CLINICAL RESEARCH IN INFECTIOUS DISEASES

ANALYSIS PLAN

for

DMID Protocol 17-0088

Study Title:

A Phase 1, Three-Part, Randomized, Double-Blind, Single and Multiple Subcutaneous Dose Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of Rezafungin in Healthy Adult Subjects

NCT04117607

Version 1.0

DATE: 06-JUL-2020

STUDY TITLE

Protocol Number Code:	**DMID Protocol 17-0088**
Development Phase:	Phase 1
Products:	Rezafungin and Placebo
Form/Route:	Solution/Subcutaneous (SC) or Solution/Intravenous (IV)
Indication Studied:	Fungal infections
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	04DEC2019
Clinical Trial Completion Date:	11MAY2020
Date of the Analysis Plan:	06JUL2020
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

TABLE OF CONTENTS

Table of Contents *(continued)*

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Code
AUC	Area under the plasma concentration versus time curve
AUC_{inf}	Area under the plasma concentration versus time curve from time 0 to infinite time
AUC_{last}	Area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration
BA	Bioavailability
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per minute
BUN	Blood Urea Nitrogen
BQL	Below Limit of Quantification
CI	Confidence Interval
CL	Total clearance
CL/F	Apparent clearance
C_{max}	Maximum measured plasma concentration
CSR	Clinical Study Report
CV %	Coefficient of Variation
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
GM	Geometric Mean
λz	The terminal phase elimination rate constant
IV	Intravenous
LLOQ	Lower Limit of Quantification
MAD	Multiple Ascending Dose
Max	Maximum
MedDRA®	Medical Dictionary for Regulatory Activities
Min	Minimum
MOP	Manual of Procedures
MTD	Maximum tolerated dose
N	Number (typically refers to subjects)
NCA	Noncompartmental Analysis
PE	Physical Examination
PI	Principal Investigator
PK	Pharmacokinetics
PR (interval)	Interval measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by electrocardiogram
PT	Preferred Term
PTT	Partial Thromboplastin Time
QNS	Quantity Not Sufficient

List of Abbreviations *(continued)*

QRS (interval)	The interval between the Q wave and the S wave in the heart's electrical cycle as measured by electrocardiogram; principal deflection in the electrocardiogram
QT (interval)	A measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by electrocardiogram
QTc (interval)	A measure of time between the start of the Q wave and the end of the T wave in the heart's electrical cycle measured by electrocardiogram corrected for heart rate
SAD	Single Ascending Dose
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SDTM	Study Day Tabulation Model
SOC	System Organ Classes
$t_{1/2}$	Terminal phase half-life
TFL	Tables, Figures, and Listings
T_{max}	Time to reach maximum measured plasma concentration
VS	Vital Sign
V_z/F	Volume of distribution
WBC	White Blood Cell

1. PREFACE

The Analysis Plan for "A Phase 1, Three-Part, Randomized, Double-Blind, Single and Multiple Subcutaneous Dose Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of Rezafungin in Healthy Adult Subjects" (DMID Protocol 17-0088) describes and expands upon the statistical information presented in the protocol.

The sponsor terminated the study on 27APR2020 due to safety concerns. No subjects were enrolled into Single Ascending Dose (SAD) Cohort 3 (30 mg) and above, any Multiple Ascending Dose (MAD) cohort, or the Bioavailability (BA) cohort. Accordingly, this SAP describes analyses of data from subjects in SAD Cohort 1 (1 mg) and Cohort 2 (10 mg) only.

Due to early termination of the study, the sponsor confirmed an abbreviated clinical study report (CSR) will be provided. The statistical analysis plan noted in the protocol was not drafted and approved prior to study closure and was therefore deemed by the sponsor as not required. This document includes sufficient description of analyses, definitions, tables, figures, and listings (TFLs) for programming of the abbreviated CSR. Within the TFL mock-ups (Appendices 1, 2, and 3), references to abbreviated CSR sections are included. Any deviation from this SAP in the statistical analysis will be described and justified in the abbreviated CSR.

