CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 16-0110

A Phase 1, Randomized, Double-blinded, Four-period Crossover, Thorough QT/QTc (TQT) Clinical Trial to Evaluate the Effect of Zoliflodacin on Cardiac Repolarization in Healthy Male and Female Subjects

NCT03613649

Version 1.0

DATE: 19-DEC-2018

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 16-0110**
Development Phase:	Phase 1
Products:	Zoliflodacin Zoliflodacin Placebo Moxifloxacin Hydrochloride
Form/Route:	Zoliflodacin and Zoliflodacin Placebo: Suspension / Oral Moxifloxacin Hydrochloride: Tablet / 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:	04SEP2018
Clinical Trial Completion Date:	
Date of the Analysis Plan:	19DEC2018
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
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Code
AUC	Area Under the Curve
$AUC_{(0\text{-}inf)}$	AUC Extrapolated to Infinity
$AUC_{(0\text{-}last)}$	AUC from Time of Dosing to Time of the Last Measured Concentration.
$AUC_{(0\text{-}t)}$	AUC from Time of Dosing to Time *t*.
AV	Atrioventricular
BMI	Body Mass Index
bpm	Beat(s) per Minute
BQL	Below Quantification Limit
BUN	Blood Urea Nitrogen
C	Degree(s) Celsius
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CL/F	Apparent Oral Clearance
C_{last}	Last Measured Concentration above the Lower Limit of Quantification
C_{max}	Maximum Concentration
CO_2	Total Carbon Dioxide
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CTU	Clinical Trials Unit
CV	Coefficient of Variation
ΔΔQTcF	Time-Matched, Placebo-Corrected, Baseline-Adjusted Mean QTcF Interval
DCC	Data Coordinating Center
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram

List of Abbreviations *(continued)*

EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ET	Early Termination
FEV1	Forced Expiratory Volume in One Second
FDA	United States Food and Drug Administration
FSH	Follicle Stimulating Hormone
g	Gram(s)
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GM	Geometric Mean
GSD	Geometric Standard Deviation
h	Hour(s)
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISM	Independent Safety Monitor
IUD	Intrauterine Device
K_e	Terminal Phase Elimination Rate Constant
LLOQ	Lower Limit of Quantification
LQTS	Long QT Syndrome
LVH	Left Ventricular Hypertrophy
MedDRA	Medical Dictionary for Regulatory Activities
max	Maximum Value
min	Minimum Value
mg	Milligram(s)
MH	Medical History
MI	Myocardial Infarction

List of Abbreviations *(continued)*

mL	Milliliter(s)
MOP	Manual of Procedures
msec	Millisecond(s)
N	Number (typically refers to subjects)
NCA	Noncompartmental Analysis
NCS	Not Clinically Significant
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NSAID	Nonsteroidal Anti-Inflammatory Drug
OCRR	Office of Clinical Research Resources
ONR	Outside Normal Range
OTC	Over-the-Counter
PD	Pharmacodynamic(s)
PE	Physical Examination
PI	Principle Investigator
PK	Pharmacokinetic(s)
PT	Preferred Term
QTcF	QT Interval of the ECG Corrected Using Fridericia's Formula
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Standard Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
$t_{1/2}$	Apparent Terminal Elimination Half-Life
TdP	Torsades de Pointes
TFLs	Tables, Figures, and Listings
TIA	Transient Ischemic Attack
T_{max}	Time to Obtain Maximum Concentration (C_{max})
TQT	Thorough QT/QTc

List of Abbreviations *(continued)*

V_z/F	Apparent Volume of Distribution During Terminal Phase
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 1, Randomized, Double-Blinded, Four-Period Crossover, Thorough QT/QTc (TQT) Clinical Trial to Evaluate the Effect of Zoliflodacin on Cardiac Repolarization in Healthy Male and Female Subjects" (DMID Protocol 16-0110) describes and expands upon the statistical information presented in the protocol. This document describes all planned analyses and includes example tables, figures, and listings (TFLs) planned for all planned analyses. This SAP follows the International Council for Harmonisation (ICH) guidelines, including E9[1] and E14[2]. Within the TFL mock-ups (Appendices 1, 2, and 3), references to the clinical study report (CSR) sections are included. Any deviation from this SAP will be described and justified in the CSR. The main text of this SAP discusses analysis of safety and pharmacokinetic (PK) endpoints for the study. Analysis of Holter ECG endpoints is presented in the ECG SAP (Appendix 4).

2. INTRODUCTION

Single 2 gram (g) and single 4 g doses of zoliflodacin were safe and well-tolerated in previous clinical trials. The 2 g dose has been selected as the therapeutic dose for further clinical testing of zoliflodacin. The 4 g dose was shown to result in drug exposures higher than the 2 g dose and should provide exposures that will be achieved in patients when used with other drugs that may interact with zoliflodacin. For this reason, the 4 g dose was selected as the supratherapeutic dose for this TQT trial. Placebo for zoliflodacin was selected to control for natural diurnal changes in the electrocardiogram (ECG). Moxifloxacin was selected as a positive comparator to evaluate assay sensitivity for QT interval of the ECG corrected using Fridericia's formula (QTcF), as it predictably causes a mild prolongation of the QTcF interval but has a very low risk for inducing cardiac arrhythmias.

2.1. Purpose of the Analyses

The main text of this SAP discusses analysis of safety and pharmacokinetic (PK) endpoints for the study. Analyses of Holter ECG endpoints (including changes in QTcF and other ECG intervals, T-wave morphology and other ECG effects), as well as drug concentration-QTcF modeling are presented in the ECG SAP (Appendix 4).

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary:

- To evaluate the effect of zoliflodacin on the QTcF interval

Secondary:

- To evaluate the effects of zoliflodacin on other ECG parameters (PR, QRS, and RR intervals, and heart rate)
- To evaluate the sensitivity of QTcF measurement using moxifloxacin
- To evaluate the effect of zoliflodacin on T-wave morphology
- To evaluate the PK of 2 g and 4 g oral zoliflodacin under fasting state
- To evaluate the relationship between zoliflodacin PK and time-matched QTcF pharmacodynamics (PD)
- To evaluate the safety and tolerability of 2 g and 4 g oral zoliflodacin

3.2. Endpoints

Primary:

- The upper bound of the one-sided 95% confidence interval (CI) for the largest time-matched, placebo-corrected, baseline-adjusted mean QTcF interval (ΔΔQTcF) collected in the 24 hour (h) period after 2 g and 4 g dose of zoliflodacin is <10 milliseconds (msec)

Secondary:

- Time-matched, placebo-corrected, baseline-adjusted non-QT intervals (PR, QRS and RR intervals) and heart rate collected in the 24 h period after 2 g and 4 g dose of zoliflodacin
- The lower bound of the one-sided 95% CI of the ΔΔQTcF is >5 msec at one or more individual timepoints between 1 h and 4 h after a single dose of moxifloxacin 400 milligrams (mg)
- Incidence of abnormal T-wave morphology using defined categories in the 24 h period after 2 g and 4 g dose of zoliflodacin
- Single-dose plasma concentrations (and PK exposure parameters, such as maximum concentration [C_{max}] and area under the curve [AUC]) of zoliflodacin collected up to 24 h after 2 g and 4 g dose of zoliflodacin
- Relationship between plasma concentrations of zoliflodacin (and PK and exposure parameters, such as C_{max} and AUC) and ΔΔQTcF up to 24 h after 2 g and 4 g dose of zoliflodacin
- Occurrence of treatment-emergent serious adverse events (SAEs), other unsolicited treatment-emergent adverse event (AEs), and changes from baseline in vital signs, clinical laboratory values, and ECG parameters following administration of zoliflodacin and moxifloxacin from time of dosing to Final Visit, or early termination (ET) Visit

3.3. Study Definitions and Derived Variables

Dosing Periods

Dosing period may be described numerically (1, 2, 3, or 4) or in terms of the treatment received during the period (2 g zoliflodacin, 4 g zoliflodacin, placebo, or 400 mg moxifloxacin). Analysis of safety endpoints will be performed by treatment received for the period, not by the period number.

Period 1: From start of first Check-in day (Day -1) through the day before Check-in for the second dose, or ET Visit, whichever occurs first.

Period 2: From start of second Check-in day through the day before Check-in for the third dose, or ET Visit, whichever occurs first.

Period 3: From start of third Check-in day through the day before Check-in for the fourth dose, or ET Visit, whichever occurs first.

Period 4: From start of fourth Check-in day through Final Visit, or ET Visit, whichever occurs first.

Baseline

Baseline is defined for safety analyses as follows.

- Measurements prior to the first dose will not have a baseline defined.
- Measurements after the first dose, and prior to the second dose (including Period 2 check-in and pre-dose measurements and early termination measurements after the first dose and prior to the second dose) will use the last measurement prior to the first dose as baseline.
- Measurements after the second dose, and prior to the third dose (including Period 3 check-in and pre-dose measurements and early termination measurements after the second dose and prior to the third dose) will use the last measurement prior to the second dose as baseline.
- Measurements after the third dose, and prior to the fourth dose (including Period 4 check-in and pre-dose measurements and early termination measurements after the third dose and prior to the fourth dose) will use the last measurement prior to the third dose as baseline.
- Measurements after the fourth dose will use the last measurement prior to the fourth dose as baseline.
- Measurements taken during the Final Visit will use the last measurement prior to the first dose as baseline for the analysis time points labeled “Final Visit” and will use the last measurement prior to the fourth dose as baseline for the analysis time points labeled “Follow-up”. Listings will show both of the two change from baseline values for Final Visit. The justification for including the Period 1 baseline for the Final Visit is to show overall changes (ideally absence of changes) over the course of the study. Grading of change from baseline will be based on the Period 1 baseline only.

Treatment Associated with Records

Treatment associated with post-dose records will always be the last type of treatment received before the (start) date or date-time associated with the record. AEs will be summarized by treatment and listings of all safety endpoints will include treatment, as it is defined here.

Possible values of treatment, in order of presentation in the CSR, are: 2 g zoliflodacin, 4 g zoliflodacin, placebo, and 400 mg moxifloxacin.

Study Day and Day in Period

Study Day and Day in Period will primarily be used in listings to refer to timing of assessments and events relative to first dosing (Study Day) or dose for the respective period (Day in Period).

The day that the first dose of study product is received is considered Study Day 1 for each subject. The day prior to first dose is considered Study Day = -1, not Study Day = 0.

The day that the dose of study product is received is considered Day in Period = 1 for each subject and each dosing period. The day prior to dosing for each period is considered Day in Period = -1, not Day in Period = 0.

Treatment Sequence

Each subject will receive one dose orally of each of four treatments, labeled A through D:

- Treatment A: zoliflodacin 2 g
- Treatment B: zoliflodacin 4 g
- Treatment C: placebo
- Treatment D: moxifloxacin 400 mg

Each subject will be randomly allocated to one of 12 dosing sequences before dosing on Day 1, Dosing Period 1, and receive a single dose of the preceding four study drugs on different days according to their randomly-assigned dosing sequences. The 12 dosing sequences, in order that they will be presented in the report, are ABCD, ACDB, ADBC, BADC, BDCA, BCAD, CDAB, CABD, CBDA, DCBA, DBAC, and DACB. Sequences will be referred to using these labels in TFLs. The four-letter codes for sequence indicate the order that the treatments will be given to the subject. For example, sequence CABD indicates that the subject would receive placebo in period 1, 2 g zoliflodacin in period 2, 4 g zoliflodacin in period 3, and 400 mg moxifloxacin in period 4.

Tolerability

Tolerability of zoliflodacin will be defined as follows. Tolerability will be concluded for a subject unless any one of the following occurred after receiving zoliflodacin as the most recent non-placebo dose: 1) subject discontinued study drug due to an AE, 2) subject choose to withdraw from the study due to an AE at any time from first dose of zoliflodacin until end of study, or 3) subject was withdrawn from the study by the investigator due to an adverse event at any time from first dose of zoliflodacin until end of study. Withdrawal or discontinuation of study drug after moxifloxacin as the most recent dose will not lead to a conclusion that zoliflodacin was not tolerable.

Visit and Time Point Names for Analysis of Safety and PK Endpoints

Analyses of clinical laboratory results, vital signs, ECG, and PK will be performed by planned time point, expressed as time in h relative to the most recent dose, within period. Labels for each time point are shown in Table 1, including the order the time points will be shown in TFLs and abbreviated labels. The Max Severity Post-Baseline time point is a derived, conceptual time point used in tables displaying severity grading. All other time points refer to planned assessments per the protocol.

The “Follow-up” analysis time points refer to either Check-In visits for the next period (for analysis of treatments given in Period 1, 2, or 3) or to the Final Visit with Pre-dose 4 as baseline. For each treatment, if the treatment was given in Period 1, Period 2, or Period 3, then the pre-dose vital signs and ECG measurements prior to the next dose will be summarized. Listings will use protocol time point names rather

than analysis time point names, e.g. “Check-in” rather than “Follow-up” and “Pre-dose” rather than “Pre-dose (Prior to Next Dose).”

Table 1: Analysis Time Points for Safety and PK Endpoints

Order	Period	Analysis Time Point	Abbreviated Label	Endpoints	Baseline
1	1	Check-In	Day -1	Clinical Laboratory Results, Vital Signs, ECG	N/A
2	1	Pre-dose	0 h	Vital Signs, ECG, PK	N/A
3	1	Max Severity Post-Baseline	N/A	Clinical Laboratory Results, Vital Signs, and ECG Toxicity Grading	N/A
4	1	0.5 h Post-dose	0.5 h	PK	N/A
5	1	1 h Post-dose	1 h	Vital Signs, ECG, PK	Pre-dose 1
6	1	2 h Post-dose	2 h	Vital Signs, ECG, PK	Pre-dose 1
7	1	3 h Post-dose	3 h	PK	N/A
8	1	4 h Post-dose	4 h	Vital Signs, ECG, PK	Pre-dose 1
9	1	6 h Post-dose	6 h	PK	N/A
10	1	8 h Post-dose	8 h	PK	N/A
11	1	12 h Post-dose	12 h	PK	N/A
12	1	24 h Post-dose	24 h	Clinical Laboratory Results, Vital Signs, ECG, PK	Pre-dose 1
13	2	Follow-up	FU	Clinical Laboratory Results, Vital Signs, ECG	Pre-dose 1
14	2	Pre-dose (Prior to Next Dose)	0 h	Vital Signs, ECG	Pre-dose 1
14	2	Pre-dose	0 h	PK	N/A
15	2	Max Severity Post-Baseline	N/A	Clinical Laboratory Results, Vital Signs, and ECG Toxicity Grading	Pre-dose 2
16	2	0.5 h Post-dose	0.5 h	PK	N/A
17	2	1 h Post-dose	1 h	Vital Signs, ECG, PK	Pre-dose 2
18	2	2 h Post-dose	2 h	Vital Signs, ECG, PK	Pre-dose 2
19	2	3 h Post-dose	3 h	PK	N/A
20	2	4 h Post-dose	4 h	Vital Signs, ECG, PK	Pre-dose 2
21	2	6 h Post-dose	6 h	PK	N/A
22	2	8 h Post-dose	8 h	PK	N/A
23	2	12 h Post-dose	12 h	PK	N/A
24	2	24 h Post-dose	24 h	Clinical Laboratory Results, Vital Signs, ECG, PK	Pre-dose 2
25	3	Follow-up	FU	Clinical Laboratory Results, Vital Signs, ECG	Pre-dose 2
26	3	Pre-dose (Prior to Next Dose)	0 h	Vital Signs, ECG	Pre-dose 2
26	3	Pre-dose	0 h	PK	N/A
27	3	Max Severity Post-Baseline	N/A	Clinical Laboratory Results, Vital Signs, and ECG Toxicity Grading	Pre-dose 3
28	3	0.5 h Post-dose	0.5 h	PK	N/A
29	3	1 h Post-dose	1 h	Vital Signs, ECG, PK	Pre-dose 3

Order	Period	Analysis Time Point	Abbreviated Label	Endpoints	Baseline
30	3	2 h Post-dose	2 h	Vital Signs, ECG, PK	Pre-dose 3
31	3	3 h Post-dose	3 h	PK	N/A
32	3	4 h Post-dose	4 h	Vital Signs, ECG, PK	Pre-dose 3
33	3	6 h Post-dose	6 h	PK	N/A
34	3	8 h Post-dose	8 h	PK	N/A
35	3	12 h Post-dose	12 h	PK	N/A
36	3	24 h Post-dose	24 h	Clinical Laboratory Results, Vital Signs, ECG, PK	Pre-dose 3
37	4	Follow-up	FU	Clinical Laboratory Results, Vital Signs, ECG	Pre-dose 3
38	4	Pre-dose (Prior to Next Dose)	0 h	Vital Signs, ECG	Pre-dose 3
38	4	Pre-dose	0 h	PK	N/A
39	4	Max Severity Post-Baseline	N/A	Clinical Laboratory Results, Vital Signs, and ECG Toxicity Grading	Pre-dose 4
40	4	0.5 h Post-dose	0.5 h	PK	N/A
41	4	1 h Post-dose	1 h	Vital Signs, ECG, PK	Pre-dose 4
42	4	2 h Post-dose	2 h	Vital Signs, ECG, PK	Pre-dose 4
43	4	3 h Post-dose	3 h	PK	N/A
44	4	4 h Post-dose	4 h	Vital Signs, ECG, PK	Pre-dose 4
45	4	6 h Post-dose	6 h	PK	N/A
46	4	8 h Post-dose	8 h	PK	N/A
47	4	12 h Post-dose	12 h	PK	N/A
48	4	24 h Post-dose	24 h	Clinical Laboratory Results, Vital Signs, ECG, PK	Pre-dose 4
49	4	Follow-up	FU	Clinical Laboratory Results, Vital Signs, ECG	Pre-dose 4
50	4	Final Visit	N/A	Clinical Laboratory Results, Vital Signs, ECG	Pre-dose 1

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

An overall schematic of study design is shown in Figure 1. The TQT study will be performed in a single center, the Vince & Associates Clinical Research, Inc., clinical trials unit (CTU), according to a randomized, double-blinded (except for the use of moxifloxacin), placebo-controlled, four-period, four-treatment, crossover design balanced with respect to first-order carryover effect in up to 72 healthy male or female subjects, aged 18 to 45 years inclusive, to evaluate the effect of zoliflodacin on QTcF and other ECG parameters, the correlation of the drug concentrations (and PK profile) with ΔΔQTcF, and the PK and safety profiles of zoliflodacin.

Subjects who consent to participate will be enrolled in the trial if they meet all inclusion and no exclusion eligibility criteria. Laboratory assessments at Screening Visit will include routine clinical laboratory tests (chemistry, hematology, urinalysis), testing for viral serology (human immunodeficiency virus [HIV] antibody, Hepatitis B surface antigen [HBsAg], and Hepatitis C virus [HCV] antibody), drugs of abuse, and alcohol. Serum pregnancy testing will be done in all women and serum follicle stimulating hormone (FSH) levels will be measured only in post-menopausal women.

Each subject will receive one dose orally of each of four treatments: 2 g zoliflodacin (investigational drug, therapeutic dose), 4 g zoliflodacin (investigational drug, supratherapeutic dose), placebo (for zoliflodacin), and 400 mg moxifloxacin (positive control comparator). Each subject will be randomly allocated to one of 12 dosing sequences before dosing on Day 1, Dosing Period 1, and receive a single dose of the four study treatments on different days according to their randomly-assigned dosing sequence (see Section 3.3 for list of the 12 sequences).

Six (6) of the planned 72 subjects will be included in each treatment sequence. The design is balanced for period and first-order carryover effects.

Subjects will be dosed in the morning of Day 1 in each dosing period, in a staggered fashion at least several minutes apart, and will receive study drug at approximately the same time in each subsequent dosing period. Each treatment will be administered after at least an 8 h fast, which will continue for at least 4 h after dosing. Consumption of water will be permitted during the fasting period. Zoliflodacin or placebo will be reconstituted in 60 milliliters (mL) of tap water. After the cup containing the 60 mL of zoliflodacin or placebo suspension is taken, approximately 60 mL of tap water will be added to the cup (as a rinse) and consumed by the subject to chase the initial dose. Moxifloxacin will be administered orally with 120 mL of water.

Safety assessments post-dosing will include vital signs, physical examination (PE), 12-lead standard ECG, and clinical laboratory tests including hematology, chemistry, and urinalysis. Treatment-emergent AEs and SAEs will be assessed from time of dosing to end of trial.

Continuous 12-lead Holter ECGs will be performed on Day 1 starting approximately 1 h before dosing and lasting for 24 h after dosing. At timepoints for ECG extraction, subjects will be resting in the supine position for at least 10 minutes before and 5 minutes after the nominal time, without any ongoing stimulation (e.g., television). Three replicate ECGs will be extracted at each timepoint to measure ECG intervals and assess T-wave morphologies.

Plasma for PK analysis will be collected at scheduled timepoints that match timepoints for ECG extraction before and after dosing on Day 1 and through Day 2 in each period, or ET if it occurs within 24 h after dosing.

Subjects will be monitored as inpatients in the CTU up to 24 h after each dose (Day 2). They will then be discharged from the inpatient CTU and followed as outpatients for at least 5 days (Days 3-7) after dosing in Dosing Periods 1-3. The total time to wash-out of the previously-received study drug is at least 8 days. The Final Visit will be 8 ±2 days after the last dose.

A safety monitoring committee (SMC) will be appointed to oversee the safe conduct of the trial. A scheduled SMC meeting will be held after all subjects complete the trial to review safety data and advise on safety monitoring in subsequent clinical trials with zoliflodacin. If criteria for halting the trial are met in any dosing period, dosing will be suspended, and an *ad hoc* SMC meeting will be held to review all available safety data and to make recommendations about the dosing of all further subjects in the trial. An independent safety monitor (ISM), who is local to the CTU, will review SAEs and other severe safety signals and provide an independent analysis to the Site principal investigator (PI), SMC, and DMID.

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

The 4-period crossover design is consistent with recommendations made in the ICH E14[1] guidance. A crossover trial can be conducted since the half-life of zoliflodacin is approximately 6 h. A wash-out phase of at least 5 half-lives of the drug is generally recommended for crossover trials to minimize the risk of carryover. A washout of 3 days would be sufficient to meet the 5 half-lives criterion for both zoliflodacin and moxifloxacin, so the 8 days or more of washout specified in the protocol is expected to prevent a carryover effect of the study drug between treatments.

The 4 g dose will be used as the supratherapeutic dose required by the ICH E14 Guidance for TQT studies. Exposures resulting from a 4 g dose of zoliflodacin were shown to be safe in previous studies. The 400 mg dose of moxifloxacin to be used is the highest dose recommended for use in the clinic and is commonly used as a positive control in TQT studies to ensure assay sensitivity for detecting potentially clinically significant changes in the QT/QTc interval.

Placebo and both of the 2 zoliflodacin doses will be blinded. However, moxifloxacin treatment will not be blinded. Due to the 12 sequences included in the study design, knowledge of the moxifloxacin period does not provide information about what treatments are received in the other 3 periods. Furthermore, the 12 sequences included in the study are balanced for period and first-order carryover effects.

4.3. Selection of Study Population

Only subjects who meet all inclusion criteria and no exclusion criteria will be eligible for enrollment into the trial. No exemptions are granted on Inclusion/Exclusion Criteria in DMID-sponsored trials.

