CLINICAL RESEARCH IN INFECTIOUS DISEASES

Clinical Pharmacokinetic Noncompartmental Data Analysis Plan

For

DMID Protocol: 16-0118

Study Title: A Phase 1 Clinical Trial to Evaluate the Plasma Pharmacokinetics, Safety, and Tolerability of a Single Oral Dose of Zoliflodacin in Healthy Male and Female Subjects

Version 1.0

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ACRONYMS AND ABBREVIATIONS

Standard acronyms and abbreviations are listed below.

Abbreviation	Definition
AUC	Area Under the Concentration-Time Curve
$AUC_{(0\text{-last})}$	AUC to the Last Measurable Concentration
$AUC_{(0\text{-t})}$	AUC from 0 to time t
$AUC_{(0\text{-}\infty)}$	AUC Extrapolated to Infinity
BMI	Body Mass Index
BQL	Below the Quantification Limit
C_{last}	Last Measurable Concentration (above the quantification limit)
CL/F	Apparent Oral Clearance
cm	Centimeter(s)
C_{max}	Maximum Plasma Concentration
CSR	Clinical Study Report
CV	Coefficient of Variation
EDC	Electronic Data Capture
g	Gram(s)
GM	Geometric Mean
GSD	Geometric Standard Deviation
h	Hour(s)
HPLC-MS/MS	High-Performance Liquid Chromatography with Tandem Mass Spectrometry
K_e	Terminal Phase Elimination Rate Constant
kg	Kilogram(s)
L	Liter(s)
LLOQ	Lower Limit of Quantification
Max	Maximum
Min	Minimum
min	Minute(s)
mL	Milliliter(s)
NCA	Noncompartmental Analysis
ng	Nanogram(s)
PK	Pharmacokinetic(s)
SD	Standard Deviation
$t_{1/2}$	Apparent Terminal Elimination Half-Life
T_{last}	Time of Last Measurable Concentration
T_{max}	Time to Maximum Plasma Concentration (C_{max})
V_z/F	Apparent Volume of Distribution During Terminal Phase

1. PREFACE

DMID protocol 16-0118 is a Phase 1 study of zoliflodacin in healthy male and female subjects. The pharmacokinetics (PK)-related objectives of the study are:

- To evaluate the plasma PK of zoliflodacin after administration of a single 4 g oral dose under fasting conditions

This document reiterates key PK elements in the study design of DMID Protocol 16-0118 and thoroughly describes the presentations and summaries of PK data as well as the noncompartmental analysis (NCA) to be included in the PK Report and summarized in the clinical study report (CSR) for this protocol. Shells and mockups are given for all PK-related tables, figures, and listings planned for inclusion in the CSR and/or PK Report. At minimum, mean PK plots as well as listings and summaries of zoliflodacin concentrations and PK parameters will be included in the CSR, while all tables, figures, and listings described in this document will be included in the PK Report.

2. CLINICAL STUDY METHODS

2.1. Analysis Groups

This is a Phase 1, open-label clinical trial of a single 4 g oral dose of zoliflodacin after an overnight fast. Eight healthy subjects who consent to participate in the trial and meet the eligibility criteria will be enrolled into a single cohort. Stratification will not be used in this study. All subjects will be analyzed in a single analysis group and no comparisons will be performed.

2.2. Dose Administration

Eligible subjects will receive a single 4 g dose (2 sachets of 2 g of zoliflodacin reconstituted on the same day and administered in a total of [redacted]) orally after an overnight fast. The dose will be administered in a standardized cup. After the [redacted] of zoliflodacin is administered, an additional [redacted] will be added to the same cup and consumed by the subject to chase the initial dose. Both doses will be completed within a total of 5 min. After dosing, subjects will continue to fast for an additional 4 h while water is allowed *ad lib*.

2.3. PK Sampling Schedule

Blood (plasma) samples will be collected into K2EDTA tubes at the following time points: On Day 1 at 30 min before dosing, and 0.5 h (±5 min), 1 h (±5 min), 2 h (±5 min), 3 h (±10 min), 4 h (±10 min), 6 h (±10 min), 8 h (±15 min), and 12 h (±15 min) after dosing; on Day 2 at 24 h (± 2 h) and 36 h (± 2 h) after dosing; on Day 3 at 48 h (±2 h) after dosing; and on Day 4 at 72 h (±2 h) after dosing, or early termination.

2.4. Analytical Methods

Plasma concentrations of zoliflodacin will be determined using a validated HPLC-MS/MS method. The analysis will be performed by KCAS Bioanalytical Services. Details are included in the assay validation. For details of sample collection, processing, storage, transportation, and bioanalysis, see the protocol, MOP, and assay validation documents.

2.5. Collection of Pharmacodynamic or Clinical Endpoints

Not applicable.

3. PHARMACOKINETIC ANALYSIS METHODS

3.1. Analysis Population and Handling of Missing Time Points

All subjects who received the study drug and who have at least one measurable drug concentration post-dosing will be included in the PK analysis population. Additionally, there will be a PK analysis subset, which includes all subjects who completed the PK part of the trial without any protocol violations or deviations that would likely affect the PK results and who have evaluable plasma concentration data for zoliflodacin from which at least the C_{max} and T_{max} can be determined (peak concentration and at least one decreased concentration after the peak observed). Zoliflodacin concentrations will be listed and shown graphically as individual profiles for all subjects in the PK analysis population, but concentration summary statistics, mean PK profiles, and NCA will use the PK analysis subset only. All enrolled subjects excluded from the PK analysis population or the PK analysis subset will be described in the PK Report, including reason for exclusion.

Collection of plasma samples outside of the protocol defined time window for the time point will not result in exclusion of the sample result from NCA. If a sample is collected more than 10 min outside of the protocol defined time window, the sample result will be excluded from calculation of summary statistics for the respective time point, as well as from plots of mean concentration.

Values below the lower limit of quantification (LLOQ) will be referred to as below the quantification limit (BQL). BQL values that precede the first PK concentration above the LLOQ will be imputed as 0 for linear plots and for all calculations including NCA and summary statistics, but will be excluded from semi-logarithmic plots. All other BQL values will be treated as missing for all analyses.

Missing pre-dose PK samples will have concentrations imputed as 0 for analysis. All other missing PK sample concentrations will not be imputed for the NCA. A geometric mean (GM) of concentrations will be treated as missing for sets of data points containing an imputed 0 value due to a BQL value.

3.2. Demographic and Baseline Characteristics

Sex, race, age, weight, height, and body mass index (BMI) of subjects in the PK analysis population will be listed and summarized (PK Table 1, PK Listing 1).

3.3. Dosing and Pharmacokinetic Sampling Summary

Subject dose administration times will be presented (PK Listing 2). Cases that potentially affect the analysis will be discussed.

Protocol deviations related to dosing or PK sampling will be listed (PK Listing 3) and summarized in the PK Report text. Deviations to be included in the PK Report include:

- Treatment administration deviations
- Blood specimen not collected
- Plasma specimen result not obtained
- Specimen temperature excursion
- Required specimen collected out of window
- Subject vomiting within 24 h of dose

- Subject ingestion of prohibited food or within the prohibited window after dosing
- Any other deviation determined by the PK analyst to be potentially affect PK

Drug plasma concentrations will be listed by subject (PK Listing 4), with nominal and actual time associated with the sample indicated (nominal time is defined as the time in h since the start time of the dose). Both laboratory reported concentration values, and modified concentration values used for analysis (for instance, imputation of 0 for a BQL value at baseline) will be included, as separate columns, in the listing.

Plasma drug concentrations will also be summarized (PK Table 2) and plotted. PK Figure 1 and PK Figure 2 will plot all individual subject plasma PK profiles, as linear and semi-logarithmic plots, respectively. Subject ID for each individual profile in these figures will be shown in a legend. GM plots of zoliflodacin PK profiles will be shown in PK Figure 3. Semi-log mean plots of zoliflodacin PK profiles will be shown in PK Figure 4.

3.4. Definition and Estimation of Individual NCA PK Parameters

PK parameters will be estimated through a NCA using version 8.0 or later of Phoenix® WinNonlin® (Pharsight Corporation, Cary, NC). Actual post-dose time will be used for the estimation of PK parameters instead of nominal time. Individual PK parameter estimates will be listed (PK Listing 5).

Phoenix® WinNonlin® NCA will use the following settings to compute parameters from plasma PK data:

- Linear Up Log Down calculation method
- Uniform weighting
- Extravascular dose
- Plasma Model Type
- Lambda Z Acceptance Criteria
  - Rsq_adjusted ≥ 0.80
  - Span ≥ 3.0 half-lives
  - Includes ≥ 3 timepoints after T_{max}
    - In exceptional circumstances, the data at T_e may be included in computation of K_e if deemed necessary and appropriate by the PK analyst. If data at T_{max} is included in computation of K_e, the decision will be justified in the PK Report.

C_{max}

Maximum plasma concentration (C_{max}) is defined as the maximum observed drug concentration observed in plasma over all PK sample concentrations. It will be obtained from the **Cmax** parameter calculated by WinNonlin®. If there is no measurable concentration in the subject's PK profile, then C_{max} will be missing for that subject. C_{max} will be reported in units of ng/mL.

T_{max}

Time of maximum plasma concentration (T_{max}) is defined as the time at which the C_{max} occurs. It will be obtained from the **Tmax** parameter calculated by WinNonlin®. If there is no measurable C_{max} in the subject's PK profile, then T_{max} will be missing for that subject. T_{max} will be reported in units of h.

C_{last}

Last observed (quantifiable) plasma concentration (C_{last}), in units of ng/mL. C_{last} will not be included in tables or listings, but is referred to in the definitions of other PK parameters.

T_{last}

Time of C_{last} (T_{last}) will be obtained from the **Tlast** parameter calculated by WinNonlin®. If there is no measurable concentration in the subject's PK profile, then T_{last} will be missing for that subject. T_{last} will be reported in units of h.

K_e

The terminal phase elimination rate constant (K_e) is defined as the first-order rate constant describing the rate of decrease of drug concentration in the terminal phase (defined as the terminal region of the PK curve where drug concentration follows first-order elimination kinetics). K_e will be computed as the slope of a terminal region consisting of ≥3 successive points in the plot of log-transformed concentration data versus time. K_e will be estimated using uniform weighting. Time points used in the estimation of K_e will be initially selected using the WinNonlin® automatic algorithm.

The set of points chosen must contain only timepoints after T_{max} and satisfy the Lambda Z Acceptance Criteria described above. Otherwise, the elimination rate constant and all derived parameters ($t_{1/2}$, $AUC_{(0-\infty)}$, CL/F, V_z/F) will be treated as missing.

The range of concentrations used to estimate K_e for each profile will be inspected by the PK analyst, who may adjust the set of concentrations used to estimate K_e if deemed necessary, but manually selected ranges must satisfy the same acceptance criteria as those chosen automatically by the WinNonlin® algorithm. Drug concentrations used to calculate K_e will be indicated in Listing 4. This parameter will be obtained from the **Lambda_z** parameter calculated by WinNonlin®. K_e will be reported in units of 1/h.

$t_{½}$

The apparent terminal elimination half-life ($t_{½}$) is defined as the time required for the drug concentration to decrease by a factor of one-half in the terminal phase. $t_{½}$ can be estimated as ln(2) / K_e. It will be obtained from the **HL_Lambda_z** parameter calculated by WinNonlin®. $t_{1/2}$ will be reported in units of h.

AUC

$AUC_{(0\text{-}last)}$ is defined as the area under the concentration-time curve from dosing (time 0) to the time of the last measured concentration. $AUC_{(0\text{-}last)}$ will be estimated using the Linear Up Log Down calculation method and obtained from the **AUClast** parameter calculated by WinNonlin®.

$AUC_{(0\text{-}t)}$ (partial AUC) is defined as the area under the concentration-time curve from dosing (time 0) to time *t*. $AUC_{(0\text{-}t)}$ may be computed for one or more values of *t*, with specific values of *t* determined after observing the data. It may be determined that no partial AUCs are required for inclusion in the PK Report. Specific times (*t*) $AUC_{(0\text{-}t)}$ will be estimated using the Linear Up Log Down calculation method.

$AUC_{(0\text{-}\infty)}$ is defined as the total area under the concentration-time curve from dosing (time 0) taken to the limit as the end time becomes arbitrarily large. $AUC_{(0\text{-}\infty)}$ can be calculated by adding $AUC_{(0\text{-}last)}$ to an extrapolated value equal to the last measured concentration greater than the LLOQ divided by K_e:

$$AUC_{(0-\infty)} = AUC_{(0-last)} + \frac{C_{last}}{K_e}.$$

$AUC_{(0\text{-}inf)}$ will be obtained from the **AUCINF_obs** parameter calculated by WinNonlin®. If the amount extrapolated portion of $AUC_{(0\text{-}\infty)}$ is >20%, the estimated $AUC_{(0\text{-}\infty)}$ value will be flagged when listed in the report and will be excluded from statistical summaries of parameter estimates and downstream calculations.

All AUCs will be reported in units of h×ng/mL.

CL/F

Apparent oral clearance (CL/F) can be computed as Dose/$AUC_{(0-\infty)}$. It will be obtained from the **Cl_F_obs** parameter calculated by WinNonlin®. If the amount extrapolated portion of $AUC_{(0-\infty)}$ is >20%, the estimated CL/F value will be flagged when listed in the report and will be excluded from statistical summaries of parameter estimates and downstream calculations. Clearance will be reported in units of L/h.

V_z/F

Apparent volume of distribution during terminal phase (V_z/F) after non-intravenous administration can be calculated as (CL/F)/ K_e. It will be obtained from the **Vz_obs** parameter in WinNonlin®. If the amount extrapolated portion of $AUC_{(0-\infty)}$ is >20%, the estimated V_z/F value will be flagged when listed in the report and will be excluded from statistical summaries of parameter estimates and downstream calculations. Volume will be reported in units of L.

3.5. Descriptive Statistics

Subject-specific PK parameter estimates will be listed (Listing 5). PK estimates will be summarized in PK Table 3. Summary statistics will include mean, standard deviation (SD), minimum, maximum, median, coefficient of variation as a percent (CV%), GM, and geometric standard deviation (GSD).

3.6. Reporting Conventions

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values <0.001 will be reported as "<0.001" The mean, SD, and other statistics will be reported to 1 significant figure greater than the original data. The minimum and maximum will use the same number of significant figures as the original data. Percentages will be reported to the nearest whole number; values >0 but <1% will be presented as "<1"; values >99% but <100% will be reported as >99%. AUCs will be reported as whole numbers. $t_{1/2}$, T_{max}, CL, and V_z/F values will be reported to 1 decimal place. K_e will be reported to 3 decimal places. C_{max} will be reported with the same number of significant digits as the measurement. Ratios, location shifts (defined as a difference in mean or median), and associated 95% confidence intervals will be reported to 1 decimal place.

Listings of individual subject data include a Subject ID column. The subject identifiers assigned by site staff are replaced throughout this report with the SDTM variable USUBJID to protect the confidentiality of those who volunteered to participate in this protocol. USUBJID has been created as a composite of the 3-letter Electronic Data Capture (EDC) platform code followed by a numeric identifier assigned chronologically to enrolled subjects as well as screening failures across all sites and protocols in the EDC platform. Any data sharing activities will include the USUBJID and not the subject identifiers assigned at the site.

4. REFERENCES

1. European Medicines Agency. Guideline on the Investigation of Bioequivalence, January 2010.
2. Food and Drug Administration. Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications, April 2003.
3. Food and Drug Administration. Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001.
4. Food and Drug Administration. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, March 2003.
5. Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Subjects with Impaired Hepatic Function; Study Design, Data Analysis, and Impact on Dosing and Labeling, May 2003.
6. Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Subjects with Impaired Renal Function; Study Design, Data Analysis, and Impact on Dosing and Labeling, March 2010.
7. Food and Drug Administration. Guidance for Industry: Bioanalytical Method Validation, May 2001.
8. Food and Drug Administration. Guidance for Industry: Validation of Analytical Procedures and Methods Validation for Drugs and Biologics, July 2015.