2. INTRODUCTION

2.1. Purpose of the Analyses

These analyses will assess the safety of single 1 mg or 10 mg subcutaneous doses of rezafungin given subcutaneously and pharmacokinetics (PK) of a single 10 mg subcutaneous dose.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Refer to Protocol v6.0.

3.2. Endpoints

Refer to Protocol v6.0.

3.3. Study Definitions and Derived Variables

3.3.1. Dose Group

Dose Group defines a grouping of subjects used for statistical analysis, where subjects within a Dose Group received the same dose and dosing schedule under the same fasting status. Note that for data from a subject to be analyzed as part of their Dose Group, the subject must also qualify for inclusion into the respective analysis population (As described in Section 5.3) for that data. Definitions for each Dose Group to be analyzed in the report, and their ordering, are provided in the list below.

- SAD Any Dose: Subjects from SAD cohorts who receive any dose of rezafungin.
- SAD 1 mg: SAD, Cohort 1 subjects receiving 1 mg of active drug.
- SAD 10 mg: SAD, Cohort 2 subjects receiving 10 mg of active drug.
- Placebo: SAD subjects receiving placebo.

The "SAD Any Dose" Dose Group will be included in analyses of safety endpoints only.

3.3.2. Baseline

For clinical laboratory results, and vital sign (VS) measurements, the baseline assessment is the last measurement recorded prior to dosing, except for height, weight, and BMI, which baseline will be defined as the measurements recorded at the initial Screening Visit. For electrocardiogram (ECG) results, baseline is defined as the median of the triplicate measurements taken within 60 minutes of dosing. If multiple triplicate measurements are taken prior to dosing, the median of last set of triplicates will be used as baseline.

Age will be based on age at enrollment. Age at enrollment is an integer value with units of years and is calculated from the subject's enrollment date (ENROLLDT) and birth date (BRTHDT) using the following algorithm.

- If month(ENROLLDT) > month(BRTHDT), then AGE = year(ENROLLDT) – year(BRTHDT)
- If month(ENROLLDT) < month(BRTHDT), then AGE = year(ENROLLDT) – year(BRTHDT) – 1
- If month(ENROLLDT) = month(BRTHDT) and day(ENROLLDT) ≥ day(BRTHDT), then AGE = year(ENROLLDT) – year(BRTHDT)
- If month(ENROLLDT) = month(BRTHDT) and day(ENROLLDT) < day(BRTHDT), then AGE = year(ENROLLDT) – year(BRTHDT) – 1

3.3.3. Study Day

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

4. SAMPLE SIZE CONSIDERATIONS

No formal sample-size calculations based on testing a statistical hypothesis were constructed. There will be a total of 86 subjects in this three-part trial, 44 subjects in 6 cohorts will receive rezafungin or placebo via SC injection in Part 1/SAD, 32 subjects in 4 cohorts will receive rezafungin or placebo via SC injection in Part 2/MAD, and 10 subjects will receive rezafungin via both SC and IV injections in Part 3/BA. The number of subjects was selected to allow sufficient evaluation of safety, tolerability, and PK of the various dose regimens, and to be consistent with standards of practice for Phase 1 trials.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. General Principles

Safety and PK data will be summarized by Dose Group, following the order shown in Section 3.3. Summary statistics for continuous data will include the mean, standard deviation (SD), median, minimum value (min), and maximum value (max). Summary statistics for discrete data will include counts and percent and may include confidence intervals (CIs) for the percent. When 95% CIs are given for a percent, Wilson Score CIs will be used. All subjects that are randomized will be included in the summaries of demographics, the Safety Population will be used for summaries of safety endpoints, and PK Population or PK Analysis Subset will be used for summaries of PK endpoints.

Generally, for summaries of safety endpoints, denominators will use the number of subjects in the Safety Population. Denominators for study time points of solicited local reactogenicity symptoms, clinical laboratory results, VS, and ECG results will use the number of subjects with an observed result at the time point for the parameter or symptom. Denominators for the conceptual "Max Severity Post-Baseline" time point for solicited local reactogenicity symptoms, clinical laboratory results, VS, and ECG results will use the number of subjects with an observed result for the parameter obtained post-dose.