Subject 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 authorized site clinician (listed on United State Food and Drug Administration [FDA] Form 1572)
3. Willingness to comply with and be available for all protocol procedures, including inpatient confinement for 3 days in each dosing period and follow-up for the duration of the trial
4. Aged 18 to 45 years inclusive on the day of first dosing

5. Body Mass Index (BMI) ≥18.5 and ≤30 kg/m^2 and weight ≥50 kg (110 pounds) and ≤100 kg (220 pounds)
6. In all female subjects, whether of childbearing potential or post-menopausal by medical history (MH), a negative serum pregnancy test at Screening Visit and on Day -1 of each dosing period
    - *Note: A woman is considered of childbearing potential unless post-menopausal (≥1 year without menses without other known or suspected cause and with an 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 to become pregnant during the trial and for 30 days after Final Visit
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 Visit
    - *Note: A highly effective method of birth control is defined as one with a low failure rate (i.e., <1% per year) according to 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 agree to refrain from sperm donation for the duration of the trial and for 90 days after Final Visit
10. Laboratory tests, as outlined in Section 8.2 of the protocol, are in the normal reference range with acceptable exceptions as noted in Section 8.2.1 and Appendix B of the protocol
11. Vital signs, 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 8.2.5 of the protocol)
14. Urine alcohol test is negative
15. Willing to abstain from alcohol consumption for 2 days before Day -1 of Period 1 and for the duration of the trial

Subject Exclusion Criteria

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

1. History of acute or chronic cardiovascular disease or surgery
    - *Note: Conditions include: congestive heart failure; coronary artery disease (myocardial infarction, unstable angina); cerebrovascular disease (cerebrovascular accident or stroke or transient ischemic attack (TIA); chronic hypertension; or coronary revascularization surgery (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty)*

2. History of cardiac arrhythmia or syncope related to cardiac arrhythmia or unexplained, or use of a cardiac pacemaker
    - *Note: Conditions include: atrial fibrillation, atrial flutter, or non-sustained or sustained ventricular tachycardia); use of a cardiac pacemaker; personal or family history of Long QT Syndrome (LQTS); or family history of sudden death*
3. History of any other 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; 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 surgery including weight loss surgery or biliary surgery*
4. Major surgical interventions are not permitted within 4 weeks of first dosing and during the trial. Minor surgical interventions are not allowed within 2 weeks of first dosing and during the trial.
5. 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*
6. Active allergic symptoms to seasonal and animal allergens that are moderate to severe, affect daily activity, and require continuous treatment
7. A marked baseline prolongation of ECG intervals, or heart rate <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*
8. 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; any characteristics that would make QT assessment unreliable, including flat T waves; or any condition deemed clinically significant by a study investigator*
9. 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/minute] values according to Cockroft-Gault*
10. Positive serology results for HIV, HBsAg, or HCV
11. Febrile illness with temperature ≥38.0 degrees Celsius (C) for <7 days before dosing in each treatment period

12. Donated whole blood or blood products within 60 days before first dosing, or plans to donate or receive before Final Visit (Day 8 ±2 after last dose in dosing period 4)
    - *Note: Blood products include red blood cells (RBCs), white blood cells (WBCs), platelets, and plasma*
13. Known allergic reactions to fluoroquinolones or to components present in the formulation or processing of zoliflodacin and moxifloxacin
14. Treatment with another investigational product within 30 days of first 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*
15. Active drug or alcohol binge consumption, abuse, or dependence within 12 months before Screening Visit that, in the opinion of the investigator, would interfere with adherence to study requirements
16. Use of any prescription medication within 30 days before first dosing or planned use during the trial except as noted below and approved by the designated study clinician
    - *Note 1: Prohibited medications include moderate or strong CYP3A4 inducers and other drugs with known risk for QT prolongation and Torsades de pointes (TdP); 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 up to 7 days before first dosing or 7 days after last dosing*
    - *Note 2: Allowed medications include: oral contraceptives; H1 antihistamines; all medications approved for control of intraocular pressure including topical ophthalmic non-selective β-blockers, such as betaxolol, carteolol, levobunolol, metipranolol, and timolol; topical/ intranasal corticosteroids; nonsteroidal anti-inflammatory drugs (NSAIDS); licensed influenza vaccine during the flu season, 7 days before first dosing or 7 days after last dosing*
17. Use of non-prescription medications, vitamins, herbs, or nutritional supplements within 15 days before first dosing or planned use during the trial unless approved by the study clinician
    - *Note 1: Intake of nutritional supplements, juice, and herbal preparations or other foods or beverages that may affect the various drug-metabolizing enzymes and transporters (e.g., grapefruit, grapefruit juice, grapefruit-containing beverages, apple or orange juice, vegetables from the mustard green family [e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], and charbroiled meats) within 7 days before dosing*
    - *Note 2: Exceptions: St. John's wart is not allowed within 30 days of dosing; vitamins and over-the-counter (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*
18. Intake of caffeinated beverages or food within 72 h before first dosing or a history of high caffeine consumption (e.g., in the last 4 months drinking >5 cups of coffee/day)
19. Smoking or use of tobacco or nicotine-containing products within 30 days before first dosing
20. Engagement in strenuous exercise within 15 days before first dosing (e.g., marathon running, long-distance cycling, weight lifting) and during the trial

21. 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
22. 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 trial
    - *Note: Includes trials that have a study intervention such as a drug, biologic, or device*
23. Is a CTU 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: CTU employees or staff include the PIs, sub-investigators, or staff who are supervised by the PI or sub-investigators*

4.4. Treatments

4.4.1. Treatments Administered

Each subject will receive 1 dose of each of the 4 study treatments orally. The 4 study treatments are 2 g zoliflodacin (Treatment A), 4 g zoliflodacin (Treatment B), placebo for zoliflodacin (Treatment C), and 400 mg moxifloxacin hydrochloride (Treatment D). The order that the treatments will be given depends on the sequence the subject was randomized to.

As specified in the protocol, dosing, which includes ingestion of the entire 120 mL of tap water for any of the treatments (60 mL of zoliflodacin or placebo suspension and 60 mL of the rinse, or 120 mL for taking the moxifloxacin tablet), will be completed within 5 minutes of initial suspension for Treatment A, Treatment B, and Treatment C and within 5 minutes of start of ingestion for Treatment D. After dosing, subjects will continue to fast for an additional 4 h while water is allowed *ad lib*.

4.4.2. Identity of Investigational Product(s)

Treatment A: One sachet containing 2 g of zoliflodacin will be reconstituted in 60 mL of tap water by the unblinded pharmacist and dosed orally after an overnight fast. The dose will be administered as a mix-and-drink solution in a standardized cup as described in the Manual of Procedures (MOP). After the cup containing 60 mL (suspension volume) of zoliflodacin is taken, approximately 60 mL (rinse volume) of tap water will be added to the cup and consumed by the subject to chase the initial dose. The second 60 mL volume is called ‘the rinse”.

Treatment B: Two sachets containing 2 g of zoliflodacin each will be reconstituted in 60 mL of tap water by the unblinded pharmacist and dosed orally after an overnight fast. The dose will be administered as a mix-and-drink solution in a standardized cup as described in the MOP. After the cup containing 60 mL (suspension volume) of zoliflodacin suspension is taken, approximately 60 mL (rinse volume) of tap water will be added to the cup and consumed by the subject to chase the initial dose. The second 60 mL volume is called ‘the rinse”.

Treatment C: A single dose of 4 g of placebo in powder form, whose quantity will match that in the 4 g dose of zoliflodacin, will be reconstituted in 60 mL of tap water by the unblinded pharmacist and dosed orally after an overnight fast. The dose will be administered as a mix-and-drink solution in a standardized cup as described in the MOP. After the cup containing 60 mL (suspension volume) of placebo is taken, approximately 60 mL (rinse volume) of tap water will be added to the cup and consumed by the subject to chase the initial dose. The second 60 mL volume is called ‘the rinse”.

Treatment D: A single, commercially-available, film-coated, 400 mg tablet of moxifloxacin hydrochloride will be administered orally with 120 mL of tap water.

Additional details of the investigational products may be found in the protocol and MOP.

4.4.3. Method of Assigning Subjects to Sequences (Randomization)

Seventy-two healthy subjects who consent to participate in the trial and meet the eligibility criteria will be enrolled following admittance to the CTU and confirmation of eligibility. Subjects will be registered using a web-based application developed by The Emmes Corporation, the Data Coordinating Center (DCC) for the trial.

Randomized sequence assignments will be generated by a statistician at the DCC for this study. Randomization will occur following admittance to the CTU and confirmation of eligibility.

Subjects will be randomized to one of 12 treatment sequences (Section 3.3) with equal allocation (1:1:1:1:1:1:1:1:1:1:1:1). The randomization list will be generated centrally through the AdvantageEDC^{SM} (Electronic Data Capture [EDC] System, Emmes) by the unblinded study biostatistician, and a list will be transferred to the unblinded study pharmacist before starting the study for the purpose of an emergency back-up.

Enrollment of subjects will be done online using the enrollment module of AdvantageEDC. The randomization code will be prepared by statisticians at the DCC and included in the enrollment module for this trial. AdvantageEDC will assign each subject to a treatment sequence after the demographic and eligibility data have been entered into the system. A designated individual at the participating site will be provided with a code list for emergency unblinding purposes, which will be kept in a secure place. Instructions for using the enrollment module are included in the AdvantageEDC User's Guide.

4.4.4. Selection of Doses in the Study

See Section 2.2.2 of the protocol for rationale of dose selection.

4.4.5. Selection and Timing of Dose for Each Subject

Treatment sequences will be assigned by randomization. Subjects will fast for at least 8 h before dosing and 4 h after dosing. The dosing interval between dosing periods will be at least 8 days to allow for adequate wash-out of drug before the next dose.

If a subject has a Grade 3 AE judged related to study drug administration, this subject will be withdrawn from the study and will not receive subsequent dosing. For all other AEs, dosing may be delayed up to 14 days in order to follow the AE for downgrading or resolution according to the above. If the subject does not meet the criteria for dosing specified above in 14 days, this subject will be withdrawn from the study and will not receive subsequent dosing.

4.4.6. Blinding

Placebo and both of the 2 zoliflodacin doses will be blinded. However, moxifloxacin treatment will not be blinded. The DCC and study pharmacist will be unblinded to all treatments. The protocol contains no explicit provisions for emergency unblinding. According to DMID policy, the study medical monitor responds to requests for emergency unblinding and instructs the DCC to release treatment codes only if necessary to ensure that the subject receives appropriate clinical care.

4.4.7. Prior and Concomitant Therapy

See Section 6.6 of the protocol for restrictions regarding prior and concomitant therapies.

4.4.8. Treatment Compliance

Each of the 4 treatments will be administered in the CTU. Start and end times of dosing will be recorded.

Since each dose of zoliflodacin, placebo or moxifloxacin will be administered by site personnel, subject compliance is not anticipated to be an issue. Complete information regarding any partial or interrupted dosing will be documented. Subjects unable to ingest the full amount of the initial 60 mL zoliflodacin or placebo suspension or the moxifloxacin tablet, or who vomit up to 5 h after dosing with zoliflodacin, placebo or moxifloxacin will be withdrawn from data analysis for the period when the event occurred, but will not be withdrawn from the trial and may complete the remaining treatment periods in the assigned dosing sequence. Subjects who do not ingest the content of the second 60 mL (the rinse) will not be withdrawn from the trial.

4.5. Safety and PK Variables

The following section describes the safety and PK endpoints. Endpoints related to Holter ECG time points are described separately in the ECG SAP (Appendix 4). For a detailed schedule of procedures refer to Table 2. Refer to Section 3 for a list of the primary and secondary objectives and outcomes.

Incidence, relatedness, and severity of treatment-emergent AEs and SAEs will be recorded from time of dose to Final Visit, or ET Visit.

The following other safety parameters will be assessed for each dosing period and at the Final Visit or ET Visit:

- Change from baseline in clinical safety laboratory parameters, as measured at the In-Patient Follow-up visit (the day after dosing), after a minimum 4 h fast.
  - Chemistry: Sodium, Potassium, Magnesium, Chloride, Total Carbon Dioxide (CO_2), Glucose (Fasting), Blood Urea Nitrogen (BUN), Creatinine, Estimated Glomerular Filtration Rate (GFR), Total Protein, Albumin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (AP), Total Bilirubin, and Direct Bilirubin
  - Hematology: Hemoglobin, Hematocrit, Erythrocytes, Leukocytes, Neutrophils (absolute count), Lymphocytes (absolute count), Monocytes (absolute count), Eosinophils (absolute count), Basophils (absolute count), and Platelets
  - Urinalysis: Glucose by Dipstick, Protein by Dipstick, Hemoglobin by Dipstick. If dipstick testing is abnormal, a complete urinalysis with microscopic evaluation will be performed. Urinalysis microscopic evaluation parameters that will be graded and summarized may include Erythrocytes by Microscopic Evaluation, Leukocytes by Microscopic Evaluation, and Bacteria by Microscopic Evaluation.
- Change from baseline in vital signs parameters, as measured at 1 h (±10 minutes), 2 h (±10 minutes), 4 h (±10 minutes), and 24 h (±2 h) after dosing.
  - Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiratory Rate, and Temperature
- Change from baseline in 12-lead standard ECG with 10-sec rhythm strip parameters, as measured 1 h (±10 minutes), 2 h (±10 minutes), 4 h (±10 minutes) and 24 h (±2 h) after dosing.

- Overall interpretation of standard 12-lead ECGs (normal, abnormal not clinically significant [NCS], or abnormal clinically significant [CS]), and the following parameters: PR Interval; QRS Duration, QT Interval; QTcF Interval, RR Interval, ECG Mean Ventricular Rate

Glomerular filtration rate, as estimated by the Cockcroft-Gault equation, will entered directly into the clinical database.

AEs will be graded for severity and relationship to study product, as described in Section 9.2 of the protocol v3.0. Adverse and serious adverse events are defined in Section 9.2 of protocol. Vital signs and ECG results will be graded according to toxicity scales in Table 3. Clinical laboratory results will be graded according to toxicity scales in Table 4.

Blood (plasma) samples for PK analysis will be collected at the following time points for each dosing period: within 30 minutes before dosing, and at 0.5 h (±5 minutes), 1 h (±5 minutes), 2 h (±5 minutes), 3 h (±10 minutes), 4 h (±10 minutes), 6 h (±10 minutes), 8 h (±15 minutes), 12 h (±15 minutes), and 24 h (±2 h) after dosing, or ET if it occurs within 24 h of dosing. Zoliflodacin concentrations will be measured from plasma samples by the bioanalytical laboratory.

5. SAMPLE SIZE CONSIDERATIONS

Enrollment of 72 subjects would provide at least 84% power to conclude a negative effect, given that up to 16 subjects may withdraw early prior to beginning to replace subjects (at least 56 subjects evaluable), and assuming a standard deviation (SD) of ΔΔQTcF of 7 msec and an underlying effect of 5 msec.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Safety, and PK will be summarized by treatment (see Section 3.3), with the order of treatments presented as: 1) 2 g zoliflodacin, 2) 4 g zoliflodacin, 3) placebo, and 4) 400 mg moxifloxacin. Summaries of frequencies and percentages will be presented for categorical data, and summary statistics including the mean, median, SD, minimum value (min), and maximum value (max) will be presented for continuous demographic and safety data. The method of Wilson will be used for CIs of proportions for safety data. The safety population will be used for summaries of demographics and safety endpoints.

Sort order of listings will be by parameter, followed by sequence, followed by subject ID, followed by date (or day) and time. If a listing will not follow this sort order, the sort order to be used can be found in Instruction text for the listing. The sort order of clinical laboratory, vital signs, and ECG parameters is described in Section 9.

6.2. Timing of Analyses

The final analysis will be performed after database lock. There are no planned interim analyses.

6.3. Analysis Populations

All analysis populations to be used in the final analysis are described below. Reasons for exclusion from each analysis population will be summarized by sequence in Table 8 and listed (Listing 4). Although there may be multiple reasons for exclusion from the PK population, only one reason will be counted when summarizing reasons for exclusion from analysis populations in the table. The order that reasons will be considered are the same as the order shown in the table shell. For example, if a subject was excluded from the PK Population and had insufficient concentration data to compute any PK parameters, the subject would be counted for exclusion from the PK analysis subset for reason of exclusion from the PK population only, because that reason appears in the table before the reason of insufficient concentration data.

6.3.1. Safety Population

All subjects who received at least one dose of study drug (zoliflodacin, placebo, or moxifloxacin) will be included in the safety population and analyzed as treated.

6.3.2. PK Population and PK Analysis Subset

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. If any subjects are found to be noncompliant with respect to dosing or have incomplete data, a decision to include them in the analysis will be made on a case-by-case basis.

6.3.3. Holter ECG Analysis Population

The Holter ECG Analysis Population will include all subjects who have received at least one dose of zoliflodacin, moxifloxacin or placebo, treatment, without protocol deviations potentially impacting the ECG intervals and have baseline ECGs and at least one post-dose ECG assessment.

6.3.4. Pharmacokinetic-ECG (PK-ECG) Analysis Population

PK-ECG Analysis Population will be a subset of the Holter ECG Analysis Population and will include all subjects in the Holter ECG Analysis Population with at least one plasma concentration value in the zoliflodacin treatment with a corresponding Holter ECG measurement value at the same nominal timepoint.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses.

6.5. Missing Data

No imputation of missing data is planned.

6.6. Interim Analyses and Data Monitoring

No interim analysis is planned.

6.7. Multicenter Studies

This is a single site study.

6.8. Multiple Comparisons/Multiplicity

Safety and PK analyses will not adjust for multiple comparisons. For multiplicity in the ECG analysis, see the ECG SAP (Appendix 4).

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Screened subjects who were ineligible for enrollment in the study (screen failures) or eligible but not enrolled will be summarized by inclusion and exclusion criteria (Table 6).

Subject disposition will be summarized by sequence (Table 7), showing the number of subjects by sequence who were screened, enrolled, dosed, completed sample collection, or completed follow up. Eligibility for each analysis population will be summarized by sequence (Table 8).

A flow diagram will summarize screening, enrollment, and disposition of subjects by sequence, including number of subjects dosed, number of subject completing ECG follow-up, and reasons for early termination or discontinuation of study product (Figure 2).

Subjects who terminated early from the study will be listed (Listing 1). Subjects who were excluded from an analysis population will be listed (Listing 4).

7.2. Protocol Deviations

A summary of protocol deviations will be presented by deviation category and deviation type (Table 5). 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).

8. EFFICACY EVALUATION

Not Applicable. For analysis of Holter ECG endpoints, see the ECG SAP (Appendix 4).

9. SAFETY EVALUATION

All safety analyses will be presented using the safety population. Subjects will be grouped for summary statistics by Treatment, as defined in Section 3.3.

When calculating the incidence of AEs (i.e., on a per subject basis), each subject will be counted once and any repetitions of unsolicited AEs within a subject (by treatment) will be ignored for events coded in the same category by the Medical Dictionary for Regulatory Activities (MedDRA®). The denominators for percent values will be indicated within the table or table header and denominators will consist of the maximal size of the safety population in the indicated observation period. Moreover, events thus summarized will be coded to the highest severity observed. If the time interval defined by the start date and end date of the AE overlaps more than 1 period, the AE will be associated with treatment immediately preceding the AE start date only, and the AE will be graded according to the maximum severity of the event at any time prior to the AE end date. Abnormal laboratory values or clinical findings measured after dosing will be reported using the toxicity scales in Table 3 and Table 4.

All laboratory, vital signs, and ECG results obtained after the first dose that have programmable criteria described in the toxicity scales will be graded for the CSR according to the programmable criteria, and toxicity grades of mild, moderate, or severe will be indicated for the result in the listings. For criteria involving a change from baseline, the baseline to be used is described in Section 3.3.

If a subject was accepted into the trial with a laboratory, vital signs, or ECG parameter value that overlaps with values used for grading Grade 1 laboratory abnormalities, the result will only be graded (mild or worse) if the post-dose measurement of the parameter is different (worse) than baseline. In other words, a result will be graded as mild, moderate, or severe if and only if it both meets the grading criteria in Table 3 or Table 4 and is worse than baseline by any amount.

9.1. Demographic and Other Baseline Characteristics

Sex, ethnicity, and race of all subjects will be summarized by sequence (Table 9). Ethnicity will be categorized as “Hispanic or Latino,” “Not Hispanic or Latino,” “Unknown,” or “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 case report form (CRF) as “No” to each racial option. Age, height, weight, and BMI will be summarized by sequence (Table 10).

Individual subject listings will be presented for all demographic and baseline characteristics (Listing 5). Note that while weight may be measured once prior to the first dose, the height, weight, and BMI from the first screening visit will be considered the baseline values.

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be 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 by sequence and overall (Table 11). Individual subject listings will be presented for all medical conditions (Listing 6).

9.1.2. Prior and Concomitant Medications

All medications will be coded using the current version of the World Health Organization (WHO) Drug dictionary (WHO Drug Dictionary Enhanced C3 September 1, 2018 or higher). The use of prior and concomitant medications taken during the study will be summarized by treatment and by Anatomical Therapeutic Code ATC 1 and ATC 2 (separately in Table 30 for prior medications and Table 31 for

concomitant medications). Individual subject listings will be presented for all prior and concomitant medications (separately in Listing 19 for prior medications and Listing 20 for concomitant medications).

Drugs will be listed and summarized as prior medications when the end date for the medication is before the first dose of study product and listed and summarized as concomitant medications otherwise.

9.2. Measurements of Treatment Compliance

Date and time of each treatment will be included in Listing 7.

9.3. Adverse Events

When calculating the incidence of AEs (i.e., on a per subject basis) within a given AE class (MedDRA category), each subject will only be counted once for each treatment and any repetitions of AEs within a subject/treatment will be ignored. For each treatment received, the worst severity observed for the subject within the observation period and AE class will be reported. The denominators for percent values will be indicated within the table or table header and denominators will consist of the maximal size of the safety population in the indicated observation period.

9.3.1. Unsolicited Adverse Events

A brief overall summary of AEs by treatment will be shown (Table 12), including number of subjects with at least 1 AE of any severity, number of subjects with at least 1 related AE of any severity, and number of subjects with at least 1 SAE.

AEs by subject will be presented in Listing 8. A subject listing of non-serious AEs of moderate or greater severity will be reported (Table 16).

The following summaries for unsolicited AEs will be presented:

- Tabularly, the total number of AEs and the number and proportion of subjects reporting at least one unsolicited AE, summarized by treatment, MedDRA SOC, HLGT, and PT (Table 13). Denominators for percentages are the number of subjects who received the treatment being summarized. 95% CIs (Wilson CIs) will be presented for proportions.
- Tabularly, the number and proportion of subjects reporting at least one unsolicited AE, summarized by treatment, SOC, HLGT, PT, severity, and relatedness (Table 14).
- Graphically, by treatment, bar charts of frequency of related serious and non-serious AEs by severity and MedDRA SOC (and overall for any SOC) (Figure 3, Figure 4, Figure 5, Figure 6, Figure 7). These figures describe the total number of occurrences of each event, including multiple occurrences per subject.
- Graphically, by treatment, bar chart of incidence of related serious and non-serious AEs by severity and MedDRA SOC (and overall for any SOC) (Figure 8, Figure 9, Figure 10, Figure 11, Figure 12). These figures describe the number of subjects with an event (each subject counted once per SOC).

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

Individual data listings of deaths and serious AEs (Table 15) will be provided. The listing will include: subject ID, treatment, AE description, duration, reason reported as an SAE, severity, relationship to treatment,

alternate etiology if not related, action taken with study treatment, whether subject discontinued due to AE, outcome, MedDRA SOC, MedDRA HLGT, and MedDRA PT.

9.5. Birth Control and Pregnancies

An individual data listing of pregnancy reports will be provided (Listing 21, Listing 22, Listing 23, Listing 24, Listing 25) if a pregnancy occurs post dosing.

Birth control method(s) will be listed for each subject with start date and end date (Listing 26).

9.6. Clinical Laboratory Evaluations

Toxicity grade criteria for laboratory results can be found in Table 4.

Unplanned clinical laboratory evaluations will be listed, but excluded from tabular and graphical summaries, except when calculating the maximum severity post-baseline.

Screening and safety clinical laboratory results (chemistry, hematology, and urinalysis) will be listed (Listing 9, Listing 10, Listing 11). Additionally, abnormal laboratory results (graded mild, moderate, or severe) will be listed in Table 17, Table 18, and Table 19. Measurements outside of the normal range, but not graded as mild, moderate, or severe, will be flagged as "ONR" (outside normal range) in the listings.

Laboratory results will be summarized in tables and figures:

- Tabularly, by parameter, treatment, time point, and toxicity grade (including maximum severity post-baseline)
  - Chemistry Parameters: Table 20
  - Hematology Parameters: Table 22
  - Urinalysis Parameters: Table 24
- Tabularly, by summary statistics for change from baseline, reported by parameter, treatment, and time point
  - Chemistry Parameters: Table 21
  - Hematology Parameters: Table 23
- Graphically, using box plots showing the change from baseline by parameter, treatment, and time point
  - Chemistry Parameters: Figure 13, Figure 14, Figure 15, Figure 16, Figure 17, Figure 18, Figure 19, Figure 20, Figure 21, Figure 22, Figure 23, Figure 24, Figure 25, Figure 26, Figure 27, Figure 28
  - Hematology Parameters: Figure 29, Figure 30, Figure 31, Figure 32, Figure 33, Figure 34, Figure 35, Figure 36, Figure 37, Figure 38

The following parameters will be presented (in order):

- Chemistry: Sodium, Potassium, Magnesium, Chloride, CO_2, Glucose (Fasting), BUN, Creatinine, Estimated GFR, Total Protein, Albumin, AST, ALT, AP, Total Bilirubin, and Direct Bilirubin
- Hematology: Hemoglobin, Hematocrit, Erythrocytes, Leukocytes; absolute counts of Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils; and Platelets

- Urinalysis: Glucose by Dipstick, Protein by Dipstick, Hemoglobin by Dipstick, Erythrocytes by Microscopic Evaluation, Leukocytes by Microscopic Evaluation, Bacteria by Microscopic Evaluation

Only laboratory parameters reported as continuous values will be included in tables of summary statistics for change from baseline and in box plots for change from baseline. Because microscopic urinalysis evaluation is only performed in subjects with an abnormal urine dipstick result, urinalysis parameters assessed by microscopic evaluation will be excluded from tables of summary statistics for change from baseline and in box plots for change from baseline. However, urinalysis parameters assessed by microscopic evaluation will be included in summaries of toxicity grading, where the toxicity grade will be imputed as "Normal" for subjects where microscopic evaluation was not performed.

Laboratory parameters that have grading criteria for both decreases (result lower than normal range and baseline measurement) and increases (result higher than normal range and baseline measurement) will be summarized separately by direction of change. For example, sodium will be summarized separately as "Sodium, Decrease" and "Sodium, Increase."