5. LISTING OF PROPOSED TABLES, FIGURES, AND LISTINGS

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

6. APPENDICES

APPENDIX 1. LIST OF PROPOSED PK TABLES

LIST OF PK TABLES

PK Table 1: Summary of Demographic and Baseline Characteristics of Subjects Included in the PK Analysis Population

Parameter	PK Analysis Population (N=X)
Sex – N (%)	
Male	
Female	
Age (years)	
Mean (SD)	
Median	
Min, Max	
Height (cm)	
Mean (SD)	
Median	
Min, Max	
Weight (kg)	
Mean (SD)	
Median	
Min, Max	
BMI (kg/m^2)	
Mean (SD)	
Median	
Min, Max	
Race – N (%)	
American Indian or Alaska Native	
Asian	
Black or African American	
Native Hawaiian or other Pacific Islander	
White	

PK Table 2: Summary Statistics for Concentrations by Nominal Time

	Zoliflodacin Concentration (ng/mL) by Nominal Time[1] After Dose (h)												
Subject ID	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**
99ZZZ001	x	x	x	x	x	x	x	x	x	x	x	x	x
99ZZZ002	x	x	x	x	x	x	x	x	x	x	x	x	x
99ZZZ003	x	x	x	x	x	x	x	x	x	x	x	x	x
…	x	x	x	x	x	x	x	x	x	x	x	x	x
Statistics													
N[2]	x	x	x	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
(Min, Max)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)

[1] Times are relative to time of dosing.
[2] Number of data points used to compute the summary statistics. For calculation of summary statistics, BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

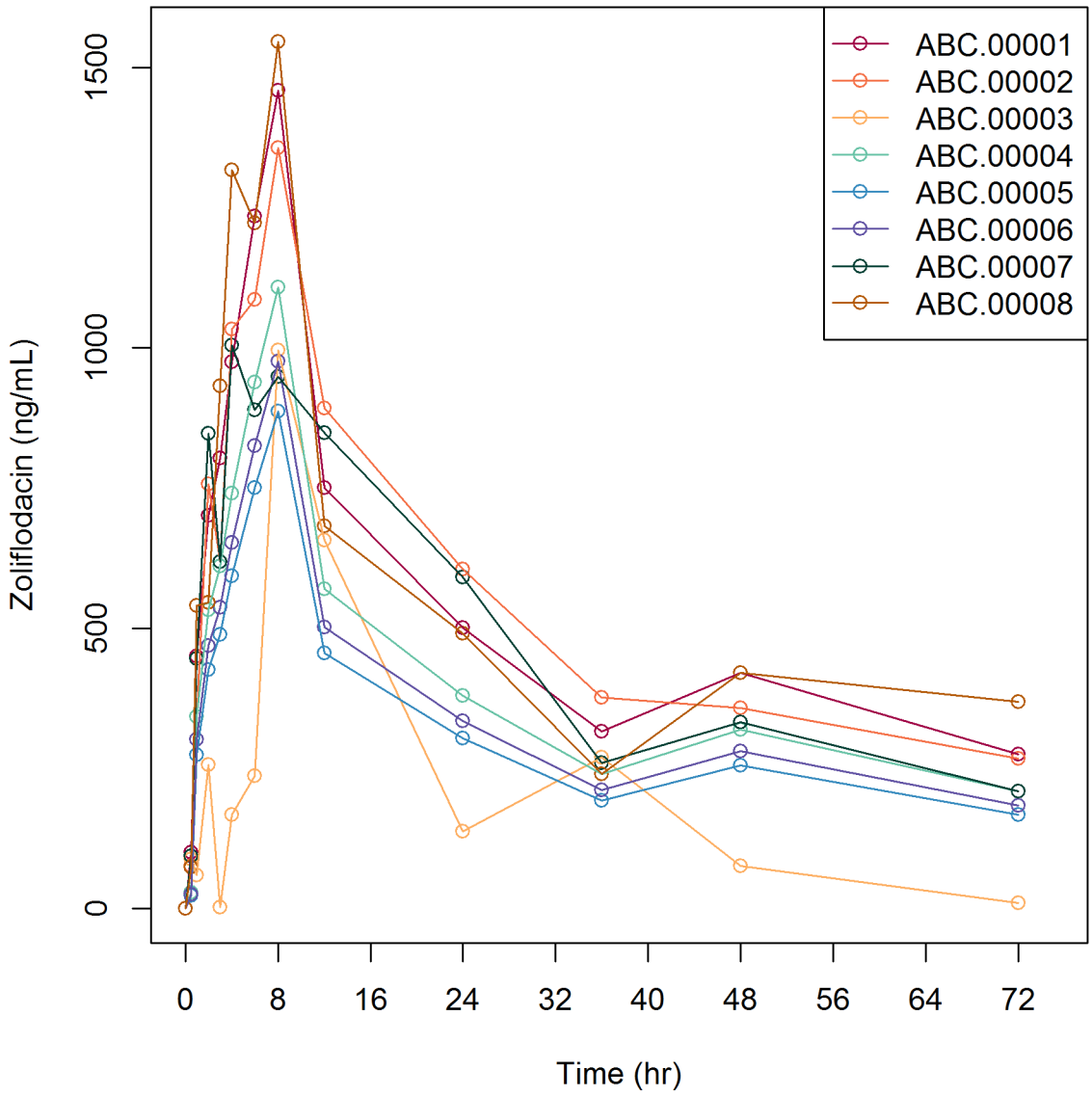
PK Table 3: Summary Statistics for PK Parameters

Statistic	C_{max} (ng/mL)	T_{max} (h)	T_{last} (h)	$AUC_{(0\text{-}last)}$ (h×ng/mL)	$AUC_{(0\text{-}\infty)}$ (h×ng/mL)	K_e (1/h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
N									
Mean									
SD									
Min									
Median									
Max									
CV %									
GM									
GSD									

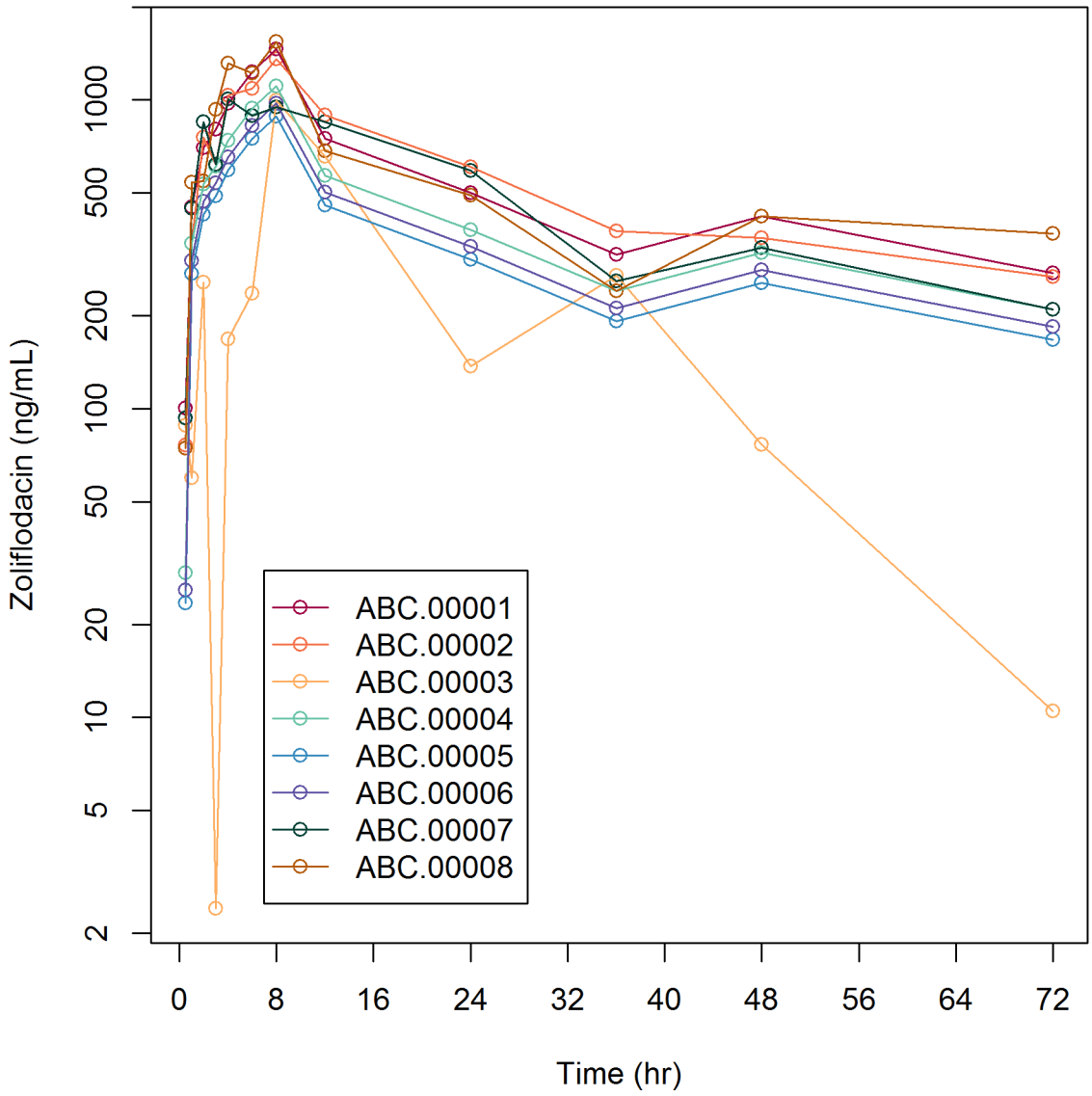
APPENDIX 2. LIST OF PROPOSED PK FIGURES

LIST OF PK FIGURES

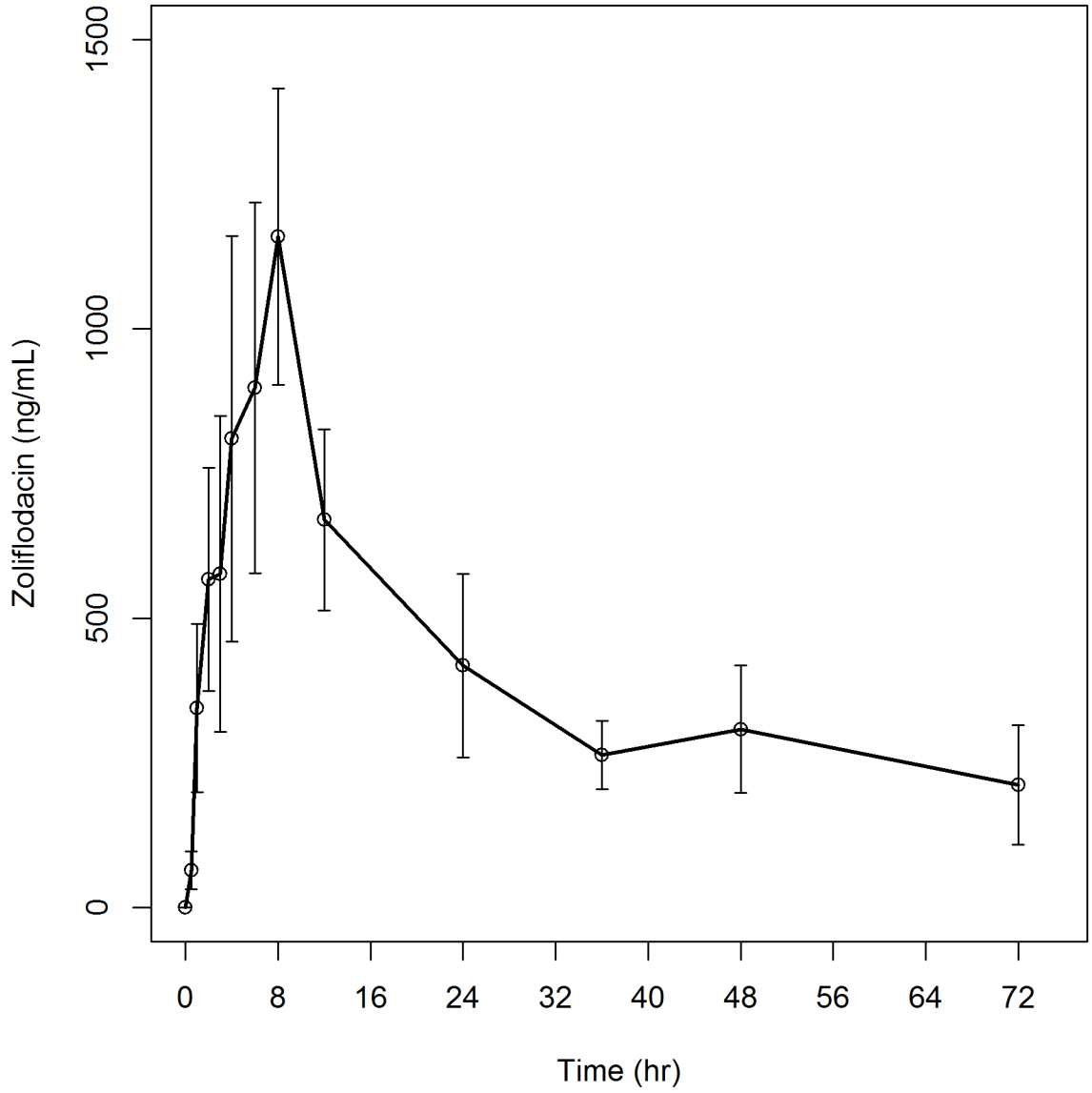
PK Figure 1: Concentration Profiles for All Subjects by Time



PK Figure 2: Semi-log Concentration Profiles for All Subjects by Time

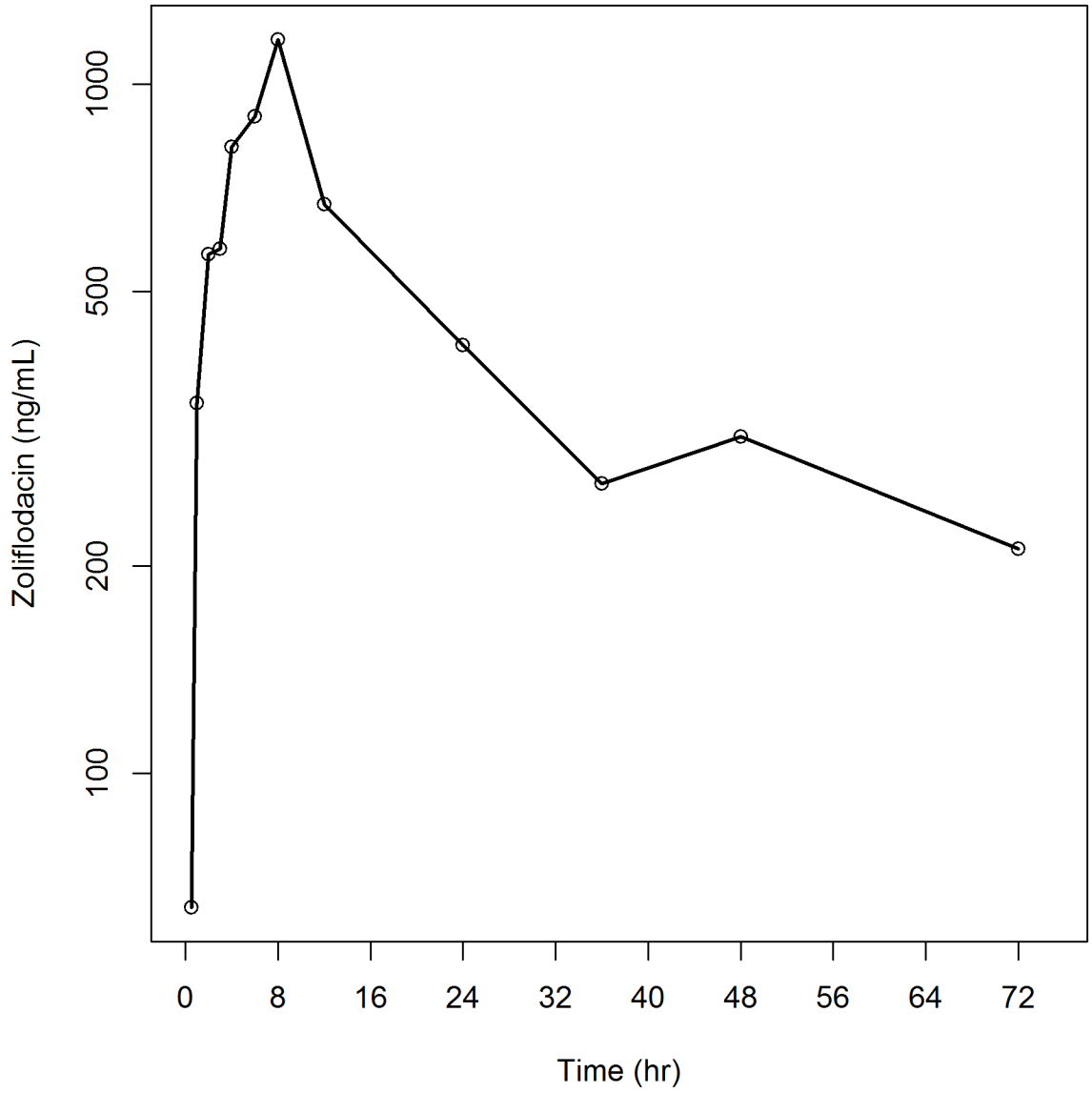


PK Figure 3: Mean Concentration by Nominal Time



Note: Error bars give ± 1 standard deviation.

PK Figure 4: Mean Concentration by Nominal Time (Semi-Log)



APPENDIX 3. LIST OF PROPOSED PK LISTINGS

TABLE OF PK LISTINGS

PK Listing 1: Subject Level Demographic and Baseline Characteristics

Subject ID	Sex	Race	Age (years)	Height (kg)	Weight (cm)	BMI (kg/m^2)

PK Listing 2: Zoliflodacin Dosing

Subject ID	Dose (g)	Start Date Dose	Start Time of Dose	End Time of Dose

PK Listing 3: Protocol Deviations Related to Dosing or PK Samples

Subject ID	DV Number	Deviation Description	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Specimen Type	Affected Visit Number	Deviation Category
Note: This listing contains a subset of the protocol deviations in the clinical database relevant to the PK analysis										

PK Listing 4: Subject Level Zoliflodacin Concentrations in Plasma

Subject ID	Nominal Time[1] (h)	Actual Time[1] (h)	Lab Reported Drug Concentration (ng/mL)	Analysis Drug Concentration (ng/mL)	Used in K_e Calculations	Excluded from NCA	Reason for Exclusion from NCA
XXX.99999	0	0	BQL	0	No	No	
XXX.99999	0.5	0.5	50.1	50.1	No	No	
XXX.99999	24	24.0	BQL	missing	No	No	

[1]Times are relative to time of dose. For Actual Times, out-of-window times are indicated by an asterisk.

PK Listing 5: Subject-Specific Pharmacokinetic Parameters

Subject ID	C_{max} (ng/mL)	T_{max} (h)	T_{last} (h)	$AUC_{(0\text{-}last)}$ (h×ng/mL)	$AUC_{(0\text{-}\infty)}$ (h×ng/mL)	$t_{1/2}$ (h)	K_e (1/h)	CL/F (L/h)	V_z/F (L)

CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 16-0118

Study Title:

A Phase 1 Clinical Trial to Evaluate the Plasma Pharmacokinetics, Safety, and Tolerability of a Single Oral Dose of Zoliflodacin in Healthy Male and Female Subjects

NCT03404167

Version 1.0

DATE: 03-APR-2018

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 16-0118**
Development Phase:	Phase 1
Products:	Zoliflodacin
Form/Route:	Oral
Indication Studied:	*Neisseria gonorrhoeae*
Sponsor:	Division of Microbiology and Infectious Diseases (DMID) National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH)
Clinical Trial Initiation Date:	02 February 2018
Clinical Trial Completion Date:	
Date of the Analysis Plan:	03 April 2018
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
$AUC_{(0\text{-last})}$	AUC to the Last Measurable Concentration
$AUC_{(0\text{-}\infty)}$	AUC Extrapolated to Infinity
BMI	Body Mass Index
BQL	Below Quantification Limit
C_{max}	Maximum Plasma Concentration
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CL/F	Clearance
CSR	Clinical Study Report
CV	Coefficient of Variation
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
ECG	Electrocardiograph
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ET	Early Termination
F	Bioavailability
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
g	Gram(s)
GM	Geometric Mean
h	Hour(s)
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus

List of Abbreviations *(continued)*

HLGT	Higher Level Group Term
HPLC-MS/MS	High-Performance Liquid Chromatography with Tandem Mass Spectrometry
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ITT	Intention to Treat (Analysis)
k_e	Elimination Rate Constant
kg	Kilogram(s)
LLOQ	Lower Limit of Quantification
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MH	Medical History
min	Minute(s)
mITT	Modified Intention to Treat (Analysis)
mmHg	Millimeters of Mercury
msec	Millisecond(s)
N	Number / Denominator (typically refers to subjects)
n	Number / Count / Numerator
NCA	Noncompartmental Analysis
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
ng	Nanogram(s)
OCRR	Office of Clinical Research Resources
PE	Physical Examination
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Preferred Term
QTc	Corrected QT Interval
QTcF	QT Interval with Fridericia Correction
RBC	Red Blood Cell
sec	Second(s)

List of Abbreviations *(continued)*

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
$t_{1/2}$	Terminal Elimination Half-Life
T_{max}	Time of Maximum Plasma Concentration
V_z/F	Volume of Distribution
VS	Vital Sign(s)
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 1 Clinical Trial to Evaluate the Plasma Pharmacokinetics, Safety, and Tolerability of a Single Oral Dose of Zoliflodacin in Healthy Male and Female Subjects" (Division of Microbiology and Infectious Diseases (DMID) protocol 16-0118) describes and expands upon the statistical information presented in the protocol.