The sort order of the listings as is indicated in the Implementation Note for each listing shell (Appendix 3).

5.2. Timing of Analyses

The final analysis will be performed after the clinical and non-clinical databases are locked.

5.3. Analysis Populations

A tabular listing (Listing 5) and summary table (Table 3) of all randomized and enrolled subjects excluded from the Safety Population, PK Analysis Population, or PK Analysis Subset will be included in the abbreviated CSR. Although there may be multiple reasons for exclusion from a PK Analysis Population or PK Analysis Subset, only one reason will be counted when summarizing reasons for exclusion from analysis populations. Priority for assigning reasons for exclusions will follow the order listed in Table 3.

5.3.1. Safety Population

All subjects that received any amount of study product will be included in the Safety Population.

5.3.2. PK Analysis Population

The PK Analysis Population will consist of all subjects who complete one full (as randomized, according to cohort) rezafungin dose and have one post-dose plasma sample with measurable rezafungin Note that all rezafungin concentration results will be included in listings, including results from placebo subjects.

5.3.3. PK Analysis Subset

The PK Analysis Subset will be a subset of the PK Analysis Population and will include all subjects in the PK Analysis Population 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 rezafungin from which at least a subset of the designated PK parameters can be determined. The statistician will review protocol deviations to determine a list of recommended exclusions due to protocol deviations likely to affect PK. The principal

investigator will review the list prior to unblinding and provide confirmation of any exclusions of subjects due to protocol deviations.

5.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses.

5.5. Missing Data

No imputation of missing data is planned.

5.6. Interim Analyses and Data Monitoring

No interim analysis was conducted prior to study termination.

5.7. Multicenter Studies

This is a single-site study.

5.8. Multiple Comparisons/Multiplicity

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

6. STUDY SUBJECTS

6.1. 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 4). Enrolled subjects who were ineligible for inclusion in analysis populations will be summarized by reason for subject exclusion and Dose Group (Table 3). Individual subject listings of subjects who were excluded from the Safety Population or a PK Analysis Population will be listed (Listing 5).

Subject disposition will be summarized (Table 2), showing the number of subjects who screened, enrolled, received study product, completed all PK blood draws, completed final study visit, and early termination.

Subjects who discontinued dosing or terminated early from the study will be listed (Listing 2).

A flowchart showing the disposition of study subjects will be included (Figure 1). This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed, by Dose Group.

6.2. Protocol Deviations

A summary of protocol deviations will be presented by deviation category, deviation type, and Dose Group (Table 1). 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 3 and Listing 4).

7. SAFETY EVALUATION

All safety analyses will be performed using the Safety Population.

Any medical condition that is present at the time that the subject is screened will be considered baseline and not reported as an AE unless it worsens in severity or increases in frequency during the study. The denominators for percent values will be indicated within the table or table header and denoted as N. Moreover, events summarized by subject will be coded to the highest severity observed over the indicated time period. Toxicity grading scales for adverse events, solicited reactogenicity symptoms, safety labs, VS, and ECG are provided in the protocol v6.0.

7.1. Demographic and Other Baseline Characteristics

Demographic summaries will include all subjects that were randomized. Sex, ethnicity, and race of all subjects will be summarized categorically by Dose Group (Table 5). Age at enrollment and height, weight, and BMI at screening will be summarized as continuous variables by Dose Group (Table 6). Individual subject listings will be presented for all demographic and baseline characteristics (Listing 6).

7.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA coded using MedDRA dictionary version 23.0 or higher. Summaries of subjects' pre-existing medical conditions by MedDRA system organ class (SOC) will be presented by Dose Group (Table 7). Individual subject listings will be presented for all medical conditions (Listing 7).

7.1.2. Prior and 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 33 for prior medications and Table 34 for concomitant medications). Individual subject listings will be presented for all prior and concomitant medications (separately in Listing 23 for prior medications and Listing 24 for concomitant medications).

