Summary of Adverse Events *(continued)*

	Mild Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N = X)	
Subjects[a] with	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
At least one serious adverse event[b]	x	x	x	x	x	x	x	x	x	x
At least one related, serious adverse event	x	x	x	x	x	x	x	x	x	x
At least one adverse event leading to early termination[c]	x	x	x	x	x	x	x	x	x	x

N = Number of subjects in the Safety Population

[a] Subjects are counted once for each category regardless of the number of events.

[b] A listing of Serious Adverse Events is included in Table 18.

[c] As reported on the Adverse Event eCRF.

14.3.1.1 Solicited Adverse Events

Not Applicable.

14.3.1.2 Unsolicited Adverse Events

Table 15: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, and Impairment Group – Mild Hepatic Impairment

MedDRA System Organ Class	MedDRA Preferred Term	Day 1-5 (N=X)				Day 6-12 (N=X)				Any Time Post Dose (N=X)			
		n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events
Any SOC	Any PT	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = number of subjects in the Safety Population. This table presents number and percentage of subjects. A subject is only counted once per PT/time point.

Tables with similar format:

Table 16: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, and Impairment Group – Moderate Hepatic Impairment

Table 17: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, and Impairment Group – Severe Hepatic Impairment

Table 18: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, and Impairment Group – Matched Controls

Table 19: Incidence of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Impairment Group

MedDRA System Organ Class	Preferred Term	Severity	Mild Hepatic Impairment (N = X)						Moderate Hepatic Impairment (N = X)						Severe Hepatic Impairment (N = X)						Matched Controls (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
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
	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

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

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 20: Listing of Serious Adverse Events

Adverse Event	MedDRA System Organ Class	MedDRA Preferred Term	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	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome
Impairment Group: Subject ID: **AE Number:**												
Comments:												
Impairment Group: Subject ID: **AE Number:**												
Comments:												

Table 21: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

Adverse Event	MedDRA System Organ Class	MedDRA Preferred Term	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	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome
Impairment Group: Subject ID: AE Number:												
Comments:												
Impairment Group: Subject ID: 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 Subject)

Table 22: Listing of Abnormal Laboratory Results - Chemistry

Impairment Group	Subject ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

Table 23: Listing of Abnormal Laboratory Results - Hematology

Impairment Group	Subject ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

Table 24: Listing of Abnormal Laboratory Results - Urinalysis

Impairment Group	Subject ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

Table 25: Listing of Abnormal Laboratory Results - Coagulation

Impairment Group	Subject ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 26: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Any Chemistry Parameter

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 2	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 5	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 12	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Table 26: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Any Chemistry Parameter *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format:

Table 27: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Total Bilirubin

Table 28: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Serum Albumin

Table 29: Chemistry Laboratory Results by Range, Maximum Severity, Time Point, and Impairment Group – Potassium

			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)		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Day 2	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Day 5	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Table 29: 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)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 12	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Max Severity Post Baseline	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N=Number of subjects in the Safety Population with labs available at each visit.

Table 30: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Magnesium

			None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 2	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 5	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 12	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Table 30: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Magnesium *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Table 31: Chemistry Laboratory Results by Range, Maximum Severity, Time Point, and Impairment Group – Calcium

			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)		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Day 2	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Day 5	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Table 31: Chemistry Laboratory Results by Range, Maximum Severity, Time Point, and Impairment Group – Calcium *(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)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 12	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Max Severity Post Baseline	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N=Number of subjects in the Safety Population with labs available at each visit.

Table with similar format:

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

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

			None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 2	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 5	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 12	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

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

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with Similar format:

Table 34: Chemistry Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Alkaline Phosphatase

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

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

Table 37: Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Any Chemistry Parameter

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

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format:

Table 38: Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Total Bilirubin

Table 39: Abnormal Chemistry Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Serum Albumin

Table 40: Abnormal Chemistry Laboratory Results Related to Study Treatment by Range, Maximum Severity, Time Point, and Impairment Group – Potassium

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)	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 2	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 5	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 12	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													

Table 40: Abnormal Chemistry Laboratory Results Related to Study Treatment by Range, Maximum Severity, Time Point, and Impairment Group – Potassium *(continued)*

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)	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N=Number of subjects in the Safety Population with labs available at each visit.

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

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

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

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

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)	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 2	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 5	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 12	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													

Table 42: Abnormal Chemistry Laboratory Results Related to Study Treatment by Range, Maximum Severity, Time Point, and Impairment Group – Calcium *(continued)*

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)	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N=Number of subjects in the Safety Population with labs available at each visit.

Table with Similar Format:

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

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

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

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with Similar Format:

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

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

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

Table 48: Chemistry Laboratory Summary Statistics by Time Point and Impairment Group – Total Bilirubin (mg/dL)

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Mild Hepatic Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 2	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 2, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 12	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 48: Chemistry Laboratory Statistics by Time Point, and Impairment Group – Total Bilirubin (mg/dL) *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Day 12, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Note: N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format:

Table 49: Chemistry Laboratory Summary Statistics by Time Point and Impairment Group – Serum Albumin (g/dL)

Table 50: Chemistry Laboratory Summary Statistics by Range, Time Point, and Impairment Group – Potassium (mmol/dL)

Table 51: Chemistry Laboratory Summary Statistics by Time Point and Impairment Group – Magnesium (mg/dL)

Table 52: Chemistry Laboratory Summary Statistics by Time Point and Impairment Group – Calcium (mg/dL)

Table 53: Chemistry Laboratory Summary Statistics by Time Point and Impairment Group – Serum Creatinine (mg/dL)

Table 54: Chemistry Laboratory Summary Statistics by Time Point and Impairment Group – BUN (mg/dL)

Table 55: Chemistry Laboratory Summary Statistics by Time Point and Impairment Group – Alkaline Phosphatase (U/L)

Table 56: Chemistry Laboratory Summary Statistics by Time Point and Impairment Group – ALT (U/L)

Table 57: Chemistry Laboratory Summary Statistics by Time Point and Impairment Group – AST (U/L)

14.3.5.2 Hematology Results

Table 58: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Any Hematology Parameter

			None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 2	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 5	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 12	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Table 58: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Any Hematology Parameter *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format:

Table 59: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Hematocrit

Table 60: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Hemoglobin

Table 61: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Red Blood Cell Count

Table 62: Hematology Laboratory Results by Range, Maximum Severity, Time Point, and Impairment Group – White Blood Cell Count

			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)		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Day 2	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Day 5	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Table 62: Hematology Laboratory Results by Range, Maximum Severity, Time Point, and Impairment Group – White Blood Cell Count *(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)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 12	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Max Severity Post Baseline	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N=Number of subjects in the Safety Population with labs available at each visit.

Table 63: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Absolute Neutrophils

			None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 2	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 5	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 12	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Table 63: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Absolute Neutrophils *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format

Table 64: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Absolute Eosinophils

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

Table 66: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Absolute Lymphocytes

Table 67: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Absolute Monocytes

Table 68: Hematology Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Platelets

Table 69: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Any Hematology Parameter

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

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format:

Table 70: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Hematocrit

Table 71: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Hemoglobin

Table 72: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Red Blood Cell Count

Table 73: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – White Blood Cell Count

			Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 2	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 5	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 12	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													

Table 73: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – White Blood Cell Count *(continued)*

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)	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N=Number of subjects in the Safety Population with labs available at each visit.

Table 74: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Absolute Neutrophils

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

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format

Table 75: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Absolute Eosinophils

Table 76: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Absolute Basophils

Table 77: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Absolute Lymphocytes

Table 78: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Absolute Monocytes

Table 79: Abnormal Hematology Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Platelets

Table 80: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – Hematocrit (%)

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Mild Hepatic Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 2	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 2, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 12	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 80: Hematology Laboratory Statistics by Time Point and Impairment Group – Hematocrit (%) *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Day 12, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Note: N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format:

Table 81: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – Hemoglobin (g/dL)

Table 82: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – Red Blood Cell Count ($x10^{12}$/L)

Table 83: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – White Blood Cell Count ($x10^{9}$/L)

Table 84: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – Absolute Neutrophils ($x10^{9}$/L)

Table 85: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – Absolute Eosinophils ($x10^{9}$/L)

Table 86: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – Absolute Basophils ($x10^{9}$/L)

Table 87: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – Absolute Lymphocytes ($x10^{9}$/L)

Table 88: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – Absolute Monocytes ($x10^{9}$/L)

Table 89: Hematology Laboratory Summary Statistics by Time Point and Impairment Group – Platelets ($x10^{9}$/L)

14.3.5.3 Urinalysis Results

Table 90: Urinalysis Laboratory Results by Parameter, Time Point, and Impairment Group

Time Point	Impairment Group	N	Urine Blood		Urine Protein		Urine Glucose		Any Parameter	
			n	%	n	%	n	%	n	%
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
Day 2	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
Day 5	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
Day 12	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									

N= Number in the safety population with labs available at each visit.
n= Number with positive dipstick results.

Table 91: Urinalysis Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Any Urinalysis Parameter

			None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 2	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 5	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 12	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Table 91: Urinalysis Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Any Urinalysis Parameter *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format:

Table 92: Urinalysis Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Protein

Table 93: Urinalysis Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Glucose

Table 94: Urinalysis Laboratory Results by Maximum Severity, Time Point, and Impairment Group – Urine Blood

Table 95: Abnormal Urinalysis Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Any Urinalysis Parameter

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

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Tables with similar format:

Table 96: Abnormal Urinalysis Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Protein

Table 97: Abnormal Urinalysis Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Glucose

Table 98: Abnormal Urinalysis Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – Urine Blood

Table 99: Urinalysis Laboratory Summary Statistics by Time Point and Impairment Group – Blood (rbc/hpf)

[Implementation Note: Microscopic urine analysis is only performed if there is an abnormal urine result. Therefore, there may not be enough data to present this table.]

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Mild Hepatic Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 2	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 2, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 99: Urinalysis Laboratory Summary Statistics by Time Point and Impairment Group – Blood (rbc/hpf) *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Day 12	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 12, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Note: N= Number of subjects in the Safety Population with a positive urine dipstick result and with labs available at each visit.

Table 100: Urinalysis Laboratory Summary Statistics by Time Point and Impairment Group – Protein

[Implementation Note: Microscopic urine analysis is only performed if there is an abnormal urine result. Therefore, there may not be enough data to present this table.]

Time Point	Impairment Group	N	Negative		Trace		1+		2+		3+		4+	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 2	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Day 5	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													

vvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvTable 100: Urinalysis Laboratory Summary Statistics by Time Point and Impairment Group – Protein *(continued)*

Time Point	Impairment Group	N	Negative		Trace		1+		2+		3+		4+	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 12	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													
Max Post Baseline	Mild Hepatic Impairment													
	Moderate Hepatic Impairment													
	Severe Hepatic Impairment													
	Matched Controls													

Note: The "Max Post Baseline" rows indicate the maximum experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Table with similar format:

Table 101: Urinalysis Laboratory Summary Statistics by Time Point and Impairment Group – Glucose

14.3.5.4 Coagulation Results

Table 102: Coagulation Laboratory Results by Maximum Severity, Time Point, and Impairment Group – INR

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 2	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 5	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 12	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Table 102: Coagulation Laboratory Results by Maximum Severity, Time Point, and Impairment Group – INR *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Table 103: Abnormal Coagulation Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, and Impairment Group – INR

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

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population with labs available at each visit.

Table 104: Coagulation Laboratory Summary Statistics by Time Point and Impairment Group – INR

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Mild Hepatic Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 2	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 2, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 12	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 104: Coagulation Laboratory Summary Statistics by Time Point and Impairment Group – INR *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Day 12, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Note: N= Number of subjects in the Safety Population with labs available at each visit.

Table 105: Chemistry Shift Tables by Time Point and Impairment Group – Total Bilirubin

[Implementation Note: If there is no low range then those columns will be removed.]