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

This document contains five sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for efficacy and safety outcomes, (4) planned statistical analyses for pharmacokinetic (PK) endpoints, and (5) a list of proposed tables and figures. Any deviation from this SAP will be described and justified in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol and manual of operating procedures for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

This Phase 1 trial is an open-label, non-randomized evaluation of the PK and safety profiles of a single 4-g oral dose of zoliflodacin [2 x 2 gram (g) sachets] in 8 healthy male or female subjects, aged 18-45 years.

2.1. Purpose of the Analyses

A single oral dose of zoliflodacin has been shown to be effective against uncomplicated gonorrhea caused by *N. gonorrhoeae* strains susceptible or resistant to currently available therapies. These findings supported the ongoing clinical development of zoliflodacin as a potential new therapeutic option for uncomplicated gonorrhea. A recently completed Phase 2 clinical trial suggests that zoliflodacin doses in the range of 2 g to 3 g are therapeutic. In the current study, a 4-g dose of zoliflodacin, using a different formulation than in the prior PK studies, is given to 8 healthy subjects. The purpose of analyses is to characterize the PK characteristics and safety profile of a 4-g dose of this formulation of zoliflodacin.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objective:

- To evaluate the plasma PK of zoliflodacin after administration of a single 4-g oral dose under fasting conditions

Secondary Objective:

- To evaluate the safety and tolerability of a single 4-g oral dose of zoliflodacin

3.2. Endpoints

Primary Endpoints:

- C_{max}, T_{max}, area under the curve (AUC) until last measurable concentration ($AUC_{(0\text{-last})}$), and other PK parameters for zoliflodacin determined using plasma concentrations of zoliflodacin in blood samples collected on Day 1 [baseline (30 min before dosing) and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 h after dosing], Day 2 [24 h and 36 h after dosing], Day 3 [48 h after dosing], and Day 4 [72 h after dosing], or early termination (ET), and measured using a validated high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) method

Secondary Endpoints:

- The occurrence of treatment-emergent serious adverse events (SAEs) from administration of zoliflodacin on Day 1 to Final Visit (Day 8 ± 2), or ET
- The occurrence of unsolicited treatment-emergent adverse events (AEs) from administration of zoliflodacin on Day 1 to Final Visit (Day 8 ± 2), or ET
- The changes from baseline (up to 60 min before dosing) in vital signs (VS) following administration of zoliflodacin, as measured on Day 1 [1 h, 2 h, and 4 h after dosing], Days 2, 3, and 4 [24 h, 48 h, and 72 h, respectively, after dosing], and Final Visit (Day 8 ± 2), or ET
- The changes from baseline (Day -1) in clinical laboratory values following administration of zoliflodacin, as measured on Day 4, or ET
- The changes from baseline (up to 60 min before dosing) in electrocardiograph (ECG) parameters following administration of zoliflodacin, as measured on Day 1 [1 h, 2 h, and 4 h after dosing] and Day 4 [72 h after dosing], or ET

3.3. Study Definitions and Derived Variables

The baseline value will be defined as the last value obtained prior to the dosing with zoliflodacin.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

The trial will be performed as an open-label, non-randomized, single-dose design in 8 healthy male or female subjects to evaluate the PK and safety profiles of the zoliflodacin formulation. Zoliflodacin is presented as granules for oral suspension, 50 % weight(wt)/wt, packaged in a single sachet. Each subject will receive a single 4g dose of zoliflodacin (2 sachets of 2 g of zoliflodacin reconstituted on the same day and administered in a total of [redacted]) orally after an overnight fast. After the [redacted] of zoliflodacin is administered, an additional [redacted] should be added to the same cup and consumed by the subject to chase the initial dose. Ingestion of the content of both the initial [redacted] volume and the [redacted] wash should be completed within 5 min. All subjects will be dosed in the morning of Day 1 in a staggered fashion with a minimum of several minutes apart. There is no placebo used in this study.

Subjects will participate in the study for approximately 4 weeks, including a 3-week screening period, a 4-day inpatient stay with dosing on Day 1, and a 1-week follow-up period after study product administration. The last follow-up visit is scheduled on Day 8. Safety oversight will be conducted by a Safety Monitoring Committee (SMC), which is an independent group of experts that monitors subject safety and advises DMID. The SMC will review safety data and advise on using the 4-g dose of zoliflodacin in a subsequent thorough QT study.

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

Zoliflodacin is a spiropyrimidinetrione antibacterial drug, which inhibits bacterial Deoxyribonucleic acid (DNA) synthesis by a novel mechanism. Zoliflodacin demonstrates in vitro activity against *N. gonorrhoeae* strains that are susceptible or resistant to current available therapies and in vivo efficacy, including in patients with uncomplicated gonorrhea.[5,6]

Regulatory guidance ICH/FDA E14 has emphasized the need to obtain robust data on the effect of new chemical entities on ECG parameters, focusing on cardiac repolarization as measured by the corrected QT interval (QTc).[6] To obtain these data, the potential of a single therapeutic dose and a single supratherapeutic dose of the study drug to prolong cardiac repolarization is measured. Single zoliflodacin doses ranging from 200 mg to 4 g were generally safe and well tolerated in the Phase 1 and Phase 2 clinical trials conducted to date in healthy subjects and patients with uncomplicated gonorrhea.[5,7,8] The current trial will further characterize the PK and safety profiles of the 4-g dose of a new zoliflodacin formulation. This dose could result in drug exposures that are multiples of the proposed 2-g therapeutic dose and meet the requirements for a supratherapeutic dose. Since the main objective is to characterize the PK of zoliflodacin, this study does not use a control group.

4.3. Selection of Study Population

Only subjects who meet all of the inclusion and none of the exclusion criteria will be eligible for enrollment into this study. No exemptions are granted on Inclusion/Exclusion Criteria in DMID-sponsored studies.

Eight healthy male and female subjects, aged 18-45 years inclusive, will be enrolled in a single cohort. Up to two alternates will be recruited.

Inclusion Criteria

All must be answered YES for the subject to be eligible for study participation:

1. Informed consent form (ICF) understood and signed before initiating any study procedures
2. Healthy male or female, as assessed by the authorized site clinician (listed on FDA Form 1572)
3. Willingness to comply with and be available for all protocol procedures including inpatient confinement for about 4 days and availability for follow-up for the duration of the trial
4. Aged 18 to 45 years inclusive on the day of study drug dosing
5. Body Mass Index (BMI) ≥18.5 and ≤30 kg/m^2 and weight ≥50 kg (110 lbs.) and ≤100 kg (220 lbs.)
6. In female subjects of childbearing potential, a negative serum pregnancy test at Screening Visit and on Day -1
    - *Note: A woman is considered of childbearing potential unless post-menopausal (≥ 1 year without menses without other known or suspected cause and with a Follicle-stimulating hormone (FSH) level in the menopausal range), or surgically sterilized (hysterectomy, salpingectomy, oophorectomy or tubal ligation/occlusion)*
7. If female, not pregnant, not breast feeding, and not planning on becoming pregnant during the trial and for 30 days after study participation
8. Females of childbearing potential and males agree to use acceptable contraception for the duration of the trial and for 30 days (females) or 90 days (males) after final study visit
    - *Note: A highly effective method of birth control is defined as one with a low failure rate (i.e., less than 1 percent per year) according to the Centers for Disease Control and Prevention (CDC) criteria. These include progestin implants, intrauterine devices (IUDs), surgical (hysterectomy, salpingectomy, oophorectomy or tubal ligation/occlusion; vasectomy), or abstinence. Use of methods with higher failure rate (such as progestin injectables, combined oral hormonal contraceptives, condoms, and diaphragms) will not be acceptable when used alone, but they could be considered if used in combination with another method (e.g., a female using combined oral contraceptives if her male partner is sterile, or if she and her non-sterile male partner use a double-barrier method), after consultation with the DMID Medical Officer.*
9. Male subjects must agree to refrain from sperm donation for the duration of the trial and for 90 days after final study visit
10. Laboratory tests, as outlined in Section 8.2.1.1 of the protocol, are in the normal reference range with acceptable exceptions as noted in Section 8.2.1.1 and Appendix B of the protocol
11. VS, as outlined in Section 8.1.6 of the protocol, are within the acceptable range per Appendix B of the protocol
12. Has adequate venous access for blood collection
13. Urine drug screen is negative for tested substances (see Section 8.2.1.5 of the protocol)
14. Alcohol test (breathalyzer) is negative
15. Willing to abstain from alcohol consumption for 2 days before Day -1 and during the trial

Exclusion Criteria

All must be answered NO for the subject to be eligible for study participation:

1. History of a chronic medical or surgical condition that would interfere with the accurate assessment of the trial's objectives or increase the subject's risk profile

   Note: Chronic medical conditions include: diabetes mellitus; asthma requiring use of medication in the year before screening; autoimmune disorder such as lupus erythematosus, Wegener's, rheumatoid arthritis, thyroid disease; cardiovascular disease, including coronary artery disease or cerebrovascular disease, or surgery; syncope related to cardiac arrhythmia or unexplained; chronic hypertension; malignancy except low-grade (squamous and basal cell) skin cancer thought to be cured; chronic renal, hepatic, pulmonary, or endocrine disease, myopathy, or neuropathy; gastrointestinal or biliary surgery.

2. History of hypersensitivity or severe allergic reaction of any type to medications, bee stings, food, or environmental factors

   Note: Severe allergic reaction is defined as any of the following: anaphylaxis, urticaria, or angioedema

3. Active allergic symptoms to seasonal and animal allergens that require treatment
4. A marked baseline prolongation of ECG intervals, or heart rate (HR) <45 bpm or >100 bpm on ECG measurements

   Note: The following are considered prolonged ECG intervals: QTc/QTcF >449 msec in males and females; PR >209 msec; and QRS >110 msec

5. Clinically significant abnormal ECG results

   Note: Clinically significant abnormal ECG results include: complete left or right bundle branch block; other ventricular conduction block; 2nd degree or 3rd degree atrioventricular (AV) block; sustained atrial or ventricular arrhythmia; two premature ventricular contractions in a row; pattern of ST elevation felt consistent with cardiac ischemia; evidence of a previous myocardial infarction (MI), left ventricular hypertrophy (LVH), or more than minor non-specific ST-T wave changes; or any condition deemed clinically significant by a study investigator.

6. Abnormal renal function

   Note: Normal renal function is defined as normal creatinine [per criteria in Appendix B of the protocol] and normal estimated glomerular filtration rate (eGFR) [i.e., >80.0 mL/min] values according to Cockroft-Gault.

7. Positive serology results for Human Immunodeficiency Virus (HIV), Hepatitis B Surface Antigen (HBsAg), or Hepatitis C Virus (HCV)
8. Febrile illness with temperature >37.6 °C for <7 days before dosing
9. Donated whole blood or blood products within 60 days before dosing, or plans to donate before Final Visit (Day 8 ± 2)

   Note: Blood products include red blood cells (RBCs), white blood cells (WBCs), platelets, and plasma

10. Known allergic reactions to any of the study drug components present in the formulation or in its processing, as listed in the Investigator's Brochure (IB)
11. Treatment with another investigational product within 30 days of dosing or 5 half-lives or twice the duration of the biological effect of the study drug (whichever is longer)

    Note: Investigational products include a drug, vaccine, biologic, device or blood product
12. Active drug or alcohol use, abuse, or dependence within 12 months before Screening Visit that, in the opinion of the investigator, would interfere with adherence to study requirements
13. Use of any prescription medication within 30 days before dosing or planned use during the study period except as noted below and approved by the designated study clinician

    Note 1: Prohibited medications include moderate or strong CYP3A4 inducers (per Section 6.9); antibiotics; injectable or oral antidiabetic drugs; anti-lipid drugs; immunosuppressive agents; immune modulators; oral corticosteroids; anti-neoplastic agents; any vaccine (licensed or investigational) except licensed influenza vaccine during the flu season, which is allowed 7 days before or after dosing.
    Note 2: Allowed medications include: oral contraceptives; H1 antihistamines; topical/ intranasal corticosteroids; nonsteroidal anti-inflammatory drugs [NSAIDS]; licensed influenza vaccine during the flu season, 7 days before or after dosing.
14. Use of any non-prescription medication, herbal preparation, or nutritional supplement within 15 days before dosing or planned use during the study unless approved by the study clinician

    Note: Exceptions: St. John's wart is not allowed within 30 days of dosing, vitamins and OTC medications taken for a brief period (<48 h) for the treatment of common symptoms (such as headache, indigestion, muscle pain) may be allowed as approved by the designated study clinician.
15. Intake of caffeinated beverages or food within 72 h before dosing or a history of high caffeine consumption (e.g., in the last 4 months drinking >5 cups of coffee/day)
16. Smoking or use of tobacco or nicotine-containing products within 15 days before dosing
17. Engagement in strenuous exercise within 15 days before dosing (e.g., marathon running, long distance cycling, weight lifting) and during the study period
18. Any specific behavioral or clinical condition that in the judgment of the investigator precludes participation because it could affect compliance with study procedures or subject safety
19. Plans to enroll or is already enrolled in another clinical trial that could interfere with safety assessment of the study drug at any time during the study period

    Note: Includes trials that have a study intervention such as a drug, biologic, or device.
20. Is a study site employee or staff member who is paid entirely or partially by the Office of Clinical Research Resources (OCRR)/NIAID contract for the DMID-funded trial

    Note: Site employees or staff include the Principal Investigators (PIs), sub-investigators, or staff who are supervised by the PI or sub-investigators.

4.4. Treatments

4.4.1. Treatments Administered

Zoliflodacin is a spiropyrimidinetrione antibacterial agent, with a novel mode of action. It is a first-in-class oral gyrase inhibitor being developed for treatment of uncomplicated gonococcal infection, including cases caused by isolates with resistance to currently available treatments. A single oral dose of zoliflodacin has been shown to be effective against uncomplicated gonorrhea caused by *N. gonorrhoeae* strains susceptible or resistant to currently available therapies. These findings supported the ongoing clinical development of zoliflodacin as a potential new therapeutic option for uncomplicated gonorrhea.

4.4.2. Identity of Investigational Product(s)

Zoliflodacin is presented as granules for oral suspension, 50 % wt/wt, packaged in a single sachet. Each sachet contains 2 g of spray-dried zoliflodacin, co-formulated with [redacted].

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

This is a single arm trial. All subjects will receive a single 4 g oral dose of zoliflodacin.

4.4.4. Selection of Doses in the Study

Single zoliflodacin doses ranging from 200 mg to 4 g were generally safe and well tolerated in the Phase 1 and Phase 2 clinical trials conducted to date in healthy subjects and patients with uncomplicated gonorrhea.[1,2,3] The current trial will further characterize the PK and safety profiles of the 4-g dose of a new zoliflodacin formulation. This dose could result in drug exposures that are multiples of the proposed 2-g therapeutic dose and meet the requirements for a supratherapeutic dose according to the ICH/FDA E14 Guidance for thorough QTc studies.[4]

4.4.5. Selection and Timing of Dose for Each Subject

Eligible subjects will receive a single 4-g dose (2 sachets of 2 g of zoliflodacin reconstituted on the same day and administered in a total of [redacted]) orally after an overnight fast. After the [redacted] of zoliflodacin is administered, an additional [redacted] will be added to the same cup and consumed by the subject to chase the initial dose. Ingestion of the content of both the initial [redacted] volume and the [redacted] should be completed within 5 min. After dosing, subjects will continue to fast for an additional 4 h while water is allowed *ad lib*. All subjects will receive zoliflodacin in the morning of Day 1 in a staggered fashion several minutes apart.

4.4.6. Blinding

This is an open-label study, no blinding procedures are required.

4.4.7. Prior and Concomitant Therapy

Concomitant medications include the following: prescription drugs, birth control hormonal preparations, non-prescription medication, herbs, vitamins, nutritional supplements, and illicit and recreational substances. Any of these taken before or after dosing will be reported as Prior Medications or Concomitant Medications, respectively.

Prior prescription medication information will be recorded at Screening Visit and, except for hormonal contraceptives, should not be taken for 30 days before dosing or during the study period.

Zoliflodacin should not be co-administered in subjects using strong (i.e., avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort) or moderate (i.e. efavirenz, bosentan, etravirine, modafinil, and nafcillin) inducers of CYP3A4. These drugs should not be taken for 30 days before dosing and during the study period.

A vaccine should not be received within 30 days before dosing or before the end of the trial, except for licensed influenza vaccine during the flu season, which may be administered up to 7 days before or after dosing.

Non-prescription medications, herbs, vitamins, and nutritional supplements should not be taken within 15 days before dosing. OTC medications taken for a brief period (<48 h) for the treatment of common symptoms (such as headache, indigestion, muscle pain) may be allowed as approved by the designated study clinician.

Allowed medications include: oral contraceptives; H1 antihistamines; topical/ intranasal corticosteroids; nonsteroidal anti-inflammatory drugs (NSAIDS); licensed influenza vaccine during the flu season, 7 days before or after dosing.

Blood/blood products (RBCs, WBCs, platelets, and plasma) should not be donated within 60 days of dosing or received before Final Visit.