7.2. Measurements of Treatment Compliance

Date and time of dosing will be presented in Listing 8. Concentration in plasma for Cohort 2 (including placebo) will be presented in Listing 31.

7.3. Adverse Events

When calculating the proportions of subjects with AEs within a given MedDRA category, each subject will only be counted once and any repetitions of AEs within a subject will be ignored, and the event will be reported according to the worst severity recorded (separately for related and unrelated AEs, when both severity and relatedness are tabulated).

7.3.1. Solicited Reactogenicity Symptoms

For each solicited local reactogenicity symptom, the number and percentage of subjects reporting each symptom will be summarized by maximum severity for a specified time point and Dose Group.

Maximum severity for each symptom based on functional grading and measurement grading criteria as described in protocol v6.0 will be summarized separately. All pre-dose and post-dose solicited local reactogenicity will be presented in Listing 9.

The following summaries for solicited local reactogenicity symptoms will be presented:

- The number and proportion of subjects with local symptoms, summarized by Dose Group and symptom. A 95% CI will be presented by Dose Group for each local symptom (Table 9).
- The number and proportion of subjects with local symptoms, summarized by Dose Group, symptom, and maximum severity. A 95% CI will be presented by Dose Group for each local symptom (Table 10).
- The number and proportion of subjects with local symptoms, summarized by Dose Group, symptom, time point, and maximum severity (including maximum severity post-baseline) (Table 11).
- By Dose Group, bar charts of proportions of subjects with local symptoms by maximum severity (each subject counted once per symptom) (Figure 2).
- By Dose Group and time point, bar charts of proportions of subjects with each local symptom by maximum severity (starting at Figure 3, continuing through Figure 16).

The following solicited local reactogenicity symptoms will be presented (in order):

- Pain, tenderness, pruritus (itching), ecchymosis (bruising) (functional grade), ecchymosis (bruising) (measurement grade), induration (hardness)/ swelling (functional grade), induration (hardness)/ swelling, (measurement grade), erythema (redness) (functional grade), erythema (redness) (measurement grade), nodule (functional grade), nodule (measurement grade), ulceration (functional grade), and ulceration (measurement grade).

7.3.2. Unsolicited Adverse Events

A brief overall summary of AEs by Dose Group including number of subjects with at least one solicited reactogenicity event of any severity, number of subjects with ulceration, number of subjects with at least one AE of any severity, number of subjects with at least one related AE of any severity, and number of subjects with at least one SAE (Table 8).

All AEs will be presented in listings (Listing 10). A subject listing of non-serious AEs of moderate or greater severity will also be reported (Table 15).

The following summaries for unsolicited adverse events will be presented:

- The total number of AEs and the number and proportion of subjects reporting at least one unsolicited AE will be summarized by Dose Group, SOC, and PT. Denominators for percentages are the number of subjects in the Safety Population. A 95% CI will be presented by Dose Group for each SOC and PT (Table 12).
- The number and proportion of subjects reporting at least one AE, summarized by Dose Group, SOC, PT, maximum severity, and relatedness (Table 13).
- By Dose Group, bar charts of proportions of subjects with related serious and non-serious AEs by maximum severity and SOC. This figure describes the number of subjects with an event (each subject counted once per SOC) (Figure 17).

- By Dose Group, bar charts of numbers of related serious and non-serious AEs by severity and SOC. This figure describes the total number of occurrences of each event, including multiple occurrences per subject (Figure 18).

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

Individual data listings of deaths and other SAEs will be provided (Table 14).

7.5. Pregnancies

An individual data listing of pregnancy reports will be provided if a pregnancy occurs pose-dosing (Listing 25, Listing 26, Listing 27, Listing 28, Listing 29). Contraceptive method will be listed in Listing 30.

7.6. Clinical Laboratory Evaluations

If the time of sample collection for clinical laboratory evaluations was prior to 23DEC2019, then grading will follow toxicity grade criteria from protocol v3.0. If the time of sample collection was on or after 23DEC2019, then grading will follow toxicity grade criteria from protocol v4.0. Note that toxicity ranges from protocol v4.0 through v6.0 were identical.