	Mild Hepatic Impairment (N=X) Baseline				**Moderate Hepatic Impairment (N=X) Baseline**				**Severe Hepatic Impairment (N=X) Baseline**				**Matched Controls (N=X) Baseline**			
Day Post Dose	**Low**	**Normal**	**High**	**Total**	**Low**	**Normal**	**High**	**Total**	**Low**	**Normal**	**High**	**Total**	**Low**	**Normal**	**High**	**Total**
Day 2																
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Day 5																
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Day 12																
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Tables with similar format:

Table 106: Chemistry Shift Tables by Time Point and Impairment Group – Serum Albumin

Table 107: Chemistry Shift Tables by Time Point and Impairment Group – Potassium

Table 108: Chemistry Shift Tables by Time Point and Impairment Group – Magnesium

14.3.6 Displays of Vital Signs

Table 129: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Any Assessment

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
Admission	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
Baseline	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
1 hour post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
2 hours post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
4 hours post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									

Table 129: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Any Assessment *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
5 hours post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
6 hours post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
8 hours post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
12 hours post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
16 hours post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									

Table 129: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Any Assessment *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
24 hours post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
36 hours post-dose	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
Day 3	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
Day 4	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
Day 5	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									

Table 129: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Any Assessment *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
Day 12	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									
Max Severity Post Baseline	Mild Hepatic Impairment									
	Moderate Hepatic Impairment									
	Severe Hepatic Impairment									
	Matched Controls									

Table with similar format:

Table 130: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Oral Temperature

Table 131: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Pulse

			None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Admission	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Baseline	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
1 hour post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
2 hours post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Table 131: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Pulse *(continued)*

Time Point	Impairment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
4 hours post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
5 hours post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
6 hours post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
8 hours post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Table 131: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Pulse *(continued)*

Time Point	Impairment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
12 hours post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
16 hours post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
24 hours post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
36 hours post-dose	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Table 131: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Pulse *(continued)*

Time Point	Impairment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 3	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Day 4	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Day 5	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	
Day 12	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Table 131: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Pulse *(continued)*

Time Point	Impairment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Mild Hepatic Impairment																	
	Moderate Hepatic Impairment																	
	Severe Hepatic Impairment																	
	Matched Controls																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = [define the population for this table, e.g., Number of subjects in the Safety Population]

Table with similar format:

Table 132: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Systolic Blood Pressure

Table 133: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Diastolic Blood Pressure

			None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
Time Point	**Impairment Group**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Admission	Mild Hepatic Impairment	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Baseline	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
1 hour post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
2 hours post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
4 hours post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Table 133: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Diastolic Blood Pressure *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
5 hours post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
6 hours post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
8 hours post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
12 hours post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
16 hours post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Table 133: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Diastolic Blood Pressure *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
24 hours post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
36 hours post-dose	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 3	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 4	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Day 5	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Table 133: Vital Signs by Maximum Severity, Time Point, and Impairment Group – Diastolic Blood Pressure *(continued)*

Time Point	Impairment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Day 12	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											
Max Severity Post Baseline	Mild Hepatic Impairment											
	Moderate Hepatic Impairment											
	Severe Hepatic Impairment											
	Matched Controls											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N= Number of subjects in the Safety Population at each visit.

Table 134: Vital Signs Summary Statistics by Time Point and Impairment Group – Oral Temperature

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Admission	Mild Hepatic Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
1 hour post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
1 hour post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
2 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
2 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 134: Vital Signs Summary Statistics by Time Point and Impairment Group – Oral Temperature *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
4 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
4 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
5 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
5 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
6 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
6 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 134: Vital Signs Summary Statistics by Time Point and Impairment Group – Oral Temperature *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
8 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
8 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
12 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
12 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
16 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
16 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 134: Vital Signs Summary Statistics by Time Point and Impairment Group – Oral Temperature *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
24 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
24 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
36 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
36 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 3	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 3, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 134: Vital Signs Summary Statistics by Time Point and Impairment Group – Oral Temperature *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Day 4	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 4, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 12	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 12, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 134: Vital Signs Summary Statistics by Time Point and Impairment Group – Oral Temperature *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Max Severity Post Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Note: N= Number of subjects in the Safety Population at each visit						

Tables with similar format:

Table 135: Vital Signs Summary Statistics by Time Point and Impairment Group – Pulse

Table 136: Vital Signs Summary Statistics by Time Point and Impairment Group – Systolic Blood Pressure

Table 137: Vital Signs Summary Statistics by Time Point and Impairment Group – Diastolic Blood Pressure

Table 138: Summary of Abnormal Physical Exam Findings by Impairment Group

Time Point		Mild Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N=X)	
	Body System	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Admission	Any Body System	x	xx	x	xx	x	xx	x	xx	x	xx
	Abdomen										
	Cardiovascular/Heart										
	Extremities										
	General Appearance										
	HEENT										
	Lymph Nodes										
	Musculoskeletal										
	Neck (Thyroid)										
	Neurological										
	Pulmonary/Chest										
	Skin										
Day 12	Any Body System	x	xx	x	xx	x	xx	x	xx	x	xx
	Abdomen										
	Cardiovascular/Heart										
	Extremities										
	General Appearance										
	HEENT										
	Lymph Nodes										

Table 138: Summary of Abnormal Physical Exam Findings by Impairment Group *(continued)*

Time Point		Mild Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N=X)	
	Body System	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	Musculoskeletal										
	Neck (Thyroid)										
	Neurological										
	Pulmonary/Chest										
	Skin										

Note: N= Number of subjects in the Safety Population at each visit
n = Number of subjects with physical exam findings.

Table 139: Physical Exam Summary Statistics by Time Point and Impairment Group – Weight

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Admission	Mild Hepatic Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
1 hour post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
1 hour post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
2 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
2 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 139: Physical Exam Summary Statistics by Time Point and Impairment Group – Weight *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
4 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
4 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
5 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
5 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
6 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
6 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 139: Physical Exam Summary Statistics by Time Point and Impairment Group – Weight *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
8 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
8 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
12 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
12 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
16 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
16 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 139: Physical Exam Summary Statistics by Time Point and Impairment Group – Weight *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
24 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
24 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
36 hours post-dose	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
36 hours post-dose, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 3	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 3, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 139: Physical Exam Summary Statistics by Time Point and Impairment Group – Weight *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Day 4	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 4, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 5, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 12	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 12, Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Table 139: Physical Exam Summary Statistics by Time Point and Impairment Group – Weight *(continued)*

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Max Severity Post Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					

Note: N= Number of subjects in the Safety Population at each visit

14.4 Summary of Concomitant Medications

Table 140: Number and Percentage of Subjects 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 Hepatic Impairment (N=X)		Moderate Hepatic Impairment (N=X)		Severe Hepatic Impairment (N=X)		Matched Controls (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	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 subjects in the Safety Population
n=Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

14.5 Other Safety Measures

Table 141: ECG Summary Statistics by Time Point and Impairment Group – RR

Time Point	Impairment Group	N	Mean	Standard Deviation	Median	Min, Max
Admission	Mild Hepatic Impairment	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Day 12	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Change from Baseline	Mild Hepatic Impairment					
	Moderate Hepatic Impairment					
	Severe Hepatic Impairment					
	Matched Controls					
Note: N= Number of subjects in the Safety Population at each visit.						

Tables with similar format:

Table 142: ECG Summary Statistics by Time Point and Impairment Group – QRS

Table 143: ECG Summary Statistics by Time Point and Impairment Group – QT

Table 144: ECG Summary Statistics by Time Point and Impairment Group – QTcF

Table 145: ECG Summary Statistics by Time Point and Impairment Group – PR

Table 146: ECG Summary Statistics by Time Point and Impairment Group – Ventricular Rate

Table 147: Number and Percentage of Subjects Experiencing ECG Events by Symptom, and Impairment Group

Symptom	Visit	Mild Hepatic Impairment (N=X)			Moderate Hepatic Impairment (N=X)			Severe Hepatic Impairment (N=X)			Matched Controls (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	Admission	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
	Day 12												
Bradycardia	Admission												
	Day 12												
Tachycardia	Admission												
	Day 12												
Conduction System Disease	Admission												
	Day 12												
Arrhythmia	Admission												
	Day 12												
Brugada Pattern	Admission												
	Day 12												

Note: N = Number of subjects in the Safety Population at each visit.

14.6 Pharmacokinetics Results

Table 148: Individual and Summary Statistics for Plasma Concentrations by Nominal Time (hours) – Mild Hepatic Impairment

	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														

[a] LLOQ=10 ng/mL

Tables with similar format:

Table 149: Individual and Summary Statistics for Plasma Concentrations by Nominal Time (hours) – Moderate Hepatic Impairment

Table 150: Individual and Summary Statistics for Plasma Concentrations by Nominal Time (hours) – Severe Hepatic Impairment

Table 151: Individual and Summary Statistics for Plasma Concentrations by Nominal Time (hours) – Matched Controls

Table 152: Individual and Summary Statistics for Noncompartmental PK Parameters – Mild Hepatic Impairment

Subject ID	$AUC_{0\text{-last}}$ (ng·hr/mL)	$AUC_{0\text{-}\infty}$ (ng·hr/mL)	T_{max} (hr)	C_{max} (ng/mL)	CL/F (L/hr)	V_d/F (L)	$t_{1/2}$ (hr)
001							
002							
003							
N							
Mean							
SD							
Min							
Max							
CV %							
GM							

Tables with similar format:

Table 153: Individual and Summary Statistics for Noncompartmental PK Parameters – Moderate Hepatic Impairment

Table 154: Individual and Summary Statistics for Noncompartmental PK Parameters – Severe Hepatic Impairment

Table 155: Individual and Summary Statistics for Noncompartmental PK Parameters – Matched Controls

Table 156: 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	$AUC_{0\text{-last}}$ (ng·hr/mL)	$AUC_{0\text{-}\infty}$ (ng·hr/mL)	C_{max} (ng/mL)
Duke	Mild	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Mean			
	Moderate	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Mean			
	Severe	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Mean			
	Matched Controls	Mean			
		90% CI of Mean			
Saint Louis	Mild	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Mean			
	Moderate	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Mean			
	Severe	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Mean			
	Matched Controls	Mean			
		90% CI of Mean			
Overall	Mild	Mean			
		90% CI of Mean			
		Fold Change[a]			

Table 156: Estimated Impairment Group Fold Change for Noncompartmental PK Parameters *(continued)*

Site	Impairment Group	Statistic	$AUC_{0\text{-last}}$ (ng·hr/mL)	$AUC_{0\text{-}\infty}$ (ng·hr/mL)	C_{max} (ng/mL)
		90% CI of Mean			
	Moderate	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Mean			
	Severe	Mean			
		90% CI of Mean			
		Fold Change[a]			
		90% CI of Mean			
	Matched Controls	Mean			
		90% CI of Mean			

[a] Comparison is to matched controls

Table 157: 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)
Duke	Mild	Median	
		90% CI[a]	
		Shift[b]	
		90% CI[a]	
	Moderate	Median	
		90% CI[a]	
		Shift[b]	
		90% CI[a]	
	Severe	Median	
		90% CI[a]	
		Shift[b]	
		90% CI[a]	
	Matched Controls	Median	
		90% CI[a]	
Saint Louis	Mild	Median	
		90% CI[a]	
		Shift[b]	
		90% CI[a]	
	Moderate	Median	
		90% CI[a]	
		Shift[b]	
		90% CI[a]	
	Severe	Median	
		90% CI[a]	
		Shift[b]	
		90% CI[a]	
	Matched Controls	Median	
		90% CI[a]	

Table 157: Estimated Impairment Group Shift for Noncompartmental PK Parameters *(continued)*