In tables summarizing toxicity grading, maximum severity observed for the parameter after dosing and within the same dosing period will be summarized (max severity post-baseline). Results of maximum severity for "Any Parameter" will be included for chemistry, hematology, and urinalysis laboratory results. For "Any Parameter" results, the maximum severity across all laboratory parameters in the respective category is summarized by time point, and from maximum severity post baseline.

By protocol, up to one repeat of a planned clinical laboratory assessment is allowed (*Laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or due to collection or laboratory error may be repeated once.*). If replicates for clinical laboratory results are present in the database, then only the second replicate will be summarized and reported. Replicates not used in the analysis will not be listed.

Viral serology screening results (Listing 12), urine toxicology and alcohol screening results (Listing 13), and serum hCG (Human Chorionic Gonadotropin) pregnancy test results (Listing 14) will be listed. If FSH is measured for any subject during the study, FSH will be included in Listing 14.

9.7. Vital Signs and Physical Evaluations

Toxicity grade criteria for vital signs can be found in Table 3. Unplanned vital signs measurements will be listed, but excluded from tabular and graphical summaries, except when calculating the maximum severity post-baseline.

Vital signs results will be listed (Listing 15).

Vital signs results will be summarized in tables and figures:

- Tabularly, by parameter, treatment, time point, and toxicity grade (including maximum severity post-baseline) (Table 25)
- Tabularly, by summary statistics for change from baseline, reported by parameter, treatment, and time point (Table 26)
- Graphically, using box plots showing the change from baseline by parameter, treatment, and time point (Figure 39, Figure 40, Figure 41, Figure 42, Figure 43)

The following parameters will be presented (in order): Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiratory Rate, and Temperature

Vital signs parameters that have grading criteria for both decreases (result lower than normal range and baseline measurement) and increases (result higher than normal range and baseline measurement) will be summarized separately by direction of change.

In tables summarizing toxicity grading, maximum severity observed for the parameter after dosing and within the same period will be summarized (max severity post-baseline). Results of maximum severity for "Any Parameter" will be included. For "Any Parameter" results, the maximum severity across all vital signs parameters is summarized by time point, and from maximum severity post baseline.

The study protocol allows measurements of vital signs to be repeated in the case of an abnormal measurement. The following rules will be used to decide which measurement to include in summaries if more than one replicate was entered into the clinical database.

- If the first replicate is normal, then it will be used for analysis
- If the first replicate is abnormal, and the second replicate is also abnormal, then the first replicate will be used if has a severity equal to or greater to the second replicate, or the second replicate will be used if the second replicate has a higher severity than the first replicate.
- If the first replicate is abnormal, the second replicate is normal, and a third replicate measurement was not performed, then the first replicate will be used in the analysis.
- If the first replicate is abnormal, the second replicate is normal, and the third replicate is normal, then the second replicate will be used in the analysis.
- If the first replicate is abnormal, the second replicate is normal, and the third replicate is abnormal, then the first replicate will be used if has a severity equal to or greater to the third replicate, or the third replicate will be used if the third replicate has a higher severity than the first replicate.

Vital signs replicates not used in the analysis will not be listed.

PE findings will be listed (Listing 16).

9.8. 12-Lead Standard ECG

Toxicity grade criteria for 12-lead standard ECG parameters (PR and QTcF intervals) can be found in Table 3. 12-lead standard ECG interval measurements (Listing 17), and overall interpretation and comments (Listing 18) will be listed. Unplanned 12-lead standard ECG measurements will be listed but excluded from tabular and graphical summaries.

12-lead standard ECG results will be summarized in tables and figures:

- Tabularly, 12-lead standard ECG change in overall interpretation from baseline will be shown by treatment and time point in Table 27.
- Tabularly, by parameter, treatment, time point, and toxicity grade (including maximum severity post-baseline) (Table 28)
- Tabularly, by summary statistics for change from baseline, reported by parameter, treatment, and time point (Table 29)

- Graphically, using box plots showing the change from baseline by parameter, treatment, and time point (Figure 44, Figure 45, Figure 46, Figure 47, Figure 48, Figure 49)

The following parameters will be presented (in order): PR Interval; QRS Duration, QT Interval; QTcF Interval, RR Interval; ECG Mean Ventricular Rate.

9.9. 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 Anatomical Therapeutic Code ATC 1 and ATC 2 (separately in Table 30 for prior medications and Table 31 for concomitant medications). Individual subject listings will be presented for all prior and concomitant medications (separately in Listing 19 for prior medications and Listing 20 for concomitant medications).

9.10. Tolerability

Tolerability to zoliflodacin (see Section 3.3) will be summarized for all subjects in the safety population who have received a dose of zoliflodacin (Table 32). Each subcomponent of tolerability will be included in the summaries: 1) subject discontinued study drug due to an AE, 2) subject choose to withdraw from the study due to an AE at any time from first dose of zoliflodacin until end of study, or 3) subject was withdrawn from the study by the investigator due to an adverse event at any time from first dose of zoliflodacin until end of study.

10. PHARMACOKINETICS

The PK Analysis Population and PK Analysis Subset are defined in Section 6.3. If there are subjects who do not have sufficient samples for a complete analysis, a modified analysis will be conducted in which some or all PK parameters may not be estimated for those subjects, but available PK concentrations will still be tabulated and graphed.

Summaries of PK data across subjects will be performed using the PK Analysis Subset by treatment (dose of zoliflodacin). Zoliflodacin concentrations will be reported in units of ng/mL. Moxifloxacin concentrations will not be measured in this study.

The below describes the basic tabular and graphical summaries of zoliflodacin PK data as well as the noncompartmental analysis (NCA). Analysis of zoliflodacin concentration and exposure data in the context of Holter ECG results is discussed in the ECG SAP.

10.1. Missing Data and Imputations

Analyte concentrations identified as laboratory errors will be indicated as such in the report and may be excluded from analyses. Time points below the lower limit of quantification (LLOQ; 1.00 ng/mL), referred to as below quantification limit (BQL), preceding the first PK concentration above the LLOQ will be imputed as 0 for plotting and for all calculations including NCA and summary statistics. All other BQL values will be missing for analysis purposes.

If the exact time of sample collection for PK is not recorded, the collection time will be imputed as the planned time for analysis. If the exact time is not known, but it is known that the sample was collected outside of the protocol defined time window for collection, then the time point may be excluded from analysis at the discretion of the PK analyst. Rationale for excluding results from analysis will be described in the CSR.

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 or, typically, exclusion from calculation of summary statistics for the respective time point. PK samples collected out of window will be evaluated on a case to case basis and in extreme cases may be excluded from concentration summary statistics and plots of mean concentration. Exclusion of time points, including the justification, will be stated clearly in the report.

Missing data due to non-collection of samples will not be imputed. A geometric mean (GM) of concentrations will be treated as missing for sets of data points containing a BQL value.

10.2. Tabular and Graphical Summaries of Zoliflodacin Concentration-Time Profiles

Zoliflodacin concentrations in plasma will be listed by subject and dosing period with separate columns for concentrations reported by the lab and concentrations used for analysis (Listing 27). The listings will indicate both the nominal time, and actual time associated with the sample. All times will be in units of h.

Zoliflodacin concentrations in plasma will be summarized by dose and time point (Table 33, Table 34) and plotted.

- Individual profiles by zoliflodacin dose as linear plots (Figure 50, Figure 51, Figure 52, Figure 53, Figure 54, Figure 55, Figure 56, Figure 57)
- Individual profiles by zoliflodacin dose as semi-logarithmic plots (Figure 58, Figure 59, Figure 60, Figure 61, Figure 62, Figure 63, Figure 64, Figure 65)
- Figure 66 will plot GM concentration-time profiles by zoliflodacin dose as linear plots.

- Figure 67 will plot GM concentration-time profiles by zoliflodacin dose as semi-logarithmic plots.

10.3. Definition and Estimation of Individual NCA PK Parameters

PK parameters will be estimated through a NCA using Phoenix® WinNonlin® version 8.0 or later (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 (Listing 28).

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

- Linear Up Log Down calculation method
- Uniform weighting
- Oral dosing
- Lambda Z Acceptance Criteria
  - Rsq_adjusted ≥ 0.80
  - Span ≥ 2.5 half-lives
  - Includes at least 3 timepoints after T_{max}

C_{max}

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.

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. Manually chosen time points may be used at the discretion of the PK analyst after examination of the automatically chosen points in the context of the semi-log profile. The set of points chosen must contain only timepoints after T_{max}, include at least 3 timepoints, and satisfy the Lambda Z Acceptance Criteria described above. Otherwise, the elimination rate constant and all derived parameters (apparent terminal elimination half-life [$t_{1/2}$], AUC Extrapolated to Infinity [$AUC_{(0\text{-inf})}$], Apparent Oral Clearance [CL/F], and Apparent Volume of Distribution During Terminal Phase [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. Sets of drug

concentrations used to calculate K_e will be indicated in Listing 27. This parameter will be obtained from the **Lambda_z** parameter calculated by WinNonlin®. K_e will be reported in units of /h.

$t_{1/2}$

The half-life ($t_{1/2}$) is defined as the time required for the drug concentration to decrease by a factor of one-half in the terminal phase. The $t_{1/2}$ can be estimated as ln(2) / K_e. It will be obtained from the **HL_Lambda_z** parameter calculated by WinNonlin®. Half-life 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 CSR. Specific times (*t*) $AUC_{(0\text{-t})}$ will be estimated using the Linear Up Log Down calculation method.

$AUC_{(0\text{-inf})}$ 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. $AUC_{(0\text{-inf})}$ 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:

$$AUC_{(0-inf)} = AUC_{(0-last)} + \frac{C_{last}}{K_e},$$

where C_{last} is the last measured concentration ≥ LLOQ. $AUC_{(0\text{-inf})}$ will be obtained from the **AUCINF_obs** parameter calculated by WinNonlin®. If the amount extrapolated portion of $AUC_{(0\text{-inf})}$ is >20%, the estimated $AUC_{(0\text{-inf})}$ 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/$AUC_{(0\text{-inf})}$. It will be obtained from the **Cl_F_obs** parameter calculated by WinNonlin®. 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®. Volume will be reported in units of L.

10.4. Descriptive Statistics

Subject specific PK parameter estimates will be listed (Listing 28). PK Estimates will be summarized (Table 35, Table 36) by zoliflodacin dose. Summary statistics will include mean, SD, min, max, median, coefficient of variation as a percent (CV%), GM, and geometric SD (GSD). The individual ratio of exposure parameters (C_{max}, $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$) will be summarized by min, max, median, CV%, GM, and 95% CI (t-intervals using log-transformed parameters) (Table 37).

11. IMMUNOGENICITY

Not applicable.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

The number of decimal places reported for listings and certain summary statistics (min and max) of height, weight, and safety parameters (clinical safety laboratory results, vital signs, etc.) will match the number of decimal places reported by the CTU, while other summary statistics (mean, median, GM, GSD) will be reported to an additional decimal place. Drug concentrations, AUCs, and C_{max} and their summary statistics will have the same number of significant digits as the drug concentrations reported by the bioanalytical laboratory. K_e will be reported to 3 decimal places. Other PK parameters will be reported to 1 decimal place. P-values $\geq$0.001 and $\leq$0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001." Percentages (including CV) will be reported as whole numbers.

Listings of individual subject data include a Subject ID column. The subject identifiers assigned by site staff are replaced throughout this report with the Standard Data Tabulation Model (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 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.

14. TECHNICAL DETAILS

SAS version 9.4 or above or R versions 3.2 or above will be used to generate tables, figures, and listings. PK parameters will be estimated through a NCA using Phoenix® WinNonlin® version 8.0 or later (Pharsight Corporation, Cary, NC).

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

None to report.

16. REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical Principles for Clinical Trials E9. 1998.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs E14. 2005.

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 Efficacy/Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 2: Schedule of Study Procedures

Study Visit	Screening[1]	Inpatient Periods 1-4			Outpatient Periods 1-4	Final Visit (after Dose 4)	Unscheduled	Early Termination
		Check-in	Dosing	Follow-up				
Study Day / Assessments	**-21 to -2**	**-1**	**1**	**2**	**3 - 7**	**8 (± 2)**		
Informed consent	X							
Inclusion/Exclusion criteria[2]	X	X	X					
Demographics	X							
Medical history	X							
Medical history update		X						
Prior and Concomitant Medications[3]	X	X	X	X	X	X	X	X
Complete PE[4]	X					X		X
Abbreviated PE[5]		X						
Symptom-directed PE[6]			X	X			X	
Height, weight, BMI[7]	X							
Weight		X				X		X
Vital signs[8]	X	X	X	X		X	X	X
Clinical labs[9]	X	X		X		X	X	X
Viral serology[10]	X							
Serum pregnancy test[11]	X	X				X		X
Serum FSH level[11]	X							
Urine toxicology	X	X						
Alcohol urine test	X	X						
12-lead standard ECG[12]	X	X	X	X		X	X	X
Continuous Holter ECG[13]			X	X				
Randomization[14]			X					
Study drug dosing			X					
PK samples[15]			X	X				X
Counsel on use of appropriate contraception and avoidance of pregnancy[16]	X			X		X	X	X
Counsel to avoid use of prohibited medications, alcohol, marijuana and illicit drugs	X			X				
Counsel to avoid rigorous physical activity	X	X		X				

Study Visit	Screening[1]	Inpatient Periods 1-4			Outpatient Periods 1-4	Final Visit (after Dose 4)	Unscheduled	Early Termination
		Check-in	Dosing	Follow-up				
Study Day / Assessments	**-21 to -2**	**-1**	**1**	**2**	**3 - 7**	**8 (± 2)**		
AE and SAE review[17]			X	X	X	X	X	X
Admit to CTU		X						
Discharge from CTU				X				
Discharge from trial						X		

1. Screening is completed within 21 days before study drug dosing and may require more than one visit.
2. Inclusion/Exclusion criteria at Screening and on Day -1 and Day 1 before dosing in Dosing Period 1 to determine eligibility for enrollment and randomization. I/E criteria will be confirmed before each subsequent dosing period.
3. Prior Medications include prescription during the period 30 days before first dosing and non-prescription drugs, herbs, vitamins, and nutritional supplements taken during the period 15 days before first dosing. ConMeds include those taken after dosing. (See Section 6.6 of Protocol) for prohibited medications and exclusions).
4. Complete PE (except genital, breast, and rectal exams): at Screening, and Final Visit, or ET.
5. Abbreviated PE: on Day -1 (not performed if the complete PE was performed ≤7 days from this visit) in each inpatient period.
6. Symptom-directed PE: on Day 1 (pre-dose and post-dose) and Day 2 in each dosing period to evaluate new symptoms before dosing and AEs after dosing.
7. BMI is calculated as weight in kg divided by height (in meters) squared.
8. Vital signs at Screening; on Days -1, 1, and 2 in each dosing period; and at Final Visit after Dose 4, or ET. On Day 1 of each dosing period, VS at baseline (within 1 h before dosing) and at 1 h (±10 minutes), 2 h (±10 minutes), and 4 h (±10 minutes) after dosing.
9. Clinical laboratory testing with a minimum 4-h fast.
10. Viral serology (HIV1/2 test, HBsAg, HCV antibody): at Screening.
11. Serum pregnancy test in all women at Screening and within 24 h before each dosing period, and at the Final Visit, or ET. FSH only at Screening in postmenopausal women.
12. 12-lead standard ECG with 10-sec rhythm strip: at Screening, Day -1, Day 1 [within 1 h before dosing, and at 1 h (±10 minutes), 2 h (±10 minutes), and 4 h (±10 minutes) after dosing], Day 2 (24 h ±2 h) or ET. At an Unscheduled Visit, a 12-lead standard ECG will be done only if needed for the evaluation of an AE.
13. Continuous Holter ECG recorded from 1 h before dosing to 24 h after dosing in each dosing period. ECGs are extracted (three replicates per timepoint) before dosing (at 45, 30, and 15 minutes before dosing) and at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, and 24 h after dosing in each dosing period.
14. Eligible subjects are randomized to a treatment sequence on Day 1 before receiving Dose 1. Randomization confirmed at each dosing period.
15. Blood (plasma) PK samples: within 30 minutes before dosing, and at 0.5 h (±5 minutes), 1 h (±5 minutes), 2 h (±5 minutes), 3 h (±10 minutes), 4 h (±10 minutes), 6 h (±10 minutes), 8 h (±15 minutes), 12 h (±15 minutes), and 24 h (±2 h) after dosing in each dosing period, or ET if it occurs within 24 h of dosing.
16. Female subjects to use appropriate contraception and avoid pregnancy for 30 days after Final Visit or ET. Male subjects to use appropriate contraception and avoid donating sperm for 90 days after Final Visit or ET.
17. Collect all AEs from the time of dosing in Dosing Period 1 through Final Visit after Dose 4. Follow up AEs and SAEs to resolution or stabilization in the clinical judgment of the study investigator.

12.2.2 Displays of Adverse Events

Table 3: Toxicity Grading Tables – Clinical Adverse Events

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Vital Signs			
Fever - °C	38.0-38.4	38.5-38.9	>38.9
Fever - °F	100.4-101.1	101.2-102.0	>102.0
Tachycardia - bpm	101-115	116-130	>130 or ventricular dysrhythmias
Bradycardia - bpm	50-54 OR 45-50 if baseline <60	45-49 OR 40-44 if baseline <60	<45 OR <40 if baseline <60
Hypertension (systolic) - mmHg	141-150	151-160	>160
Hypertension (diastolic) - mmHg	91-95	96-100	>100
Hypotension (systolic) - mmHg	85-89	80-84	<80
Tachypnea – breaths per minutes	23-25	26-30	>30
12-Lead Standard ECG			
QTcF interval prolonged (msec)	Asymptomatic, QTcF 450-479 msec	Asymptomatic, QTcF 480-500 msec OR increase in interval 30-59 msec above baseline	Asymptomatic, QTcF >500 msec OR increase in interval ≥60 msec above baseline
PR interval prolonged (msec)	210-250 msec	>250 msec	Type II 2nd degree AV block OR ventricular pause >3.0 sec
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
Respiratory			
Cough	Transient cough; no treatment required	Persistent cough; treatment required	Interferes with daily activities
Bronchospasm, Acute	Transient bronchospasm; no treatment required; forced expiratory volume in one second (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

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
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
Allergic Reaction	Pruritus without rash	Localized urticaria OR requires oral therapy	Generalized urticaria OR angioedema OR anaphylaxis OR requires epinephrine
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

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
All Other Conditions			
Illness or clinical AE (as defined according to applicable regulations)	Require minimal or no treatment; does not interfere with the subject's daily activities.	Result in a low level of inconvenience or concern with therapeutic measures; may cause some interference with functioning.	Interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment; are usually incapacitating

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)
Chemistry			
Sodium decrease – mmol/L	130 - 131	125 –129	<125
Sodium increase – mmol/L	149 - 150	151 – 153	>153
Potassium increase – mmol/L	5.6 – 6.0	6.1 – 6.4	≥6.5
Potassium decrease – mmol/L	3.0 – 3.2	2.5 – 2.9	<2.5
Bicarbonate (CO_2) increase – mmol/L	34 – 35	36 – 37	>37
Bicarbonate (CO_2) decrease – mmol/L	17 - 18	14 - 16	<14
Glucose decrease, fasting – mg/dL	47 - 49	45 –46	<45
Glucose increase, fasting – mg/dL	116 – 125	126 – 249	≥250
Glucose increase, non-fasting – mg/dL	116 – 160	161 – 249	≥250
Blood urea nitrogen – mg/dL	25 - 27	28 – 32	>32
Creatinine increase, male – mg/dL	1.46 – 1.70	1.71 – 2.30	>2.30
Creatinine increase, female – mg/dL	1.21 – 1.50	1.51 – 2.00	>2.00
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
Total protein decrease – g/dL	5.1 – 5.7	4.6 – 5.0	<4.6
Albumin decrease – g/dL	2.8 – 3.4	2.5 – 2.7	<2.5
AST increase, male – U/L	46 – 115	116 – 220	>220
AST increase, female – U/L	36 - 90	91 - 175	>175
ALT increase, male – U/L	53 – 115	116 - 230	>230
ALT increase, female – U/L	39 – 95	96 – 190	>190
Alkaline phosphatase increase – U/L	151 – 240	241 – 360	>360
Total bilirubin (serum) increase – mg/dL (with other LFTs in the normal range)	1.5 – 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)**	1.5 – 1.7	1.8 – 2.1	>2.1
Hematology			
Hemoglobin decrease, female – g/dL	10.8 – 11.2	9.4 – 10.7	<9.4
Hemoglobin decrease, male – g/dL	11.8 – 12.9	10.0 – 11.7	<10.0
WBC increase – cells/µL	11,000 – 15,000	15,001 – 20,000	>20,000
WBC decrease – cells/µL	2,500 – 3,500	1,500 – 2,499	<1,500
Neutrophils decrease – cells/µL	1,200 – 1,499	1,000 – 1,199	<1,000
Lymphocytes decrease – cells/µL	750 – 849	500 – 749	<500
Monocytes increase – cells/µL	1,101 – 2,000	2,001 – 3000	>3,000
Eosinophils increase – cells/µL	500 – 750	751 – 1,500	>1,500
Basophils increase – cells/µL	201 – 500	501 – 800	>800
Platelets decrease – cells/µL	120,000 – 124,000	100,000 – 119,000	<100,000

Laboratory AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Urinalysis			
Protein	1+	2+	>2+
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

10.2 Protocol Deviations

Table 5: 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		
	Other specimen not collected		
	Too few aliquots obtained		
	Specimen result not obtained		
	Required procedure not conducted		
	Required procedure done incorrectly		
	Required specimen collected out of window		
	Required procedure done out of window		
	Study product temperature excursion		
	Specimen temperature excursion		
	Other		
Treatment administration	Any type		
	Required procedure done incorrectly		
	Study product temperature excursion		
	Other		

Category	Deviation Type	All Subjects (N=X)	
		No. of Subj.	No. of Dev.
Blinding policy/procedure	Any type		
	Treatment unblinded		
	Other		

14.1 Description of Study Subjects

Table 6: Ineligibility Summary of Screen Failures

[Implementation Note: Only inclusion and exclusion criteria resulting in at least 1 screen failure will be included in the table.]

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n (%)
Any	Number of subjects failing any eligibility criterion or eligible but not enrolled	x
Inclusion	Any inclusion criterion	x (x)
	[inclusion criterion 1]	x (x)
	[inclusion criterion 2]	x (x)
Exclusion	Any exclusion criterion	x (x)
	[exclusion criterion 1]	x (x)
	[exclusion criterion 2]	x (x)
Eligible but not Enrolled	Any Reason	x (x)
	[Reason 1]	x (x)
	[Reason 2]	x (x)

Note: More than one criterion may be marked per subject. Denominator for percentages is the total number of screen failures.

Table 7: Subject Disposition by Sequence

Subject Disposition[a]	ABCD (N=X)	ACDB (N=X)	ADBC (N=X)	BADC (N=X)	BDCA (N=X)	BCAD (N=X)	CDAB (N=X)	CABD (N=X)	CBDA (N=X)	DCBA (N=X)	DBAC (N=X)	DACB (N=X)	All Subjects (N=X)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Screened	x	x	x	x	x	x	x	x	x	x	x	x	x
Enrolled/Randomized	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)
Dosing Period 1: Received Treatment	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)
Dosing Period 1: Completed 24 h of Holter ECG after Dose	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)
Dosing Period 2: Received Treatment	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)
Dosing Period 2: Completed 24 h of Holter ECG after Dose	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)
Dosing Period 3: Received Treatment	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)
Dosing Period 3: Completed 24 h of Holter ECG after Dose	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)
Dosing Period 4: Received Treatment	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)
Dosing Period 4: Completed 24 h of Holter ECG after Dose	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)
Completed Final Visit	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)

Note: N= number of subject randomized to each sequence.
[a] Refer to Listing 16.2.1 for reasons subjects discontinued or terminated early.
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

Table 8: Analysis Population Exclusions by Sequence

[Implementation Note: Although subjects may meet multiple criteria for exclusion, they will be counted under only one reason for exclusion in this table. Priority for assigning reasons for exclusions is consistent with the order in the table.]