- CHEM: Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were removed from clinical lab collection after protocol v3.0.
- COAG: Prothrombin time and activated PTT toxicity ranges were updated after protocol v3.0.
- UA: Blood in urine (microscopic) toxicity ranges were updated after protocol v3.0.

All screening and safety laboratory results will be listed in Listing 11 (CHEM), Listing 12 (HEM), Listing 13 (COAG), Listing 14 (UA), Listing 15 (serology), Listing 16 (urine toxicity), and Listing 17 (pregnancy test). Abnormal laboratory results (laboratory results outside of the normal range on time of collection) will be listed in Table 16 (CHEM), Table 17 (HEM), Table 18 (COAG), and Table 19 (UA).

Laboratory results will be summarized in tables and figures:

- Tabularly, by parameter, Dose Group, time point, and toxicity grade (including maximum severity post-baseline). Summaries will be presented in Table 20 (CHEM), Table 22 (HEM), Table 24 (COAG), and Table 26 (UA). When calculating the proportions of subjects with a laboratory toxicity, each subject will only be counted once per toxicity grade and any repetitions of laboratory toxicities within a subject will be ignored, and the event will be reported according to the worst severity recorded. Parameters with no specified toxicity ranges listed in protocol will be excluded from this summary.
- Tabularly, by summary statistics for change from baseline, reported by parameter, Dose Group, and time point. Summaries will be presented in Table 21 (CHEM), Table 23 (HEM), and Table 25 (COAG).
- Graphically, using box plots of change from baseline by parameter, Dose Group, and time point.
  - CHEM: Beginning at Figure 19 and continuing through Figure 35.
  - HEM: Beginning at Figure 36 and continuing through Figure 45.
  - COAG: Figure 46, Figure 47, and Figure 48.

The following laboratory parameters will be presented (in order):

- Chemistry (CHEM): sodium, potassium, calcium, phosphorus, chloride, total carbon dioxide, glucose, blood urea nitrogen, creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin, creatine phosphokinase. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides parameters were removed after Protocol v3.0. Only Cohort 1 subjects have results for the specified parameters. Due to limited number of subjects with available results, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides will only be presented in Table 21 and Listing 11 and will be excluded from the change from baseline figures.
- Hematology (HEM): hemoglobin, hematocrit, RBC count, WBC count, neutrophil count, lymphocyte count, monocyte count, eosinophil count, basophil count, platelet count.
- Coagulation (COAG): prothrombin time, activated PTT, INR
- Urinalysis (UA): protein, glucose, occult blood.

By protocol, microscopic evaluation of urine or complete urinalysis is only performed if dipstick urinalysis is positive for blood. If complete UA or microscopic results were obtained in the absence of an abnormal dipstick result (or without dipstick tests being done), results of the complete UA or microscopy will still be summarized. Results determined using both methods will be listed. In tables, dipstick results will be presented prior to complete UA or microscopy results.

Laboratory parameters that have grading criteria for both decreases (result lower than normal range) and increases (result higher than normal range) 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 after dosing will be summarized (max severity post-baseline, including unscheduled visits) for each parameter. Results of maximum severity for “Any Parameter” will be included for all clinical laboratory results. For “Any Parameter” results, the maximum severity across all laboratory parameters in the respective category is summarized by time point.

Unscheduled clinical laboratory evaluations will be listed, but excluded from tabular and graphical summaries, except when calculating the maximum severity post-baseline. Any pre-existing abnormal lab results at screening will be graded and presented in listings but will not be reported as an AE unless they are treatment-emergent (i.e. it worsens after dosing, meaning for continuous parameters that an increase toxicity can only be assigned if the result is numerically higher than baseline and a decrease toxicity can only be assigned if the result is numerically lower than baseline.)

7.7. Vital Signs and Physical Evaluations

All VS measurements will be presented in Listing 18.