Site	Impairment Group	Statistic	T_{max} (h)
Overall	Mild	Median	
		90% CI[a]	
		Shift[b]	
		90% CI[a]	
	Moderate	Median	
		90% CI[a]	
		Shift[b]	
		90% CI[a]	
	Severe	Median	
		90% CI[a]	
		Shift[b]	
		90% CI[a]	
	Matched Controls	Median	
		90% CI[a]	

[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

LIST OF FIGURES *(continued)*

LIST OF FIGURES *(continued)*

10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram

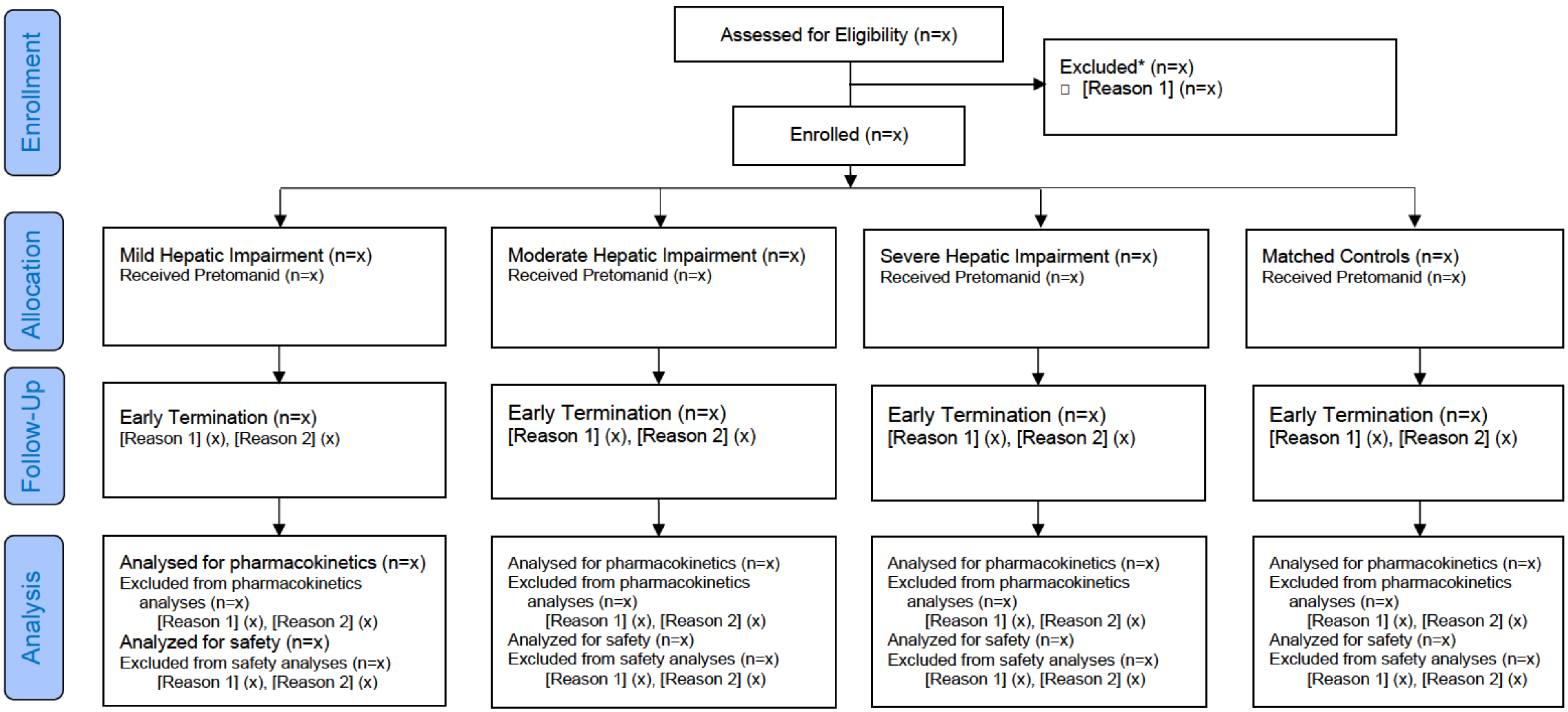
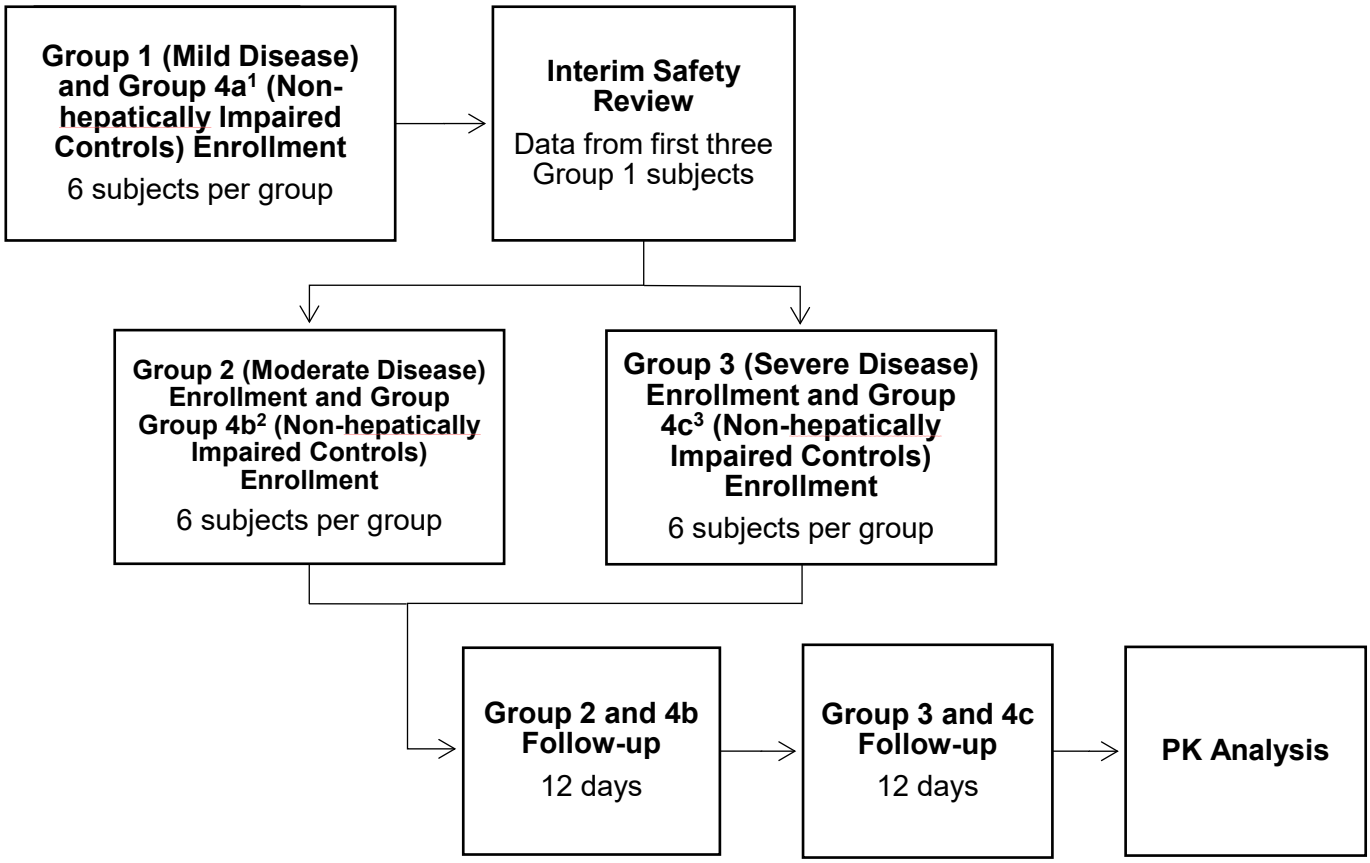


Figure 2: Schematic of Study Design



[1]Group 4a is referring to the non-hepatically impaired controls matched with Group 1
[2]Group 4b is referring to the non-hepatically impaired controls matched with Group 2
[3]Group 4c is referring to the non-hepatically impaired controls matched with Group 3

14.2.2 Efficacy/Immunogenicity Response Figures by Measure, Treatment/Vaccination, and Time Point

Not Applicable.

14.3.1.2 Unsolicited Adverse Events

Figure 3: Frequency of Related Adverse Events by MedDRA System Organ Class, Severity, and Impairment Group