Analysis Populations	Reason Subjects Excluded	ABCD (N=X)	ACDB (N=X)	ADBC (N=X)	BADC (N=X)	BDCA (N=X)	BCAD (N=X)	CDAB (N=X)	CABD (N=X)	CBDA (N=X)	DCBA (N=X)	DBAC (N=X)	DACB (N=X)	All Subjects (N=X)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Safety Population	Any reason	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)
PK Population	Any reason	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)
	Did not receive zoliflodacin	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)
	Incomplete dose of zoliflodacin	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)
	No quantifiable post-dose zoliflodacin concentration	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)
PK Analysis Subset	Any Reason	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)
	Exclusion from PK Population	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)
	Has protocol deviations that potentially impact PK	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)
	PK data insufficient to estimate any PK parameters	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)
Holter ECG Analysis Population	Any Reason	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)
	No dose of zoliflodacin, moxifloxacin or placebo received	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)
	Has protocol deviations that potentially impact the ECG intervals	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)
	Does not have at least one baseline and at least one post-dose Holter ECG assessment	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)
Pharmacokinetic-ECG (PK-ECG) Analysis Population	Any Reason	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)

Analysis Populations	Reason Subjects Excluded	ABCD (N=X)	ACDB (N=X)	ADBC (N=X)	BADC (N=X)	BDCA (N=X)	BCAD (N=X)	CDAB (N=X)	CABD (N=X)	CBDA (N=X)	DCBA (N=X)	DBAC (N=X)	DACB (N=X)	All Subjects (N=X)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Exclusion from Holter ECG Analysis Population	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)
	Does not have at least one ECG and PK concentration at the same nominal time point	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)

Note: N= number of subject randomized to each sequence.
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

14.1.2 Demographic Data by Study Group

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

Variable		ABCD (N=X)	ACDB (N=X)	ADBC (N=X)	BADC (N=X)	BDCA (N=X)	BCAD (N=X)	CDAB (N=X)	CABD (N=X)	CBDA (N=X)	DCBA (N=X)	DBAC (N=X)	DACB (N=X)	All Subjects (N=X)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex	Male	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)
	Female	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)
Ethnicity	Not Hispanic or Latino	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)
	Hispanic or Latino	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)
	Not Reported	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)
	Unknown	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)
Race	American Indian or Alaska Native	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)
	Asian	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)
	Native Hawaiian or Other Pacific Islander	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)
	Black or African American	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)
	White	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)
	Multi-Racial	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)
	Unknown	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)

Note: N= number of subject randomized to each sequence
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

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

[Implementation Note: Height, Weight, and BMI values summarized will be from the initial screening visit for each subject.]

Variable	Statistic	ABCD	ACDB	ADBC	BADC	BDCA	BCAD	CDAB	CABD	CBDA	DCBA	DBAC	DACB	All Subjects
Age (years)	N	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
	Standard Deviation	x	x	x	x	x	x	x	x	x	x	x	x	x
	Median	x	x	x	x	x	x	x	x	x	x	x	x	x
	Minimum	x	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x	x	x	x	x
Height (cm)	N	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
	Standard Deviation	x	x	x	x	x	x	x	x	x	x	x	x	x
	Median	x	x	x	x	x	x	x	x	x	x	x	x	x
	Minimum	x	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight (kg)	N	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
	Standard Deviation	x	x	x	x	x	x	x	x	x	x	x	x	x
	Median	x	x	x	x	x	x	x	x	x	x	x	x	x
	Minimum	x	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x	x	x	x	x
BMI (kg/m^2)	N	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
	Standard Deviation	x	x	x	x	x	x	x	x	x	x	x	x	x
	Median	x	x	x	x	x	x	x	x	x	x	x	x	x

Variable	Statistic	ABCD	ACDB	ADBC	BADC	BDCA	BCAD	CDAB	CABD	CBDA	DCBA	DBAC	DACB	All Subjects
	Minimum	x	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: N=Number of subjects in the Safety Population
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

14.1.3 Prior and Concurrent Medical Conditions

Table 11: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class

MedDRA System Organ Class	ABCD (N=X)	ACDB (N=X)	ADBC (N=X)	BADC (N=X)	BDCA (N=X)	BCAD (N=X)	CDAB (N=X)	CABD (N=X)	CBDA (N=X)	DCBA (N=X)	DBAC (N=X)	DACB (N=X)	All Subjects (N=X)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any SOC	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)
[SOC 1]	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)
[SOC 2]	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)

Note: N= number of subject randomized to each sequence
n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 12: Overall Summary of Adverse Events by Treatment

	2 g Zoliflodacin (N=X)		4 g Zoliflodacin (N=X)		Placebo (N=X)		400 mg Moxifloxacin (N=X)		Any Treatment (N=X)	
Subjects[a] with	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**
At least one unsolicited adverse event	x	x	x	x	x	x	x	x	X	x
At least one related unsolicited adverse event	x	x	x	x	x	x	x	x	X	x
At least one Mild related unsolicited adverse event	x	x	x	x	x	x	x	x	X	x
At least one Moderate related unsolicited adverse event	x	x	x	x	x	x	x	x	X	x
At least one Severe related unsolicited adverse event	x	x	x	x	x	x	x	x	X	x
At least one SAE[b]	x	x	x	x	x	x	x	x	X	x
At least one related SAE	x	x	x	x	x	x	x	x	X	x
At least one adverse event leading to early termination[c]	x	x	x	x	x	x	x	x	X	x

N= Number of subjects in the Safety Population given a dose of the respective treatment
[a] Subjects are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Table 15.
[c] As reported on the Adverse Event eCRF.

14.3.1.2 Unsolicited Adverse Events

Table 13: Summary of Unsolicited Adverse Events by MedDRA System Organ Class, High Level Group Term, Preferred Term, and Treatment

MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Treatment	N	n	%	95% CI	No. of Events
Any SOC	Any HLGT	Any PT	Any Treatment		x	xx	xx, xx	x
			2 g Zoliflodacin					
			4 g Zoliflodacin					
			Placebo					
			400 mg Moxifloxacin					
SOC 1	Any HLGT	Any PT	Any Treatment					
			2 g Zoliflodacin					
			4 g Zoliflodacin					
			Placebo					
			400 mg Moxifloxacin					
SOC 1	HLGT 1	Any PT	Any Treatment					
			2 g Zoliflodacin					
			4 g Zoliflodacin					
			Placebo					
			400 mg Moxifloxacin					
SOC 1	HLGT 1	PT 1	Any Treatment					
			2 g Zoliflodacin					
			4 g Zoliflodacin					
			Placebo					
			400 mg Moxifloxacin					
SOC 1	HLGT 1	PT 2	Any Treatment					
			2 g Zoliflodacin					
			4 g Zoliflodacin					
			Placebo					
			400 mg Moxifloxacin					

Note: N=Number of subjects in the Safety Population given a dose of the respective treatment.
This table presents number and percentage of subjects. A subject is only counted once per PT / treatment.

Table 14: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment

MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Severity	2 g Zoliflodacin (N=X)		4 g Zoliflodacin (N=X)		Placebo (N=X)		400 mg Moxifloxacin (N=X)		Any Treatment (N=X)	
				Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)
Any SOC	Any HLGT	Any PT	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
SOC 1	Any HLGT	Any PT	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
SOC 1	HLGT 1	Any PT	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
SOC 1	HLGT 1	PT 1	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
SOC 1	HLGT 1	PT 2	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
			Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Note: N= Number of subjects in the Safety Population given a dose of the respective treatment.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 15: Listing of Serious Adverse Events

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. If the event is ongoing (no stop date), indicate "ongoing" for the "Duration". If more than one reason is selected for the reason reported as an SAE, list all reasons in the column, separated by a comma. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. Listing is ordered by Subject ID, then by AE Number.]

Adverse Event	Treatment	No. of Days Post Treatment (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term
Subject ID: PHU.00123, Period 2 of Sequence:BACD , AE Number:001												
Anaphylaxis	2 g Zoliflodacin	5 (1)	5	Hospitalization	Severe	Not Related, Flu Vaccine	None	Yes	Resolved			
Comments:												
Subject ID: ,Period of Sequence: , AE Number:												
Comments:												
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin												

Table 16: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

[Implementation Note: This listing is included in the tables document, as it is included in the body of the CSR. If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. Dosing Period will be given a treatment label (2 g Zoliflodacin, 4 g Zoliflodacin, Placebo, or 400 mg Moxifloxacin).]

Adverse Event	Treatment	No. of Days Post Treatment (Duration)	Severity	Relationship to Study Treatment, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term
Subject ID: PHU.00123, Period 2 of Sequence:BACD , AE Number:001										
Headache	2 g Zoliflodacin	5 (1)	Moderate	Related	…					
Comments:										
Subject ID: , Period _ of Sequence: , AE Number:										
Comments:										
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin										

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

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

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 17: Listing of Abnormal Laboratory Results - Chemistry

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing will contain abnormal laboratory results of mild, moderate, or severe severity. A complete listing of all laboratory results is included in the listings document. In the Laboratory Parameter column, indicate the units after the parameter, e.g., Hemoglobin (g/dL). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 16.2 (mild).]

Subject ID	Sequence	Sex	Treatment	Period Number	Planned Time Point	Study Day (Day in Period)	Laboratory Parameter (Units)	Result (Severity)	Change from Baseline[a]	Clinical Significance
PHU.00123	ABCD	Male	4 g zoliflodacin	2	24 h Post-dose	11 (2)	Glucose (mg/dL)	130 (Moderate)	+40	No

[a] For Final Visit, listings show change from baseline values using the last measurement prior to first dose as baseline.

Table 18: Listing of Abnormal Laboratory Results - Hematology

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing will contain abnormal laboratory results of mild, moderate, or severe severity. A complete listing of all laboratory results is included in the listings document. In the Laboratory Parameter column, indicate the units after the parameter, e.g., Hemoglobin (g/dL). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 16.2 (mild).]

Subject ID	Sequence	Sex	Treatment	Period Number	Planned Time Point	Study Day (Day in Period)	Laboratory Parameter (Units)	Result (Severity)	Change from Baseline[a]	Clinical Significance

[a] For Final Visit, listings show change from baseline values using the last measurement prior to first dose as baseline.

Table 19: Listing of Abnormal Laboratory Results - Urinalysis

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing will contain abnormal laboratory results of mild, moderate, or severe severity. A complete listing of all laboratory results is included in the listings document. In the Laboratory Parameter column, indicate the units after the parameter, e.g., Erythrocytes (/hpf). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 16.2 (mild).]

Subject ID	Sequence	Sex	Treatment	Period Number	Planned Time Point	Study Day (Day in Period)	Laboratory Parameter (Units)	Result (Severity)	Clinical Significance

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 20: Chemistry Clinical Safety Laboratory Results by Parameter, Maximum Severity, Time Point, and Dosing Period

[Implementation Note: If there is not at least 1 Mild, Moderate, or Severe Event for Any Period, Max Severity Post-Baseline, then only the Any Period, Max Severity Post-Baseline row will be shown for the parameter.]

Dosing Period	Time Point	N	Mild		Moderate		Severe	
			n	%	n	%	n	%
Chemistry - Any Parameter								
Any Period	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Final Visit[b]	x	x	x	x	x	x	x
2 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
4 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
Placebo	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
400 mg Moxifloxacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
Chemistry – Sodium, Decrease								
Any Period	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Final Visit[b]	x	x	x	x	x	x	x
2 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
4 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
Placebo	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x

Dosing Period	Time Point	N	Mild		Moderate		Severe	
			n	%	n	%	n	%
400 mg Moxifloxacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
Chemistry – Sodium, Decrease								
…								

Note: The "Max Severity Post-Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline within the period, including unscheduled assessments. N=Number of subjects in the Safety Population that had clinical safety labs measured at the respective visit.

[a] The "Follow-up" analysis time points refer to either Check-In visits for the next period (for analysis of treatments given in Period 1, 2, or 3) or to the Final Visit with Pre-dose 4 as baseline.

[b] The "Final Visit" analysis time point uses the last measurement prior to the first dose as baseline.

Table 21: Chemistry Clinical Safety Laboratory Results Change from Baseline – Summary Statistics by Parameter, Time Point, and Dosing Period

Dosing Period	Time Point	N	Mean	SD	Median	Min, Max
Chemistry, Sodium (mmol/L)						
2 g Zoliflodacin	24 h Post-dose					
	Follow-up[a]					
4 g Zoliflodacin	24 h Post-dose					
	Follow-up[a]					
Placebo	24 h Post-dose					
	Follow-up[a]					
400 mg Moxifloxacin	24 h Post-dose					
	Follow-up[a]					
Dosing Period 4	Final Visit[b]					
Chemistry, Potassium (mmol/L)						
2 g Zoliflodacin	24 h Post-dose					
	Follow-up[a]					
4 g Zoliflodacin	24 h Post-dose					
	Follow-up[a]					
Placebo	24 h Post-dose					
	Follow-up[a]					
400 mg Moxifloxacin	24 h Post-dose					
	Follow-up[a]					
Dosing Period 4	Final Visit[b]					
Chemistry, Chloride (mmol/L)						
…						

Note: N=Number of subjects in the Safety Population that had clinical safety labs measured at the respective visit.

[a] The "Follow-up" analysis time points refer to either Check-In visits for the next period (for analysis of treatments given in Period 1, 2, or 3) or to the Final Visit with Pre-dose 4 as baseline.

[b] The "Final Visit" analysis time point uses the last measurement prior to the first dose as baseline.

14.3.5.2 Hematology Results

Table 22: Hematology Clinical Safety Laboratory Results by Parameter, Maximum Severity, Time Point, and Dosing Period

This table will repeat Table 20 for Hematology parameters.

Table 23: Hematology Clinical Safety Laboratory Results Change from Baseline – Summary Statistics by Parameter, Time Point, and Dosing Period

This table will repeat Table 21 for Hematology parameters.

14.3.5.3 Urinalysis Results

Table 24: Urinalysis Clinical Safety Laboratory Results by Parameter, Maximum Severity, Time Point, and Dosing Period

This table will repeat Table 20 for Urinalysis parameters.

14.3.6 Displays of Vital Signs

Table 25: Vital Signs Results by Parameter, Maximum Severity, Time Point, and Dosing Period

[Implementation Note: If there is not at least 1 Mild, Moderate, or Severe Event for Any Period, Max Severity Post-Baseline, then only the Any Period, Max Severity Post-Baseline row will be shown for the parameter.

Dosing Period	Time Point	N	Mild		Moderate		Severe	
			n	%	n	%	n	%
Systolic Blood Pressure, Decrease								
Any Period	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
	Final Visit[b]	x	x	x	x	x	x	x
2 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
4 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
Placebo	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
400 mg Moxifloxacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x

Dosing Period	Time Point	N	Mild		Moderate		Severe	
			n	%	n	%	n	%
Systolic Blood Pressure, Increase								
…								

Note: The "Max Severity Post-Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline within the period, including unscheduled assessments. N=Number of subjects in the Safety Population that had vital signs measured at the respective time point.

[a] The "Follow-up" analysis time points refer to either Check-In visits for the next period (for analysis of treatments given in Period 1, 2, or 3) or to the Final Visit with Pre-dose 4 as baseline.

[b] The "Final Visit" analysis time point uses the last measurement prior to the first dose as baseline.

Table 26: Vital Signs Change from Baseline – Summary Statistics by Parameter, Time Point, and Dosing Period

[Implementation Note: The following vital signs parameters will be summarized, in order: Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiration Rate, Temperature.]

Dosing Period	Time Point	N	Mean	SD	Median	Min, Max
Systolic Blood Pressure (mmHg)						
2 g Zoliflodacin	1 h Post-dose	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x
4 g Zoliflodacin	1 h Post-dose	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x
Placebo	1 h Post-dose	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x
400 mg Moxifloxacin	1 h Post-dose	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x
Dosing Period 4	Final Visit[b]	x	x	x	x	x
Diastolic Blood Pressure (mmHg)						
…						

Note: N= Number of subjects in the Safety Population that had vital signs measured at the respective time point.

[a] The "Follow-up" analysis time points refer to either Check-In visits for the next period (for analysis of treatments given in Period 1, 2, or 3) or to the Final Visit with Pre-dose 4 as baseline.

[b] The "Final Visit" analysis time point uses the last measurement prior to the first dose as baseline.

14.3.7 Displays of 12-Lead Standard Measurements

Table 27: 12-Lead Standard ECG Overall Interpretations, Post Dose Compared to Baseline

Change from Baseline in ECG Interpretation	2 g Zoliflodacin n (%)	4 g Zoliflodacin n (%)	Placebo n (%)	400 mg Moxifloxacin n (%)	Any Period n (%)
1 h Post-dose					
	N=X	N=X	N=X	N=X	N=X
Normal at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, NCS	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Normal	x (x)	x (x)	x (x)	x (x)	x (x)
2 h Post-dose					
	N=X	N=X	N=X	N=X	N=X
Normal at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, NCS	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Normal	x (x)	x (x)	x (x)	x (x)	x (x)
4 h Post-dose					
	N=X	N=X	N=X	N=X	N=X
Normal at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, NCS	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Normal	x (x)	x (x)	x (x)	x (x)	x (x)
24 h Post-dose					
	N=X	N=X	N=X	N=X	N=X
Normal at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, NCS	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Normal	x (x)	x (x)	x (x)	x (x)	x (x)

Change from Baseline in ECG Interpretation	2 g Zoliflodacin n (%)	4 g Zoliflodacin n (%)	Placebo n (%)	400 mg Moxifloxacin n (%)	Any Period n (%)
Follow-up[a]					
	N=X	N=X	N=X	N=X	N=X
Normal at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, NCS	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Normal	x (x)	x (x)	x (x)	x (x)	x (x)
Pre-dose (Prior to Next Dose)					
	N=X	N=X	N=X	N=X	N=X
Normal at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, NCS	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Normal	x (x)	x (x)	x (x)	x (x)	x (x)
Final Visit[b]					
	N=X	N=X	N=X	N=X	N=X
Normal at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, NCS	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Normal	x (x)	x (x)	x (x)	x (x)	x (x)

Note: N = number of subjects in safety population with the ECG measurement at the respective time point.
CS = clinically significant; NCS = not clinically significant.

[a] The "Follow-up" analysis time points refer to either Check-In visits for the next period (for analysis of treatments given in Period 1, 2, or 3) or to the Final Visit with Pre-dose 4 as baseline.

[b] The "Final Visit" analysis time point uses the last measurement prior to the first dose as baseline.

Table 28: 12-Lead Standard ECG Results by Parameter, Maximum Severity, Time Point, and Dosing Period

[Implementation Note: If there is not at least 1 Mild, Moderate, or Severe Event for Any Period, Max Severity Post-Baseline, then only the Any Period, Max Severity Post-Baseline row will be shown for the parameter.]

Dosing Period	Time Point	N	Mild		Moderate		Severe	
			n	%	n	%	n	%
PR Interval Prolongation								
Any Period	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
	Final Visit[b]	x	x	x	x	x	x	x
2 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
4 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
Placebo	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
400 mg Moxifloxacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x

Dosing Period	Time Point	N	Mild		Moderate		Severe	
			n	%	n	%	n	%
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
QTcF Prolongation								
Any Period	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
	Final Visit[b]	x	x	x	x	x	x	x
2 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
4 g Zoliflodacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x
Placebo	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x	x	x

Dosing Period	Time Point	N	Mild		Moderate		Severe	
			n	%	n	%	n	%
400 mg Moxifloxacin	Max Severity Post-Baseline	x	x	x	x	x	x	x
	1 h Post-dose	x	x	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	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 within the period, including unscheduled assessments. N = number of subjects in safety population with the ECG measurement at the respective time point.

[a] The "Follow-up" analysis time points refer to either Check-In visits for the next period (for analysis of treatments given in Period 1, 2, or 3) or to the Final Visit with Pre-dose 4 as baseline.

[b] The "Final Visit" analysis time point uses the last measurement prior to the first dose as baseline.

Table 29: 12-Lead Standard ECG Change from Baseline – Summary Statistics by Parameter, Time Point, and Dosing Period

[Implementation Note: The following 12-lead standard ECG parameters will be summarized, in order:]

Dosing Period	Time Point	N	Mean	SD	Median	Min, Max
PR Interval (msec)						
2 g Zoliflodacin	1 h Post-dose	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x
4 g Zoliflodacin	1 h Post-dose	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x
Placebo	1 h Post-dose	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x
400 mg Moxifloxacin	1 h Post-dose	x	x	x	x	x
	2 h Post-dose	x	x	x	x	x
	4 h Post-dose	x	x	x	x	x
	24 h Post-dose	x	x	x	x	x
	Follow-up[a]	x	x	x	x	x
	Pre-dose (Prior to Next Dose)	x	x	x	x	x
Dosing Period 4	Final Visit[b]	x	x	x	x	x
QRS Duration (msec)						
…						

Note: N= number of subjects in safety population with the ECG measurement at the respective time point.
[a] The "Follow-up" analysis time points refer to either Check-In visits for the next period (for analysis of treatments given in Period 1, 2, or 3) or to the Final Visit with Pre-dose 4 as baseline.
[b] The "Final Visit" analysis time point uses the last measurement prior to the first dose as baseline.

14.4 Summary of Prior and Concomitant Medications

Table 30: Number and Percentage of Subjects with Prior Medications by WHO Drug Classification and Sequence

[Instruction: Include prior medications (medications with an end date prior to first dose) only.]

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	ABCD (N=X)	ACDB (N=X)	ADBC (N=X)	BADC (N=X)	BDCA (N=X)	BCAD (N=X)	CDAB (N=X)	CABD (N=X)	CBDA (N=X)	DCBA (N=X)	DBAC (N=X)	DACB (N=X)	All Subjects (N=X)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Level 1 Codes	Any Level 2 Codes	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)
[ATC Level 1 - 1]	Any [ATC 1 – 1]	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)
	[ATC 2 - 1]	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)
	[ATC 2 - 2]	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)
	[ATC 2 - 3]	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)
[ATC Level 1 – 2]	[ATC 2 - 1]	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)
	[ATC 2 - 2]	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)
	[ATC 2 - 3]	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)
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin														

Table 31: Number and Percentage of Subjects with Concomitant Medications by WHO Drug Classification and Treatment

[Instruction: Include concomitant medications (medications that are ongoing or that have an end date after first dose) only. The associated treatment for a concomitant medication should be the last treatment received prior to the start of the medication.]

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	2 g Zoliflodacin (N=X)	4 g Zoliflodacin (N=X)	Placebo (N=X)	400 mg Moxifloxacin (N=X)	Any Treatment (N=X)
		n (%)	n (%)	n (%)	n (%)	n (%)
Any Level 1 Codes	Any Level 2 Codes	x (x)	x (x)	x (x)	x (x)	x (x)
[ATC Level 1 - 1]	Any [ATC 1 – 1]	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 1]	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 2]	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 3]	x (x)	x (x)	x (x)	x (x)	x (x)
[ATC Level 1 – 2]	[ATC 2 - 1]	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 2]	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 3]	x (x)	x (x)	x (x)	x (x)	x (x)

14.5 Tolerability

Table 32: Assessment of Tolerability

	All Subjects (N=X)	
	n	%
Tolerability to zoliflodacin		
Subject did not discontinue study drug due to AE		
Subject did not choose to withdraw from the study due to an AE		
Subject was not withdrawn from the study due to an AE		

Note: Tolerability was concluded for a subject unless any one of the following occurred after receipt of a dose of zoliflodacin: 1) subject discontinued study drug due to an AE, 2) subject choose to withdraw from the study due to an AE at any time from first receipt of zoliflodacin until end of study, or 3) subject was withdrawn from the study by the investigator due to an adverse event at any time from first receipt of zoliflodacin until end of study
N = Number of subjects in the Safety Population who received a dose of zoliflodacin

14.6 Pharmacokinetics

Table 33: Summary Statistics for Zoliflodacin Concentrations by Nominal Time, after Single 2 g Zoliflodacin Dose

	Zoliflodacin Concentration (ng/mL) by Nominal Time[a] After Dose (h)									
Subject ID	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**
PHU.00101	x	x	x	x	x	x	X	x	x	x
PHU.00102	x	x	x	x	x	x	X	x	x	x
PHU.00102	x	x	x	x	x	x	X	x	x	x
…	x	x	x	x	x	x	X	x	x	x
Statistics	x	x	x	x	x	x	X	x	x	x
N[b]	x	x	x	x	x	x	X	x	x	x
Mean	x	x	x	x	x	x	X	x	x	x
SD	x	x	x	x	x	x	X	x	x	x
Min	x	x	x	x	x	x	X	x	x	x
Median	x	x	x	x	x	x	X	x	x	x
Max	x	x	x	x	x	x	X	x	x	x
CV%	x	x	x	x	x	x	X	x	x	x
GM	x	x	x	x	x	x	X	x	x	x
GSD	x	x	x	x	x	x	X	x	x	x

[a] Times are relative to time of dosing.
[b] 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.

Table 34: Summary Statistics for Zoliflodacin Concentrations by Nominal Time, after Single 4 g Zoliflodacin Dose

This table will repeat Table 32 for zoliflodacin concentrations after a single 4 g zoliflodacin dose.

Table 35: Summary Statistics for Zoliflodacin PK Parameters, after Single 2 g Zoliflodacin Dose

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

Table 36: Summary Statistics for Zoliflodacin PK Parameters, after Single 4 g Zoliflodacin Dose

This table will repeat Table 34 for zoliflodacin PK parameters after a single 4 g zoliflodacin dose.