VS will be summarized in tables and figures:

- Tabularly, by parameter, Dose Group, time point, and toxicity grade (including maximum severity post-baseline). Respiratory rate measurements are not graded, and so will not be included in this summary. (Table 27).
- Tabularly, by summary statistics for change from baseline, reported by parameter, Dose Group, and time point. (Table 28).

- Graphically, using box plots of change from baseline by parameter, Dose Group, and time point. (Figure 49, Figure 50, Figure 51, Figure 52, Figure 53).

The following parameters will be reported (in order): systolic blood pressure (BP), diastolic BP, heart rate, respiratory rate, and temperature.

VS parameters that have grading criteria for both decreases (result lower than normal range) and increases (result higher than normal range) will be summarized separately by direction of change. For example, systolic blood pressure will be summarized separately as "Systolic Blood Pressure, Decrease" and "Systolic Blood Pressure, Increase."

In tables summarizing toxicity grading, maximum severity observed after dosing will be summarized for each parameter. Results of maximum severity for "Any Parameter" will also be included. For "Any Parameter" results, the maximum severity across all vital sign parameters is summarized by time point.

Unscheduled VS measurements will be listed, but excluded from tabular and graphical summaries, except when calculating the maximum severity post-baseline. Baseline for height, weight, and BMI will be the measurement taken at Screening Visit, baseline for the rest of the VS parameters is defined as the last vital sign parameter taken before dosing on Day 1 (including any repeats). Repeated VS due to clinic error or technical problem will be used for all analyses instead of the original vital sign result. Additional measurements taken as follow-up for safety will be included in listings and in computing maximum severity post baseline, but not as separate time points in summary tables. For repeats that were done due to delayed dosing, the last measurement prior to dosing will be considered as baseline for that subject.

Abnormal PE findings will be listed in Listing 19.

7.8. 12-Lead Standard Electrocardiogram

All 12-lead standard ECG measurement results, overall interpretation, and findings will be listed in Listing 20, Listing 21, and Listing 22.

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 Dose Group and time point (Table 29).
- Tabularly, by parameter, Dose Group, time point, and toxicity grade (including maximum severity post-baseline) (Table 30).
- Tabularly, by summary statistics for change from baseline, reported by parameter, Dose Group, and time point (Table 31).
- Tabularly, by Dose Group, time point, and sex based on QTcF categories according to the ICH Guideline E14 "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (protocol v6.0 Section 10.5.2). (Table 32).
- Graphically, using box plots of change from baseline by parameter, Dose Group, and time point (Figure 54, Figure 55, Figure 56, Figure 57, Figure 58, Figure 59).

The following parameters will be presented (in order): PR interval, QRS duration, QT interval, QTcF interval, RR interval, and mean ventricular rate.

Unscheduled 12-lead standard ECG measurements will be listed but excluded from tabular and graphical summaries. Individual interval measurements will be presented in listings along with overall interpretation

and comments. Other ECG findings besides interpretation will also be included in listings. Repeated ECG due to clinic error or technical problem will be used for all analyses instead of the original ECG result. Additional ECG measurements taken as follow-up for safety will be included in listings and in computing maximum severity post baseline, but not as separate time points in summary tables. For repeats that were done due to delayed dosing, the median of the last triplicate ECG measurement prior to dosing will be considered as baseline for that subject.

7.9. 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 ATC 1 and ATC 2 (separately in Table 33 for prior medications and Table 34 for concomitant medications). Individual subject listings will be presented for all prior and concomitant medications (separately in Listing 23 for prior medications and Listing 24 for concomitant medications).

8. PHARMACOKINETICS

Time points below the lower limit of quantification (LLOQ), referred to as below limit of quantification (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. There will be no imputation of missing concentrations. A geometric mean (GM) of concentrations will be treated as missing for sets of data points containing more than 1 BQL value.