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

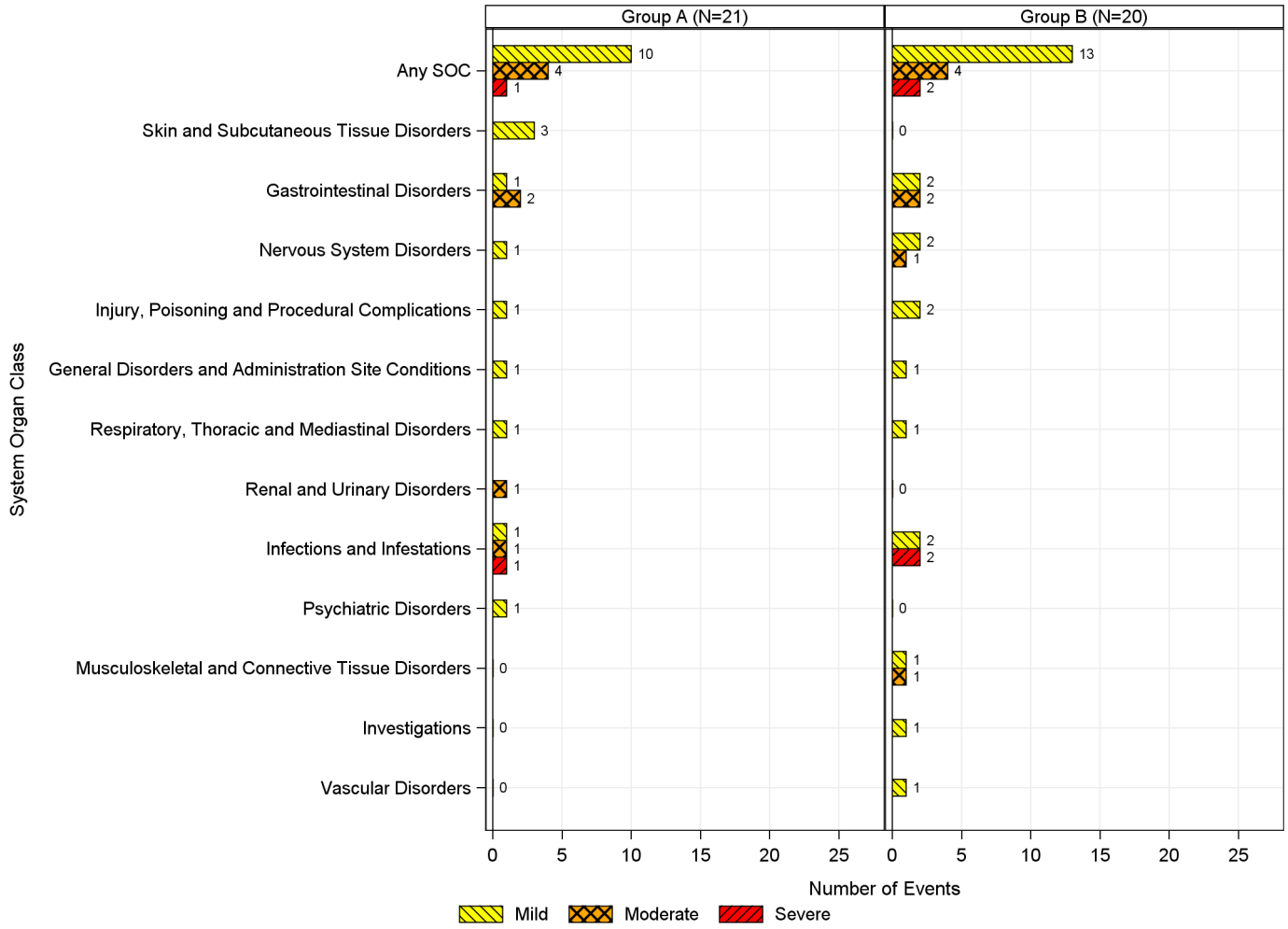
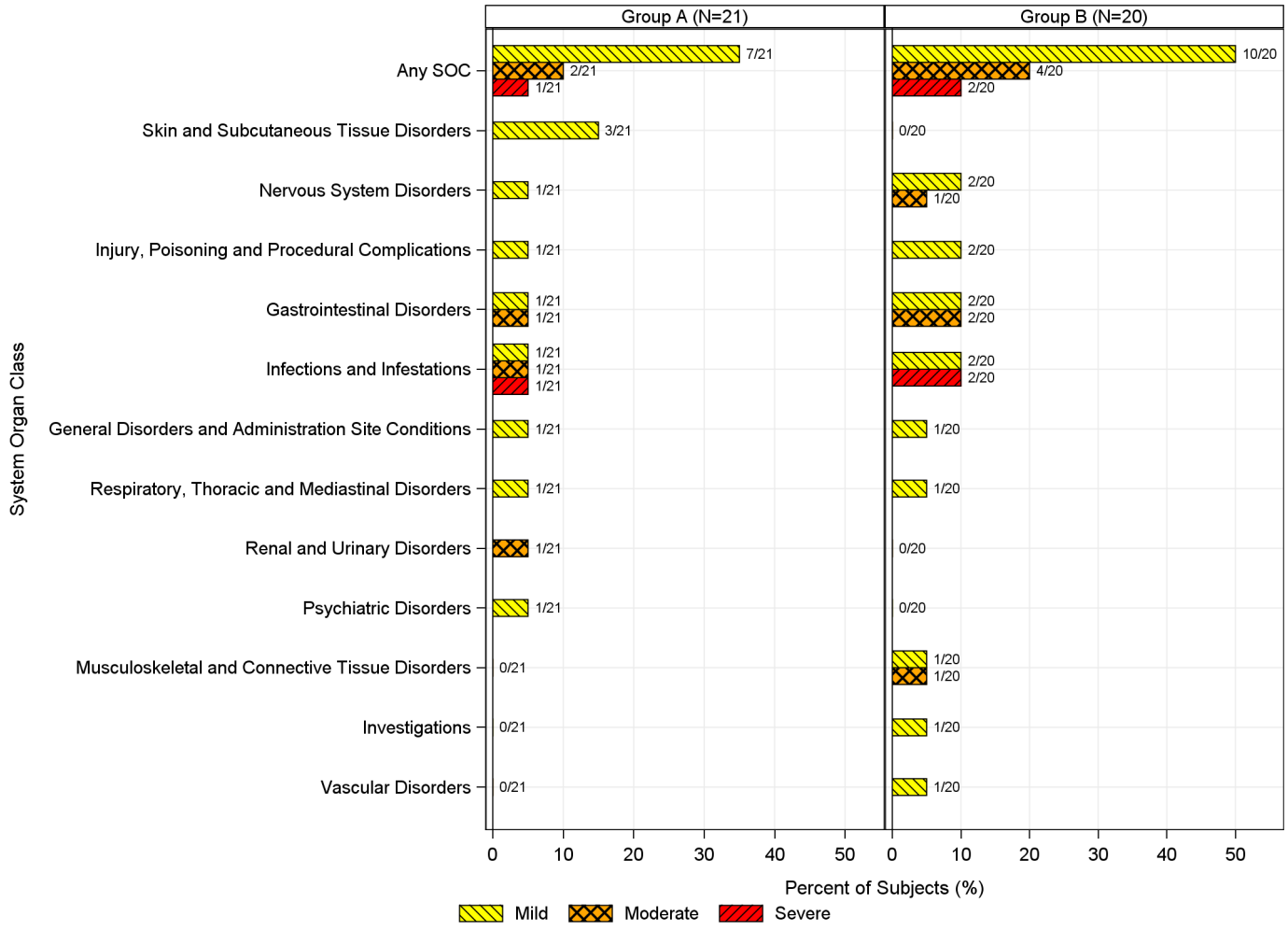


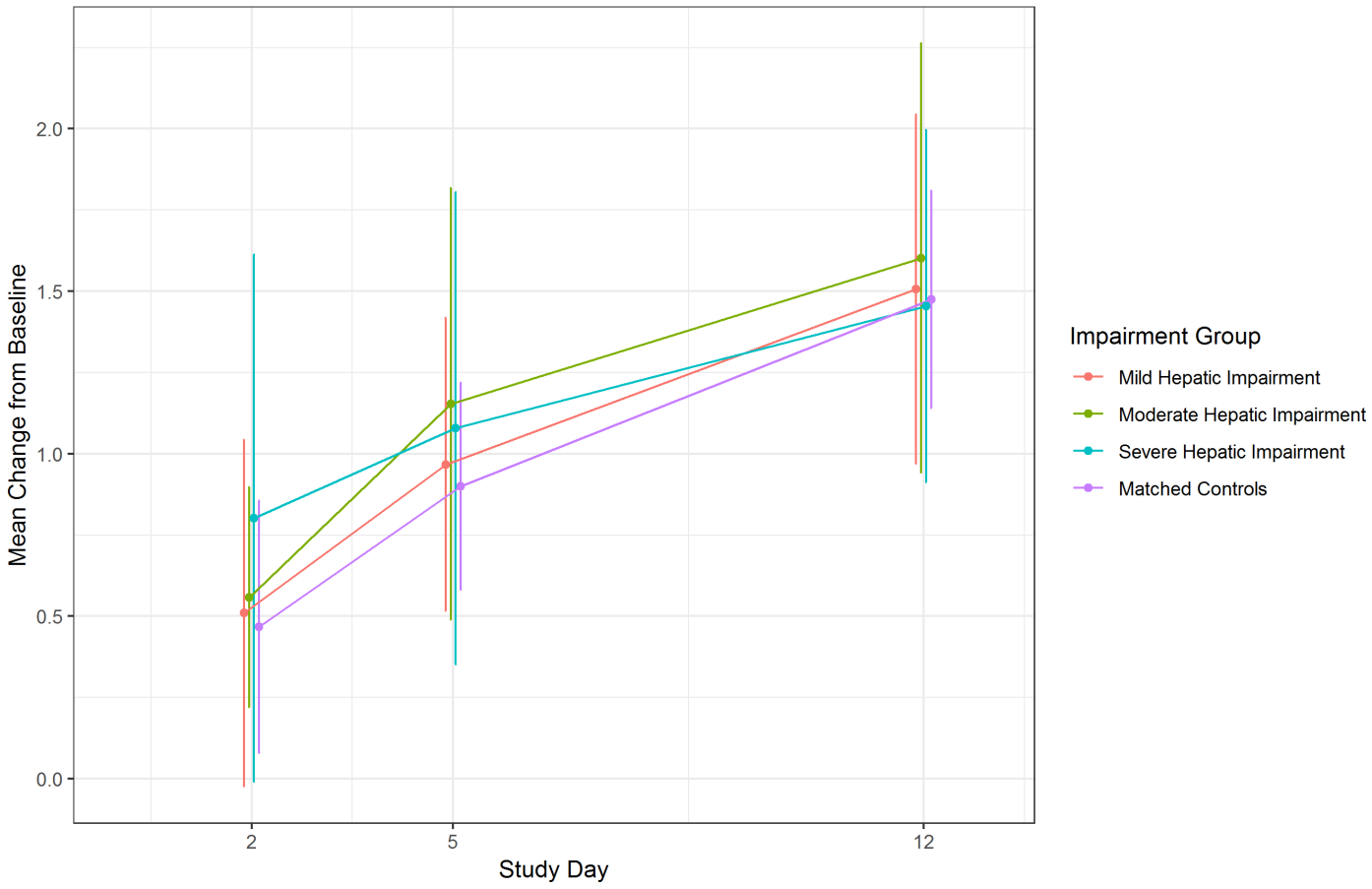
Figure 4: Incidence of Related Adverse Events by MedDRA® System Organ Class, Maximum Severity, and Impairment Group

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



14.3.5 Displays of Laboratory Results

Figure 5: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Impairment Group – Total Bilirubin



Figures with similar format:

Figure 6: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Impairment Group – Serum Albumin

Figure 7 Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Impairment Group – Potassium

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

Figure 9: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Impairment Group – Calcium

Figure 10: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Sex and Impairment Group – Serum Creatinine

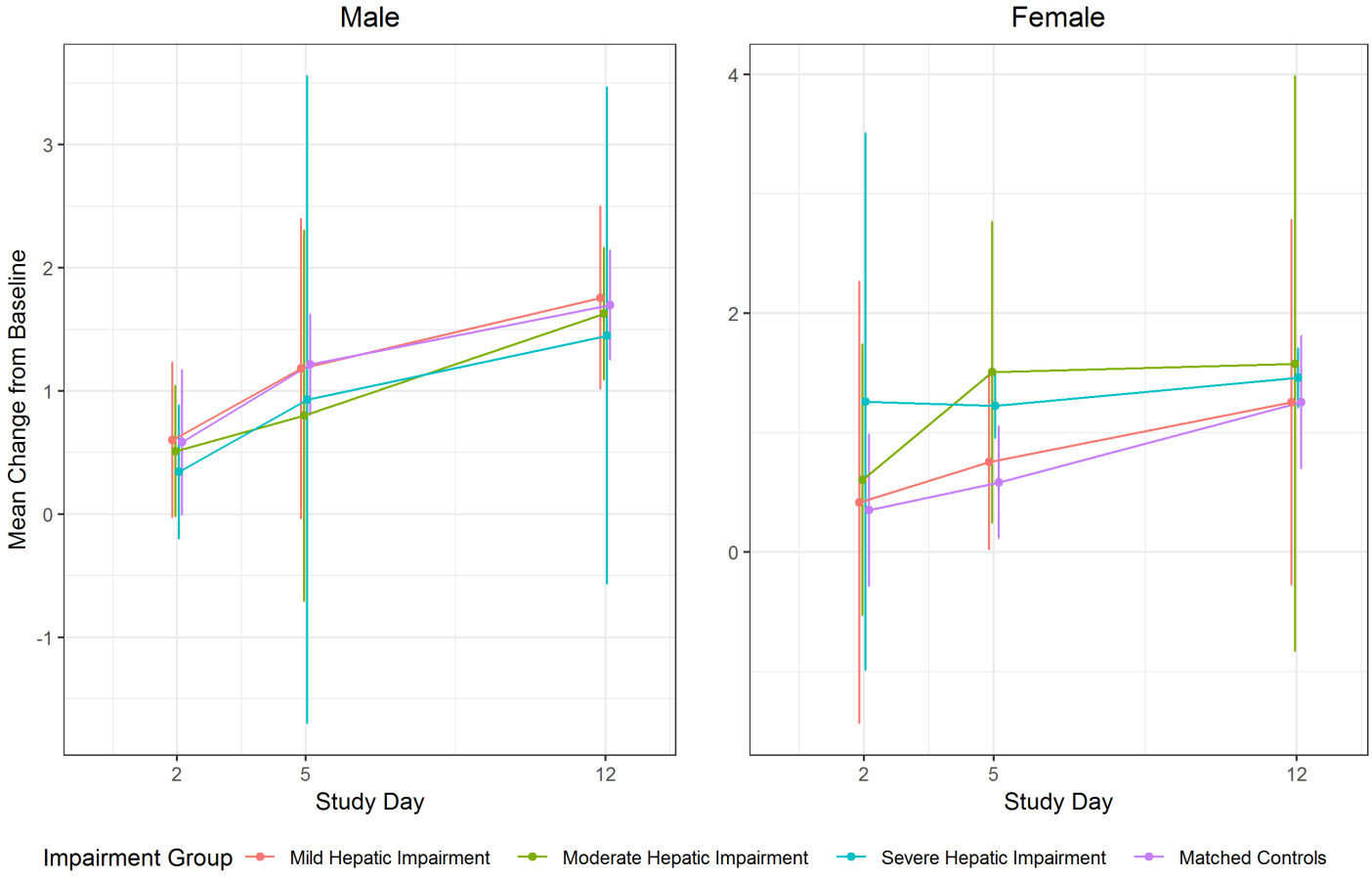


Figure 11: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Impairment Group – BUN