Table 37: Summary Statistics for Zoliflodacin Exposure Measure Ratios Comparing a Single 4 g Oral Dose to a Single 2 g Oral Dose

Statistic	C_{max} Ratio	$AUC_{(0\text{-last})}$ Ratio	$AUC_{(0\text{-inf})}$ Ratio
N	x	X	x
Min	x	X	x
Median	x	X	x
Max	x	X	x
CV%	x	X	x
GM	x	X	x
95% CI	(x, x)	(x, x)	(x, x)

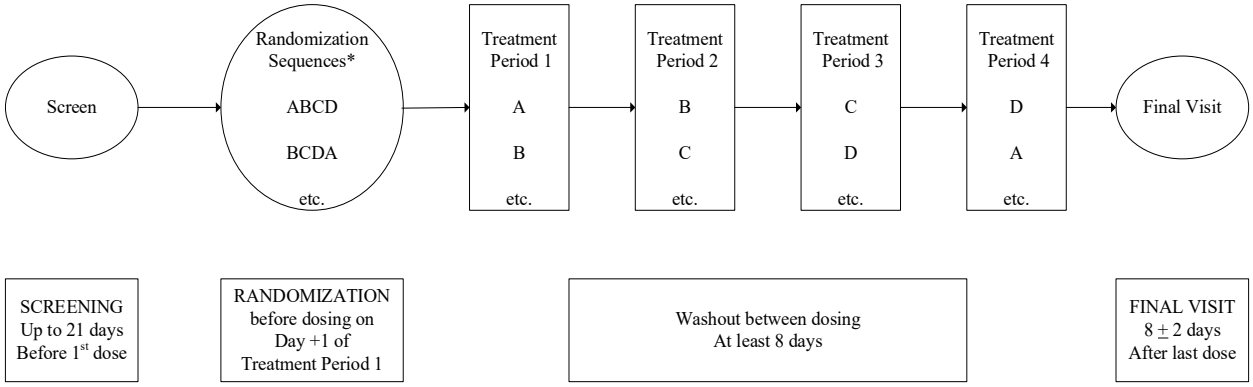
APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

10.1 Disposition of Subjects

9.1 Overall Study Design and Plan Description

Figure 1: Study Design



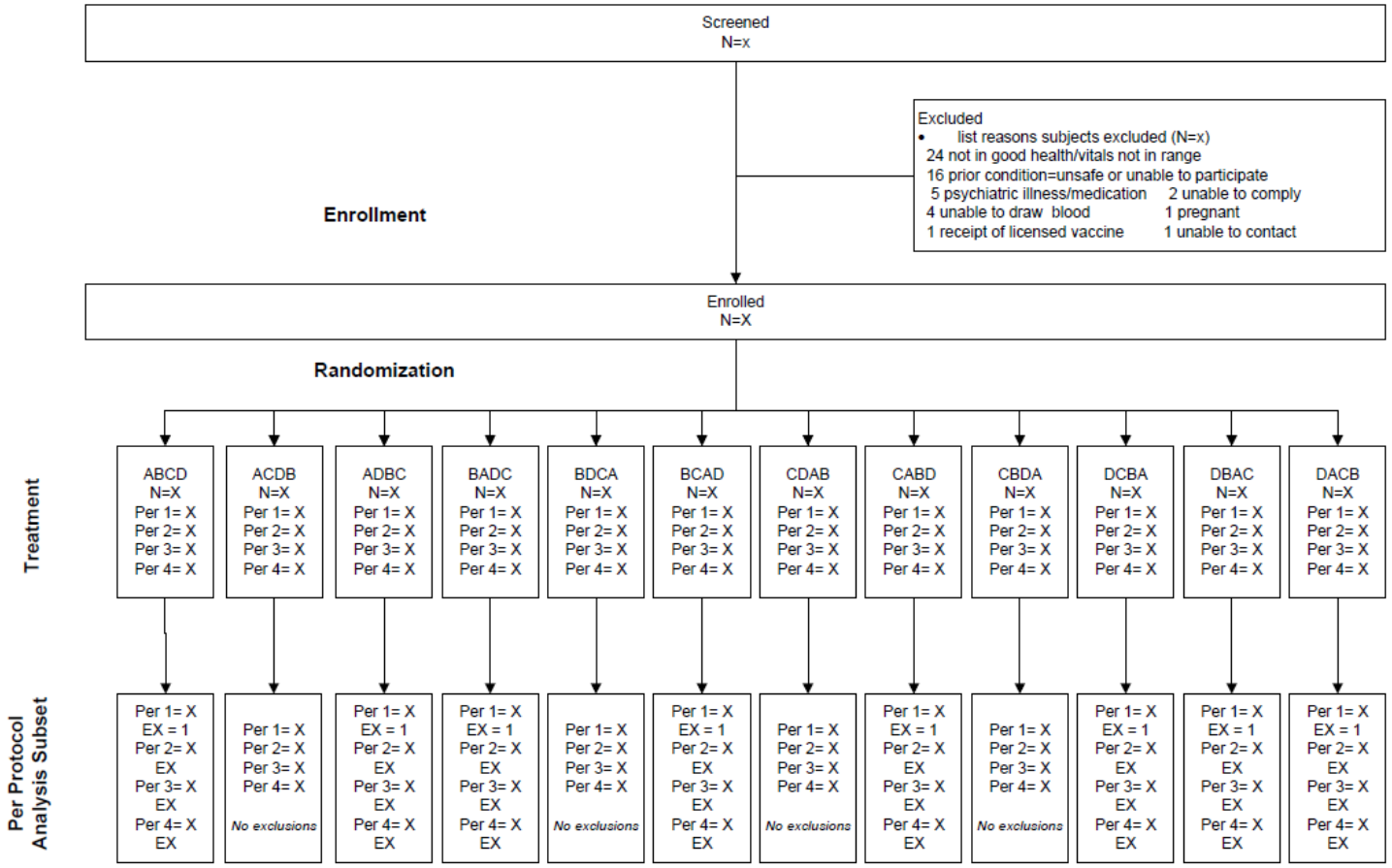
NOTE: A, B, C, and D refer to each of the study treatments: Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin. This is a four-treatment, four-period, crossover trial. Treatments and treatment sequences will be randomized using a 12-sequence design balanced for period and first-order carryover effects, and double-blinded, except for administration of moxifloxacin. Six subjects will be randomized to each treatment sequence. The schematic displays only two of the 12 sequences.

* See Section 3.3 for details and a complete list of planned treatment sequences.

Figure 2: Study Flow Diagram

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

The below mockup for the flow diagram is preliminary. The flow diagram will show the number of subjects screened and enrolled, the reasons for screening failures, the number of subjects completing each period by sequence, and reasons for early termination or exclusion from the primary analysis.



14.3.1.2 Unsolicited Adverse Events

Figure 3: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity, Any Time after First Dose

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events deemed related to study product. Instead of "Group A", report figure will say "Any Time After First Dose" at the top of the figure. Figure will be repeated for each dose group. Note that this figure will present total counts of adverse events, and a subject may be represented by more than one count for the same type of adverse event.]

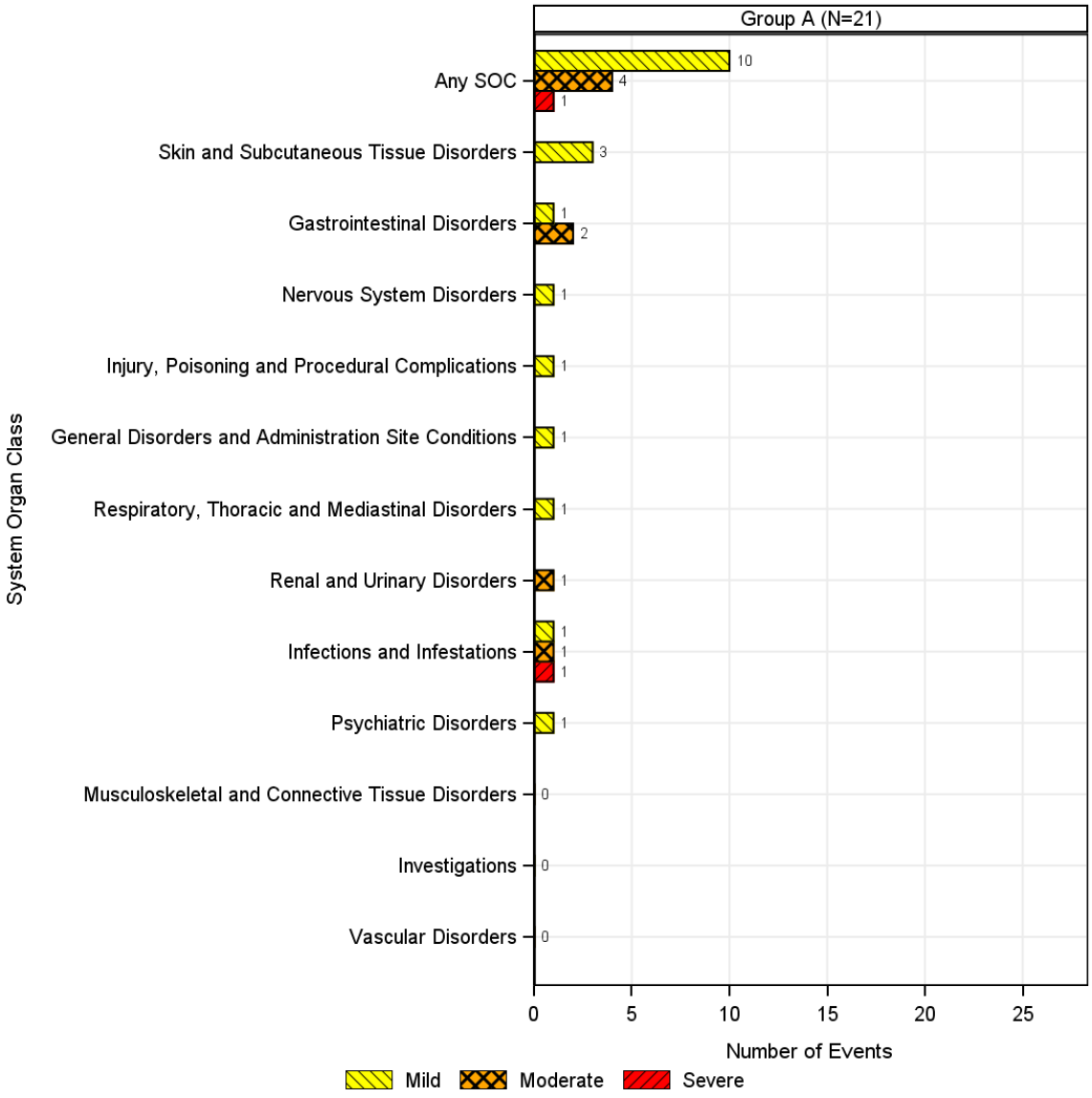


Figure 4: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity, after 2 g Zoliflodacin and Prior to Next Dose

This figure will repeat Figure 4 for AEs occurring after 2 g Zoliflodacin.

Figure 5: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity, after 4 g Zoliflodacin and Prior to Next Dose

This figure will repeat Figure 4 for AEs occurring after 4 g Zoliflodacin.

Figure 6: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity, after Placebo and Prior to Next Dose

This figure will repeat Figure 4 for AEs occurring after Placebo.

Figure 7: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity, after 400 mg Moxifloxacin and Prior to Next Dose

This figure will repeat Figure 4 for AEs occurring after 400 mg Moxifloxacin

Figure 8: Incidence of Related Adverse Events by MedDRA System Organ Class and Maximum Severity, Any Time after First Dose

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events deemed related to study product. Instead of "Group A", report figure will say "Any Time After First Dose" at the top of the figure. Figure will be repeated for each dose group. Note that this figure will present the number of subjects with types of adverse events, and a subject may not be counted more than once for the same type of adverse event, but will be counted only once for the maximum severity of the respective type.]

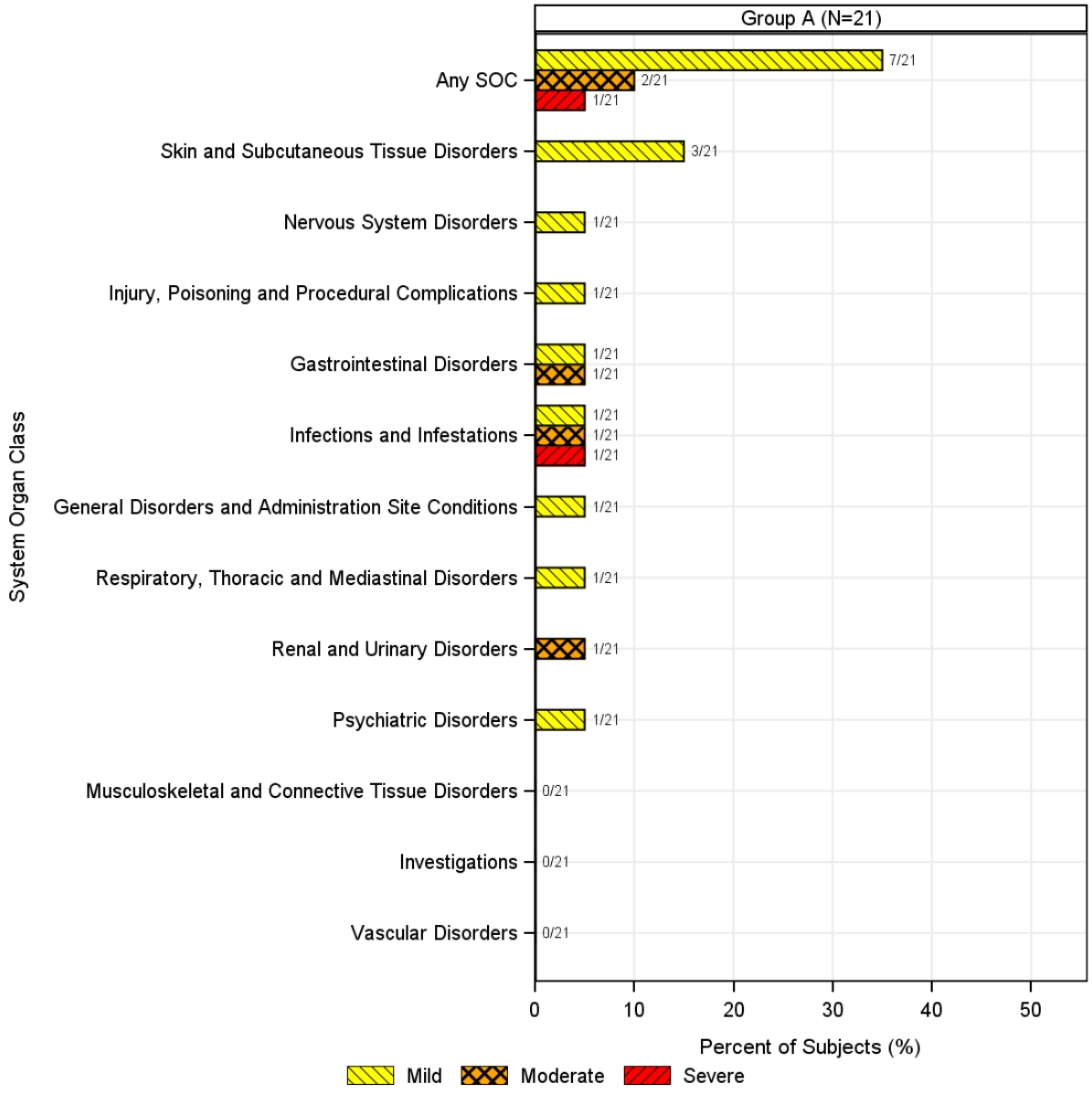


Figure 9: Incidence of Related Adverse Events by MedDRA System Organ Class and Severity, after 2 g Zoliflodacin and Prior to Next Dose

This figure will repeat Figure 8 for AEs occurring after 2 g Zoliflodacin.

Figure 10: Incidence of Related Adverse Events by MedDRA System Organ Class and Severity, after 4 g Zoliflodacin and Prior to Next Dose

This figure will repeat Figure 8 for AEs occurring after 4 g Zoliflodacin.

Figure 11: Incidence of Related Adverse Events by MedDRA System Organ Class and Severity, after Placebo and Prior to Next Dose

This figure will repeat Figure 8 for AEs occurring after Placebo.

Figure 12: Incidence of Related Adverse Events by MedDRA System Organ Class and Severity, after 400 mg Moxifloxacin and Prior to Next Dose

This figure will repeat Figure 8 for AEs occurring after 400 mg Moxifloxacin.

14.3.5.1 Chemistry Results

Figure 13: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Sodium

[Implementation Note: Figure in CSR should show Follow-up time points in addition to 24 h Post-dose time points. The x-axis labels should lead "24 h Post-dose" rather than "1 day Post-dose".]

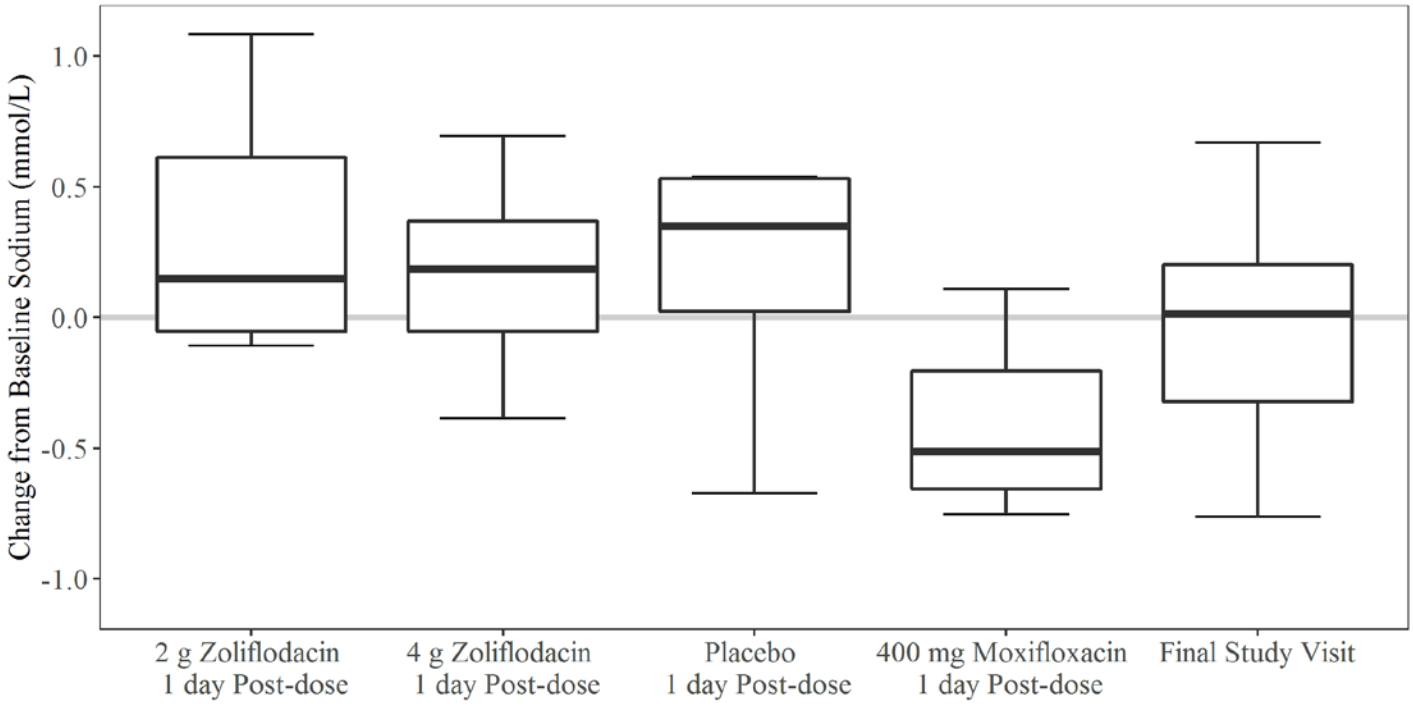


Figure 14: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Potassium

This figure will repeat Figure 13 for Chemistry, Potassium

Figure 15: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Magnesium

This figure will repeat Figure 13 for Chemistry, Magnesium

Figure 16: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Chloride

This figure will repeat Figure 13 for Chemistry, Chloride

Figure 17: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, CO_2

This figure will repeat Figure 13 for Chemistry, CO2

Figure 18: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Glucose (Fasting)

This figure will repeat Figure 13 for Chemistry, Glucose (Fasting)

Figure 19: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, BUN

This figure will repeat Figure 13 for Chemistry, BUN

Figure 20: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Creatinine

This figure will repeat Figure 13 for Chemistry, Creatinine

Figure 21: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Estimated Glomerular Filtration Rate

This figure will repeat Figure 13 for Chemistry, Estimated Glomerular Filtration Rate

Figure 22: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Total Protein

This figure will repeat Figure 13 for Chemistry, Total Protein

Figure 23: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Albumin

This figure will repeat Figure 13 for Chemistry, Albumin

Figure 24: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, AST

This figure will repeat Figure 13 for Chemistry, AST

Figure 25: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, ALT

This figure will repeat Figure 13 for Chemistry, ALT

Figure 26: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, AP

This figure will repeat Figure 13 for Chemistry, Alkaline Phosphatase

Figure 27: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Total Bilirubin

This figure will repeat Figure 13 for Chemistry, Total Bilirubin

Figure 28: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point – Chemistry, Direct Bilirubin

This figure will repeat Figure 13 for Chemistry, Direct Bilirubin

14.3.5.2 Hematology Results

Figure 29: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Hemoglobin

This figure will repeat Figure 13 for Hematology, Hemoglobin

Figure 30: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Hematocrit

This figure will repeat Figure 13 for Hematology, Hematocrit

Figure 31: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Erythrocytes

This figure will repeat Figure 13 for Hematology, Erythrocytes

Figure 32: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Leukocytes

This figure will repeat Figure 13 for Hematology, Leukocytes

Figure 33: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Neutrophils

This figure will repeat Figure 13 for Hematology, Neutrophils

Figure 34: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Lymphocytes

This figure will repeat Figure 13 for Hematology, Lymphocytes

Figure 35: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Monocytes

This figure will repeat Figure 13 for Hematology, Monocytes

Figure 36: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Eosinophils

This figure will repeat Figure 13 for Hematology, Eosinophils

Figure 37: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Basophils

This figure will repeat Figure 13 for Hematology, Basophils

Figure 38: Clinical Laboratory Results: Change from Baseline by Parameter, Dosing Period, and Time Point– Hematology, Platelets

This figure will repeat Figure 13 for Hematology, Platelets

14.3.6 Displays of Vital Signs

Figure 39: Vital Signs: Change from Baseline by Parameter, Dosing Period, and Time Point – Systolic Blood Pressure

[Implementation Note: Figure in CSR should show "Follow-up" and "Pre-dose (Prior to Next Dose)" time points in addition to those shown in the mock-up.]

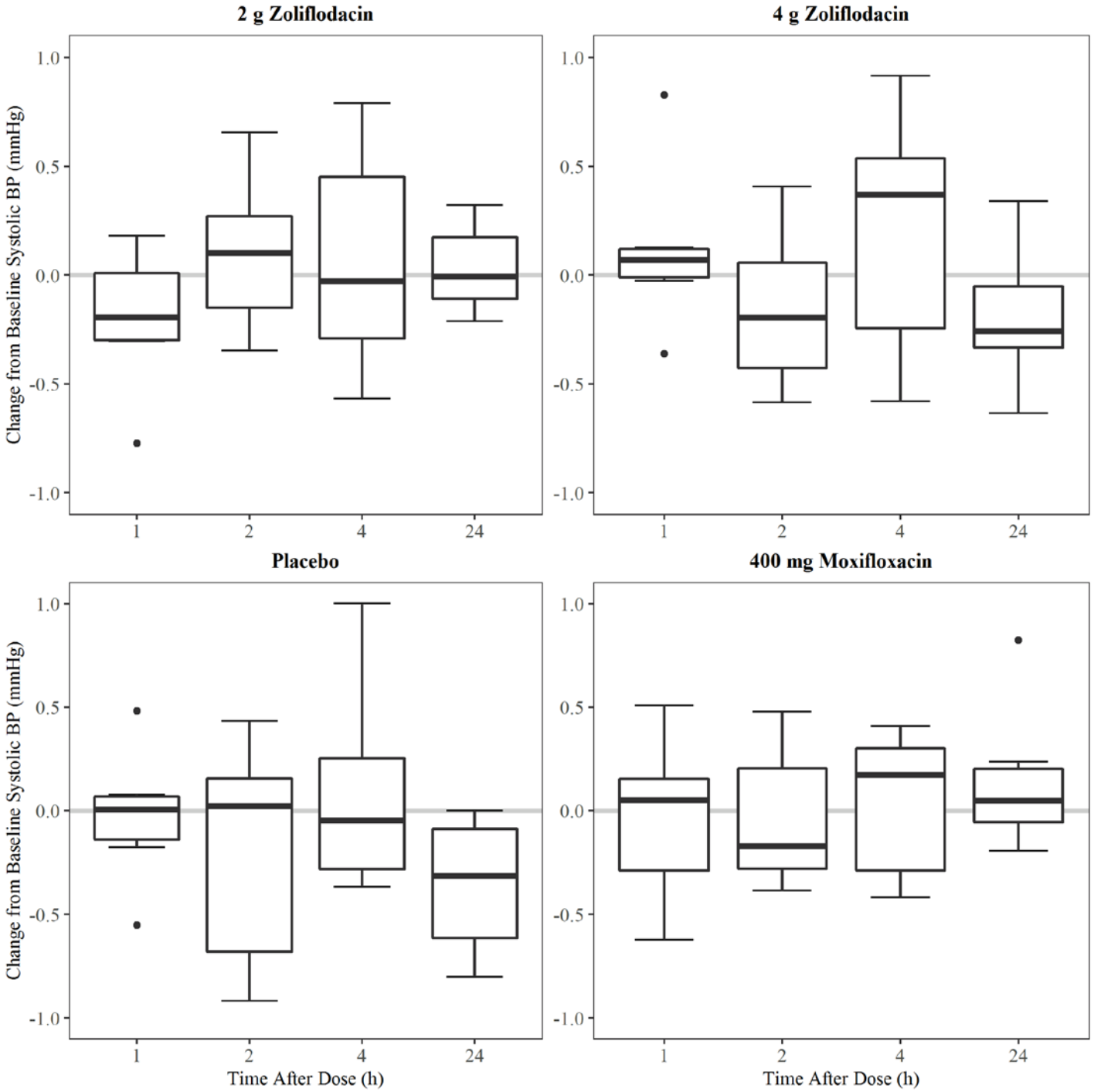


Figure 40: Vital Signs: Change from Baseline by Parameter, Dosing Period, and Time Point – Diastolic Blood Pressure

This figure will repeat Figure 38 for Diastolic Blood Pressure

Figure 41: Vital Signs: Change from Baseline by Parameter, Dosing Period, and Time Point – Heart Rate

This figure will repeat Figure 38 for Heart Rate

Figure 42: Vital Signs: Change from Baseline by Parameter, Dosing Period, and Time Point – Respiratory Rate

This figure will repeat Figure 38 for Respiratory Rate

Figure 43: Vital Signs: Change from Baseline by Parameter, Dosing Period, and Time Point – Temperature

This figure will repeat Figure 38 for Temperature

14.3.7 Displays of ECG Measurements

Figure 44: 12-Lead Standard ECG: Change from Baseline by Parameter, Dosing Period, and Time Point – PR Interval

[Implementation Note: Figure in CSR should show "Follow-up" and "Pre-dose (Prior to Next Dose)" time points in addition to those shown in the mock-up.]