Following dosing, each new concomitant medication and changes to existing medications will be recorded. Subjects will be required not to utilize non-study medication during the trial except those deemed necessary by the Site PI or sub-investigator.

Any drug (e.g., non-prescription medications, herbal supplements, vitamins, or prescription medications) or vaccine or blood/blood products used by the subject during the trial will be recorded in the subject's source documents and on the appropriate electronic case report form (eCRF), and the PI or authorized study clinician (listed on FDA Form 1572) will note whether the use was medically indicated and immediately necessary. Any use of medications not authorized by the study PI or authorized clinician will be recorded as a deviation.

4.4.8. Treatment Compliance

All subjects will receive a single 4 g dose of zoliflodacin administered in the clinic. Dates and times of administration will be recorded by site personnel. Complete information regarding any partial or interrupted dosing will be documented.

4.5. Efficacy and Safety Variables

As this study is a Phase I clinical trial in healthy adult subjects, there will be no assessment of drug efficacy. Safety endpoints are briefly listed below. For a detailed schedule of activities, refer to Appendix A of the protocol. For a complete list of primary and secondary objectives and outcomes, refer to Section 3 of the SAP.

Safety will be assessed by the timing, frequency, relatedness to study drug, and severity of:

1. Treatment-emergent SAEs occurring from dosing through Final Visit (Day 8 ± 2), or ET
2. Clinical laboratory AEs occurring from dosing through Final Visit (Day 8 ± 2), or ET
3. Non-serious, unsolicited treatment-emergent AEs occurring from dosing through Final Visit (Day 8 ± 2), or ET.

Details of the study safety parameters can be found in the protocol.

5. SAMPLE SIZE CONSIDERATIONS

Since this is a pilot Phase 1, open-label trial with a single 4-g dose cohort of zoliflodacin, no formal sample size calculations based on testing a statistical hypothesis were constructed. Eight subjects will be enrolled, and it is planned to have seven evaluable subjects given zoliflodacin. This sample size will provide sufficient information to estimate exposure to the 4-g dose of zoliflodacin and to assess its safety.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Tabulations will be used extensively to summarize the data. Summary statistics for continuous data will include the mean, median, standard deviation, and range (minimum and maximum values). Summary statistics for discrete data will include counts and percentages, contingency tables, and associated confidence intervals (CIs). Denominators will be shown for all percentages (as N=X). When 95% CIs are given for a binary variable, Wilson Score CIs will be used. Parameters will be summarized overall and not by any subgroup.

In general, all data will be listed, sorted by subject ID, and when appropriate, by visit number within subject. The total population size relevant to specific tables or to columns or rows within tables will be displayed.

Listings of individual subject data include a Subject ID column. The subject identifiers assigned by site staff are replaced throughout this report with the SDTM variable USUBJID to protect the confidentiality of those who volunteered to participate in this protocol. USUBJID has been created as a composite of the 3-letter Electronic Data Capture (EDC) platform code followed by a numeric identifier assigned chronologically to enrolled subjects as well as screening failures across all sites and protocols in the EDC platform. Any data sharing activities will include the USUBJID and not the subject identifiers assigned at the site.

6.2. Timing of Analyses

The final analysis will be performed after database lock.

6.3. Analysis Populations

A tabular listing of all subjects, visits, and observations excluded from the analysis of PK data will be provided in the CSR (Listing 4).

6.3.1. Intention-to-Treat Analysis (ITT) Population

Not applicable.

6.3.2. Full Analysis Population

Not applicable.

6.3.3. Modified Intention-to-Treat (mITT) Population

Not applicable.

6.3.4. Evaluable Population

Not applicable.

6.3.5. Per Protocol Population

Not applicable.

6.3.6. Safety Population

All subjects who received the study drug will be included in the safety population and analyzed as treated.

6.3.7. PK Population

The PK analysis population will consist of all subjects who received zoliflodacin and have at least one quantifiable post-dosing drug concentration measured. The PK analysis subset will be based on the PK population, which includes all subjects who completed the PK part of the trial without any protocol violations that would likely affect the PK results and who have evaluable plasma concentration data for zoliflodacin from whom at least a subset of the designated PK parameters can be determined.

6.3.8. Immunogenicity Population

Not applicable.

6.4. Covariates and Subgroups

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

6.5. Missing Data

All attempts will be made to collect all data per protocol. Clinical labs will not be collected for Day -1 if collected ≤7 days of dosing. Therefore, missing clinical laboratory results on Day -1 only will be imputed using last observation carried forward when results with 7 days prior to dosing are available. Missing clinical laboratory results on Day 4 or "Day 4 or ET" will not be imputed. Missing pre-dose PK samples will have concentrations imputed as BQL (below quantification limit). No other imputation will be performed for missing values. Outliers will not be excluded from the primary analyses. Outliers identified during the PK analysis will be discussed in the analysis report.

6.6. Interim Analyses and Data Monitoring

There are no planned interim analyses for this study.

An SMC will review all the safety data to Day 8 or ET in the study cohort. If any of the predefined objective criteria for halting the study, listed in Section 9.5.1 of the protocol, are met, a SMC ad hoc meeting will be held to review all available safety data (see Section 9.6.2 of the protocol for more details).

6.7. Multicenter Studies

Not applicable. This is a single site study.

6.8. Multiple Comparisons/Multiplicity

This is a small Phase 1 first-in-human study with multiple primary endpoints. The primary endpoints are descriptive rather than hypothesis tests, no adjustments for multiple testing are planned.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Screened subjects who were ineligible for enrollment in the study will be summarized by inclusion and exclusion criteria in Table 7, and enrolled subjects who were ineligible for inclusion in the analysis populations will be presented by reason for subject exclusion in Table 6.

Subject disposition will be summarized (Table 5), showing the number of subjects who screened, enrolled, dosed, completed sample collection, and completed follow-up. Subjects who terminated early from the study will be listed (Listing 1). Subjects who were excluded from the PK population, then PK analysis subset, or safety population will be listed, including reason for exclusion (Listing 4).

7.2. Protocol Deviations

A summary of protocol deviations will be presented by the deviation category and reason in Table 2. This table will provide both the number of subjects and the number of deviations for each category.

All subject-specific protocol deviations and non-subject-specific protocol deviations will be listed (Listing 2 and Listing 3, respectively).

8. EFFICACY EVALUATION

There are no efficacy endpoints for this trial

8.1. Primary Efficacy Analysis

Not applicable.

8.2. Secondary Efficacy Analyses

Not applicable.

8.3. Exploratory Efficacy Analyses

Not applicable.

9. SAFETY EVALUATION

All safety analyses will be presented using the safety population. When calculating the incidence of AEs (i.e., on a per subject basis), each subject will be counted once and any repetitions of AEs within a subject will be ignored for events coded in the same category by the Medical Dictionary for Regulatory Activities (MedDRA); the denominator will be the total safety population size. Moreover, events thus summarized will be coded to the highest severity observed per toxicity tables (Table 3 and Table 4).

9.1. Demographic and Other Baseline Characteristics

Sex, ethnicity, and race of all subjects will be summarized (Table 8). Ethnicity will be categorized as "Hispanic or Latino," or "Not Hispanic or Latino," or "Unknown/Not Reported." 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 eCRF as "No" to each racial option. Age (in years), height (in m), weight (in kg), and BMI (in kg/m^2) will be summarized (Table 9).

Individual subject listings will be presented for all demographic and baseline characteristics (Listing 5).

9.1.1. Prior and Concurrent Medical Conditions

Medical history (MH) including all current illnesses and past pre-existing medical conditions will be MedDRA coded using MedDRA dictionary version 20.1 or higher. Summaries of subjects' pre-existing medical conditions by MedDRA system organ class (SOC) will be presented (Table 10). Individual subject listings including medical history term, condition start and end day, SOC, and PT will be presented for all medical conditions (Listing 6). Surgeries, and the underlying illness indicating the surgery, were collected as separate medical history terms, and will be reported as separate rows in the listing.

9.1.2. Prior and Concomitant Medications

All medications will be coded using the current version of the World Health Organization (WHO) Drug dictionary. The use of prior and concomitant medications taken during the study will be summarized by Anatomical Therapeutic Chemical (ATC) classification codes ATC 1 and ATC 2 (separately in Table 117 for prior medications and Table 118 for concomitant medications). Individual subject listings will be presented for all prior and concomitant medications (separately in Listing 18 for prior medications and Listing 19 for concomitant medications).

9.2. Measurements of Treatment Compliance

All subjects were to receive a single 4 g dose of zoliflodacin administered in the clinic. The dates and times of administration are listed for each subject in Listing 7. Subjects unable to ingest the full amount of the initial [redacted] of study drug suspension or who vomit within 24 h after dosing will be withdrawn from the study and replaced (See Section 5.3.3 and 5.3.4 of the protocol). Subjects who do not ingest the content of the second [redacted] of study drug suspension will not be withdrawn from the study. Subjects who received any amount of the study drug but withdraw from the trial will be encouraged to continue follow-up (with subjects' consent) for safety assessments and PK sample collection.

Subjects receiving the full initial [redacted] suspension and the full [redacted] wash ([redacted]) will be reported in Listing 7 as receiving "4 g" of the drug. Subjects receiving an incomplete dose will be reported in Listing 7 as receiving "<4 g" of the drug.

9.3. Adverse Events

When calculating the incidence of AEs within each category (i.e., on a per subject basis), each subject will only be counted once and any repetitions of AEs within a subject will be ignored; the denominator will be the total safety population size. When multiple AEs of different severities are observed for a subject within a category, the worst severity will be tabulated for calculations of incidence. All reported AEs will be included in the summaries and analyses.

9.3.1. Solicited Events and Symptoms

There are no solicited symptoms or AEs in this trial.

9.3.2. Unsolicited Adverse Events

The proportion of subjects reporting at least one unsolicited AE after dosing and prior to Day 8 or ET will be summarized by MedDRA SOC, higher level group term (HLGT), and preferred term (PT). A 95% Wilson Score CI will be presented for each MedDRA SOC, HLGT, and PT. Tables, figures, and listings of AEs will include clinical laboratory AEs and ECG AEs.

AEs by subject will be presented in Listing 8. Additionally, moderate and severe non-serious AEs will be listed in Table 15.

A brief overall summary of AEs will be given in Table 11. The following summaries for unsolicited AEs will be presented by MedDRA SOC, HLGT, and PT:

- Frequency (number and percent of subjects with an AE of mild severity or greater, with 95% Wilson Score intervals) and number of AE, regardless of severity or relationship to study product (Table 12)
- Frequency of AEs by severity and relationship to study product (Table 13);
- Bar chart of frequency of related AEs by severity and MedDRA SOC (Figure 2). This figure describes the total number of occurrences of each AE, including multiple occurrences per subject.
- Bar chart of incidence of serious and non-serious AEs by maximum severity and MedDRA SOC (Figure 1). This figure describes the number and percent of subjects with an AE.

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

Individual data listings of deaths and Serious AEs (Table 14) will be provided. The listing will include: Subject ID, AE Description, Duration, Reason Reported as an SAE, Severity, Relationship to Treatment, Alternate Etiology if not Related, Outcome, MedDRA SOC, and MedDRA PT.

9.5. Pregnancies

A female subject who participates in the trial and becomes pregnant will be asked to inform study personnel of a pregnancy occurring 30 days after the final study visit. A male subject who participates in the trial and whose female partner becomes pregnant 90 days after the final study visit will be asked to inform study personnel of the pregnancy. For all reported pregnancies, subjects will be asked to provide pregnancy outcome upon delivery or pregnancy termination to the clinical trial unit.

An individual data listing of pregnancy reports will be provided in Listing 21, Listing 22, Listing 23, Listing 24, and Listing25 if a pregnancy occurs post dosing. A by-subject list of birth control methods can be found in Listing 20.

9.6. Clinical Laboratory Evaluations

Toxicity grade criteria can be found in Table 3 and Table 4. Unscheduled or repeated follow-up tests for medical or safety reasons will be listed but excluded from tabular and graphical summaries.

Clinical labs will not be collected for Day -1 if collected ≤7 days of dosing. In all cases, the most recent result in the database prior to dosing will be used as baseline. Missing clinical laboratory results on Day 4 or ET will not be imputed. If multiple Day -1 results exist for a subject, the latest result prior to dosing will be regarded as the baseline value.

All clinical laboratory results (chemistry, hematology, and urinalysis) will be listed (Listing 9, Listing 10, and Listing 11). Other laboratory results (viral serology, pregnancy tests, and confirmation of menopause) will be listed separately (Listing 12). Toxicology results will be shown in Listing 13 and Breathalyzer results will be shown in Listing 14. Abnormal laboratory results will be listed in Table 16, Table 17, and Table 18.

Chemistry laboratory results will be summarized by parameter and severity (including maximum severity post-baseline) regardless of relatedness (Table 19, Table 20, Table 21, Table 22, Table 23, Table 24, Table 25, Table 26, Table 27, Table 28, Table 29, Table 30 and Table 31) and additionally the frequency of *related* laboratory toxicities will be summarized by parameter and severity (including maximum severity post-baseline; Table 32, Table 33, Table 34, Table 35, Table 36, Table 37, Table 38, Table 39, Table 40, Table 41, Table 42, Table 43, and Table 44). Summary statistics will be reported by parameter and scheduled visit, including change from baseline (Table 45, Table 46, Table 47, Table 48, Table 49, Table 50, Table 51, Table 52, Table 53, Table 54, Table 55, Table 56, Table 57, Table 58, and Table 59). Individual line plots showing the laboratory result over time will be shown by chemistry parameter (Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8, Figure 9, Figure 10, Figure 11, Figure 12, Figure 13, Figure 14, Figure 15, Figure 16 and Figure 17). Subjects will not be labeled in the line plots, as the purpose of the figures is to give an overall trend of trajectory. The following chemistry parameters will be included in summaries of severity: sodium, potassium, bicarbonate, glucose, blood urea nitrogen, creatinine, protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin. The following chemistry parameters will be included in tables of summary statistics and in graphical plots: sodium, potassium, magnesium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, protein, albumin, AST, ALT, alkaline phosphatase, bilirubin, and direct bilirubin.

Hematology laboratory results will be summarized by parameter and severity (including maximum severity post-baseline) regardless of relatedness (Table 60, Table 61, Table 62, Table 63, Table 64, Table 65, Table 66, Table 67 and Table 68) and additionally the frequency of *related* laboratory toxicities will be summarized by parameter and severity (including maximum severity post-baseline; Table 69, Table 70, Table 71, Table 72, Table 73, Table 74, Table 75, Table 76 and Table 77). Summary statistics will be reported by parameter and scheduled visit, including change from baseline (Table 78, Table 79, Table 80, Table 81, Table 82, Table 83, Table 84, Table 85, Table 86, and Table 87). Individual line plots showing the laboratory result over time will be shown by hematology parameter (Figure 18, Figure 19, Figure 20, Figure 21, Figure 22, Figure 23, Figure 24, Figure 25, Figure 26, and Figure 27). Subjects will not be labeled in the line plots, as the purpose of the figures is to give an overall trend of trajectory. The following hematology parameters will be included in summaries of severity: hemoglobin, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets. The following hematology parameters will be included in tables of summary statistics

and in graphical plots: hemoglobin, hematocrit, erythrocytes, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets.

Urinalysis laboratory results will be summarized by parameter (protein, glucose, and hemoglobin) and severity (including maximum severity post-baseline) regardless of relatedness (Table 88, Table 89, Table 90, and Table 91) and additionally the frequency of *related* laboratory toxicities will be summarized by parameter and severity (including maximum severity post-baseline; Table 92, Table 93, Table 94, and Table 95). Because urinalysis parameters are not continuous (except for microscopy follow-up parameters in the event of abnormal urine), no tables of summary statistics or line plots will be produced for urinalysis results. If performed, results of microscopy follow-up tests to abnormal urine dipstick tests will be included in listings of urinalysis results.

In tables of severity, maximum severity observed for the parameter after dosing will be summarized. Tables of maximum severity for "Any Parameter" will be included for chemistry, hematology, and urinalysis laboratory results. In these tables, the maximum severity across all laboratory results in the respective category is summarized by visit, and from maximum severity post baseline. Ordinarily, only the maximum severity event will be counted in the summary tables. For instance, if subject has a mild decrease and a moderate increase observed post-dose, they will be counted once as a moderate increase for maximum severity post-baseline. In the exceptional case that a subject has an increase and a decrease of equal maximum severity, they will be counted twice for maximum severity post baseline, once for an increase and once for a decrease.

9.7. Vital Signs and Physical Evaluations

VS measurements include systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and oral temperature. VS will be assessed within 60 min of dosing (baseline), 1 h (±10 min), 2 h (±10 min), and 4 h (±10 min) after dosing, and at Day 2, Day 3, Day 4, and Day 8 or ET. VS will be tabulated by parameter, severity grading, and visit (Table 96, Table 97, Table 98, Table 99, Table 100, and Table 101) and listed (Listing 15). Additionally, descriptive statistics, including mean, standard deviation, median, minimum and maximum will be presented to summarize VS at baseline and post-dose and will also present change from baseline (Table 102, Table 103, Table 104, Table 105 and Table 106). For each vital sign, individual line plots showing the vital sign over time will be shown by parameter (Figure 28, Figure 29, Figure 30, Figure 31 and Figure 32). Subjects will not be labeled in the line plots, as the purpose of the figures is to give an overall trend of trajectory.

In tables of severity, maximum severity observed for the parameter after dosing will be summarized. Tables of maximum severity for "Any Parameter" will be included for VS results. In these tables, the maximum severity across all VS is summarized by visit, and from maximum severity post baseline. Ordinarily, only the maximum severity event will be counted in the summary tables. For instance, if subject has a mild decrease and a moderate increase observed post-dose, they will be counted once as a moderate increase for maximum severity post-baseline. In the exceptional case that a subject has an increase and a decrease of equal maximum severity, they will be counted twice for maximum severity post baseline, once for an increase and once for a decrease.

A complete physical examination (PE), except genital, rectal and breast exams, will be conducted at Screening and at Day 8 (± 2) or ET. This examination will assess general appearance, HEENT (head, eyes, ears, nose and throat), heart, lungs, abdomen, skin, musculoskeletal system, and lymph nodes, and include an abbreviated neurological exam. An abbreviated PE will be performed on Day -1 (unless a complete PE was performed < 7 days before dosing) and Day 4. An abbreviated PE differs from a complete PE in that the

abdomen and neurological system are not evaluated. A symptom-directed PE will be performed before dosing on Day 1 and after dosing on Days 1, 2, and 3, to evaluate new symptoms or treatment-emergent AEs, respectively. Results of physical examinations, scheduled and unscheduled, will be presented in Listing 16.