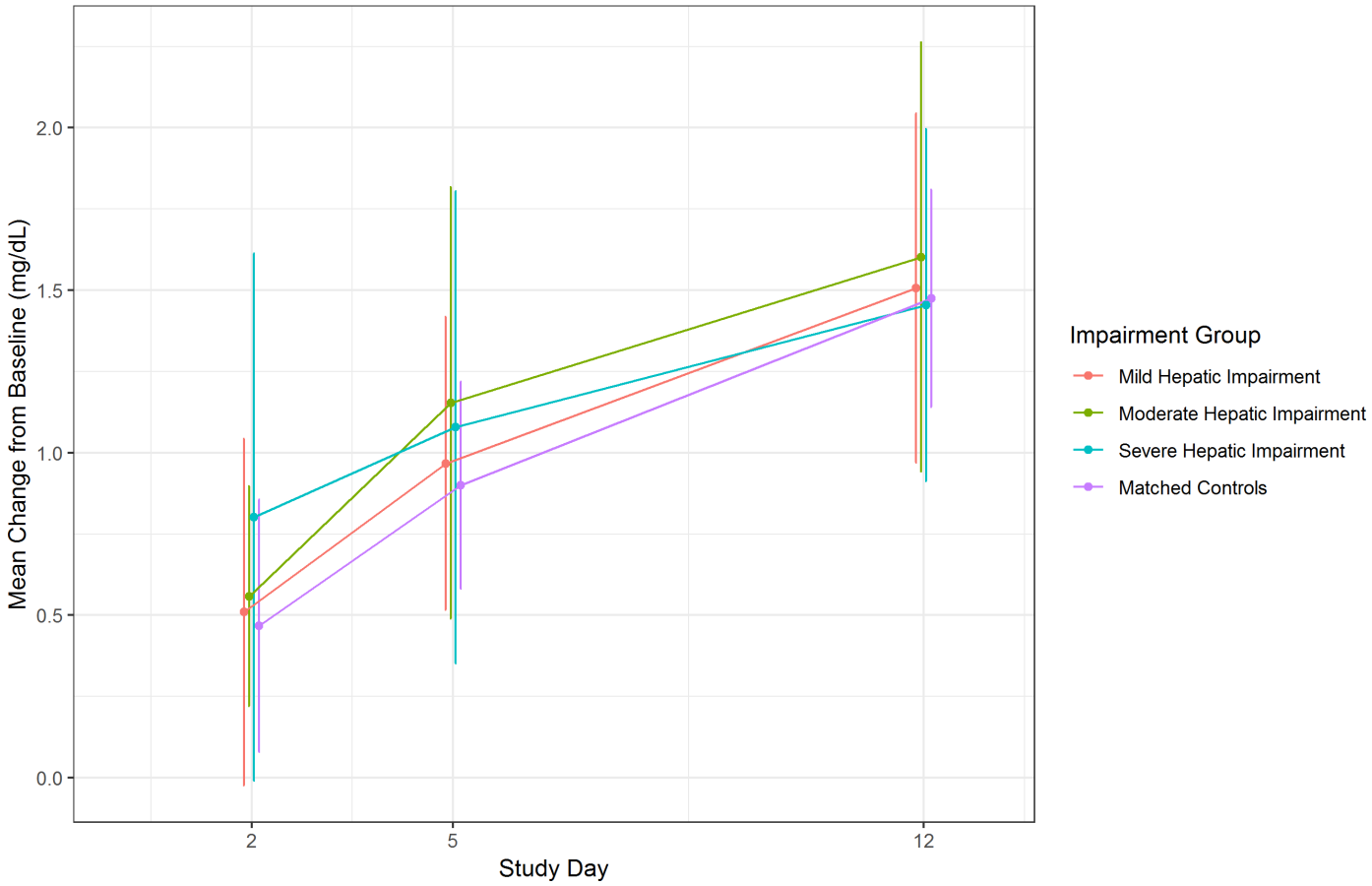


Figure 12: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Sex and Impairment Group – Alkaline Phosphatase

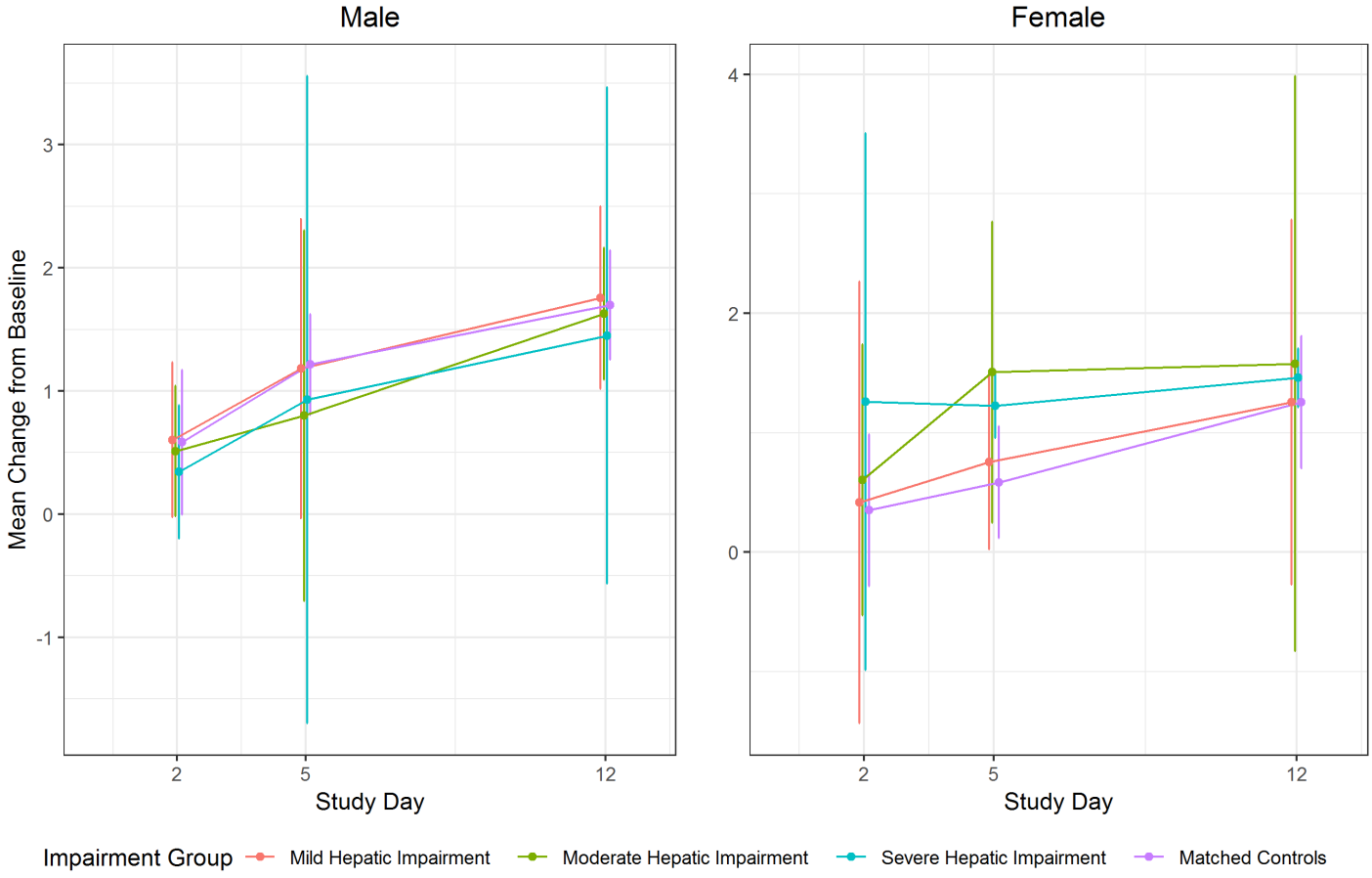


Figure with Similar format:

Figure 13: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Sex and Impairment Group – ALT

Figure 14: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Impairment Group – AST