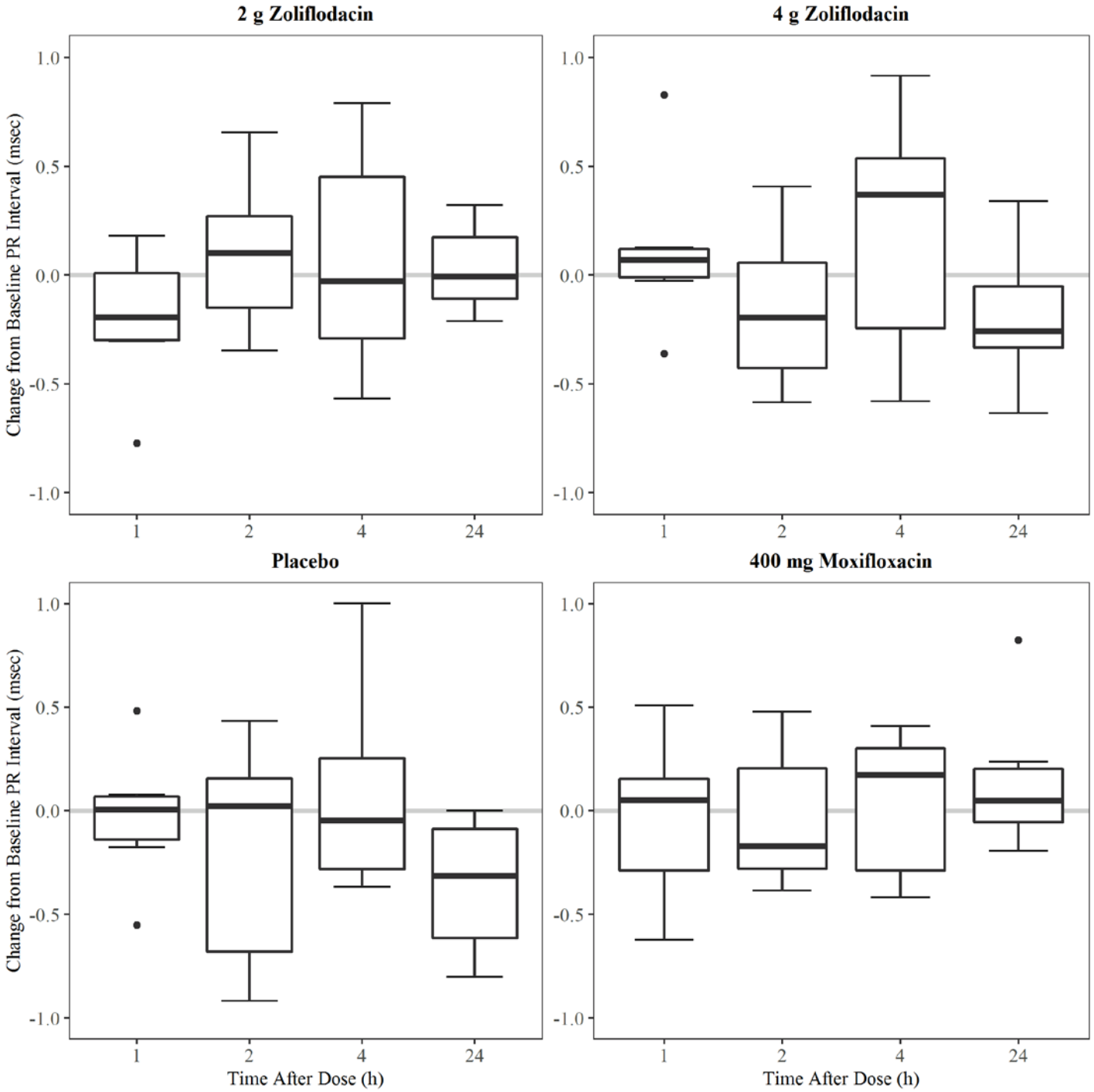


Figure 45: 12-Lead Standard ECG: Change from Baseline by Parameter, Dosing Period, and Time Point – QRS Duration

This figure will repeat Figure 43 for QRS Duration

Figure 46: 12-Lead Standard ECG: Change from Baseline by Parameter, Dosing Period, and Time Point – QT Interval

This figure will repeat Figure 43 for QT Interval

Figure 47: 12-Lead Standard ECG: Change from Baseline by Parameter, Dosing Period, and Time Point – QTcF Interval

This figure will repeat Figure 43 for QTcF Interval

Figure 48: 12-Lead Standard ECG: Change from Baseline by Parameter, Dosing Period, and Time Point – RR Interval

This figure will repeat Figure 43 for RR Interval

Figure 49: 12-Lead Standard ECG: Change from Baseline by Parameter, Dosing Period, and Time Point – ECG Mean Ventricular Rate

This figure will repeat Figure 43 for ECG Mean Ventricular Rate

Figure 50: Individual Profiles of Zoliflodacin Concentrations - Part 1

[Instruction: First 9 subjects (sorted by USUBJID) will go into Part 1. There are 8 figures of individual plots (72 subjects w/ 9 subjects per figure).]

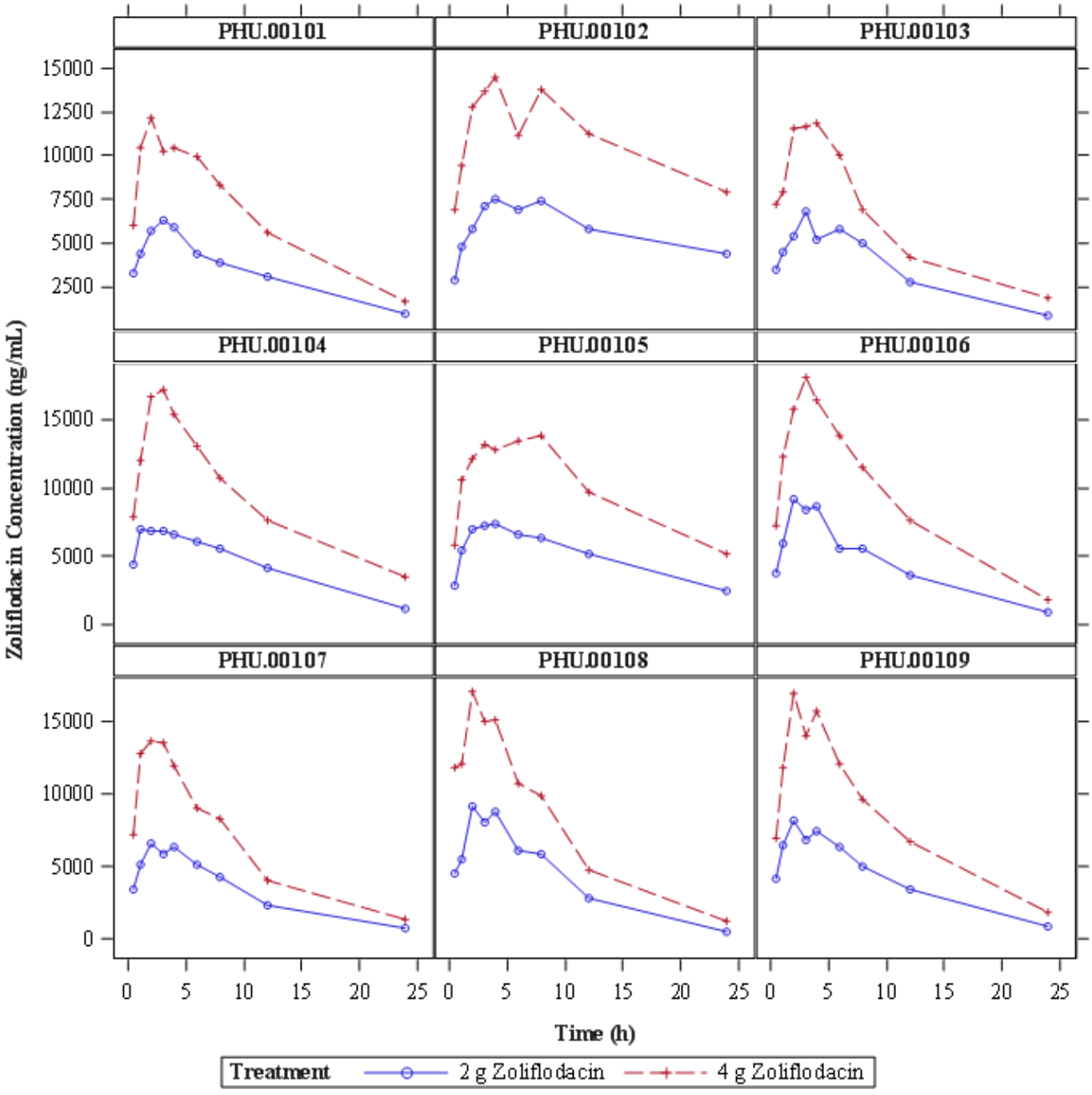


Figure 51: Individual Profiles of Zoliflodacin Concentrations - Part 2

This figure will repeat Figure 49 for 9 other subjects (in order of increasing USUBJID).

Figure 52: Individual Profiles of Zoliflodacin Concentrations - Part 3

This figure will repeat Figure 49 for 9 other subjects (in order of increasing USUBJID).

Figure 53: Individual Profiles of Zoliflodacin Concentrations - Part 4

This figure will repeat Figure 49 for 9 other subjects (in order of increasing USUBJID).

Figure 54: Individual Profiles of Zoliflodacin Concentrations - Part 5

This figure will repeat Figure 49 for 9 other subjects (in order of increasing USUBJID).

Figure 55: Individual Profiles of Zoliflodacin Concentrations - Part 6

This figure will repeat Figure 49 for 9 other subjects (in order of increasing USUBJID).

Figure 56: Individual Profiles of Zoliflodacin Concentrations - Part 7

This figure will repeat Figure 49 for 9 other subjects (in order of increasing USUBJID).

Figure 57: Individual Profiles of Zoliflodacin Concentrations - Part 8

This figure will repeat Figure 49 for 9 other subjects (in order of increasing USUBJID).

Figure 58: Semi-log Individual Profiles of Zoliflodacin Concentrations - Part 1

[Instruction: First 9 subjects (sorted by USUBJID) will go into Part 1. There are 8 figures of individual plots (72 subjects w/ 9 subjects per figure).]

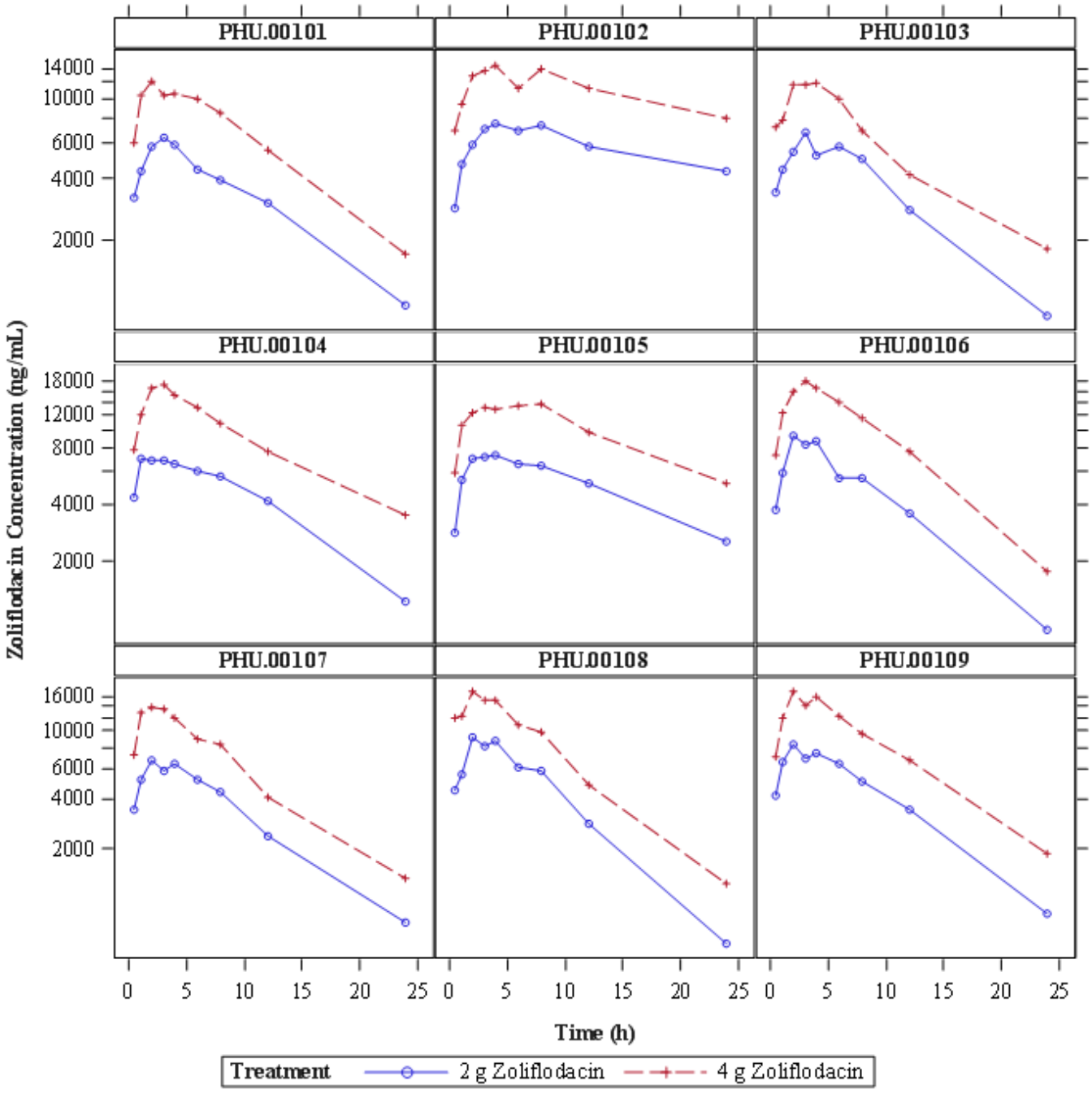


Figure 59: Semi-log Individual Profiles of Zoliflodacin Concentrations - Part 2

This figure will repeat Figure 57 for 9 other subjects (in order of increasing USUBJID).

Figure 60: Semi-log Individual Profiles of Zoliflodacin Concentrations - Part 3

This figure will repeat Figure 57 for 9 other subjects (in order of increasing USUBJID).

Figure 61: Semi-log Individual Profiles of Zoliflodacin Concentrations - Part 4

This figure will repeat Figure 57 for 9 other subjects (in order of increasing USUBJID).

Figure 62: Semi-log Individual Profiles of Zoliflodacin Concentrations - Part 5

This figure will repeat Figure 57 for 9 other subjects (in order of increasing USUBJID).

Figure 63: Semi-log Individual Profiles of Zoliflodacin Concentrations - Part 6

This figure will repeat Figure 57 for 9 other subjects (in order of increasing USUBJID).

Figure 64: Semi-log Individual Profiles of Zoliflodacin Concentrations - Part 7

This figure will repeat Figure 57 for 9 other subjects (in order of increasing USUBJID).

Figure 65: Semi-log Individual Profiles of Zoliflodacin Concentrations - Part 8

This figure will repeat Figure 57 for 9 other subjects (in order of increasing USUBJID).

Figure 66: Mean Profiles of Zoliflodacin Concentrations by Dose

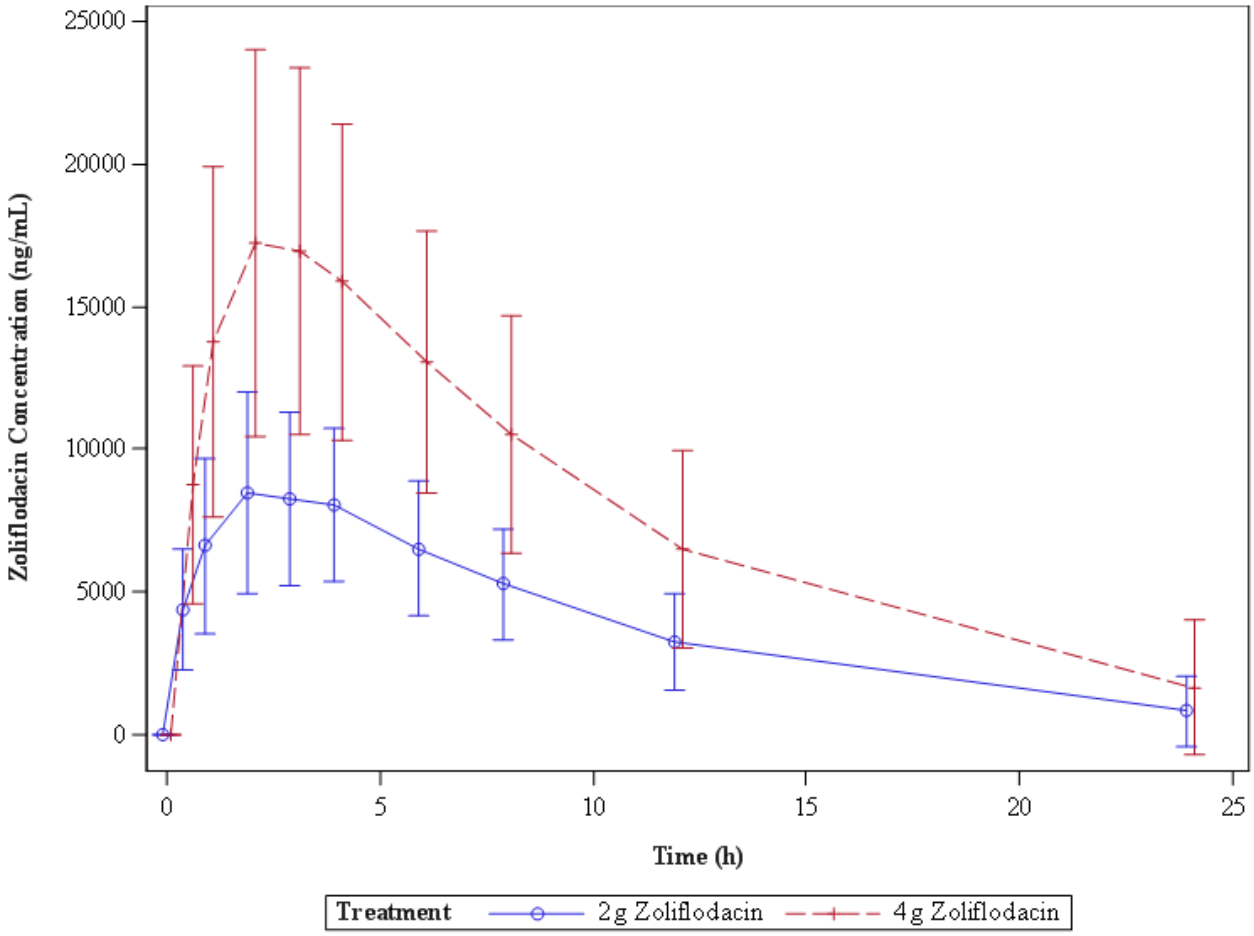
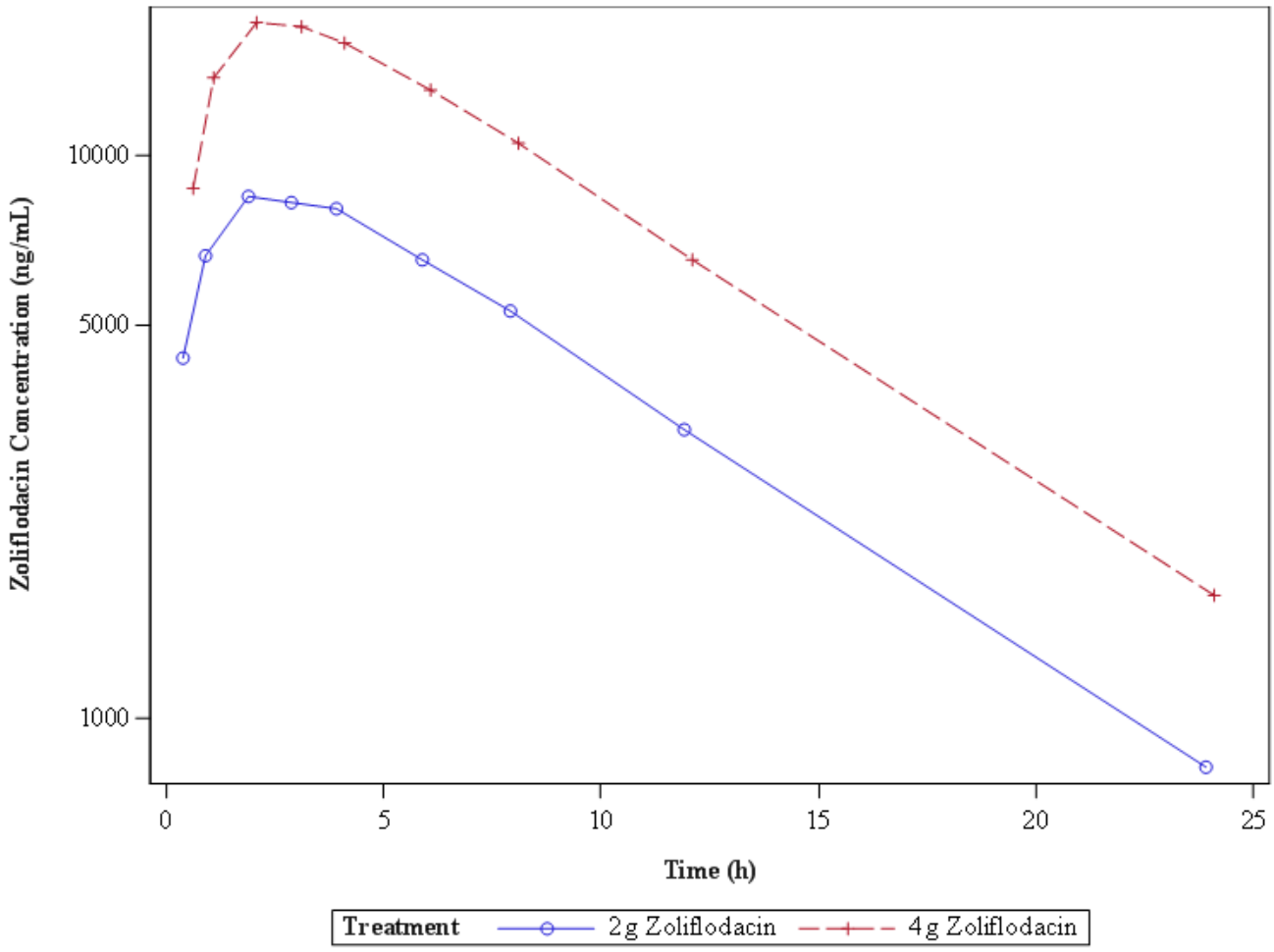


Figure 67: Semi-log Mean Profiles of Zoliflodacin Concentrations by Dose



APPENDIX 3. LISTINGS MOCK-UPS

LIST OF LISTINGS

16.1.6 Listing of Subjects Receiving Investigational Product

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

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 1: 16.2.1 Early Terminations or Discontinued Subjects

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

Sequence	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Last Treatment Prior to Termination or Discontinuation	Period Number	Study Day (Day in Period)
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin						

16.2.2 Protocol Deviations

Listing 2: 16.2.2.1: Subject-Specific Protocol Deviations

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

Sequence	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
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin											

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

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

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

16.2.3 Subjects Excluded from Analysis

Listing 4: 16.2.3: Subjects Excluded from Analysis Populations

[Implementation Note: This data in this listing should be congruent with the "Analysis Populations by Sequence" table. The reasons included here should match the SAP text that describes who will be excluded from analyses.]