9.8. Concomitant Medications

All medications will be coded using the current version of the WHO Drug dictionary. The use of prior and concomitant medications taken during the study will be summarized by ATC 1 and ATC 2 (separately in Table 117 for prior medications and Table 118 for concomitant medications). Individual subject listings will be presented for all prior and concomitant medications (separately in Listing 18 for prior medications and Listing 19 for concomitant medications).

9.9. Other Safety Measures

A 12-lead ECG and 10-sec rhythm strip will be obtained at Screening Visit and on Days -1, 1, and 4 (72 h ± 2 h post dose), or ET. On Day 1, a 12-lead ECG and 10-sec rhythm strip will be recorded within 1 h before dosing and 1 h (±10 min), 2 h (±10 min), and 4 h (±10 min) after dosing. ECG change in overall interpretation from baseline will be shown by study visit in Table 107. For PR interval and QT intervals with Fridericia correction (QTcF), ECG results will be tabulated by parameter, severity grading, and visit (Table 108 and Table 109). Summary statistics of ECG results, including change from baseline, will be reported by parameter (PR interval, QRS duration, QT interval, QTcF interval, RR interval, and ECG mean ventricular rate) in tabular form by study visit (Table 110, Table 111, Table 112, Table 113, Table 114, and Table 115) and will be shown graphically as line plots by visit (Figure 33, Figure 34, Figure 35, Figure 36, Figure 37, Figure 38, and Figure 39). Subjects will not be labeled in the line plots, as the purpose of the figures is to give an overall trend of trajectory. Line plots of change from baseline will be shown for QTcF intervals (Figure 37) but change from baseline will not be shown graphically for other ECG parameters. Frequency of QTcF prolongation (between 30 and <60 msec or ≥60 msec) will be given by post-dose visit (Table 116). Individual data listings of ECG results (interpretation, PR interval, QRS duration, QT interval, QTcF interval, RR interval, and ECG mean ventricular rate) will be presented (Listing 17).

10. PHARMACOKINETICS

The PK analysis plan is described in the PK SAP. The summary from the PK Report and key tables, figures and listings (concentrations, parameters, and mean time-concentration profiles) will be included in the CSR.

11. IMMUNOGENICITY

There are no immunogenicity endpoints in this trial.

12. OTHER ANALYSES

There are no other analyses in this trial.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values <0.001 will be reported as "<0.001"; p-values >0.999 will be reported as "> 0.999". All summary statistics besides the minimum value and maximum value 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; proportions >0 but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; percentages >0 but <1% will be presented as "<1".

14. TECHNICAL DETAILS

SAS version 9.4 or above or R version 3.2 or above will be used to generate tables, figures, and listings.

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

No changes.

16. REFERENCES

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3. Randomized, Open-label Phase 2 Study of Oral AZD0914 in the Treatment of Gonorrhea. ClinicalTrials.gov Identifier: NCT02257918. https://clinicaltrials.gov/ct2/show/NCT02257918?term=AZD0914&rank=1 (accessed 27 July 2017

4. Guidance for Industry. E14: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. FDA, October 2005. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf (Accessed on 27 July 2017)

5. Basarab GS, Kern GH, McNulty J, et al. Responding to the challenge of untreatable gonorrhea: ETX0914, a first-in-class agent with a distinct mechanism-of-action against bacterial Type II topoisomerases. Sci Rep. 2015 Jul 14;5:11827

6. Huband MD, Bradford PA, Otterson LG, et al. In vitro antibacterial activity of AZD0914, a new spiropyrimidinetrione DNA gyrase/topoisomerase inhibitor with potent activity against Gram-positive, fastidious Gram-Negative, and atypical bacteria. Antimicrob Agents Chemother. 2015 Jan; 59(1): 467-74.

7. Centers for Disease Control and Prevention, (CDC). CDC Fact Sheet: STD Trends in the United States: 2011 National Data for Chlamydia, Gonorrhea, and Syphilis, 2013. Available at: http://www.cdc.gov/std/stats11/trends-2011.pdf (accessed on 10 July 2014)

8. Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States, 2013. Available at: http://www.cdc.gov/drugresistance/threatreport-2013/pdf/ar-threats-2013-508.pdf (accessed on 10 July 2014)

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

9.5.1 Overall Study Design and Plan Description

Table 1: Study Design

9.5.1 Safety Measurements Assessed and Flow Chart

Study Visit	Screening [1]	Check-in	Inpatient Period				Final Visit	Unscheduled	Early termination
			Dosing	Follow Up					
Study Day / Assessments	**-21 to -2**	**-1**	**1**	**2**	**3**	**4**	**8 (± 2)**		
Informed consent	X								
Inclusion/Exclusion criteria	X	X	X						
Demographics	X								
Medical history	X								
Medical history update		X	X	X	X	X	X	X	X
Prior and ConMeds [2]	X	X	X	X	X	X	X	X	X
Complete PE [3]	X						X		X
Abbreviated PE [4]		X				X			
Symptom-directed PE [5]			X	X	X			X	
Height, weight, BMI [6]	X								
Weight		X					X		
Vital signs [7]	X	X	X	X	X	X	X	X	X
Clinical labs (hematology, chemistry, urinalysis) [8]	X	X				X		X	X
Viral serology [9]	X								
Serum pregnancy test	X[13]	X					X		X
Serum FSH level	X[13]								
Urine toxicology	X	X							
Alcohol breathalyzer test	X	X							
12-lead ECG [10]	X	X	X			X			X
Study drug dosing			X						
PK samples [11]			X	X	X	X			X
Counsel on use of contraception and avoidance of pregnancy[14]	X					X	X		X
Counsel to avoid use of prohibited medications, alcohol, marijuana and illicit drugs	X	X				X	X		
Interim medical history			X	X	X	X	X	X	X

Study Visit	Screening [1]	Check-in	Inpatient Period				Final Visit	Unscheduled	Early termination
			Dosing	Follow Up					
Study Day / Assessments	**-21 to -2**	**-1**	**1**	**2**	**3**	**4**	**8 (± 2)**		
AE and SAE review [12]			X	X	X	X	X	X	X
Admit to CTU		X							
Discharge from CTU						X			
Discharge from trial							X		

1.Screening Visit is completed within 21 days before study drug dosing and may require more than one visit.
2.Prior medications include prescription drugs taken 30 days before dosing, and non-prescription drugs, herbs, vitamins, and nutritional supplements taken 15 days before dosing. Concomitant medications include those taken after dosing.
3.Complete PE (except genital, breast, and rectal exam): at Screening, Day -1 (if complete PE was done >7 days before this visit), and Final Visit, or ET.
4.Abbreviated PE: on Day -1 (not performed if the complete PE was performed ≤7 days from this visit) and Day 4.
5.Symptom-directed PE: on Days 1 (predose and postdose), 2, and 3 for evaluation of new symptoms pre-dose and AEs post-dose.
6.BMI is calculated as wt (kg) / ht (m^2).
7.Vital Signs (blood pressure, pulse rate, respiratory rate, and temperature): at Screening Visit; on Days -1, 1, 2, 3, and 4; and at Final Visit, or ET. On Day 1, VS at baseline (approximately 1 h before dosing) and at 1 h (±5 min), 2 h (±10 min), and 4 h (±10 min) after dosing.
8.Clinical laboratory testing with minimum 4 h fast: HEM (Hemoglobin, Hct, RBC, WBC with differential absolute count, platelet count); CHEM (creatinine with estimation of GFR, blood urea nitrogen, glucose, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, total protein, albumin, electrolytes (sodium, potassium, chloride, bicarbonate (CO_2), magnesium); and dipstick urinalysis (blood, protein, glucose): at Screening, Day -1 (if not collected ≤7 days before dosing), Day 4, or ET.
9.Viral Serology (HIV antibody, HBsAg, HCV antibody): at Screening Visit.
10.12-lead ECG with 10 sec rhythm strip: at Screening Visit, Day -1, Day 1 [within 1 h before dosing, and at 1 h (±10 min), 2 h (±10 min), and 4 h (±10 min) after dosing], and Day 4 [72 h (±2 h)] after dosing, or ET.
11.Blood (plasma) PK samples: within 30 min before dosing, and at 0.5 h (±5 min), 1 h (±5 min), 2 h (±5 min), 3 h (±10 min), 4 h (±10 min), 6 h (±10 min), 8 h (±15 min), 12 h (±15 min), 24 h (±2 h), 36 h (± 2 h), 48 h (± 2 h), and 72 h (± 2 h) after dosing, or ET.
12.Collect all AEs from the time of dosing to and including Final Visit. Follow-up AEs and SAEs to resolution or stabilization in the clinical judgment of the study investigator.
13.Serum pregnancy test in all women. FSH only in post-menopausal women.
14.Females to use appropriate contraception and avoid pregnancy to 30 days after last study visit. Males to use appropriate contraception and refrain from donating sperm for 90 days after last study visit.

10.2 Protocol Deviations

Table 2: Distribution of Protocol Deviations by Category, and Type

Category	Deviation Type	All Subjects (N=X)	
		No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type		
	Did not meet inclusion criterion	x	x
	Met exclusion criterion		
	ICF not signed prior to study procedures		
	Other		
Treatment administration schedule	Any type		
	Out of window visit		
	Missed visit/visit not conducted		
	Missed treatment administration		
	Delayed treatment administration		
	Other		
Follow-up visit schedule	Any type		
	Out of window visit		
	Missed visit/visit not conducted		
	Other		
Protocol procedure/assessment	Any type		
	Incorrect version of ICF signed		
	Blood not collected		
	Urine not collected		
	Stool not collected		
	Other specimen not collected		
	Too few aliquots obtained		
	Specimen result not obtained		
	Required procedure not conducted		
	Required procedure done incorrectly		
	Study product temperature excursion		
	Specimen temperature excursion		
	Other		
Treatment administration	Any type		
	Required procedure done incorrectly		
	Study product temperature excursion		
	Other		
N = number of subjects enrolled.			

12.2.2 Displays of Adverse Events

Table 3: Toxicity Grading Scale

Toxicity Grading Tables

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Comments
VITAL SIGNS				
Fever - °C Fever - °F	38.0-38.4 100.4-101.1	38.5-38.9 101.2-102.0	>38.9 >102.0	No recent hot or cold beverages or smoking. A protocol should select either ^{0}C or ^{0}F for inclusion
Tachycardia - bpm	101-115	116-130	>130 or ventricular dysrhythmias	Assume awake and in supine position for 5 min at rest; for AE, measurements at least 3 times with 2 concordant results (Section 8.1.6 of the protocol)
Bradycardia - bpm	50-54 OR 45-50 if baseline <60	45-49 OR 40-44 if baseline <60	<45 OR <40 if baseline <60	as above
Hypertension (systolic) - mm Hg	141-150	151-160	>160	Assume awake, and in supine position for 5 min at rest; for AE, measurements on same arm at least 3 times with 2 concordant results (Section 8.1.6 of the protocol)
Hypertension (diastolic) - mm Hg	91-95	96-100	>100	As above
Hypotension (systolic) - mm Hg	85-89	80-84	<80	As above
Tachypnea – breaths per min	23-25	26-30	>30	Assume awake and in supine position for 5 min at rest; for AE, measurements at least 3 times with 2 concordant results (Section 8.1.6 of the protocol)
Note: Isolated/individual abnormalities of vital signs would not be considered toward halting criteria. Abnormalities of vital signs should be described as "increase X" or "decrease X" (X = heart rate, blood pressure, respiratory rate, temperature) if asymptomatic, transient and not associated with a systemic or organ-specific disorder, and coded by MedDRA within the System Organ Class (SOC) "Investigations." These abnormalities should be graded per criteria in Appendix C of the protocol, but not considered in determining whether study stopping criteria have been met. On the other hand, abnormalities of vital signs that are either secondary to systemic or organ-specific clinical syndrome or primary disorders should be coded in the appropriate SOC (e.g., "cardiac disorders", respiratory disorders", "immunological disorders", etc.). These abnormalities should be considered in determining whether stopping criteria have been met.				
CARDIOVASCULAR				
Arrhythmia		Asymptomatic or transient signs; no medical intervention required	Recurrent and/or persistent signs; symptomatic medical intervention required	
Hemorrhage	Estimated blood loss ≤100 mL	Estimated blood loss >100 mL; no transfusion required	Blood transfusion required	

Toxicity Grading Tables

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Comments
RESPIRATORY				
Cough	Transient cough; no treatment required	Persistent cough; treatment required	Interferes with daily activities	
Bronchospasm, Acute	Transient bronchospasm; no treatment required; FEV1 71-80% of predicted peak flow	Requires treatment; normalizes with bronchodilator; FEV1 60-70% of predicted peak flow	No normalization with bronchodilator; FEV1 <60% of predicted peak flow	
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities; no treatment	Prevents usual and social activities, OR requires treatment	
GASTROINTESTINAL				
Nausea	No interference with normal activity	Some interference with normal activity	Prevents daily activities	
Vomiting	No interference with activity, OR 1-2 episodes in a 24-h period	Some interference with activity, OR >2 episodes in a 24-h period	Prevents daily activity, OR requires medical intervention	
Diarrhea	2-3 loose or watery stools in a 24-h period	4-5 loose OR watery stools in a 24-h period	6 or more loose or watery stools in a 24-h period, OR requires IV hydration OR requires medical intervention	
Oral Discomfort / Dysphagia	Mild discomfort; no difficulty swallowing	Some limits on eating / drinking	Eating / talking very limited; unable to swallow solid foods	
LOCAL IV CATHETER REACTION				
IV site reaction	Not Applicable	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	
SYSTEMIC REACTIONS				
Anaphylaxis **	--	--	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema or angioedema; hypotension	
***Definition*: *A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.*				
Allergic Reaction	Pruritus without rash	Localized urticaria OR requires oral therapy	Generalized urticaria; angioedema OR anaphylaxis OR requires epinephrine	

Toxicity Grading Tables

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Comments
Hypersensitivity (including drug fever)	Transient flushing or rash; temperature 38.0-38.4 °C (100.4-101.1°F)	Rash; flushing; urticaria; dyspnea; temperature 38.5 - 38.9°C (101.2 – 102.0°F)	Symptomatic bronchospasm with or without urticaria; parenteral medication indicated; allergy-related edema or angioedema; hypotension; temperature >38.9°C (>102.0°F)	
Headache	No interference with activity	Repeated use of non-narcotic pain reliever for more than 24 h OR some interference with activity	Significant; any use of narcotic pain reliever OR prevents daily activity OR requires triptans	
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	
SKIN				
Mucocutaneous	Erythema, pruritus	Diffuse, maculo-papular rash, dry desquamation	Vesiculation OR moist desquamation OR ulceration	
Pruritus	No or minimal interference with usual social and functional activities	Greater than minimal interference with usual social and functional activities	Inability to perform usual social and functional daily activities	
ALL OTHER CONDITIONS				
Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity but not requiring medical intervention	Prevents daily activity and requires medical intervention	

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 4: Laboratory Adverse Event Grading Scale

Laboratory AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Blood, serum, or plasma *			
Sodium decrease – mmol/L	130 –132	125 –130	<125
Sodium increase – mmol/L	148 – 149	150 – 153	≥154
Potassium increase – mmol/L	5.3 – 6.0	6.1 – 6.4	≥6.5
Potassium decrease – mmol/L	3.0 – 3.3	2.5 – 2.9	<2.5
Bicarbonate (CO_2) increase – mmol/L	32 - 34	35 – 36	>36
Bicarbonate (CO_2) decrease – mmol/L	18 -- 20	14 - 17	<14
Glucose decrease, fasting – mg/dL	50 – 73	45 – 49	<45
Glucose increase, fasting – mg/dL	107– 125	126 - 249	≥250
Glucose increase, non-fasting – mg/dL	107- 160	161 - 249	≥250
Blood urea nitrogen – mg/dL	21 – 26	27 – 31	>31
Creatinine increase – mg/dL	1.4 – 1.7	1.8 – 2.3	>2.3
Calcium decrease – mg/dL	7.8 –8.0	7.0 – 7.7	<7.0
Calcium increase – mg/dL	11.0 – 11.4	11.5 – 12.4	≥12.5
Phosphorous increase – mg/dL	4.8 – 5.0	5.1 – 5.5	>5.5
Phosphorous decrease – mg/dL	2.0 – 2.4	1.4 – 1.9	<1.4
Total protein decrease – g/dL	5.2 – 6.0	4.8 – 5.1	<4.8
Albumin decrease – g/dL	2.8 – 3.4	2.5 – 2.7	<2.5
AST increase – U/L	43 – 104	105 – 209	≥210
ALT increase, male – U/L	73 – 179	180 – 359	≥360
ALT increase, female – U/L	45 – 109	110 – 219	≥220
Alkaline phosphatase increase – U/L	151 – 240	241 – 360	>360
Total bilirubin (serum) increase – mg/dL (with other LFTs in the normal range)	1.4 – 2.0	2.1 – 2.5	>2.5
Total bilirubin (serum) increase – mg/dL (accompanied by a >3 x ULN increase in ALT or AST)**	1.4 – 1.6	1.7 – 2.0	>2.0
Hemoglobin decrease, female – g/dL	11.0 – 11.5	9.5 – 10.9	< 9.5
Hemoglobin decrease, male – g/dL	12.0 –13.5	10.0 – 11.9	<10.0
WBC increase – cell/mm^3	11,000 – 15,000	15,001 – 20,000	>20,000
WBC decrease – cell/mm^3	2,500 –3,500	1,500 – 2,499	<1,500
Neutrophils decrease – cell/mm^3	1,200 – 1,399	1,000 – 1,199	<1,000
Lymphocytes decrease – cell/mm^3	750 – 999	500 – 749	<500
Monocytes increase – cell/mm^3	1,101 – 2,000	2,001– 3000	>3,000
Eosinophils increase – cell/mm^3	500 – 750	751 – 1,500	>1,500
Basophils increase – cell/mm^3	201 – 500	501 – 800	>800
Platelets decrease – cell/mm^3	120,000 – 125,000	100,000 – <120,000	<100,000
Urine*			
Protein	1+	2+	>2+

Laboratory AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Glucose	1+	2+	>2+
Blood (dipstick)	1+	2+	>2+
Blood (microscopic) - RBCs per HPF	6-10	11-50	>50 and/or gross blood
WBC (microscopic) – WBC per HPF	5-10	11-50	>50
Bacteria (microscopic)	few	moderate	Many

* Institutional normal reference ranges and allowable ranges at screening are provided in Appendix B of the protocol.
**ALT, males: >216 U/mL; ALT, females: >132 U/mL; AST, male or female: >126 U/mL)
Note 1: If a subject was accepted into the trial with a laboratory value of an analyte that overlaps with values used for grading Grade 1 (mild) laboratory abnormalities, an AE will be reported if the on-study value of the same analyte is different (worse) from the baseline.
Note 2: Safety laboratory results that are abnormal according to the local laboratory reference range, but not considered a Grade 1 abnormality, will be evaluated by the study site clinician and reported as Grade 1 abnormality if clinically significant. If not clinically significant, these will not be considered laboratory AEs and will thus not be graded, but will be recorded in the source document and followed-up clinically at the discretion of the study site clinician.
Note 3: Other laboratory parameters performed and reported as parted of the complete blood count, metabolic panel and urinalysis will be evaluated by the study physician, recorded in the source document, and reported as laboratory AEs if clinically significant, and graded according to the criteria in Section 9.2.1 of the protocol.
Note 4: If US by dipstick is abnormal, a microscopic urinalysis will be performed and the results will supersede the results of the dipstick urinalysis.
Note 5: Menstruating females with a positive urine dipstick or microscopic urinalysis may be retested following cessation of menses.