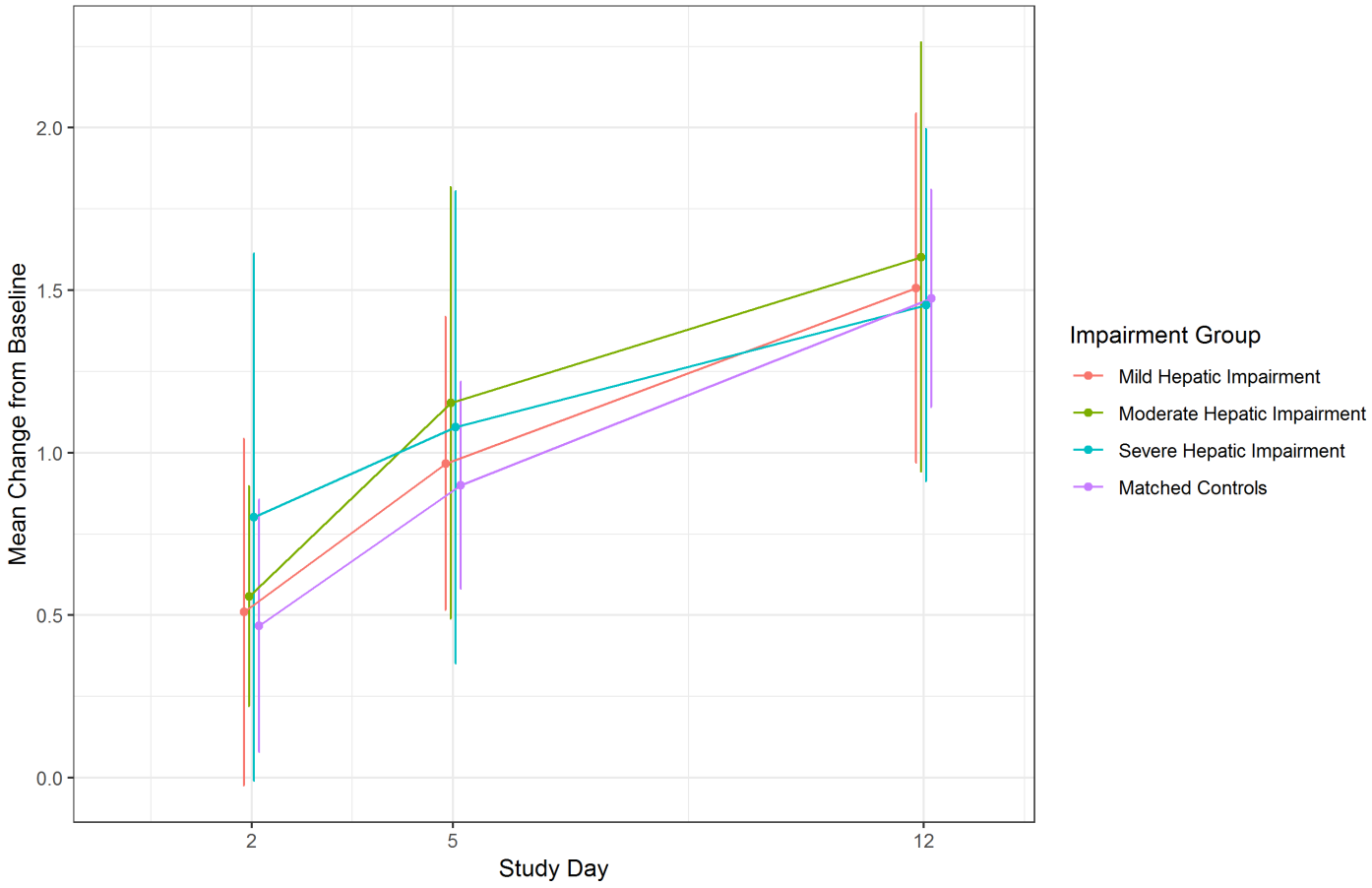
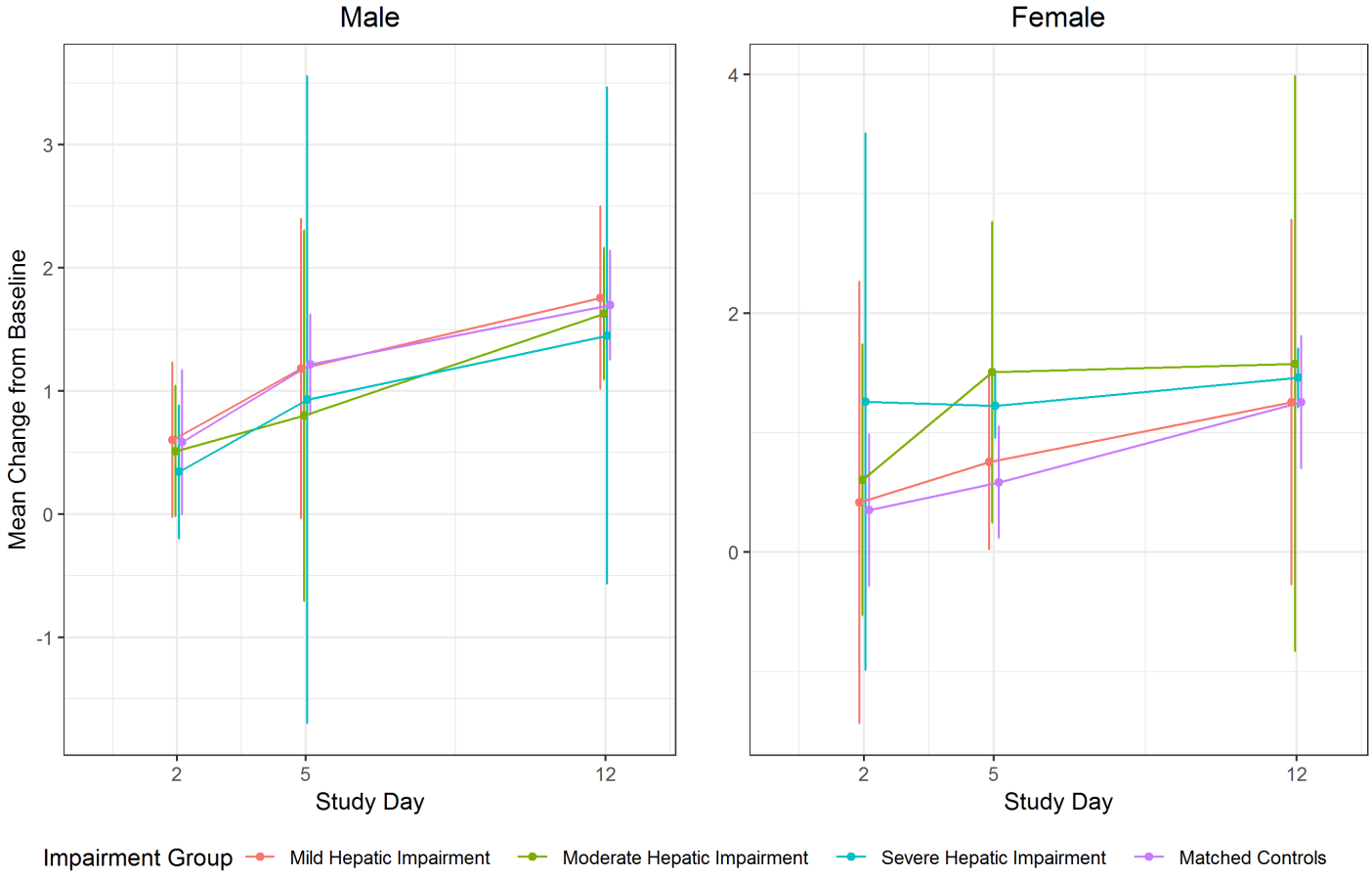


Figure 15: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Sex and Impairment Group – Hematocrit

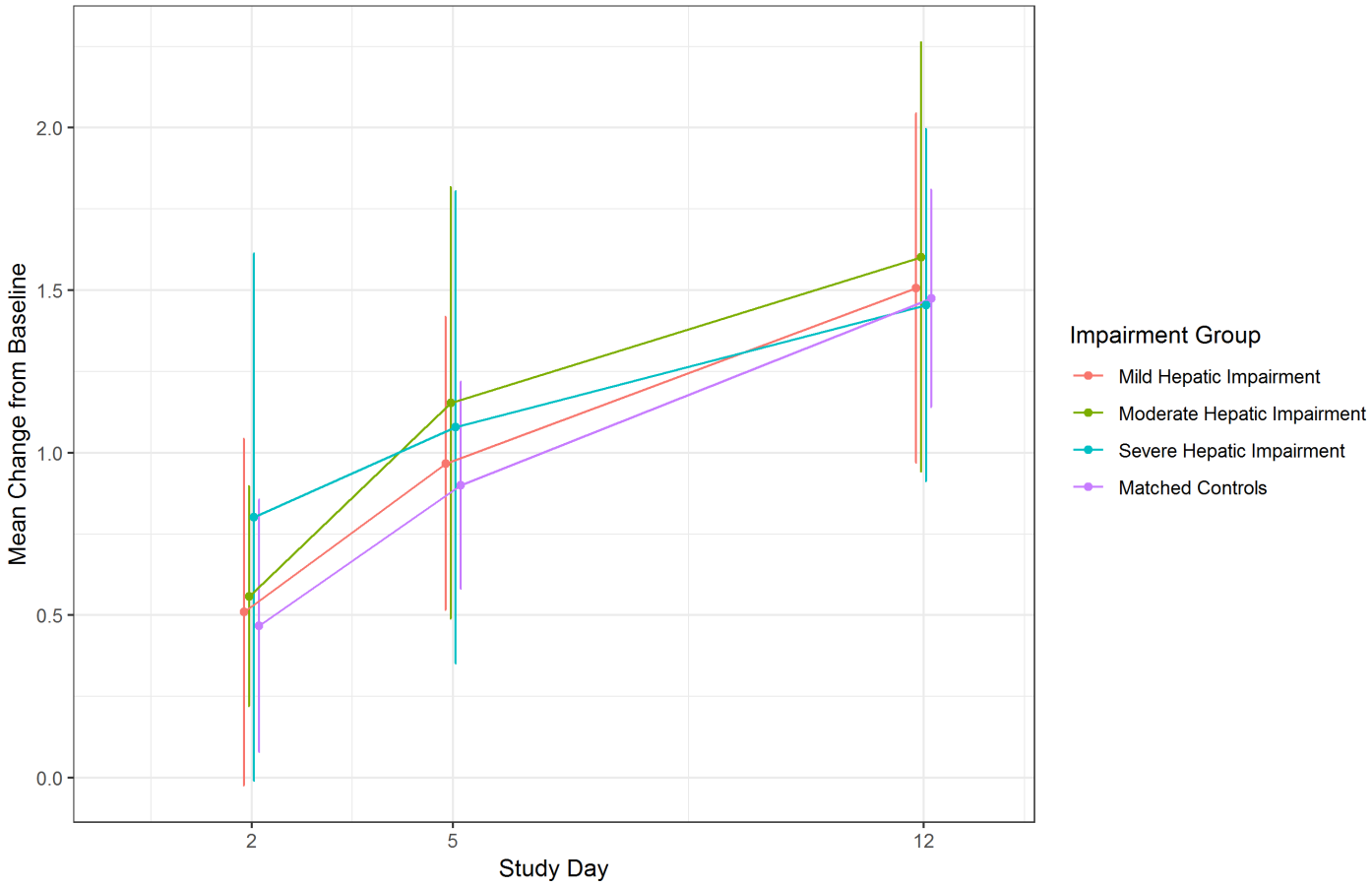


Figures with Similar Format:

Figure 16: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Sex and Impairment Group – Hemoglobin

Figure 17: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Sex and Impairment Group – Red Blood Cell Count

Figure 18: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by and Impairment Group – White Blood Cell Count



Figures with Similar Format:

Figure 19: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by and Impairment Group – Neutrophils

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

Figure 21: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by and Impairment Group – Basophils

Figure 22: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by and Impairment Group – Lymphocytes

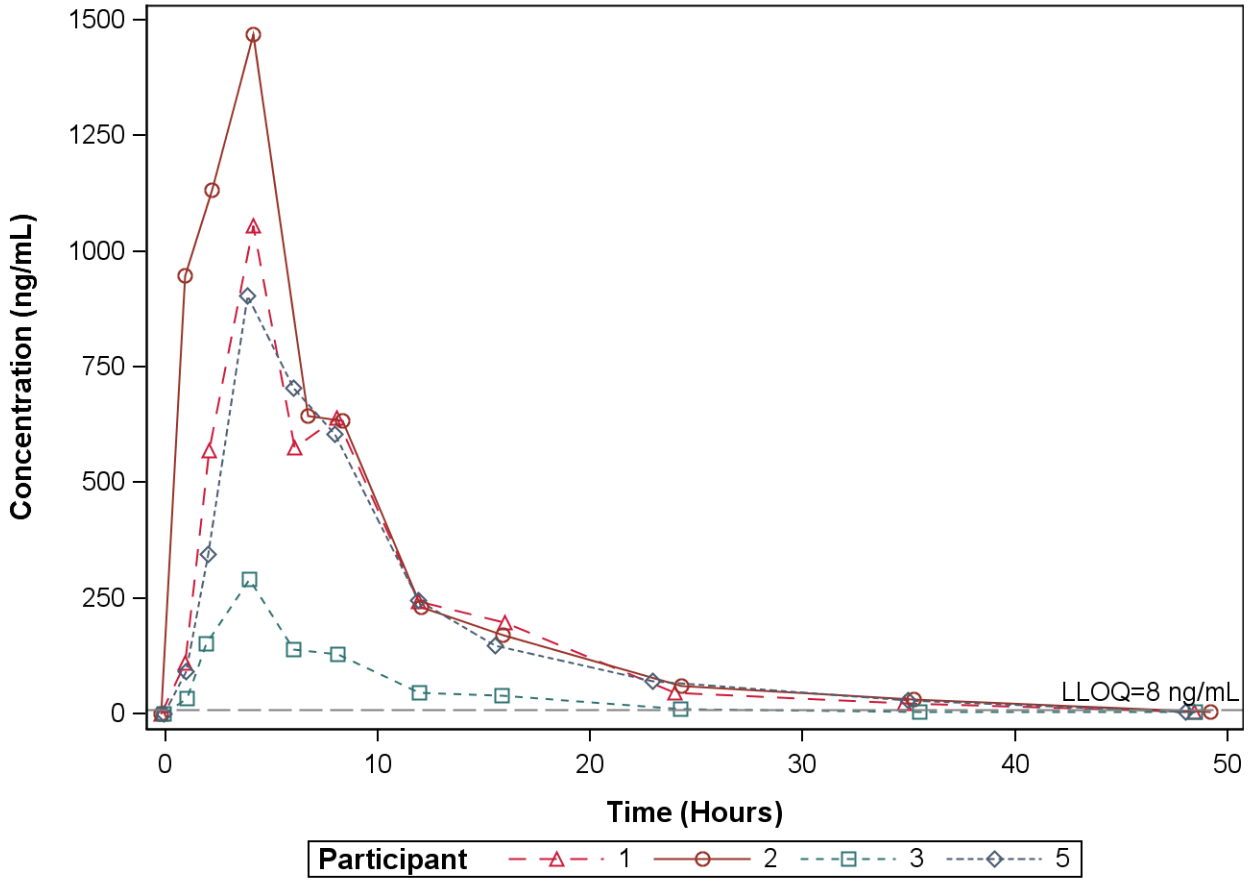
Figure 23: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by and Impairment Group – Monocytes

Figure 24: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by and Impairment Group – Platelets

Figure 25: Coagulation Laboratory Results by Scheduled Visits: Mean Changes from Baseline by and Impairment Group – INR

14.6 Pharmacokinetics

Figure 26: Linear Plot of Pretomanid Concentration Profiles by Nominal Time – Mild Hepatic Impairment



Note: Values below the lower limit of quantification (LLOQ) are plotted as LLOQ/2.