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 noncompartmental analysis (NCA). Plasma samples collected out of window will be evaluated on a case-by-case basis. Samples will be considered substantially out of window if PK samples were not collected within ± 10 min for the 0.5 hour time point, ± 20 min of the targeted collection time (nominal time point) for time points 12 hours post-dose and earlier and within ± 1 hour for nominal time points from 24 to 144 hours post-dose, and ± 2 days on Day 14 and Day 30. Results from substantially out of window samples will be excluded from concentration summary statistics by nominal time points and plots of mean concentration, but included in NCA and in plots of individual concentrations.

Drug concentrations in plasma will be listed for subjects in Cohort 2, including placebo, with BQL and PK analyses-excluded samples indicated and with separate columns for concentrations reported by the lab and concentrations used for analysis (Listing 31). The column containing concentrations reported from the lab may include codes such as “BQL” or “QNS” (Quantity Not Sufficient) while the column containing concentrations used for analysis will contain numeric data only, including imputed values such as zeros for pre-dose timepoints reported as BQL. The listings will also indicate the nominal time (i.e., the planned time) and actual post-dose time in h associated with the sample.

The PK Analysis Subset will be used when summarizing PK concentrations. Summary statistics will be given for rezafungin concentrations by nominal time (Table 35).

Rezafungin concentrations will be also be shown graphically:

- Individual subject concentration-time profiles within 144 hours post-dose (Day 7) with y-axis on the linear scale (Figure 60).
- Individual subject concentration-time profiles within 144 hours post-dose (Day 7) with y-axis on the logarithmic scale (Figure 61).
- Individual subject concentration-time profiles for all time points with y-axis on the linear scale (Figure 62).
- Individual subject concentration-time profiles for all time points with y-axis on the logarithmic scale (Figure 63).
- GM concentration-time profiles within 144 hours post-dose (Day 7) y-axis on the linear scale. Error bars will show the mean ± 1 SD (Figure 64).
- GM concentration-time profiles within 144 hours post-dose (Day 7) y-axis on the logarithmic scale (Figure 65).
- GM concentration-time profiles for all time points with y-axis on the linear scale. Error bars will show the mean ± 1 SD (Figure 66).
- GM concentration-time profiles for all time points with y-axis on the logarithmic scale (Figure 67).

8.1. Noncompartmental Analysis

PK parameters will be estimated through an NCA using Phoenix® WinNonlin® version 8.2 or later (Certara, Princeton, NJ). Actual post-dose time will be used for the estimation of PK parameters instead of nominal time. Individual PK parameter estimates will be listed. PK Analysis Subset will be used when summarizing PK parameters. Summary tables including mean, SD, min, max, median, coefficient of variation (CV %), and GM will be presented (Table 36). Definition of CV is provided below.

For an independent identically distributed random sample $\{x_1, x_2, \ldots, x_n\}$ from a log-normal distribution, let s^2 be the sample variance statistic of the natural log-transformed values of the sample. The CV was defined as:

$$\text{CV} = \sqrt{\exp(s^2) - 1}$$

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

- Linear Up Log Down calculation method
- Uniform weighting
- Extravascular Dosing
- Lambda Z Acceptance Criteria
  - Rsq_adjusted ≥ 0.90
  - Span ≥ 3.0 half-lives
  - Includes at least 3 timepoints after T_{max}

All estimable PK parameters and terminal phase PK parameters that meet Lambda Z acceptance criteria will be listed in Listing 32. A definition for each PK parameter for the SAD cohorts are defined below.

C_{max}

Maximum concentration (C_{max}) is defined as the maximum observed drug concentration observed 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 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.

λz

The terminal phase elimination rate constant (λz) 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). λz 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. λz will be estimated using uniform weighting.

Time points used in the estimation of λz 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 Clearance [CL/F], Apparent volume of distribution during terminal phase [V_z/F]) will be treated as missing.

The range of concentrations used to estimate λz for each profile will be inspected by the PK analyst, who may adjust the set of concentrations used to estimate λz 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 λz will be indicated in the listing for concentration. This parameter will be obtained from the **Lambda_z** parameter calculated by WinNonlin®. λz will be reported in units of 1/h.

$t_{1/2}$

The $t_{1/2}$ 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) / λz. 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®.