ECG interval abnormality	Grade 1	Grade 2	Grade 3
QT/QTc interval (Fridericia's correction) prolonged (msec)	Asymptomatic, QTc 450-479 msec, OR increase in interval <30 msec above baseline	Asymptomatic, QTc 480-499 msec OR increase in interval 30-59 msec above baseline	Asymptomatic, QTc ≥500 msec OR increase in interval ≥60 msec above baseline
PR interval prolonged - sec	0.21-0.25 sec	>0.25 sec	Type II 2nd degree AV block OR ventricular pause >3.0 sec

Note: The events will be coded as SAE if there are life-threatening associated symptoms or signs (arrhythmia, CHF, hypotension, syncope, torsade's de pointes, etc.)
Note: If a male subject was accepted into the trial with a QT/QTc value that overlaps with values used for grading Grade 1 (mild) QT/QTc prolongation, an AE will be reported if the on-study value of the QT/QTc is higher than the baseline

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 5: Subject Disposition

Subject Disposition	All Subjects (N=X)	
	n	%
Screened	x	--
Enrolled	x	100
Received Treatment	x	Xx
Completed Final Blood Draw		
Completed Follow-up (Study Day 8)		
Early Termination [a]		
Discontinued Study Product		

Note: N = number of subjects enrolled
[a] Refer to Listing 1 for reasons subjects discontinued or terminated early.

Table 6: Analysis Populations

Analysis Populations	Reason Subjects Excluded	All Subjects (N=X)	
		%	N
Safety Population	Subject not dosed	x	Xx
PK Analysis Population	Any Reason		
	Subject not dosed		
	No measurable PK concentration		
PK Subset	Any Reason		
	Subject not dosed		
	Disqualifying protocol deviation		
	No measurable PK concentration		

Note: N = number of subjects enrolled

Table 7: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	X	100
Inclusion	Any inclusion criterion	X	xx
	Informed consent form (ICF) understood and signed before initiating any study procedures	X	xx
	Healthy male or female, as assessed by the authorized site clinician	X	xx
	Willingness to comply with and be available for all protocol procedures including inpatient confinement for about 4 days and availability for follow-up for the duration of the trial	X	xx
	Aged 18 to 45 years inclusive on the day of study drug dosing	X	xx
	BMI ≥18.5 and ≤30 kg/m2 and weight ≥50 kg (110 lbs.) and ≤100 kg (220 lbs.)	X	xx
	In female subjects of childbearing potential, a negative serum pregnancy test at Screening Visit and on Day -1	X	xx
	If female, not pregnant, not breast feeding, and not planning on becoming pregnant during the trial and for 30 days after study participation	X	xx
	Females of childbearing potential and males agree to use acceptable contraception for the duration of the trial and for 30 days (females) or 90 days (males) after final study visit	X	xx
	Male subjects must agree to refrain from sperm donation for the duration of the trial and for 90 days after Final Visit	x	xx
	Laboratory tests, as outlined in Section 8.2.1.1 of the protocol, are in the normal reference range with acceptable exceptions as noted in Section 8.2.1.1 and Appendix B of the protocol	x	xx
	VS, as outlined in Section 8.1.6 of the protocol, are within the acceptable range per Appendix B of the protocol	x	xx
	Has adequate venous access for blood collection	x	xx
	Urine drug screen is negative for tested substances	x	xx
	Alcohol test (breathalyzer) is negative	x	xx
	Willing to abstain from alcohol consumption for 2 days before Day -1 and during the trial	x	xx

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Exclusion	Any exclusion criterion	x	xx
	History of a chronic medical or surgical condition that would interfere with the accurate assessment of the trial's objectives or increase the subject's risk profile	x	xx
	History of hypersensitivity or severe allergic reaction of any type to medications, bee stings, food, or environmental factors	x	xx
	Active allergic symptoms to seasonal and animal allergens that require treatment	x	xx
	A marked baseline prolongation of ECG intervals, or HR <45 bpm or >100 bpm on ECG measurements	x	xx
	Clinically significant abnormal ECG results	x	xx
	Abnormal renal function	x	xx
	Positive serology results for HIV, HBsAg, or HCV	x	xx
	Febrile illness with temperature >37.6°C for <7 days before dosing	x	xx
	Donated whole blood or blood products within 60 days before dosing, or plans to donate before Final Visit (Day 8 ± 2)	x	xx
	Known allergic reactions to any of the study drug components present in the formulation or in its processing, as listed in the IB	x	xx
	Treatment with another investigational product within 30 days of dosing or 5 half-lives or twice the duration of the biological effect of the study drug (whichever is longer)	x	xx
	Active drug or alcohol use, abuse, or dependence within 12 months before Screening Visit that, in the opinion of the investigator, would interfere with adherence to study requirements	x	xx
	Use of any prescription medication within 30 days before dosing or planned use during the study period except as noted below and approved by the designated study clinician	x	xx
	Use of any non-prescription medication, herbal preparation, or nutritional supplement within 15 days before dosing or planned use during the study unless approved by the study clinician	x	xx
	Intake of caffeinated beverages or food within 72 h before dosing or a history of high caffeine consumption (e.g., in the last 4 months drinking >5 cups of coffee/day)	x	xx
	Smoking or use of tobacco or nicotine-containing products within 15 days before dosing	x	xx

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
	Engagement in strenuous exercise within 15 days before dosing (e.g., marathon running, long distance cycling, weight lifting) and during the study period	x	xx
	Any specific behavioral or clinical condition that in the judgment of the investigator precludes participation because it could affect compliance with study procedures or subject safety	x	xx
	Plans to enroll or is already enrolled in another clinical trial that could interfere with safety assessment of the study drug at any time during the study period	x	xx
	Is a study site employee or staff member who is paid entirely or partially by the OCRR/NIAID contract for the DMID-funded trial	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 Study Group

Table 8: Summary of Categorical Demographic and Baseline Characteristics

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

Note: N = number of subjects enrolled.

Table 9: Summary of Continuous Demographic and Baseline Characteristics

Variable	Statistic	All Subjects (N=X)
Age	Mean	x.x
	Standard Deviation	x.x
	Median	x.x
	Minimum	x
	Maximum	x
Height	Mean	x.x
	Standard Deviation	x.x
	Median	x.x
	Minimum	x
	Maximum	x
Weight	Mean	x.x
	Standard Deviation	x.x
	Median	x.x
	Minimum	x
	Maximum	x
BMI	Mean	x.x
	Standard Deviation	x.x
	Median	x.x
	Minimum	x
	Maximum	x

Note: N = number of subjects enrolled

14.1.3 Prior and Concurrent Medical Conditions

Table 10: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class

MedDRA System Organ Class	All Subjects (N=X)	
	n	%
Any SOC	x	xx
[SOC 1]		
[SOC 2]		

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

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 11: Overall Summary of Adverse Events

	Frequency of Event in All Subjects (N = x)	
Event	**n**	**%**
At least one AE	x	x
At least one related AE, mild (grade 1)	x	x
At least one related AE, moderate (grade 2)	x	x
At least one related AE, severe (grade 3)	x	x
At least one serious AE, any	x	x
At least one serious AE, related	x	x
At least one AE leading to early termination	x	x

N = Number of subjects in the Safety Population. Subjects are counted once for each category regardless of the number of events.

14.3.1.1 Solicited Adverse Events

There are no solicited AEs.

14.3.1.2 Unsolicited Adverse Events

Table 12: Summary of Unsolicited Adverse Events by MedDRA System Organ Class, Higher Level Group Term, and Preferred Term

MedDRA System Organ Class	MedDRA Higher Level Group Term	MedDRA Preferred Term	Any Time Post Dose (N=X)			
			n	%	95% CI	Events
Any SOC	Any HLGT	Any PT	x	xx	xx, xx	X
[SOC 1]	HLGT 1	[PT 1]				
		[PT 2]				
[SOC 2]	HLGT 2	[PT 1]				
		[PT 2]				

Table 13: Unsolicited Adverse Events by MedDRA System Organ Class, Higher Level Group Term, Preferred Term, Maximum Severity, and Relationship

MedDRA System Organ Class	MedDRA Higher Level Group Term	Preferred Term	Severity	All Subjects (N = X)			
				Related		Any Relatedness	
				n	%	n	%
Any SOC	Any HLGT	Any PT	Any Severity	x	x	x	x
			Mild	x	x	x	x
			Moderate	x	x	x	x
			Severe	x	x	x	x
SOC 1	Any HLGT	Any PT	Any Severity	x	x	x	x
			Mild	x	x	x	x
			Moderate	x	x	x	x
			Severe	x	x	x	x
SOC 2	HLGT 1	Any PT	Any Severity	x	x	x	x
			Mild	x	x	x	x
			Moderate	x	x	x	x
			Severe	x	x	x	x
SOC 3	HLGT 1	PT 1	Any Severity	x	x	x	x
			Mild	x	x	x	x
			Moderate	x	x	x	x
			Severe	x	x	x	x

Note: N = Number of subjects in the Safety Analysis Population.
[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity. Events are summarized separately for related events only and all AEs regardless of relatedness.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 14: Listing of Serious Adverse Events

AE	No. of Days Post Associated 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	MedDRA System Organ Class	MedDRA Higher Level Group Term	MedDRA Preferred Term
Subject ID:, AE Number:												
Comments:												
Subject ID:, AE Number:												
Comments:												

Table 15: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

AE	No. of Days Post Associated 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	MedDRA System Organ Class	MedDRA Higher Level Group Term	MedDRA Preferred Term
Subject ID:, AE Number:												
Comments:												
Subject ID:, AE Number:												
Comments:												

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

This is a placeholder for the CSR.

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 16: Listing of Abnormal Laboratory Results - Chemistry

Subject ID	Sex	Age (years)	Fasting Status	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Clinically Significant?

Table 17: Listing of Abnormal Laboratory Results - Hematology

Subject ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Clinically Significant?

Table 18: Listing of Abnormal Laboratory Results - Urinalysis

Subject ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Clinically Significant?

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 19: Chemistry Laboratory Results by Severity and Time Point – Any Chemistry Parameter

		None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
Time Point	**N**	**n**	**%**	**N**	**%**	**n**	**%**	**N**	**%**	**n**	**%**
Baseline	x	x	x	X	X	x	x	X	x	x	X
Day 4	x	x	x	X	X	x	x	X	x	x	X
Max Severity Post Baseline	x	x	x	X	X	x	x	X	x	x	X

Note: The "Max Severity 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.

Table 20: Chemistry Laboratory Results by Severity and Time Point – Sodium

		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	**N**	**n**	**%**	**n**	**%**	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**	**n**	**%**
Baseline	x	x	x	x	x	X	x	x	x	x	x	x	x	X	x	x	x
Day 4	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x
Max Severity Post Baseline	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x

Note: The "Max Severity 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.

Table 21: Chemistry Laboratory Results by Severity and Time Point – Potassium

This table will repeat Table 20 for Potassium.

Table 22: Chemistry Laboratory Results by Severity and Time Point – Bicarbonate

This table will repeat Table 20 for Bicarbonate.

Table 23: Chemistry Laboratory Results by Severity and Time Point – Glucose

This table will repeat Table 20 for Glucose.

Table 24: Chemistry Laboratory Results by Severity and Time Point – Blood Urea Nitrogen

This table will repeat Table 19 for Blood Urea Nitrogen.

Table 25: Chemistry Laboratory Results by Severity and Time Point – Creatinine

This table will repeat Table 19 for Creatinine.

Table 26: Chemistry Laboratory Results by Severity and Time Point – Protein

This table will repeat Table 19 for Protein.

Table 27: Chemistry Laboratory Results by Severity and Time Point – Albumin

This table will repeat Table 19 for Albumin.

Table 28: Chemistry Laboratory Results by Severity and Time Point – Aspartate Aminotransferase

This table will repeat Table 19 for Aspartate Aminotransferase.

Table 29: Chemistry Laboratory Results by Severity and Time Point – Alanine Aminotransferase

This table will repeat Table 20 for Alanine Aminotransferase.

Table 30: Chemistry Laboratory Results by Severity and Time Point – Alkaline Phosphatase

This table will repeat Table 19 for Alkaline Phosphatase.

Table 31: Chemistry Laboratory Results by Severity and Time Point – Bilirubin

This table will repeat Table 19 for Bilirubin.

Table 32 Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Any Chemistry Parameter

		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
Time Point	**N**	**n**	**%**	**n**	**%**	**N**	**%**
Baseline	x	x	x	x	x	X	x
Day 4	x	x	x	x	x	X	x
Max Severity Post Baseline	x	x	x	x	x	X	x

Note: The "Max Severity 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.

Table 33: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Sodium

		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	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	x	x	x	x	x	x	x	x	x	x	x	x	x
Day 4	x	x	x	x	x	x	x	x	x	x	x	x	x
Max Severity Post Baseline	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: The "Max Severity 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.

Table 34: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Potassium

This table will repeat Table 33 for Potassium.

Table 35: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Bicarbonate

This table will repeat Table 33 for Bicarbonate.

Table 36: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Glucose

This table will repeat Table 33 for Glucose.

Table 37: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Blood Urea Nitrogen

This table will repeat Table 32 for Blood Urea Nitrogen.

Table 38: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Creatinine

This table will repeat Table 32 for Creatinine.

Table 39: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Protein

This table will repeat Table 32 for Protein.

Table 40: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Albumin

This table will repeat Table 32 for Albumin.

Table 41: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Aspartate Aminotransferase

This table will repeat Table 32 for Aspartate Aminotransferase.

Table 42: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Alanine Aminotransferase

This table will repeat Table 32 for Alanine Aminotransferase.

Table 43: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Alkaline Phosphatase

This table will repeat Table 32 for Alkaline Phosphatase.

Table 44: Chemistry Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Bilirubin

This table will repeat Table 32 for Bilirubin.

Table 45: Chemistry Laboratory Summary Statistics by Time Point – Sodium (mmol/L)

Time Point	N	Mean	Standard Deviation	Median	Min, Max
Baseline	x	x.x	x.x	x.x	x, x
Day 4	x	x.x	x.x	x.x	x, x
Day 4, Change from Baseline	x	x.x	x.x	x.x	x, x
Note: N=Number of subjects in the Safety Population with the laboratory result assessed at the respective time point.					

Table 46: Chemistry Laboratory Summary Statistics by Time Point – Potassium (mmol/L)

This table will repeat Table 45 for Potassium.

Table 47: Chemistry Laboratory Summary Statistics by Time Point – Magnesium (mg/dL)

This table will repeat Table 45 for Magnesium.

Table 48: Chemistry Laboratory Summary Statistics by Time Point – Chloride (mmol/L)

This table will repeat Table 45 for Chloride.

Table 49: Chemistry Laboratory Summary Statistics by Time Point – Bicarbonate (mmol/L)

This table will repeat Table 45 for Bicarbonate.

Table 50: Chemistry Laboratory Summary Statistics by Time Point – Glucose (mg/dL)

This table will repeat Table 45 for Glucose.

Table 51: Chemistry Laboratory Summary Statistics by Time Point – Blood Urea Nitrogen (mg/dL)

This table will repeat Table 45 for Blood Urea Nitrogen.

Table 52: Chemistry Laboratory Summary Statistics by Time Point – Creatinine (mg/dL)

This table will repeat Table 45 for Creatinine.

Table 53: Chemistry Laboratory Summary Statistics by Time Point – Protein (g/dL)

This table will repeat Table 45 for Protein.

Table 54: Chemistry Laboratory Summary Statistics by Time Point – Albumin (g/dL)

This table will repeat Table 45 for Albumin.

Table 55: Chemistry Laboratory Summary Statistics by Time Point – Aspartate Aminotransferase (U/L)

This table will repeat Table 45 for Aspartate Aminotransferase.

Table 56: Chemistry Laboratory Summary Statistics by Time Point – Alanine Aminotransferase (U/L)

This table will repeat Table 45 for Alanine Aminotransferase.

Table 57: Chemistry Laboratory Summary Statistics by Time Point – Alkaline Phosphatase (U/L)

This table will repeat Table 45 for Alkaline Phosphatase.

Table 58: Chemistry Laboratory Summary Statistics by Time Point – Bilirubin (mg/dL)

This table will repeat Table 45 for Bilirubin.

Table 59: Chemistry Laboratory Summary Statistics by Time Point – Direct Bilirubin (mg/dL)

This table will repeat Table 45 for Direct Bilirubin.

Table 60: Hematology Laboratory Results by Severity and Time Point – Any Hematology Parameter

This table will repeat Table 19 for Any Hematology Parameter.

Table 61: Hematology Laboratory Results by Severity and Time Point – Hemoglobin

This table will repeat Table 19 for Hemoglobin.

Table 62: Hematology Laboratory Results by Severity and Time Point – Leukocytes

This table will repeat Table 19 for Leukocytes.