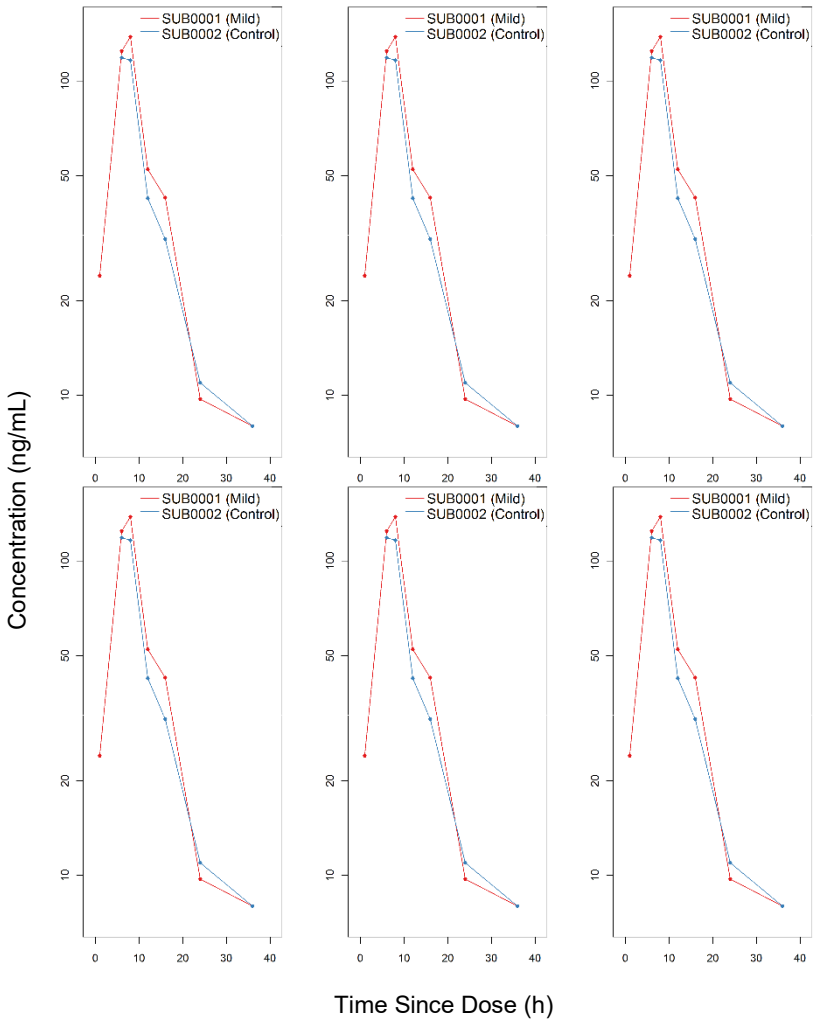
Figures with Similar Format:

Figure 27 Linear Plot of Pretomanid Concentration Profiles by Nominal Time – Moderate Hepatic Impairment

Figure 28: Linear Plot of Pretomanid Concentration Profiles by Nominal Time – Severe Hepatic Impairment

Figure 29: Linear Plot of Pretomanid Concentration Profiles by Nominal Time – Matched Controls

Figure 30: Linear Plot of Pretomanid Concentration Profiles by Nominal Time for Subjects with Mild Hepatic Impairment and Their Matched Controls

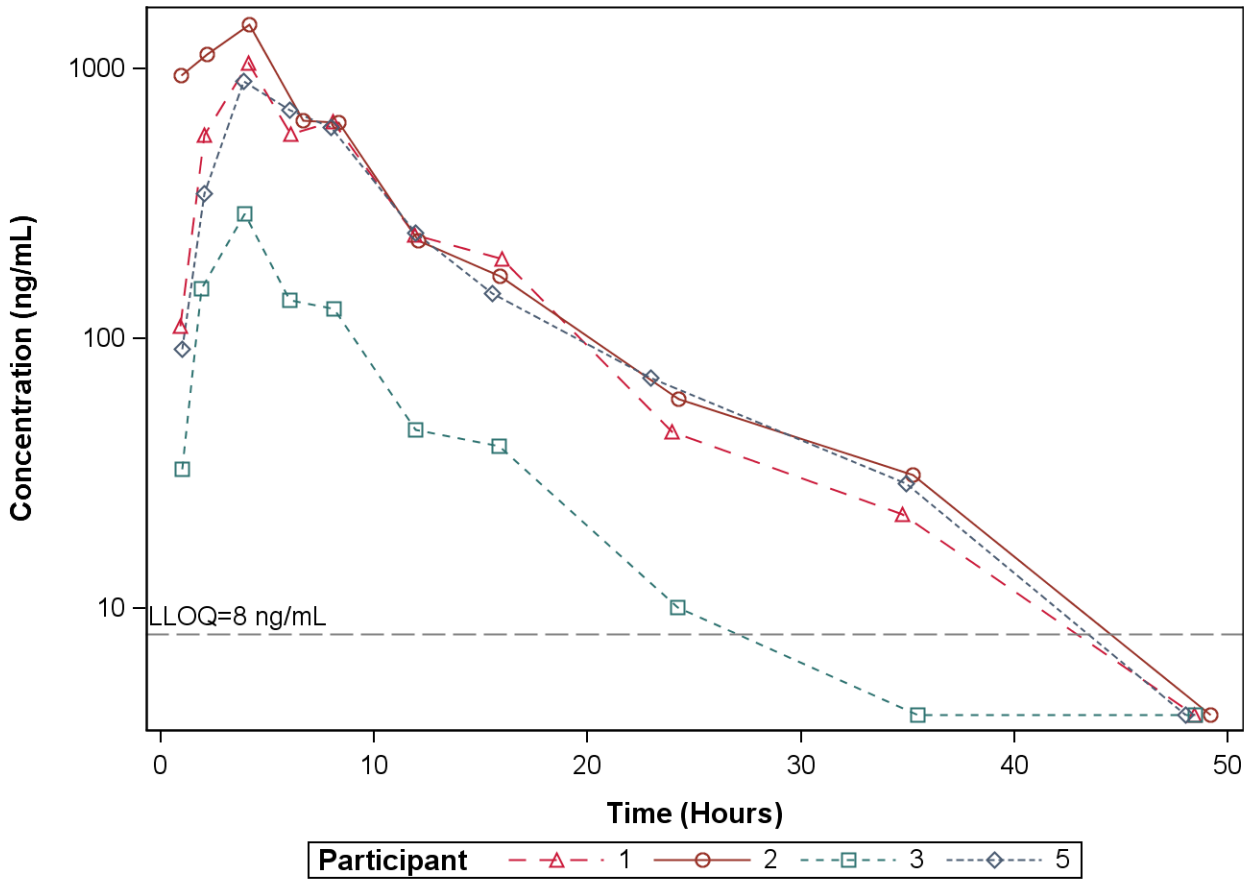


Figures with Similar Format:

Figure 31: Linear Plot of Pretomanid Concentration Profiles by Nominal Time for Subjects with Moderate Hepatic Impairment and Their Matched Controls

Figure 32: Linear Plot of Pretomanid Concentration Profiles by Nominal Time for Subjects with Severe Hepatic Impairment and Their Matched Controls

Figure 33: Semilogarithmic Plot of Pretomanid Concentration Profiles by Nominal Time – Mild Hepatic Impairment



Figures with Similar Format:

Figure 34: Semilogarithmic Plot of Pretomanid Concentration Profiles by Nominal Time – Moderate Hepatic Impairment

Figure 35: Semilogarithmic Plot of Pretomanid Concentration Profiles by Nominal Time – Severe Hepatic Impairment

Figure 36: Semilogarithmic Plot of Pretomanid Concentration Profiles by Nominal Time – Matched Controls

Figure 37: Linear Plots of Mean Pretomanid Plasma Concentration by Nominal Time

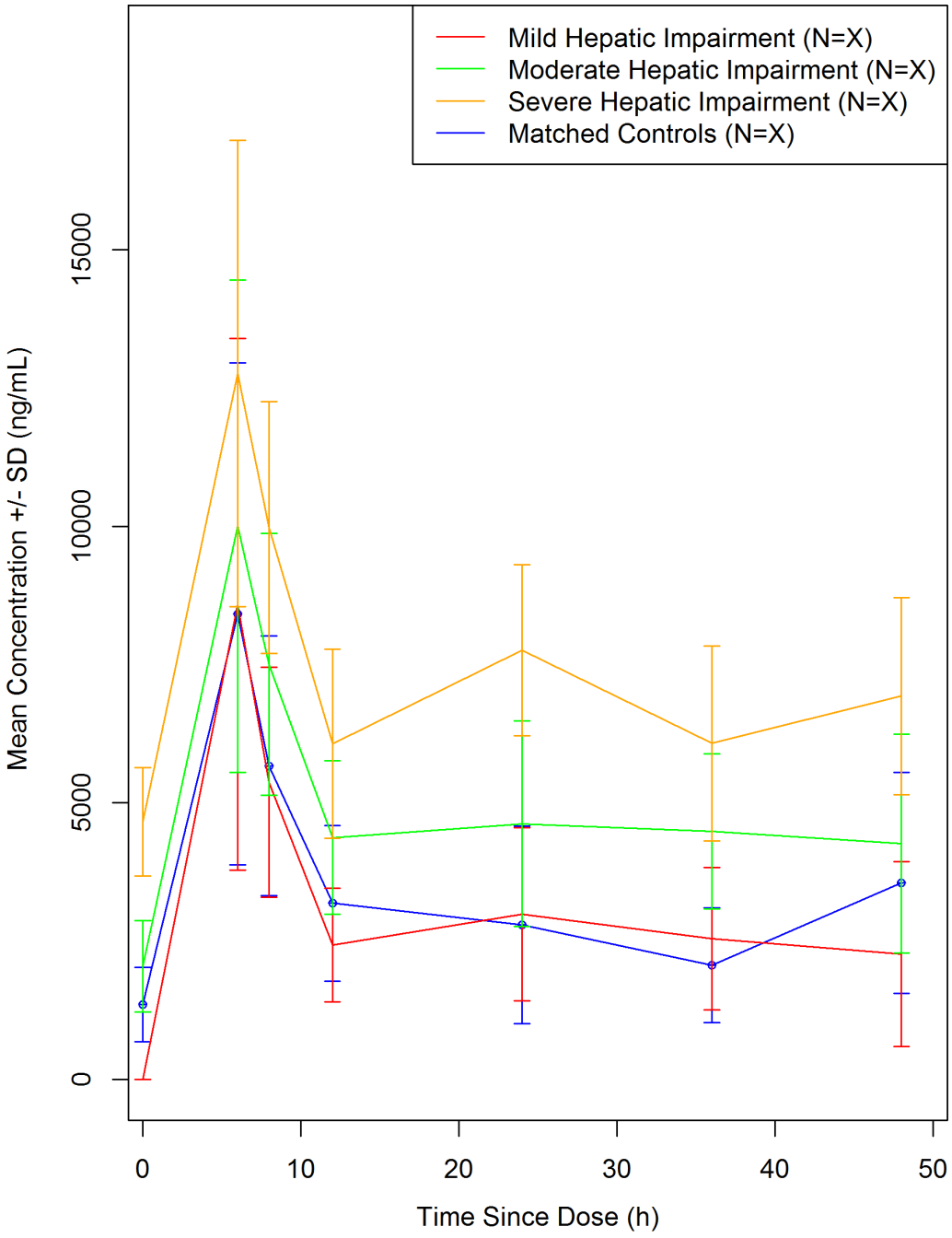


Figure 38: Semilogarithmic Plots of Mean Pretomanid Plasma Concentration by Nominal Time