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

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

16.2.4 Demographic Data

Listing 5: 16.2.4.1: Demographic Data

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

In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: Sequence, Subject ID. Height, weight, and BMI are from (first) screening visit.

Height, weight, and BMI included in this listing will be from the initial screening visit.]

Sequence	Subject ID	Sex	Age (years)	Ethnicity	Race	Height (cm)	Weight (kg)	BMI (kg/m^2)
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin								

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

[Implementation Note: "Condition Start Day" and "Condition End Day" are relative to enrollment. Rather than use exact study days, categorize as follows:

Condition Start Day

- 5 years prior to enrollment
- 1-5 years prior to enrollment
- 1-12 months prior to enrollment
- Within 1 month of enrollment

Condition End Day

- See "Condition Start Day" categories if condition ended prior to enrollment
- During study
- Ongoing]

Sequence	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin							

Listing 7: Treatments Administered

[Implementation Note: Listing will be sorted by sequence, Subject ID, and Study Day.]

Sequence	Subject ID	Treatment	Study Day	Date	Start Time of Dose	End Time of Dose
ABCD	PHU.0123	2 g Zoliflodacin	1	ddMMMyyyy	hh:mm	hh:mm
ABCD	PHU.0123	4 g Zoliflodacin	10	ddMMMyyyy	hh:mm	hh:mm
ABCD	PHU.0123	Placebo	19	ddMMMyyyy	hh:mm	hh:mm
ABCD	PHU.0123	400 mg Moxifloxacin	28	ddMMMyyyy	hh:mm	hh:mm
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin						

16.2.7 Adverse Events

Listing 8: Unsolicited Adverse Events

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. This listing includes all unsolicited adverse events. Add columns for MedDRA HLT or LLT depending on halting criteria or other study needs. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Sequence, Subject ID, Associated with Dose No., No. of Days Post Treatment. If the table will be multi-page, move the footnote/explanation to the footer so that it repeats for each page of the table.]

Adverse Event	Treatment	No. of Days Post Treatment (Duration)	Severity	SAE?	Relationship to Study Treatment, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term
Sequence: , Subject ID: , AE Number:											
Comments:											
Sequence: , Subject ID: , AE Number:											
Comments:											

Note: For additional details about SAEs, see Table: xx.
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

16.2.8 Individual Laboratory Measurements

Listing 9: Clinical Laboratory Results – Chemistry

[Implementation Note: These listings (for hematology, chemistry, and urinalysis) include all laboratory results, scheduled and unscheduled, including screening. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., 16.2 (Mild). The "extra" fields that are completed for abnormal results are not included in this listing; they are included in the listing of abnormal laboratory results that is included in the table shells document. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Sequence, Subject ID, and Planned Time Point. Measurements outside of the normal range, but not graded as mild, moderate, or severe, will be flagged as "ONR" in the listings.]

Sequence	Subject ID	Period Number	Treatment	Time Point	Study Day (Day in Period)	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline[a]	Reference Range	Clinical Significance
ABCD	PHU.0123	1	2 g Zoliflodacin	24 h Post-dose	2 (2)	Male	Sodium (mEq/L)	149 (Mild)	+5	135-146	No
ABCD	PHU.0123	2	2 g Zoliflodacin	Follow-up	8 (-1)	Male	Sodium (mEq/L)	134 (ONR)	-10	135-146	No

Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin
[a] For Final Visit, change from baseline values using the last measurement prior to first dose as baseline, followed by change from baseline using the Period 4 baseline in parentheses.

Listing 10: Clinical Laboratory Results – Hematology

Sequence	Subject ID	Period Number	Treatment	Time Point	Study Day (Day in Period)	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline[a]	Reference Range	Clinical Significance

Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

[a] For Final Visit, change from baseline values using the last measurement prior to first dose as baseline, followed by change from baseline using the Period 4 baseline in parentheses.

Listing 11: Clinical Laboratory Results – Urinalysis

Sequence	Subject ID	Period Number	Treatment	Time Point	Study Day (Day in Period)	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range	Clinical Significance
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin										

Listing 12: Screening Laboratory Results – Serology

Sequence	Subject ID	Visit	HIV Antibodies	HCV Antibodies	HBsAg
ABCD	PHU.0123	Screening	Negative	Negative	Negative

Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

Listing 13: Laboratory Results – Urine Toxicology and Alcohol Testing

[Instruction: Update columns as necessary to reflect urine toxicology tests present in the final clinical database.]

Sequence	Subject ID	Visit	Amphetamines	Barbiturates	Benzodiazepines	Benzoylecgonine	Cannabinoids	Opiates	Phencyclidine	Methadone	Alcohol
ABCD	PHU.00123	Screening	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
ABCD	PHU.00123	Unscheduled (Day 2)	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin											

Listing 14: Laboratory Results – Serum hCG Pregnancy Tests

[Instruction: If collected for any subject in the study, serum FSH will be included in this table.]

Sequence	Subject ID	Visit	Actual Study Day	Serum hCG Result
ABCD	PHU.0123	Screening	-15	Negative
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin				

16.2.9 Vital Signs and Physical Exam Findings

Listing 15: Vital Signs

Sequence	Subject ID	Treatment	Period Number	Time Point	Study Day (Day in Period)	Time (hh:mm)	Parameter (units)	Result (Severity)	Change from Baseline[a]
ABCD	PHU.00123	2 g Zoliflodacin	1	1 h Post-dose	2 (2)	hh:mm	Systolic Blood Pressure (mmHg)	142 (Mild)	+10

Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin
[a] For Final Visit, change from baseline values using the last measurement prior to first dose as baseline, followed by change from baseline using the Period 4 baseline in parentheses.

Listing 16: Physical Exam Findings

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

Sequence	Subject ID	Treatment	Period Number	Study Day (Day in Period)	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)
ABCD	PHU.0123	2 g Zoliflodacin	1	2 (2)	SKIN	MACULAR RASH ON SHOULDERS	Yes (Rash; 001)
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin							

Listing 17: Listing of 12-Lead Standard ECG Interval Measurements

Sequence	Subject ID	Treatment	Period Number	Time Point	Study Day (Day in Period)	Time (hh:mm)	Parameter (units)	Result (Severity)	Change from Baseline[a]
ABCD	PHU.0123	2 g Zoliflodacin	1	1 h Post-dose	2 (2)	hh:mm	QTcF	455 (Mild)	25

Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

[a] For Final Visit, change from baseline values using the last measurement prior to first dose as baseline, followed by change from baseline using the Period 4 baseline in parentheses.

Listing 18: Listing of 12-Lead Standard ECG Overall Interpretation and Comments

Sequence	Subject ID	Treatment	Period Number	Time Point	Study Day (Day in Period)	Time (hh:mm)	Interpretation	Comments
ABCD	PHU.0123	2 g Zoliflodacin	1	1 h Post-dose	2 (2)	hh:mm	Abnormal NCS	Sinus Bradycardia

Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

16.2.10 Prior and Concomitant Medications

Listing 19: Prior Medications

[Instruction: Include prior medications (medications with an end date prior to dosing) only. Listing will be sorted by Sequence, then by Subject ID, and then by CM Number. Medication start and end Days are relative to enrollment (Day 1). If start date is more than 30 days before enrollment then categorize as: 1-12 months prior to enrollment, 1-5 years prior to enrollment, or >5 years prior to enrollment.]

Sequence	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)
ABCD	PHU.0123	001	BENADRYL	1-12 months prior to enrollment	1-12 months prior to enrollment	ITCHING	No	DERMATOLOGICALS (ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.)
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin								

Listing 20: Concomitant Medications

[Instruction: Include concomitant medications (medications that are ongoing or that have an end date after dosing) only. Listing will be sorted by Sequence, then by Subject ID, and then by CM Number. Medication start and end Days are relative to enrollment (Day 1). If start date is more than 30 days before enrollment then categorize as: 1-12 months prior to enrollment, 1-5 years prior to enrollment, or >5 years prior to enrollment. If ongoing, display "Ongoing" in End Day column. The Treatment (Sequence) column should show the most recent treatment prior to the medication start day, with the sequence randomized to in parentheses. If the Medication Start Day is the same day zoliflodacin, moxifloxacin, or placebo is administered, then the Treatment will be the study product administered on the Medication Start Day.]

Treatment (Sequence)	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)
2 g zoliflodacin (ABCD)	PHU.0123	001	BENADRYL	2	2	ITCHING	Yes (MACULAR RASH; 001)	No	DERMATOLOGICALS (ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.)
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin									

16.2.11 Pregnancy Reports

Listing 21: Pregnancy Reports – Maternal Information

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

Sequence	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?

Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin

Listing 22: 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

Extremely PB: < 25 weeks
Very Early PB: 25 0/7 - 31 6/7 weeks
Early PB: 32 0/7 - 33 6/7 weeks
Late PB: 34 0/7 - 36 6/7 weeks
Early TB: 37 0/7 - 38 6/7 weeks
Full TB: 39 0/7 - 40 6/7 weeks
Late TB: 41 0/7 - 41 6/7 weeks
Post TB: > 42 0/7 weeks

Listing 23: Pregnancy Reports – Live Birth Outcomes

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

Listing 24: Pregnancy Reports – Still Birth Outcomes

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

Listing 25: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

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

Listing 26: Birth Control Listing

[Instruction: Listing will be sorted by Sequence, then by Subject ID, and then by CM Number. Birth control start and end Days are relative to first dose (Day 1). If start date is more than 30 days before enrollment then categorize as: 1-12 months prior to enrollment, 1-5 years prior to enrollment, or >5 years prior to enrollment. If ongoing, display "Ongoing" in End Day column. Multiple forms of birth control for a single subject will be listed on separate rows.]

Sequence	Subject ID	Sex	Child Bearing Potential	Birth Control Method	Birth Control Start Day	Birth Control End Day
Treatment A = 2 g zoliflodacin; Treatment B = 4 g zoliflodacin; Treatment C = placebo; Treatment D = 400 mg moxifloxacin						

Listing 27: Subject Level Zoliflodacin Concentrations in Plasma

Subject ID	Zoliflodacin Dose (g)	Nominal Time[a] (h)	Actual Time[a] (h)	Concentration as Reported in the Bioanalytical Report[b] (ng/mL)	Concentration as Used in Phoenix (ng/mL)	Used in K_e Calculations
PHU.00101	2	0	0	BQL	0	
PHU.00101	2	0.5	0.5	x	x	
PHU.00101	2	1	1	x	x	
PHU.00101	2	2	2	x	x	

[a] Times are relative to time of dose. For Actual Times, out-of-window times are indicated by an asterisk.
[b] <Bioanalytical report will be referenced here>

Listing 28: Subject-Specific Zoliflodacin PK Parameters

Subject ID	Zoliflodacin Dose (g)	C_{max} (ng/mL)	T_{max} (h)	T_{last} (h)	$AUC_{(0\text{-}last)}$ (h*ng/mL)	$AUC_{(0\text{-}inf)}$ (h*ng/mL)	$t_{1/2}$ (h)	K_e (/h)	CL/F (L/h)	V_z/F (L)
PHU.00101	2	x	x	x	x	x	x	x	x	x
PHU.00101	4	x	x	x	x	x	x	x	x	x
PHU.00102	2	x	x	x	x	x	x	x	x	x
PHU.00102	4	x	x	x	x	x	x	x	x	x

ECG STATISTICAL ANALYSIS PLAN

Protocol Number: DMID 16-0110

A Phase 1, Randomized, Double-blinded, Four-period Crossover, Thorough QT/QTc (TQT) Clinical Trial to Evaluate the Effect of Zoliflodacin on Cardiac Repolarization in Healthy Male and Female Subjects

Version: Final
Date: 18 Sep 2018

Authors: Pramod Kadam\Pooja Hingorani
IQVIA Reviewer: Dr. Dilip Karnad
DynPort Vaccine Company, LLC Reviewer: Dr. George Saviolakis

SIGNATURE PAGE

This statement confirms that the Report Writing team of Cardiac Safety Services, IQVIA and DynPort Vaccine Company, LLC have reviewed the ECG Statistical Analysis Plan for the Study DMID 16-0110.

Study No.:	DMID 16-0110
Study Title:	A Phase 1, Randomized, Double-blinded, Four-period Crossover, Thorough QT/QTc (TQT) Clinical Trial to Evaluate the Effect of Zoliflodacin on Cardiac Repolarization in Healthy Male and Female Subjects
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TABLE OF CONTENTS

Modification History

Unique Identifier for this Version	Date of the Document Version	Section number and text from previous version	Section number and text in new version
Draft 01	16JUL2018	Not Applicable – First Version	
Draft 02	13AUG2018	1. Inserting throughout text the appropriate references to TLFs #s	Wherever applicable in this document
		2. Reviewer from Sponsor added	Signature page
		3. Review abbreviations in Final and delete/add as needed.	Updated the abbreviation list
		4. In the entire document wherever applicable, when the abbreviation is used for the first time, it is now spelled out.	As per review comments
		5. Global comment 'Remove hyphen in DMID-16-0110'	Updated wherever applicable in this document
		6. Global comment 'Postdose' added hyphen 'post-dose' throughout the document	Updated wherever applicable in this document as per reviewer's comment
		7. Section 2.2 – Study Outcome measures	Updated as per study protocol text
		8. Section 3 – Study design	Updated as per study protocol text and review comments
		9. Section 4 – Reworded 'Analysis Set' to 'Analysis Population'	As per review comments
		10. Section 5 – reworded 'average' to 'mean'	As per review comments

		11. Added 'Calculated from RR' in parenthesis to Heart rate in Section 5 and in the rest of the document	As per review comments
		12. Added analysis for RR	As per review comments
		13. Added analysis for QTcB	As per sponsor discussion and as per ICH E14 guidance.
		14. Deleted 'groups' where 'Treatment groups' appeared in the text	As per review comments
		15. Section 5 onwards – changed 2-sided 90% confidence intervals to one-sided 95% confidence intervals	As per review comments
		16. Section 5.3 – Added Baseline to be determined for each period separately. reworded 'average' to 'mean'	As per review comments
		17. Section 5.3 – Table 3 – Added Day 2 to Day1 Hour 24 timepoint	As per review comments
		18. Section 5.4.1 – Added QTcB for categorical outlier analysis.	As per sponsor discussion and as per ICH E14 guidance.
		19. Section 5.4.2 – Clarified the baseline considered for treatment emergent morphological abnormalities	Based on review comments
		20. Section 5.5 title changed from 'Concentration-QTcF analysis' to 'Pharmacokinetic – QTcF Analysis'	As per review comments
		21. Section 5.5 deleted 'its metabolites (if available)'	As per review comments – no metabolites data available

		22. Added section numbering to methods of Concentration QTcF analysis	As per review comments
		23. Test of linearity section – Corrected ΔQTcF to ΔΔQTcF	As per reviewer's observation
Final	18SEP2018	Accepted minor edit comments throughout the document	As per Sponsor's comments
		Added reference of the scientific white paper	As per Sponsor's comments
		Modified the SAS code in section 5.4	As per IQVIA reviewer's input

Abbreviations and Definitions

Abbreviation or specialist term	Explanation
AE	Adverse event
AIC	Akaike Information Criterion
ANCOVA	Analysis of covariance
AUC	Area under the curve
AV	Atrioventricular
β2	Model-predicted estimates of slope
bpm	Beats per minute
CI	Confidence interval
C_{max}	Maximum plasma concentration
CS	Compound symmetry
CSS	Cardiac Safety Services, IQVIA
CTU	Clinical trial unit
CV	Coefficient of variation
DDFM	Denominator degrees of freedom method
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
E_{max}	Nonlinear model frequently used in dose–response analyses
ET	Early termination
g	Gram
h	Hour
HR	Heart rate
Hz	Hertz
ICH	International Council for Harmonization
LCL	Lower confidence limit
LOESS	Locally-weighted scatterplot smoothing
LS	Least square

Abbreviation or specialist term	Explanation
LVH	Left ventricular hypertrophy
Max	Maximum
mg	Milligram
MI	Myocardial infarction
Min	Minimum
msec	Milliseconds
N	Number of observations
PD	Pharmacodynamics
PK	Pharmacokinetics
PO	Oral
PR interval	Interval from onset of P-wave to the onset of the QRS complex
QRS	Duration from the start of the Q-wave to the end of the S-wave
QT interval	Interval from onset of the Q-wave to the end of the T-wave
QTc	Corrected QT interval
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
ΔQTcF	Change-from-baseline QTcF value
ΔΔQTcF	Placebo-corrected change from baseline QTcF value
RR	Interval from the peak of the R wave of a QRS complex to the peak of the R wave of the next QRS complex
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
TQT	Thorough QT/QTc
T_{max}	Time to maximum plasma concentration
T-wave	ECG wave indicative of ventricular repolarization

Abbreviation or specialist term	Explanation
UCL	Upper confidence limit
UN	Unstructured covariance
VS	Vital signs

1. Introduction

This Electrocardiogram (ECG) Statistical Analysis Plan (SAP) for the DMID 16-0110 study, for preparing the Expert ECG Report, is based on Clinical Trial Protocol Version 1.0 dated 18 Jun 2018 for the DMID 16-0110 study.[1]

2. Study Objectives and Outcome Measures

2.1. Study Objectives

2.1.1. Primary objective

- To evaluate the effect of zoliflodacin on the corrected QT interval of the ECG using Fridericia's formula (QTcF).

2.1.2. Secondary objective

- To evaluate the effects of zoliflodacin on other ECG parameters [PR, QRS, and RR intervals, and heart rate (HR)]
- To evaluate the sensitivity of QTcF measurement using moxifloxacin
- To evaluate the effect of zoliflodacin on T-wave morphology
- To evaluate the pharmacokinetics (PK) of 2 grams (g) and 4 g oral zoliflodacin under fasting state
- To evaluate the relationship between zoliflodacin PK and time-matched QTcF pharmacodynamics (PD)
- To evaluate the safety and tolerability of 2 g and 4 g oral zoliflodacin

2.2. Study Outcome Measures

2.2.1. Primary outcome measure

- The upper bound of the one-sided 95% confidence interval (CI) for the largest time-matched, placebo-corrected, baseline-adjusted mean QTcF interval (ΔΔQTcF) collected in the 24 hour (h) post-dosing period after 2 g and 4 g dose of zoliflodacin is <10 milliseconds (msec)

2.2.2. Secondary outcome measures

- Time-matched, placebo-corrected, baseline-adjusted non-QT intervals (PR, QRS, and RR intervals) and HR collected in the 24 h period after 2 g and 4 g dose of zoliflodacin
- The lower bound of the one-sided 95% CI of the ΔΔQTcF is >5 msec at one or more individual timepoints between 1 h and 4 h after a single dose of moxifloxacin 400 mg.
- Incidence of abnormal T-wave morphology using defined categories in the 24 h period after 2 g and 4 g dose of zoliflodacin

- Single-dose plasma concentrations (and PK exposure parameters, such as C_{max} and AUC) of zoliflodacin collected up to 24 h after 2 g and 4 g dose of zoliflodacin
- Relationship between plasma concentrations of zoliflodacin (and PK exposure parameters, such as C_{max} and AUC) and ΔΔQTcF up to 24 h after 2 g and 4 g dose of zoliflodacin
- Occurrence of treatment-emergent serious adverse events (SAEs), other unsolicited treatment-emergent adverse events (AEs), and changes from baseline in vital signs (VS), clinical laboratory values, and ECG parameters following administration of zoliflodacin and moxifloxacin from time of dosing to Final Visit, or Early Termination (ET) Visit

3. Study Design

This TQT study is being performed in a single center, the Vince & Associates Clinical Research, Inc., clinical trial unit (CTU). The study has a randomized, double-blinded (except for the use of moxifloxacin), placebo-controlled, four-period, four-treatment, crossover design which is balanced for period and first-order carryover effects with 72 healthy subjects (male or female), aged 18 to 45 years inclusive. In this study, the ECG and PK data from these subjects will be used to evaluate the effect of zoliflodacin on QTcF and other ECG parameters, the correlation of drug concentration (and PK profile) with ΔΔQTcF, and the PK and safety profiles of the new zoliflodacin formulation.

Each subject will receive one oral dose of each of four treatments, labeled A through D:

• Treatment A: zoliflodacin 2 g orally (PO) (investigational drug, therapeutic dose)

• Treatment B: zoliflodacin 4 g PO (investigational drug, supratherapeutic dose)

• Treatment C: placebo PO (for zoliflodacin)

• Treatment D: moxifloxacin 400 mg PO (positive control comparator)

Each subject will be randomly allocated to one of 12 dosing sequences before dosing on Day 1, Dosing Period 1. Each subject will receive a single dose of the following four study drugs on different days according to their randomly-assigned dosing sequence, as follows:

Table 1: Dosing sequences for randomization

ABCD	ACDB	ADBC	DCBA
BADC	BDCA	BCAD	DBAC
CDAB	CABD	CBDA	DACB

Six of the planned 72 subjects are to be included in each treatment sequence. The design is balanced for period and first-order carryover effects.

Subjects will be dosed on the morning of Day 1 in each dosing period, in a staggered fashion at least several minutes apart, and will receive study drug at approximately the same time in each subsequent dosing period. Each treatment will be administered after at least an 8-hour fast period, which will continue for at least 4 h after dosing. Zoliflodacin or placebo will be reconstituted in 60 mL of tap water. After the cup containing the 60 mL of zoliflodacin or placebo is taken, approximately 60 mL of tap water will be added to the cup and consumed by the subject to chase the initial dose. Moxifloxacin will be administered orally with 120 mL of water.

Continuous 12-lead Holter ECGs will be recorded on Day 1 and Day 2 of each dosing period starting approximately 1 h before dosing and lasting 25 h. At timepoints for Holter ECG extraction, subjects will rest in the supine position for at least 10 minutes before and 5 minutes after the nominal time, without any ongoing stimulation (e.g., television). Three replicate ECGs will be extracted at each timepoint for ECG interval measurement and assessment of T-wave morphology.

Plasma for PK analysis will be collected at scheduled timepoints that match the timepoints for ECG extraction before and after dosing on Day 1 and through Day 2, or ET if it occurs within 24 h after dosing.

Subjects are to be monitored as inpatients in the CTU up to 24 h after each dose (Day 2). They will be discharged from the CTU and followed up as outpatients for at least 5 days (Days 3-7) after dosing in Dosing Periods 1-3. The total time to wash-out of the previously-received study drug is at least 8 days. The Final Visit will be 8±2 days after the last dose.

Subjects will be excluded if they have any of the following cardiac criteria:

- History of acute or chronic cardiovascular disease or surgery
- History of cardiac arrhythmia or syncope related to cardiac arrhythmia or unexplained, or use of a cardiac pacemaker
- A marked baseline prolongation of ECG intervals QTc/QTcF >449 msec in males and females; PR >209 msec; and QRS >110 msec, or HR <45 bpm or >100 bpm on ECG measurements.
- Clinically significant abnormal ECG results including: 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; any characteristics that would make QT assessment unreliable, including flat T-waves; or any condition deemed clinically significant by a study investigator.

3.1. Overview of Holter ECG Data Collection in the Study

ECGs will be recorded during all four dosing periods using high resolution (1000 Hz) 12-lead Holter ECG equipment.

The continuous ECG recording will start approximately 1 h before dosing on Day 1 of all dosing periods and continue until 24 h after dosing (i.e., in the morning of Day 2). Three replicate ECG recordings will be extracted at the following timepoints in each dosing period: 45, 30, and 15 minutes before dosing (baseline) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h after dosing for a total of 12 timepoints per subject per dosing period. The subject will be in a supine position for at least 10 minutes before recording an ECG at the nominal timepoint for the ECG extractions from the Holter monitors. These timepoints are to correspond to the PK blood sampling timepoints for each dosing period with ECGs being obtained before the measurement of VS and collection of blood samples, to avoid the effect of stress on the ECG. The mean of pre-dose ECGs extracted on Day 1 of each dosing period will be used as the baseline reference for comparison with post-dose ECGs.

The primary objective and primary outcome measure in this study is based on QTcF values. However, the ICH-E14 guidance acknowledges that all formulae make assumptions about the nature of the QT-HR relationship that may not apply to those with disease or taking drugs. The ICH-E14 guidance, therefore, suggests that uncorrected QT and RR interval data, HR data, as well as QT interval data corrected using Bazett's (QTcB) and Fridericia's (QTcF) corrections should be submitted in all applications, in addition to QT interval data corrected using any other formulae.[2] Thus, this analysis plan also includes statistical analysis of QTcF, QTcB, HR (calculated from RR), RR interval, QT interval, PR interval and the QRS duration.