Table 63: Hematology Laboratory Results by Severity and Time Point – Neutrophils

This table will repeat Table 19 for Neutrophils.

Table 64: Hematology Laboratory Results by Severity and Time Point – Lymphocytes

This table will repeat Table 19 for Lymphocytes.

Table 65: Hematology Laboratory Results by Severity and Time Point – Monocytes

This table will repeat Table 19 for Monocytes.

Table 66: Hematology Laboratory Results by Severity and Time Point – Eosinophils

This table will repeat Table 19 for Eosinophils.

Table 67: Hematology Laboratory Results by Severity and Time Point – Basophils

This table will repeat Table 19 for Basophils.

Table 68: Hematology Laboratory Results by Severity and Time Point – Platelets

This table will repeat Table 19 for Platelets.

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

This table will repeat Table 32 for Any Hematology Parameter.

Table 70: Hematology Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Hemoglobin

This table will repeat Table 32 for Hemoglobin.

Table 71: Hematology Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Leukocytes

This table will repeat Table 32 for Leukocytes.

Table 72: Hematology Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Neutrophils

This table will repeat Table 32 for Neutrophils.

Table 73: Hematology Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Lymphocytes

This table will repeat Table 32 for Lymphocytes.

Table 74: Hematology Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Monocytes

This table will repeat Table 32 for Monocytes.

Table 75: Hematology Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Eosinophils

This table will repeat Table 32 for Eosinophils.

Table 76: Hematology Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Basophils

This table will repeat Table 32 for Basophils.

Table 77: Hematology Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Platelets

This table will repeat Table 32 for Platelets.

Table 78: Hematology Laboratory Summary Statistics by Time Point – Hemoglobin (g/dL)

This table will repeat Table 45 for Hemoglobin.

Table 79: Hematology Laboratory Summary Statistics by Time Point – Hematocrit (%)

This table will repeat Table 45 for Hematocrit.

Table 80: Hematology Laboratory Summary Statistics by Time Point – Erythrocytes (10^12/L)

This table will repeat Table 45 for Erythrocytes.

Table 81: Hematology Laboratory Summary Statistics by Time Point – Leukocytes (10^9/L)

This table will repeat Table 45 for Leukocytes.

Table 82: Hematology Laboratory Summary Statistics by Time Point – Neutrophils (10^9/L)

This table will repeat Table 45 for Neutrophils.

Table 83: Hematology Laboratory Summary Statistics by Time Point – Lymphocytes (10^9/L)

This table will repeat Table 45 for Lymphocytes.

Table 84: Hematology Laboratory Summary Statistics by Time Point – Monocytes (10^9/L)

This table will repeat Table 45 for Monocytes.

Table 85: Hematology Laboratory Summary Statistics by Time Point – Eosinophils (10^9/L)

This table will repeat Table 45 for Eosinophils.

Table 86: Hematology Laboratory Summary Statistics by Time Point – Basophils (10^9/L)

This table will repeat Table 45 for Basophils.

Table 87: Hematology Laboratory Summary Statistics by Time Point – Platelets (10^9/L)

This table will repeat Table 45 for Platelets.

Table 88: Urinalysis Laboratory Results by Severity and Time Point – Any Urinalysis Parameter

This table will repeat Table 19 for Any Urinalysis Parameter.

Table 89: Urinalysis Laboratory Results by Severity and Time Point – Protein

This table will repeat Table 19 for Protein.

Table 90: Urinalysis Laboratory Results by Severity and Time Point – Glucose

This table will repeat Table 19 for Glucose.

Table 91: Urinalysis Laboratory Results by Severity and Time Point – Hemoglobin

This table will repeat Table 19 for Hemoglobin.

Table 92: Urinalysis Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Any Urinalysis Parameter

This table will repeat Table 32 for Any Urinalysis Parameter.

Table 93: Urinalysis Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Protein

This table will repeat Table 32 for Protein.

Table 94: Urinalysis Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Glucose

This table will repeat Table 32 for Glucose.

Table 95: Urinalysis Abnormal Laboratory Results Related to Study Treatment by Severity and Time Point – Hemoglobin

This table will repeat Table 32 for Hemoglobin.

14.3.6 Displays of Vital Signs

Table 96: Vital Signs by Assessment, Maximum Severity, and Time Point – Any Assessment

This table will repeat Table 19 for Vital Signs – Any Assessment.

Table 97: Vital Signs by Assessment, Maximum Severity, and Time Point – Systolic Blood Pressure

This table will repeat Table 20 for Vital Signs – Systolic Blood Pressure.

Table 98: Vital Signs by Assessment, Maximum Severity, and Time Point – Diastolic Blood Pressure

This table will repeat Table 19 for Vital Signs – Diastolic Blood Pressure.

Table 99: Vital Signs by Assessment, Maximum Severity, and Time Point – Pulse Rate

This table will repeat Table 20 for Vital Signs – Pulse Rate.

Table 100: Vital Signs by Assessment, Maximum Severity, and Time Point – Respiratory Rate

This table will repeat Table 19 for Vital Signs – Respiratory Rate.

Table 101: Vital Signs by Assessment, Maximum Severity, and Time Point –Temperature

This table will repeat Table 19 for Vital Signs – Temperature.

Table 102: Vital Signs Summary Statistics by Assessment and Time Point – Systolic Blood Pressure (mmHg)

Time Point	N	Mean	Standard Deviation	Median	Min, Max
Baseline					
1 h (± 10 min) after dosing					
1 h, Change from Baseline					
2 h (± 10 min) after dosing					
2 h, Change from Baseline					
4 h (± 10 min) after dosing					
4 h, Change from Baseline					
Day 2					
Day 2, Change from Baseline					
Day 3					
Day 3, Change from Baseline					
Day 4					
Day 4, Change from Baseline					
Day 8					
Day 8, Change from Baseline					

N = number of subjects in the Safety Population with the vital sign assessed for the respective time point

Table 103: Vital Signs Summary Statistics by Assessment and Time Point – Diastolic Blood Pressure (mmHg)

This table will repeat Table 102 for Diastolic Blood Pressure.

Table 104: Vital Signs Summary Statistics by Assessment and Time Point – Pulse Rate (beats/min)

This table will repeat Table 102 for Pulse Rate.

Table 105: Vital Signs Summary Statistics by Assessment and Time Point – Respiratory Rate (breaths/min)

This table will repeat Table 102 for Respiratory Rate.

Table 106: Vital Signs Summary Statistics by Assessment and Time Point –Temperature (C)

This table will repeat Table 102 for Temperature.

14.3.7 Displays of ECG Measurements

Table 107: ECG Overall Interpretations, Post Dose Compared to Baseline

ECG Interpretation	n (%)
1 Hours (± 10 min) After Dosing (N=X)	
Normal at Both Times	x (x)
Normal to Abnormal, NCS	x (x)
Normal to Abnormal, CS	x (x)
Abnormal, NCS at Both Times	x (x)
Abnormal, NCS to Abnormal, CS	x (x)
Abnormal, NCS to Normal	x (x)
2 Hours (± 10 min) After Dosing (N=X)	
Normal at Both Times	x (x)
Normal to Abnormal, NCS	x (x)
Normal to Abnormal, CS	x (x)
Abnormal, NCS at Both Times	x (x)
Abnormal, NCS to Abnormal, CS	x (x)
Abnormal, NCS to Normal	x (x)
4 Hours (± 10 min) After Dosing (N=X)	
Normal at Both Times	x (x)
Normal to Abnormal, NCS	x (x)
Normal to Abnormal, CS	x (x)
Abnormal, NCS at Both Times	x (x)
Abnormal, NCS to Abnormal, CS	x (x)
Abnormal, NCS to Normal	x (x)
72 Hours (± 2 hours) After Dosing (N=X)	
Normal at Both Times	x (x)
Normal to Abnormal, NCS	x (x)
Normal to Abnormal, CS	x (x)
Abnormal, NCS at Both Times	x (x)
Abnormal, NCS to Abnormal, CS	x (x)
Abnormal, NCS to Normal	x (x)

Note: N = number of subjects in safety population with the ECG measurement at the visit indicated above the table. CS = clinically significant; NCS = not clinically significant.

Table 108: ECG by Parameter, Maximum Severity, and Time Point – PR Interval, Aggregate

		None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
Time Point	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	x	x	x	x	x	x	x	x	x	x	x
1 hr Post-Dose	x	x	x	x	x	x	x	x	x	x	x
2 hr Post-Dose	x	x	x	x	x	x	x	x	x	x	x
4 hr Post-Dose	x	x	x	x	x	x	x	x	x	x	x
72 hr Post-Dose	x	x	x	x	x	x	x	x	x	x	x
Max Severity Post Baseline	x	x	x	x	x	x	x	x	x	x	x

Note: The "Max Severity 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.

Table 109: ECG by Parameter, Maximum Severity, and Time Point – QTcF Interval, Aggregate

This table will repeat Table 108 for QTcF Interval, Aggregate.

Table 110: ECG Summary Statistics by Parameter and Time Point – PR Interval, Aggregate (msec)

Time Point	N	Mean	Standard Deviation	Median	Min, Max
Baseline					
1 h (± 10 min) after dosing					
1 h, Change from Baseline					
2 h (± 10 min) after dosing					
2 h, Change from Baseline					
4 h (± 10 min) after dosing					
4 h, Change from Baseline					
72 h (± 2 h) after dosing					
72 h, Change from Baseline					
N = number of subjects in the Safety Population with the ECG parameter assessed for the respective time point					

Table 111: ECG Summary Statistics by Parameter and Time Point – QRS Duration, Aggregate (msec)

This table will repeat Table 110 for QRS Duration, Aggregate.

Table 112: ECG Summary Statistics by Parameter and Time Point – QT Interval, Aggregate (msec)

This table will repeat Table 110 for QT Interval, Aggregate.

Table 113: ECG Summary Statistics by Parameter and Time Point – QTcF Interval, Aggregate (msec)

This table will repeat Table 110 for QTcF Interval, Aggregate.

Table 114: ECG Summary Statistics by Parameter and Time Point – RR Interval, Aggregate (msec)

This table will repeat Table 110 for RR Interval, Aggregate.

Table 115: ECG Summary Statistics by Parameter and Time Point – ECG Mean Ventricular Rate (msec)

This table will repeat Table 110 for ECG Mean Ventricular Rate.

Table 116: ECG Measurements, Frequency of QTcF Prolongation

Time Point	Prolongation Between 30 and <60 msec		Prolongation ≥60 msec	
	N	n (%)	N	n (%)
1 h Post Dose				
2 h Post Dose				
4 h Post Dose				
72 h Post Dose				

14.4 Summary of Prior and Concomitant Medications

Table 117: Number and Percentage of Subjects with Prior Medications by WHO Drug Classification

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	All Subjects (N=X)	
		n	%
Any Level 1 Codes	Any Level 2 Codes	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 safety population. n = Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

Table 118: Number and Percentage of Subjects with Concomitant Medications by WHO Drug Classification

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	All Subjects (N=X)	
		n	%
Any Level 1 Codes	Any Level 2 Codes	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 safety population. n = Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

14.3.1.2 Unsolicited Adverse Events

Figure 1: Incidence of Related Adverse Events by MedDRA System Organ Class and Severity

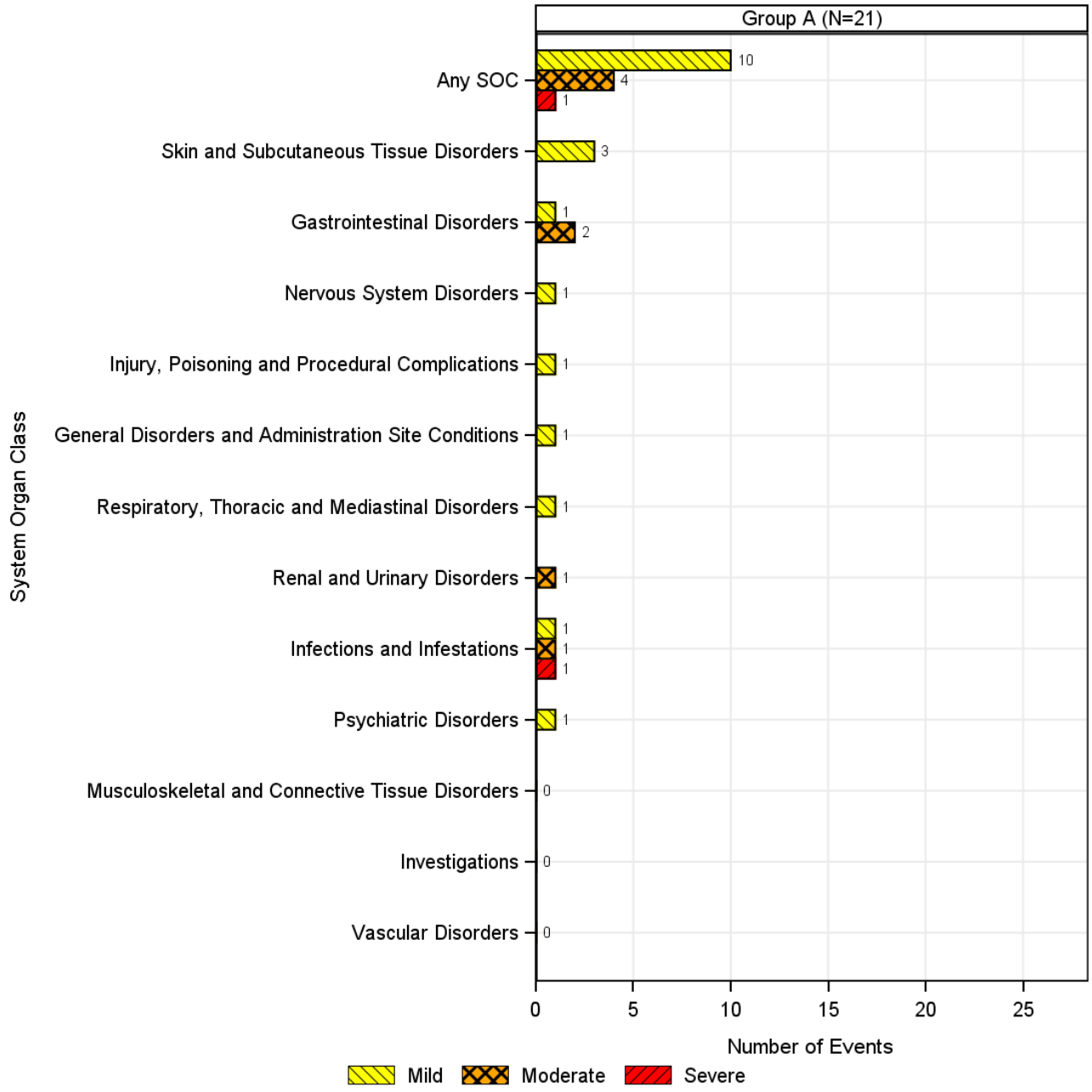
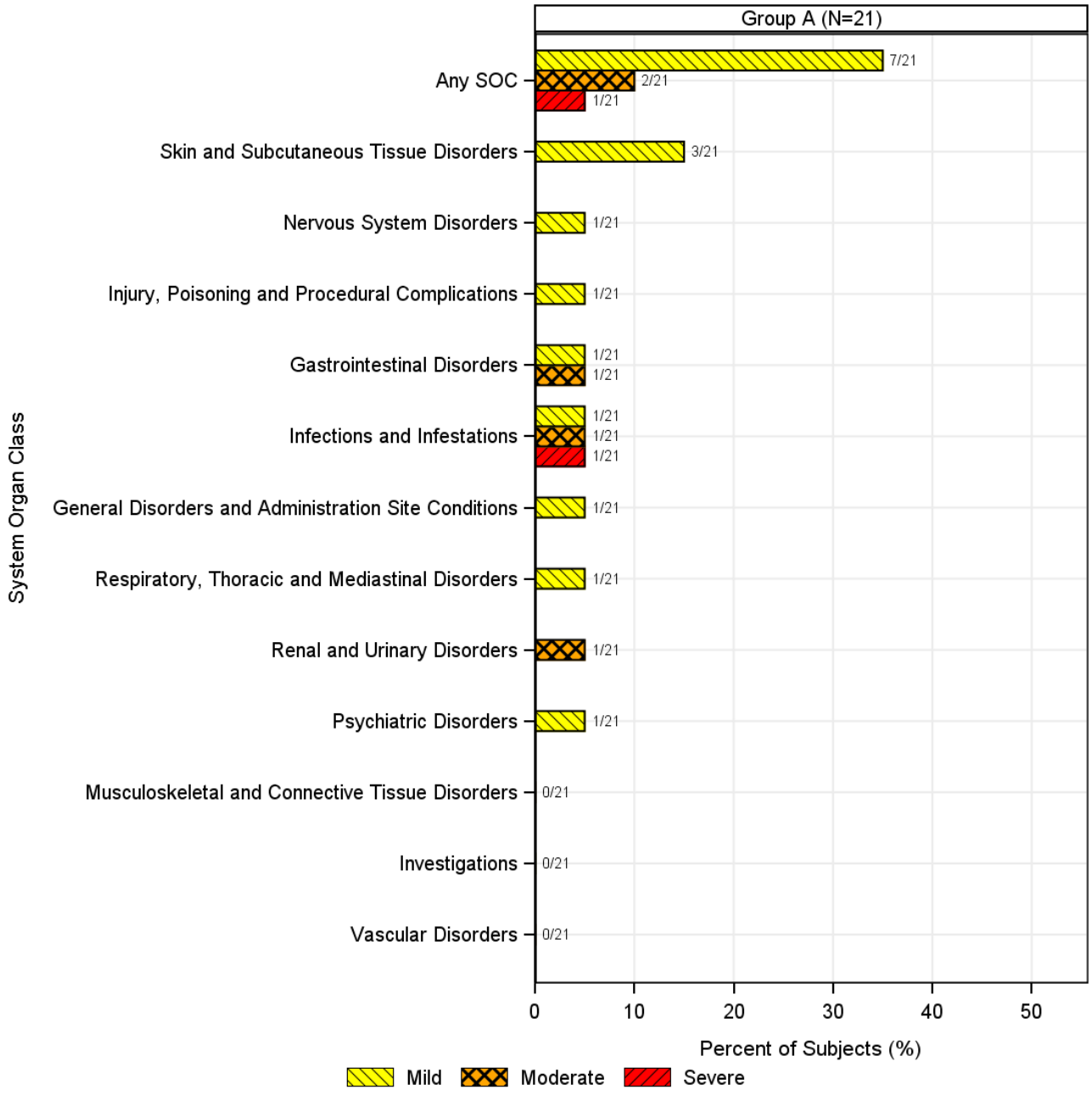