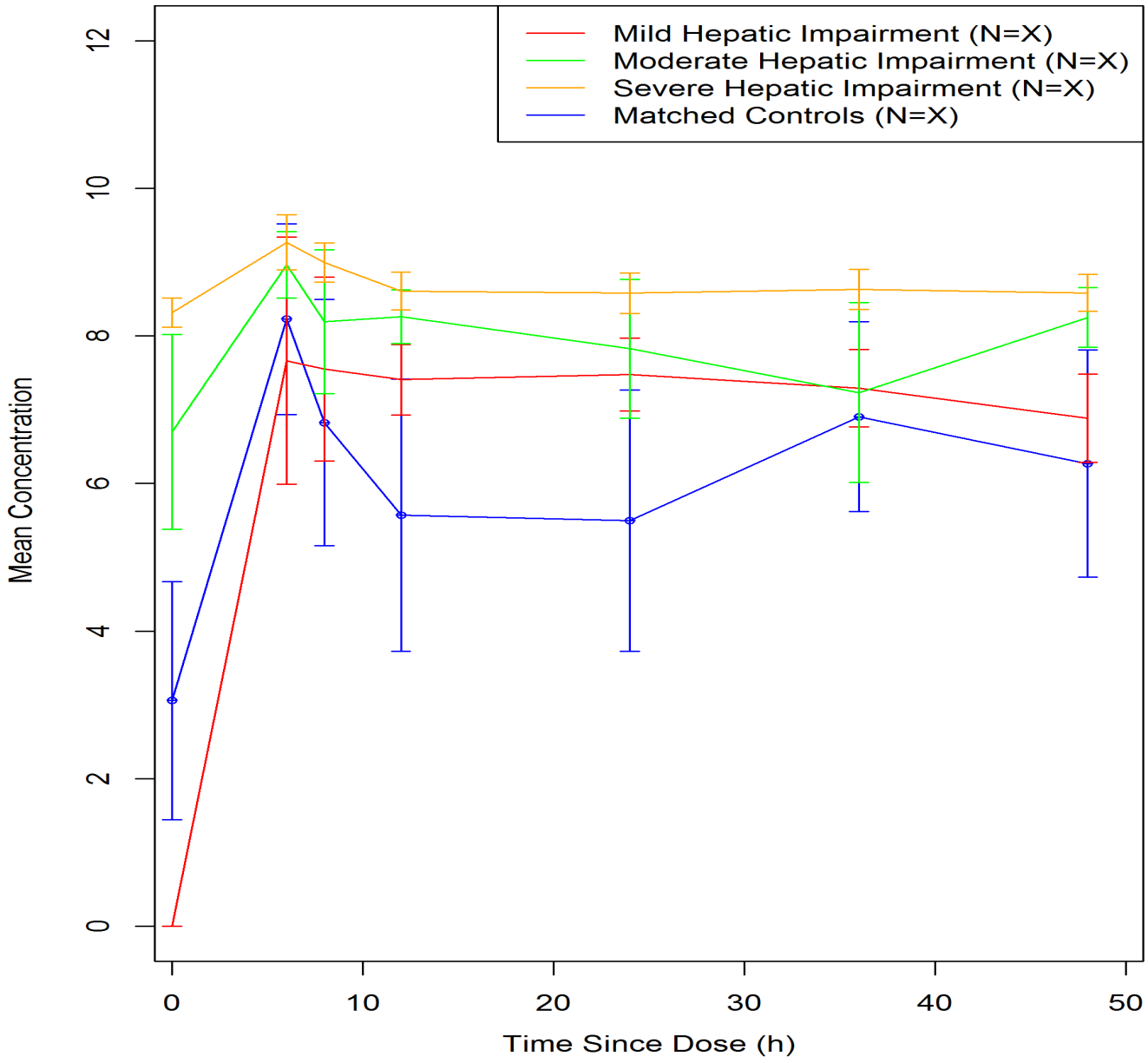


Figure 39: Impairment Group Summary for Noncompartmental PK Parameters – C_{max}

[Implementation Note: Each boxplot may include panels by site if appropriate as described in Section 10.3]

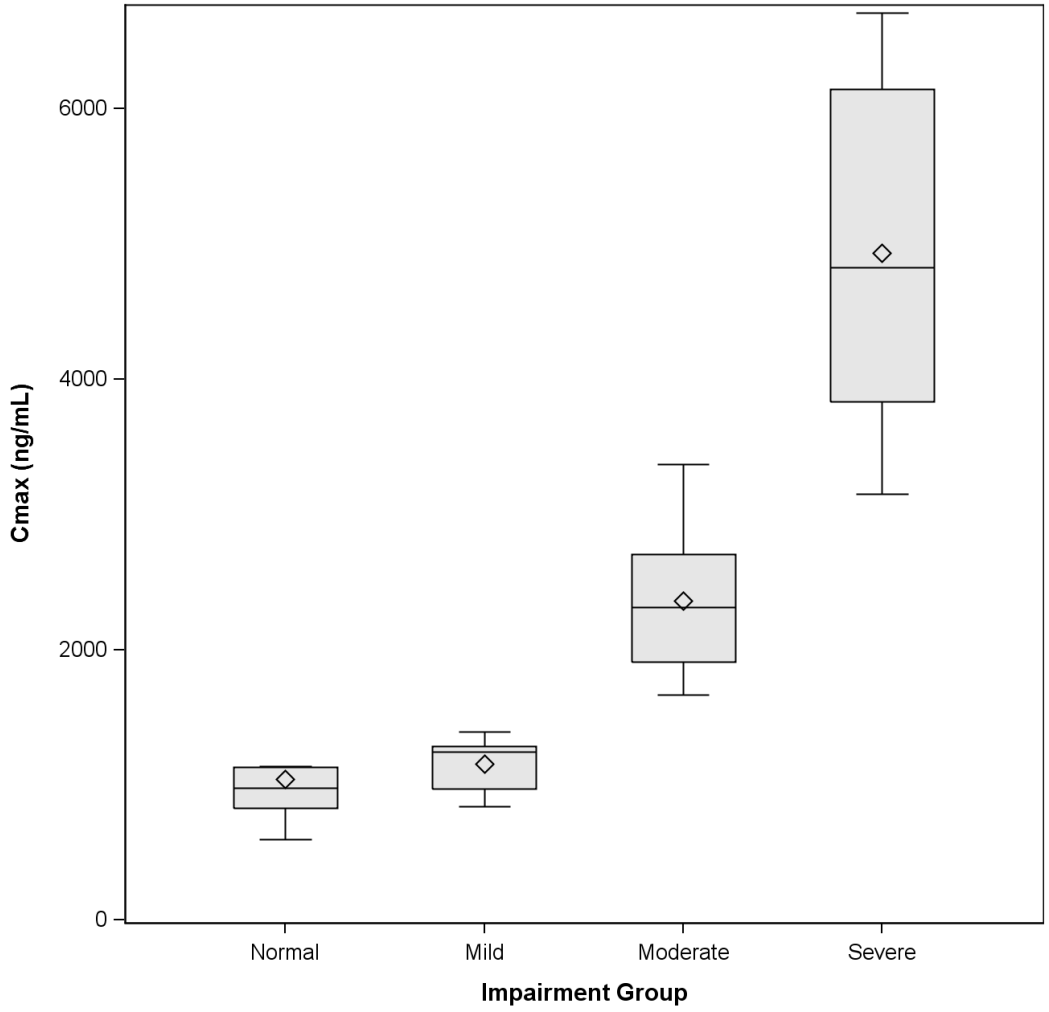


Figure 40: Impairment Group Summary for Noncompartmental PK Parameters – T_{max}

Figure 41: Impairment Group Summary for Noncompartmental PK Parameters – $AUC_{(0-\infty)}$

Figure 42: Impairment Group Summary for Noncompartmental PK Parameters –$AUC_{(0\text{-last})}$

Figure 43: Impairment Group Summary for Noncompartmental PK Parameters – CL/F

Figure 44: Impairment Group Summary for Noncompartmental PK Parameters – V_d/F

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

16.1.6 Listing of Subjects Receiving Investigational Product

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

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 1: 16.2.1 Early Terminations or Discontinued Subjects

Impairment Group	Subject ID	Category	Reason for Early Termination	Study Day

16.2.2 Protocol Deviations

Listing 2: 16.2.2.1: Subject-Specific Protocol Deviations

Impairment Group	Subject ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Resolution	Comments

Listing 3: 16.2.2.2: Non-Subject-Specific Protocol Deviations

Site	Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 4: 16.2.3: Subjects Excluded from Analysis Populations

Impairment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded

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 5: 16.2.4.1: Demographic Data

Impairment Group	Subject ID	Sex	Age at Enrollment (years)	Ethnicity	Race	Height at Screening (cm)	Weight at Screening (kg)

Listing 6: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

-

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

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 7: 16.2.7.2: Unsolicited Adverse Events

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

Note: For additional details about SAEs, see Table 20.

16.2.8 Individual Laboratory Measurements

Listing 8: 16.2.8.1: Clinical Laboratory Results – Chemistry

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

Listing 9: 16.2.8.2: Clinical Laboratory Results – Hematology

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

Listing 10: 16.2.8.3: Clinical Laboratory Results – Urinalysis

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

Listing 11: 16.2.8.3: Clinical Laboratory Results – Coagulation

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

16.2.9 Vital Signs and Physical Exam Findings

Listing 12: 16.2.9.1: Vital Signs

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

Listing 13: 16.2.9.2: Physical Exam Findings

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

16.2.10 Concomitant Medications

Listing 14: 16.2.10: Concomitant Medications

Impairment Group	Subject 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 15: 16.2.11.1: Pregnancy Reports – Maternal Information

Impairment Group	Subject 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 16: 16.2.11.2: Pregnancy Reports – Gravida and Para

			Live Births												
Subject 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 17: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

Subject 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 18: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

Subject 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 19: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject 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

Listing 20: Listing of 12-Lead Standard ECG Overall Interpretation and Comments

Impairment Group	Subject ID	Planned Time Point	Actual Study Time Point	Interpretation	Abnormal Finding	Comments

Listing 21: Listing of 12-Lead Standard ECG Interval Measurements

Impairment Group	Subject ID	Planned Time Point	Actual Study Time Point	Parameter (units)	Result (Severity)	Change from Baseline

Listing 22: Subject Level Drug Concentrations

Impairment Group	Subject 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
					yes/no			

[a] Times are relative to time of first dose. For actual time, out of window times are indicated by an asterisk.