4. Analysis Populations related to Expert ECG Report

Holter ECG Analysis Population: The Holter ECG Analysis Population will include all subjects who have received at least one dose of zoliflodacin, moxifloxacin, or placebo, treatment, without protocol deviations potentially impacting the ECG intervals and have baseline ECGs and at least one post-dose ECG assessment.

PK Analysis Population: The PK Analysis Population will include all subjects who have received at least one dose of zoliflodacin and have at least one measured zoliflodacin concentration at a scheduled post-dose PK timepoint without major protocol deviations. Subjects will be analyzed according to the actual treatment they receive.

PK-ECG Analysis Population: The PK-ECG Analysis Population will be a sub-set of the Holter ECG Analysis Population and will include all subjects in the Holter ECG Analysis

Population with at least one plasma concentration value in the zoliflodacin treatment period with a corresponding Holter ECG measurement value at the same nominal timepoint.

5. Statistical Analysis Methods

This section describes the statistical analysis methods for the Holter ECG data from the DMID 16-0110 study.

5.1. General Statistical Considerations for Cardiac Safety Evaluation

- ECG parameter measurements and morphological abnormalities from the central ECG laboratory interpretation will be evaluated in this analysis
- Continuous ECG data (QTcF, QTcB, HR [calculated from RR], RR, QT, PR, and QRS) will be described using the following descriptive statistics: number of subjects, mean, standard deviation (SD), median, coefficient of variation (CV), minimum, maximum, standard error (SE) and one-sided 95% CI. For a timepoint where N ≤3 for a treatment period, only median, minimum and maximum values will be provided. Frequencies and percentages will be used for summarizing categorical outlier values. For calculation of mean of ECG parameter values across replicates at each timepoint, the value will be rounded to nearest whole number in the derived dataset (Refer to DMID 16-0110_ECG_Table shells: Tables 3 and 4; DMID 16-0110_ECG_Listing shells: Listings 1 to 7).
- Continuous ECG data will be assumed to be normally distributed. Test of normality will not be performed.
- One-sided 95% CIs will be calculated for absolute and change from baseline values and provided in the report (Refer to DMID 16-0110_ECG_Table shells: Tables 3 and 4; DMID 16-0110_ECG_Listing shells: Listings 1 to 7).
- Repeated measures mixed effects modeling will be used to estimate the placebo-corrected effect of study drug(s) on the ECG parameters (Refer to DMID 16-0110_ECG_Table shells: Table 6).
- Additional visit windowing will not be performed as this will have already been done prior to database lock.
- Presentation of results – decimal places and significant digits (Refer to Table 2)

Table 2 Presentation of results – decimal places

ECG Reporting Precision	
Descriptive Summaries	
Minimum, Maximum	Recorded decimal places
Mean, Median	Recorded decimal places + 1
Standard Deviation, Standard Error	Recorded decimal places + 2
Inferential Statistics	
LS Mean, Difference in LS Means	Recorded decimal places + 1
CIs corresponding to LS Means and Difference in LS Means	Recorded decimal places + 2

Listings	Recorded decimal places
PK Reporting Precision	
Mean (arithmetic and geometric), Median	Recorded decimal places + 1
Listings	Recorded decimal places

5.2. Treatments for Cardiac Safety Evaluation

The DMID 16-0110 study includes four treatments:

Each subject received one dose of each of four treatments, labeled A through D:

- Treatment A: zoliflodacin 2 g PO (investigational drug, therapeutic dose)
- Treatment B: zoliflodacin 4 g PO (investigational drug, supratherapeutic dose)
- Treatment C: placebo PO (for zoliflodacin)
- Treatment D: moxifloxacin 400 mg PO (positive control comparator)

Subject disposition for Holter ECG analysis population (number of subjects enrolled, completed, discontinued, and present in Holter ECG analysis population) will be presented. In addition, subject and ECG disposition for Holter ECG analysis population (number of subjects, expected number of ECGs, ECGs extracted and missing ECGs) will be summarized for each timepoint and all treatments.

5.3. Study Holter ECG Timepoints

At each study timepoint, the mean value of an ECG parameter from all available replicate ECGs recorded at that timepoint (maximum of 3 replicates) for an individual subject will be considered as the value of the ECG parameter at the nominal timepoint for the subject.

Baseline: Baseline will be determined separately for each dosing period. Mean of triplicate ECGs recorded at 3 pre-dose assessments (mean of 9 ECGs) on Day 1 (i.e. D1PRE45MIN, D1PRE30MIN and D1PRE15MIN) of each treatment period will be considered as baseline for the corresponding treatment period.

Holter ECG analysis timepoints for the study are as follows:

Table 3: Holter ECG Timepoints as per Visit code poster and Visit codes used in ECG database

No.	Timepoints as per Visit code poster	Visit Codes in ECG database
1	Period 1 Day 1 Predose 45 minutes	P1D1PRE45MIN
2	Period 1 Day 1 Predose 30 minutes	P1D1PRE30MIN
3	Period 1 Day 1 Predose 15 minutes	P1D1PRE15MIN
4	Period 1 Day 1 Post dose 0.5 hours	P1D1H0.5
5	Period 1 Day 1 Post dose 1 hour	P1D1H1
6	Period 1 Day 1 Post dose 2 hour	P1D1H2
7	Period 1 Day 1 Post dose 3 hour	P1D1H3
8	Period 1 Day 1 Post dose 4 hour	P1D1H4
9	Period 1 Day 1 Post dose 6 hour	P1D1H6

No.	Timepoints as per Visit code poster	Visit Codes in ECG database
10	Period 1 Day 1 Post dose 8 hour	P1D1H8
11	Period 1 Day 1 Post dose 12 hour	P1D1H12
12	Period 1 Day 1 Post dose 24 hour (Day 2)	P1D1H24
13	Period 2 Day 1 Predose 45 minutes	P2D1PRE45MIN
14	Period 2 Day 1 Predose 30 minutes	P2D1PRE30MIN
15	Period 2 Day 1 Predose 15 minutes	P2D1PRE15MIN
16	Period 2 Day 1 Post dose 0.5 hours	P2D1H0.5
17	Period 2 Day 1 Post dose 1 hour	P2D1H1
18	Period 2 Day 1 Post dose 2 hour	P2D1H2
19	Period 2 Day 1 Post dose 3 hour	P2D1H3
20	Period 2 Day 1 Post dose 4 hour	P2D1H4
21	Period 2 Day 1 Post dose 6 hour	P2D1H6
22	Period 2 Day 1 Post dose 8 hour	P2D1H8
23	Period 2 Day 1 Post dose 12 hour	P2D1H12
24	Period 2 Day 1 Post dose 24 hour (Day 2)	P2D1H24
25	Period 3 Day 1 Predose 45 minutes	P3D1PRE45MIN
26	Period 3 Day 1 Predose 30 minutes	P3D1PRE30MIN
27	Period 3 Day 1 Predose 15 minutes	P3D1PRE15MIN
28	Period 3 Day 1 Post dose 0.5 hours	P3D1H0.5
29	Period 3 Day 1 Post dose 1 hour	P3D1H1
30	Period 3 Day 1 Post dose 2 hour	P3D1H2
31	Period 3 Day 1 Post dose 3 hour	P3D1H3
32	Period 3 Day 1 Post dose 4 hour	P3D1H4
33	Period 3 Day 1 Post dose 6 hour	P3D1H6
34	Period 3 Day 1 Post dose 8 hour	P3D1H8
35	Period 3 Day 1 Post dose 12 hour	P3D1H12
36	Period 3 Day 1 Post dose 24 hour (Day 2)	P3D1H24
37	Period 4 Day 1 Predose 45 minutes	P4D1PRE45MIN
38	Period 4 Day 1 Predose 30 minutes	P4D1PRE30MIN
39	Period 4 Day 1 Predose 15 minutes	P4D1PRE15MIN
40	Period 4 Day 1 Post dose 0.5 hours	P4D1H0.5
41	Period 4 Day 1 Post dose 1 hour	P4D1H1
42	Period 4 Day 1 Post dose 2 hour	P4D1H2
43	Period 4 Day 1 Post dose 3 hour	P4D1H3
44	Period 4 Day 1 Post dose 4 hour	P4D1H4
45	Period 4 Day 1 Post dose 6 hour	P4D1H6
46	Period 4 Day 1 Post dose 8 hour	P4D1H8
47	Period 4 Day 1 Post dose 12 hour	P4D1H12
48	Period 4 Day 1 Post dose 24 hour (Day 2)	P4D1H24

5.4. Analysis of Central Tendency (By-timepoint Analysis)

By-timepoint analysis will be performed using Holter ECG data from subjects in the Holter ECG Analysis Population. Absolute values, change-from-baseline and time-matched, placebo-corrected, change-from-baseline values for each ECG parameter will be considered for this analysis (Refer to DMID 16-0110_ECG_Table shells: Tables 3, 4 and 5; DMID 16-0110_ECG_Listing shells: Listings 1 to 7; DMID 16-0110_ECG_Figure shells: Figure 1 to 56). Change-from-baseline QTcF (ΔQTcF) values (and other ECG parameters QTcB, HR

[calculated from RR], RR, QT, PR and QRS duration values) will be calculated by subtracting the mean value of replicate ECGs at baseline from the mean value of replicate ECGs at post-dose timepoints.

Time-matched, placebo-corrected, change from baseline in QTcF interval (ΔΔQTcF) values (and other ECG parameters QTcB, HR [calculated from RR], RR, QT, PR and QRS duration values) will be calculated as differences between time-matched change-from-baseline QTcF values for active treatment minus time-matched change-from-baseline QTcF values for placebo for each subject (Refer to DMID 16-0110_ECG_Table shells: Table 5; DMID 16-0110_ECG_Listing shells: Listings 1 to 7).

As a primary analysis, a repeated measurement analysis on ΔΔQTcF values will be performed at each post-dose timepoint using analysis of covariance (ANCOVA) (Refer to DMID 16-0110_ECG_Table shells: Table 6; DMID 16-0110_ECG_Figure shells: Figure 57). Unless otherwise specified, a restricted maximum likelihood based, linear mixed effect model will be used. Model will include ΔΔQTcF as the dependent variable. Baseline QTcF value as continuous covariate and sequence, period, treatment, nominal timepoint (as categorical) and interactions of timepoint with treatment will be treated as fixed effects. The model will also include subject nested within sequence as a random effect. SAS PROC MIXED will be used to perform the analysis.

At each of the 9 post-dose timepoints and for each zoliflodacin dose, a one-sided 95% CI for the treatment effect on ΔΔQTcF will be estimated using least square (LS) means. There will be 18 CIs, one for each combination of zoliflodacin dose and timepoint. A negative effect of 2 g or 4 g zoliflodacin will be concluded if the maximum of the 18 one-sided 95% CI upper bounds is <10 msec. No adjustment will be made for multiplicity.

SAS code will be similar to:

```
PROC MIXED;
      CLASS TREATMENT PERIOD SEQUENCE TIME SUBJ;
      MODEL   ΔΔQTCF   =   TREATMENT   PERIOD   SEQUENCE   TIME   BASELINE_QTCF
      TIME*TREATMENT;
      RANDOM SUBJECT(SEQUENCE);
      REPEATED TIME / SUBJ=SUBJ(PERIOD) TYPE=CS;
      LSMEANS TIME*TREATMENT / ALPHA=0.1;
 RUN;
```

In the above model, treatment will be Zoliflodacin 2 g and Zoliflodacin 4 g.

Similar ANCOVA models will also be done for QTcB, HR (calculated from RR), RR, QT, PR and QRS as secondary analyses (Refer to DMID 16-0110_ECG_Table shells: Table 6; DMID 16-0110_ECG_Figure shells: Figure 57 to 63).

The analysis will also be presented in graphs. For each of the 2 active treatments, all 9 confidence intervals (corresponding to the 9 post-dose timepoints) will be presented on one graph. The change from baseline (ΔQTcF) and placebo-corrected change from baseline QTcF (ΔΔQTcF) will be presented separately (Refer to DMID 16-0110_ECG_Figure shells: Figure 57 to 63).

Assay sensitivity (i.e., the ability to detect small increases from baseline QTcF duration) will be established by comparing the time-matched placebo-corrected change from baseline in QTcF in the moxifloxacin at the following 4 timepoints, i.e., 1, 2, 3, and 4 hours post-dose. The model as described in the primary analyses will be used. If the lower bound of one-sided 95% CI for treatment effect on ΔΔQTcF in at least one timepoint is >5 msec, it will be concluded that the assay is sensitive to small increases in baseline QTcF duration. Multiplicity adjustment will be done using the Bonferroni correction method. Since 4 timepoints and overall two-sided alpha of 0.1 are included in the analysis, two-sided alpha will be set to 0.1/4 = 0.025 in the model (Refer to DMID 16-0110_ECG_Figure shells: Figures 64 and 65).

```
PROC MIXED;
      CLASS PERIOD SEQUENCE TIME SUBJ;
      MODEL ΔΔQTCF = PERIOD SEQUENCE TIME BASELINE_QTCF;
      RANDOM SUBJECT(SEQUENCE);
      REPEATED TIME / SUBJ=SUBJ(PERIOD) TYPE=CS;
      LSMEANS TIME / ALPHA=0.025;
 RUN;
```

In addition, using the above linear mixed effects model, least squares mean estimates of ΔΔQTcF and their one-sided 95% CIs for moxifloxacin will be obtained for the treatment effect at all post-dose timepoints without multiplicity correction and displayed graphically to demonstrate the time course of the moxifloxacin effect.

Descriptive statistics (number of subjects, mean, SD, median, CV, minimum, maximum, SE and one-sided 95% CI) will be used to summarize the ECG parameters for each timepoint and for each treatment. For those visits with N ≤3, only median, maximum, and minimum values will be provided. These will be provided for absolute values and change from baseline values for all 4 treatments. Time-matched, placebo-corrected, change from baseline values will be provided for the 2 g zoliflodacin, 4 g zoliflodacin, and moxifloxacin for QTcF, QTcB, HR (calculated from RR), RR, QT interval, PR interval, and QRS duration.

Descriptive statistics will also be shown graphically with the x-axis showing the nominal time and the y-axis showing the mean change from baseline and its one-sided 95% CI for each of the ECG intervals parameters separately (i.e., QTcF, QTcB, HR, RR, QT, PR and QRS) for each of the treatment periods.

5.4.1. Categorical analysis

Categorical outlier analysis will supplement the central tendency analysis by determining if there were individual subjects who had an exaggerated effect on any ECG interval that were not revealed in a mean change from baseline central tendency analysis.

ECG parameter values from individual post-dose replicate ECGs at each timepoint (not mean or median of all replicates) will be considered separately for categorical outlier analysis.

Results of categorical outlier analysis will be presented as number and percentage of subjects in each treatment. Results will be tabulated by individual treatment. If a subject has more than one categorical outlier value for a parameter at a timepoint, then the subject will be counted only

once for that timepoint. Statistical tests for comparison between treatment arms will not be performed.

For outlier analysis, the baseline value for each participant is defined as mean of 3 pre-dose assessments (9 ECGs) on Day 1 (i.e. D1PRE45MIN, D1PRE30MIN and D1PRE15MIN) of the corresponding treatment period.

ECG parameters namely QT/QTc will be flagged as normal, abnormal insignificant or significant, based on the pre-approved study specific ECG abnormality criteria based on ICH E14 guidance.[2]

The categorical outlier values for QTcF, QTcB, HR, PR, and QRS parameters (Refer to DMID 16-0110_ECG_Table shells: Table 9; DMID 16-0110_ECG_Listing shells: Listings 8 to 13) for the individual subjects in each dose cohort will be summarized as follows:

1. QTcF and QTcB will be categorized using the following study-specific criteria:
   - QTc >450 msec to 480 msec
   - QTc >480 msec to 500 msec
   - QTc >500 msec
   - QTc increase from baseline ≥30 msec to <60 msec
   - QTc increase from baseline ≥60 msec
2. Uncorrected QT will be categorized for >500 msec.
3. Categorical outliers for HR (calculated from RR) will be categorized based on the following criteria:
   - HR change-from-baseline >25% decrease resulting in HR <50 bpm
   - HR change-from-baseline >25% increase resulting in HR >100 bpm
4. Categorical outliers for PR and QRS parameters will be categorized for the following criteria:
   - PR change-from-baseline >25% resulting in PR >200 msec
   - QRS change-from-baseline >25% resulting in QRS >120 msec

5.4.2. Analysis of ECG morphological abnormalities

The ECG morphological abnormalities will be presented in terms of the number and percentage of subjects in each treatment with changes from baseline that represent the appearance or the worsening of the morphological abnormality. The ECG morphological abnormalities will be summarized by treatment using the number and percentage of subjects within each treatment based on incidence rates. The denominator for the percentage will be the number of evaluable subjects in each treatment.

Abnormalities present in any one or more of the baseline timepoint replicate ECGs recorded for a particular period will be considered to be present at baseline for post-dose ECGs from that specific period.

If a subject has an ECG morphological abnormality in more than one replicate ECG of a study timepoint, the subject will be counted only once for that timepoint.

Morphological abnormalities will be summarized by treatment and by timepoint using the number and percentage of subjects within each treatment. No statistical test of significance will be applied. Treatment emergent morphological ECG abnormalities and their significance will be discussed in detail in the report.

T-wave morphology abnormalities will be presented separately in terms of the number and percentage of subjects in each treatment. The T-wave morphology abnormalities will be summarized by the T-wave morphology categories for abnormal T-waves such as flat T-waves, biphasic T-waves, and notched T-waves, as stated in section 8.3.1.2 of the protocol[1] (Refer to DMID 16-0110_ECG_Table shells: Tables 10 and 11; DMID 16-0110_ECG_Listing shells: Listings 14 and 15).

5.5. Pharmacokinetic-QTcF Analysis

PK-QTcF analysis will be performed using individual PK and ΔΔQTcF data from all timepoints from all subjects regardless of dose of zoliflodacin, in the PK-ECG Analysis Population. Time-matched plasma concentration of zoliflodacin and corresponding ΔΔQTcF data will be used to quantify the relationship between exposure and response (ΔΔQTcF). Moxifloxacin will not be included in this analysis. A linear or nonlinear mixed effects modeling approach will be used to quantify the relationship between plasma concentration of zoliflodacin and ΔΔQTcF (Refer to DMID 16-0110_ECG_Table shells: Tables 12 to 15; DMID 16-0110_ECG_Listing shells: Listings 16 and 17; DMID 16-0110_ECG_Figure shells: Figure 66 to 71).

5.5.1. Hysteresis effect check

To assess if there is a time dependency (a hysteresis effect) between zoliflodacin concentration and ΔΔQTcF visually, zoliflodacin concentration and ΔΔQTcF will be plotted vs. timepoint in a single plot and visually inspected for a difference between T_{max} for concentration and T_{max} for ΔΔQTcF. In addition, a scatter plot of mean ΔΔQTcF and mean plasma zoliflodacin concentration values from all subjects at each timepoint will be plotted using different colors and symbols for the 2 g and 4 g dose groups and the points connected in temporal sequence. If there is a unique value of ΔΔQTcF for each value of concentration, even as time evolves, the plot suggests no hysteresis. If plot shows that the value of ΔΔQTcF for a given value of concentration differs as time evolves, and the values of ΔΔQTcF observed before T_{max} consistently differ from the values observed at a similar concentration at a timepoint after T_{max} this would suggest presence of hysteresis (Refer to DMID 16-0110_ECG_Figure shells: Figures 66 and 67). If hysteresis is present, a PK model with an additional effect compartment will be used.[4] In this case, the concentration in the effect compartment (Ce) will be calculated and used in the model instead of the original concentration.

5.5.2. Testing for linearity:

A potential non-linear relationship between zoliflodacin concentration and ΔΔQTcF will be assessed visually and statistically (Refer to DMID 16-0110_ECG_Table shells: Table 12 and 13; DMID 16-0110_ECG_Figure shells: Figure 69).

In the visual approach, a scatter plot of ΔΔQTcF versus zoliflodacin plasma concentration for all timepoints will be generated and the locally weighted scatterplot smoothing (LOESS) and its one-sided 95% CI will be plotted and inspected for nonlinearity.[3] A PK-PD model with ΔΔQTcF as the dependent variable and zoliflodacin concentration and quadratic term of zoliflodacin concentration as independent variables will be performed using PROC MIXED with slope of concentration and quadratic term of concentration and intercept as subject-specific random effects.[4]

If there is no clear indication of nonlinearity based on visual inspection of the ΔΔQTcF vs. concentration plot, or the quadratic term for concentration is non-significant at a two-sided alpha level of 0.05, a linear mixed effects modeling approach will be used.[4] If there is an indication of a nonlinear relationship, a nonlinear mixed effect modeling approach will be examined. Akaike Information Criterion (AIC) of linear and different nonlinear mixed effect models including log-linear and E_{max} will be calculated. The model with the least AIC will be considered as the final model for concentration-effect modelling.[4]

5.5.3. Model selection:

The selection of the PK-PD model for evaluating zoliflodacin concentration and ΔΔQTcF will follow the assessment of hysteresis and non-linearity.[5] If there is no evidence of hysteresis and no indication of nonlinearity, linear mixed effects modeling approach will be used to quantify the relationship between zoliflodacin plasma concentration and ΔΔQTcF.

The model will include ΔΔQTcF as the dependent variable, with zoliflodacin concentration as fixed effects and intercept and slope as subject-specific random effects. Unstructured covariance (UN) structures will be used and denominator degrees of freedom method (DDFM) will be set to Kenward-Roger.[6] The subject-specific slope random effect will be dropped from the model or concentration values will be rescaled if the model fails to converge.

Model-predicted parameter estimates (model-predicted estimates of slope {β2}, SE of β2, p-values (for slope {β2} and overall model fit), predicted ΔΔQTcF and its upper bound of the one-sided 95% confidence limit at geometric mean C_{max} [separately for zoliflodacin 2 g PO and zoliflodacin 4 g PO]) will be calculated (Refer to DMID 16-0110_ECG_Table shells: Tables 14 and 15; DMID 16-0110_ECG_Listing shells: Listings 16 and 17; DMID 16-0110_ECG_Figure shells: Figure 70).

The model derived relationship between concentration of zoliflodacin and ΔΔQTcF will be validated by calculating the mean ΔΔQTcF and its one-sided 95% CIs for each decile of concentration values in the 2 g and 4 g zoliflodacin treatments.[3] The mean ΔΔQTcF and its one-sided 95% CIs for each decile of concentration values in the 2 g and 4 g zoliflodacin treatment will then be plotted at the corresponding median concentration value in each decile (Refer to DMID 16-0110_ECG_Figure shells: Figure 71).

5.6. Graphical Analysis

The actual values, the change-from-baseline and time-matched, placebo-corrected, change from baseline in ECG parameters will also be presented in a graphical manner. For each treatment, mean value of actual values at each timepoint with one-sided 95% CIs as error bars will be plotted for each treatment for QTcF. For timepoints with less than 5 subjects 'Range' will be plotted instead of 95% CI. Similar plots will be prepared for QTcB, HR (calculated from RR), RR, QT, PR and QRS parameters for absolute values and the change-from-baseline QTcF, HR (calculated from RR), QT, PR and QRS (Refer to DMID 16-0110_Figure shells: Figure 1 to 56).

For placebo-corrected, change from baseline in ECG parameters, least square means at each timepoint with one-sided 95% CIs as error bars will be plotted for each treatment. The graphs for ECG parameter values will be separated by treatment in the same plot (Refer to DMID 16-0110_ECG_Figure shells: Figures 57 to 63).

For the time course of moxifloxacin, one-sided 95% CIs (unadjusted and adjusted for multiplicity) will be obtained for the moxifloxacin effect on ΔΔQTcF at every timepoint using a linear mixed effects ANCOVA model and displayed graphically (Refer to DMID 16-0110_ECG_Figure shells: Figures 64 and 65).

Mean and 95% CI of ΔΔQTcF and concentration of zoliflodacin will be plotted in the zoliflodacin treatment period by timepoints (Refer to DMID 16-0110_ECG_Figure shells: Figures 66 and 67).

A scatterplot of individual values of ΔΔQTcF versus plasma concentration of zoliflodacin from all subjects from all timepoints will be prepared and the LOESS curve will be plotted (Refer to DMID 16-0110_ECG_Figure shells: Figure 69).

Individual ΔΔQTcF and plasma concentration of zoliflodacin for all subjects from all visits will be plotted and the model-based (including zoliflodacin plasma concentration as independent covariate) population mean prediction line for ΔΔQTcF and its one-sided 95% CI will be plotted (Refer to DMID 16-0110_ECG_Figure shells: Figure 70).

The mean ΔΔQTcF and its one-sided 95% CIs for each decile of concentration values in the 2 g and 4 g zoliflodacin treatment periods will be plotted at the corresponding median concentration value in each decile (Refer to DMID 16-0110_ECG_Figure shells: Figure 71).

6. References

1. Clinical Trial Protocol DMID 016-0110 (version 1.0, Dated 18 Jun 2018)
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