Figure 2: Frequency of Related Adverse Events by MedDRA System Organ Class and Maximum Severity



14.3.5 Displays of Laboratory Results

Figure 3: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Sodium

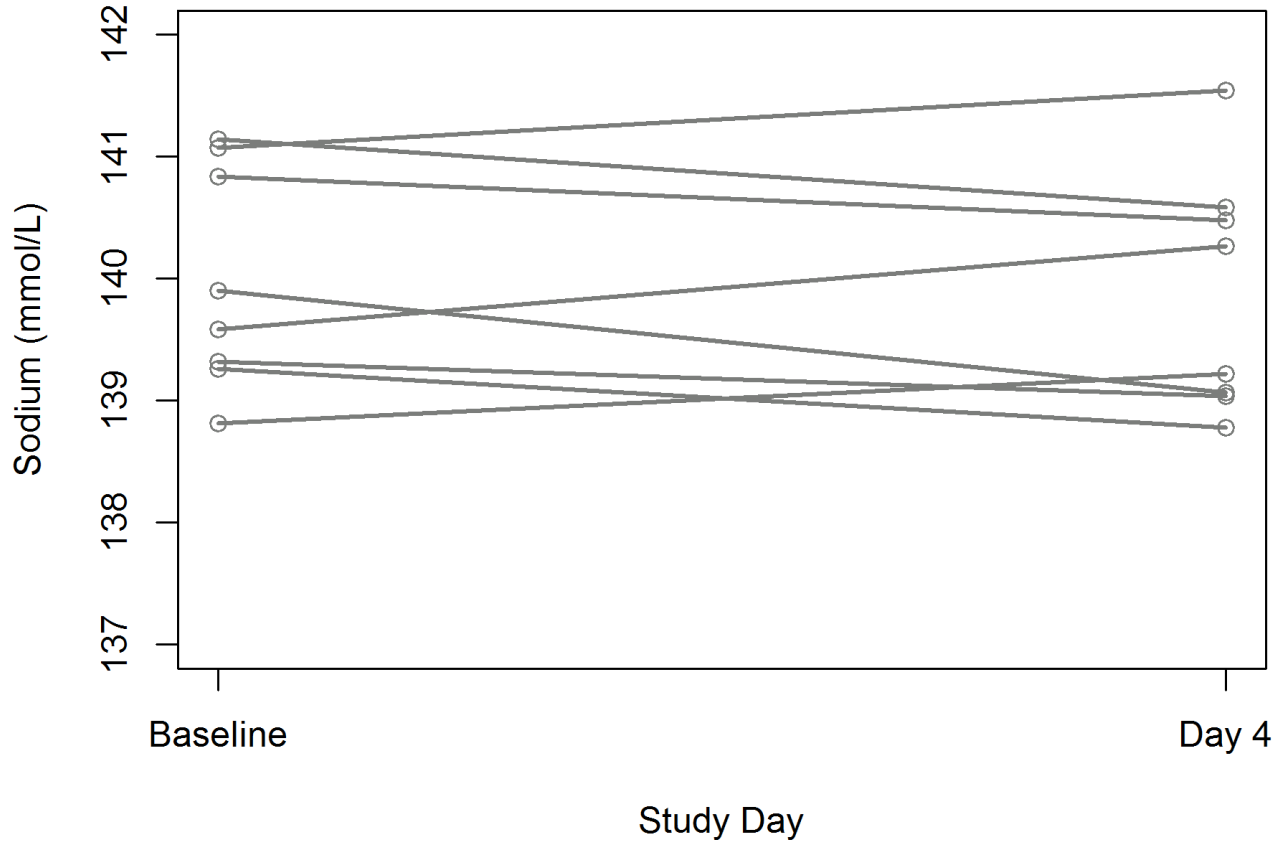


Figure 4: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Potassium

This figure will repeat Figure 3 for Potassium.

Figure 5: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Magnesium

This figure will repeat Figure 3 for Magnesium.

Figure 6: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Chloride

This figure will repeat Figure 3 for Chloride.

Figure 7: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Bicarbonate

This figure will repeat Figure 3 for Bicarbonate.

Figure 8: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Glucose

This figure will repeat Figure 3 for Glucose.

Figure 9: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Blood Urea Nitrogen

This figure will repeat Figure 3 for Blood Urea Nitrogen.

Figure 10: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Creatinine

This figure will repeat Figure 3 for Creatinine.

Figure 11: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Protein

This figure will repeat Figure 3 for Protein.

Figure 12: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Albumin

This figure will repeat Figure 3 for Albumin.

Figure 13: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Aspartate Aminotransferase

This figure will repeat Figure 3 for Aminotransferase.

Figure 14: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Alanine Aminotransferase

This figure will repeat Figure 3 for Alanine Aminotransferase.

Figure 15: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Alkaline Phosphatase

This figure will repeat Figure 3 for Alkaline Phosphatase.

Figure 16: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Bilirubin

This figure will repeat Figure 3 for Bilirubin.

Figure 17: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Direct Bilirubin

This figure will repeat Figure 3 for Direct Bilirubin.

Figure 18: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Hemoglobin

This figure will repeat Figure 3 for Hemoglobin.

Figure 19: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Hematocrit

This figure will repeat Figure 3 for Hematocrit.

Figure 20: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Erythrocytes

This figure will repeat Figure 3 for Erythrocytes.

Figure 21: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Leukocytes

This figure will repeat Figure 3 for Leukocytes.

Figure 22: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Neutrophils

This figure will repeat Figure 3 for Neutrophils.

Figure 23: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Lymphocytes

This figure will repeat Figure 3 for Lymphocytes.

Figure 24: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Monocytes

This figure will repeat Figure 3 for Monocytes.

Figure 25: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Eosinophils

This figure will repeat Figure 3 for Eosinophils.

Figure 26: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Basophils

This figure will repeat Figure 3 for Basophils.

Figure 27: Individual Laboratory Results by Scheduled Visits: Changes from Baseline – Platelets

This figure will repeat Figure 3 for Platelets.

Section 14.3.6 Displays of Vital Signs

Figure 28: Individual Vital Signs by Scheduled Visits: Systolic Blood Pressure

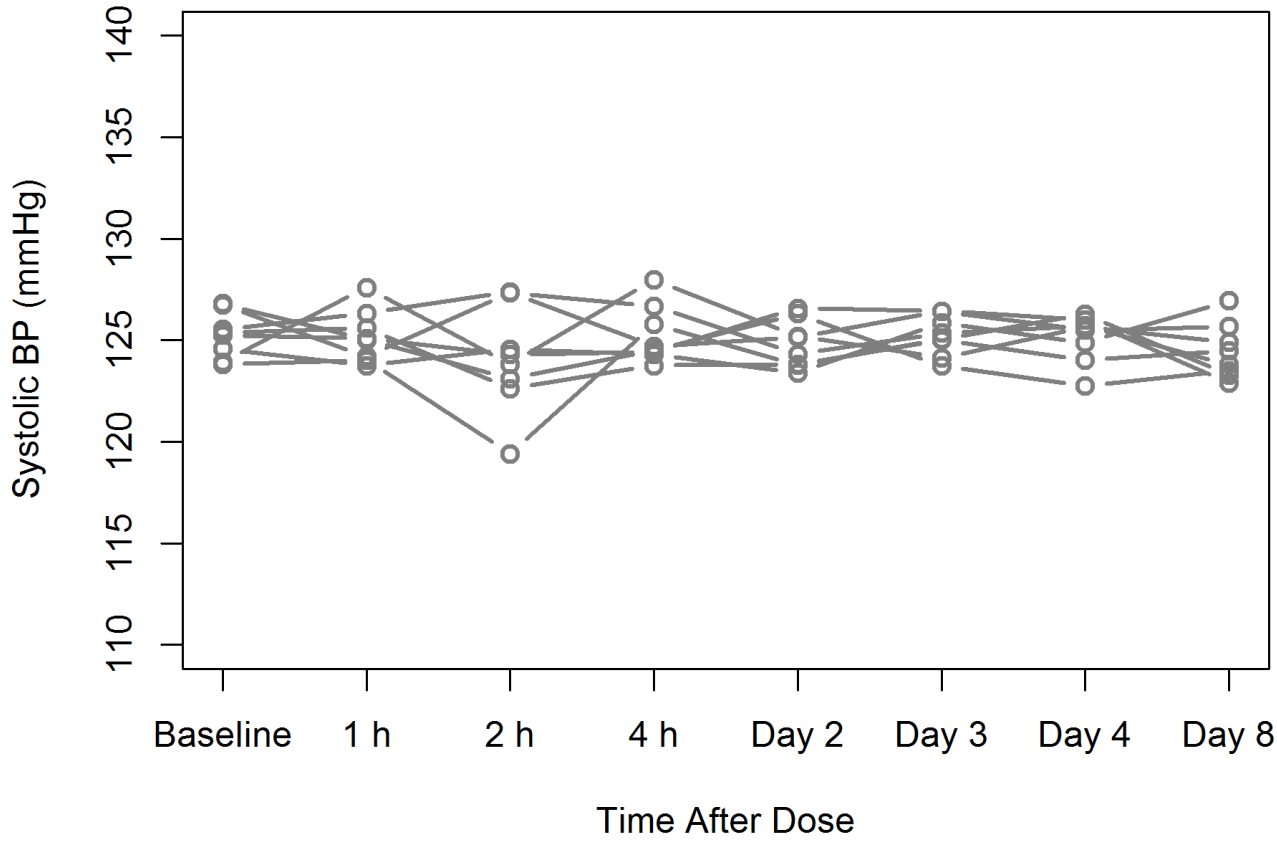


Figure 29: Individual Vital Signs by Scheduled Visits: Diastolic Blood Pressure

This figure will repeat Figure 28 for Diastolic Blood Pressure.

Figure 30: Individual Vital Signs by Scheduled Visits: Pulse Rate

This figure will repeat Figure 28 for Pulse Rate.

Figure 31: Individual Vital Signs by Scheduled Visits: Respiratory Rate

This figure will repeat Figure 28 for Respiratory Rate.

Figure 32: Individual Vital Signs by Scheduled Visits: Temperature

This figure will repeat Figure 28 for Temperature.

Figure 33: Individual ECG by Scheduled Visits: PR Interval, Aggregate

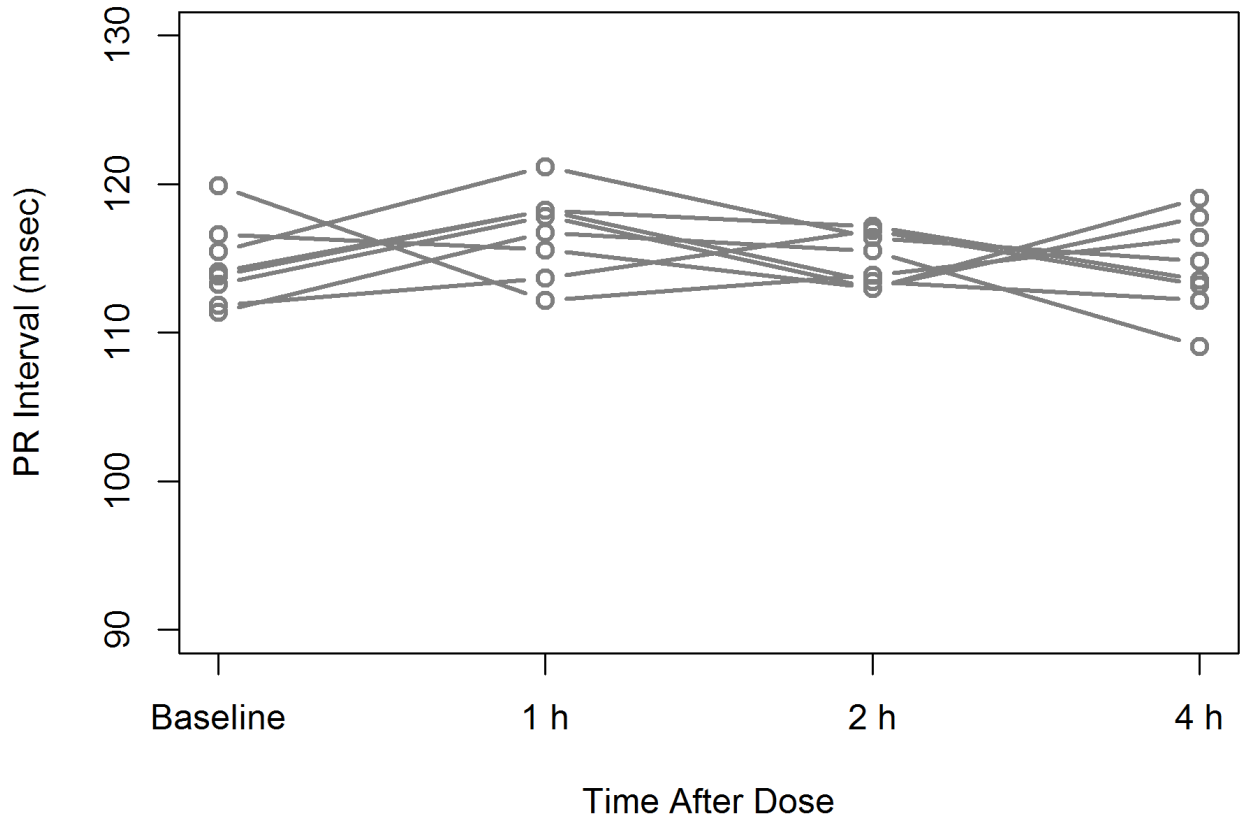


Figure 34: Individual ECG by Scheduled Visits: QRS Duration, Aggregate

This figure will repeat Figure 33 for Diastolic Blood Pressure.

Figure 35: Individual ECG by Scheduled Visits: QT Interval, Aggregate

This figure will repeat Figure 33 for Pulse Rate.

Figure 36: Individual ECG by Scheduled Visits: QTcF Interval, Aggregate

This figure will repeat Figure 33 for QTcF Interval, Aggregate.

Figure 37: Individual ECG by Scheduled Visits: QTcF Interval, Aggregate, Change from Baseline

This figure will repeat Figure 33 for QTcF Interval, Aggregate, Change from Baseline.

Figure 38: Individual ECG by Scheduled Visits: RR Interval, Aggregate

This figure will repeat Figure 33 for RR Interval, Aggregate.

Figure 39: Individual ECG by Scheduled Visits: ECG Mean Ventricular Rate

This figure will repeat Figure 33 for ECG Mean Ventricular Rate.

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

16.1.6 Listing of Subjects Receiving Investigational Product

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

Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 2: 16.2.2.1: Subject-Specific Protocol Deviations

Subject ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

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

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

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 4: 16.2.3: Subjects Excluded from Analysis Populations

Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
	[e.g., Safety, PK]	[e.g., Safety, PK]		

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

Subject ID	Sex	Age at Enrollment (years)	Height (kg)	Weight (m)	BMI (kg/m^2)	Ethnicity	Race

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

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

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

Listing 7: 16.2.5: Compliance and/or Drug Concentration Data

Subject ID	Date of Administration	Start Time of Administration	End Time of Administration	Volume of Product Administered (mL)	Amount of Product Administered (g)

16.2.7 Adverse Events

16.2.7.3 Unsolicited Adverse Events

Listing 8: Unsolicited Adverse Events

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

Note: For additional details about SAEs, see Tables 11-16.

16.2.8 Individual Laboratory Measurements

Listing 9: 16.2.8.1: Clinical Laboratory Results – Chemistry

Subject ID	Planned Time Point	Actual Study Day	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range Low	Reference Range High	Relatedness	Alternate Etiology	Clinical Significance

Listing 10: 16.2.8.2: Clinical Laboratory Results – Hematology

Subject ID	Planned Time Point	Actual Study Day	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range Low	Reference Range High	Relatedness	Alternate Etiology	Clinical Significance

Listing 11: 16.2.8.3: Clinical Laboratory Results – Urinalysis

Subject ID	Planned Time Point	Actual Study Day	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range Low	Reference Range High	Relatedness	Alternate Etiology	Clinical Significance

Listing 12: 16.2.8.4: Clinical Laboratory Results – Other Laboratory Results (Viral Serology, Pregnancy Test, Confirmation of Menopause)

Subject ID	Sex	Planned Time Point	Actual Study Day	Category	Parameter	Result

Listing 13: 16.2.8.5: Clinical Laboratory Results – Toxicology

Subject ID	Sex	Planned Time Point	Actual Study Day	Drug	Result

Listing 14: 16.2.8.6: Clinical Laboratory Results – Breathalyzer

Subject ID	Sex	Planned Time Point	Actual Study Day	Result

16.2.9 Vital Signs and Physical Exam Findings

Listing 15: 16.2.9.1: Vital Signs

Subject ID	Visit	Parameter (units)	Date of Assessment	Time of Assessment (hh:mm)	Result (Severity)	Change from Baseline
	1 hour post dose	Temperature (°C)	ddMMMyyyy		38.4 (Moderate)	0.7

Listing 16: 16.2.9.2: Physical Exam Findings

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

Listing 17: 16.2.10: Listing of ECG Measurements

Subject ID	Visit	Parameter (units)	Date of Assessment	Time of Assessment (hh:mm)	Result (Severity)	Change from Baseline

16.2.11 Prior and Concomitant Medications

Listing 18: Prior Medications

Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1	ATC Level 2	ATC Level 3

Listing 19: Concomitant Medications

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	ATC Level 3

16.2.12 Birth Control Reports

Listing 20: Birth Control Listing

Subject ID	Sex	Child Bearing Potential	Birth Control Method	Start Date	Start Date Certainty	End Date	End Date Certainty	Ongoing?

16.2.13 Pregnancy Reports

Listing 21: 16.2.13.1: Pregnancy Reports – Maternal Information

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 AE listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.

Listing 22: 16.2.13.2: 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 23: 16.2.13.3: 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 AE listing.												

Listing 24: 16.2.13.4: 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?

Listing25: 16.2.13.5: 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

APPENDIX 4. NONCOMPARTMENTAL ANALYSIS TEMPLATE

Details of the PK analysis can be found in the PK SAP.