$AUC_{0\text{-inf}}$ 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 λz:

$$\mathrm{AUC}_{0-\mathrm{inf}} = \mathrm{AUC}_{0-\mathrm{last}} + \frac{\mathrm{C}_{\mathrm{last}}}{\boldsymbol{\lambda z}},$$

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 clearance (CL/F) will be computed as Dose/$AUC_{0\text{-inf}}$. 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 will be calculated as (CL/F)/ λz. Volume will be reported in units of L.

9. REPORTING CONVENTIONS

The mean, median, SD, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Order statistics, such as the min and max, will use the same number of decimal places as the original data. Proportions will be presented as two decimal places; values <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values < 1% will be presented as "<1".

For PK, AUCs will be reported as whole numbers (or using 3 significant digits if less than 100). t1/2, Tmax, CL/F, and Vz/F values will be reported to one decimal place (or to 2 decimal places if less than 1). λz values will be reported to 3 significant digits. Cmax will be reported to 3 significant digits. The mean, median, SD, and any other statistics other than quantiles will be reported one significant digit greater than the reported data. Order statistics, such as the min and max, will use the same number of significant digits as the original data.

Listings of individual subject data include a Subject ID column. The subject identifiers assigned by site staff are replaced throughout this report with the Study Day 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.

10. 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 an NCA using Phoenix® WinNonlin® version 8.2 or later (Certara, Princeton, NJ).

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

The sponsor terminated the study on 27APR2020 due to safety concerns. No subjects were enrolled into SAD Cohort 3 (30 mg) and above, any MAD cohort, or the BA cohort. Only SAD 1 mg and SAD 10 mg Dose Groups will be included in the final safety analysis and SAD 10 mg Dose Group will be included in the final PK analysis.

12. REFERENCES

13. 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

10.2 Protocol Deviations

Table 1: Distribution of Protocol Deviations by Category, Type, and Dose Group

Category	Deviation Type	Number of Subjects (Number of Deviations)			
		SAD 1 mg (N=X)	SAD 10 mg (N=X)	Placebo (N=X)	All Subjects (N=X)
Eligibility/enrollment	Any type	x (x)	x (x)	x (x)	x (x)
	Did not meet inclusion criterion	x (x)	x (x)	x (x)	x (x)
	Met exclusion criterion	x (x)	x (x)	x (x)	x (x)
	ICF not signed prior to study procedures	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)
Treatment administration schedule	Any type	x (x)	x (x)	x (x)	x (x)
	Out of window visit	x (x)	x (x)	x (x)	x (x)
	Missed visit/visit not conducted	x (x)	x (x)	x (x)	x (x)
	Missed treatment administration	x (x)	x (x)	x (x)	x (x)
	Delayed treatment administration	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)
Follow-up visit schedule	Any type	x (x)	x (x)	x (x)	x (x)
	Out of window visit	x (x)	x (x)	x (x)	x (x)
	Missed visit/visit not conducted	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)
Protocol procedure/assessment	Any type	x (x)	x (x)	x (x)	x (x
	Incorrect version of ICF signed	x (x)	x (x)	x (x)	x (x)
	Blood not collected	x (x)	x (x)	x (x)	x (x)
	Urine not collected	x (x)	x (x)	x (x)	x (x)
	Other specimen not collected	x (x)	x (x)	x (x)	x (x)
	Too few aliquots obtained	x (x)	x (x)	x (x)	x (x)
	Specimen result not obtained	x (x)	x (x)	x (x)	x (x)
	Required procedure not conducted	x (x)	x (x)	x (x)	x (x)
	Required procedure done incorrectly	x (x)	x (x)	x (x)	x (x)
	Study product temperature excursion	x (x)	x (x)	x (x)	x (x)
	Specimen temperature excursion	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)
Treatment administration	Any type	x (x)	x (x)	x (x)	x (x)
	Required procedure done incorrectly	x (x)	x (x)	x (x)	x (x)
	Study product temperature excursion	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)
Blinding policy/procedure	Any type	x (x)	x (x)	x (x)	x (x)
	Treatment unblinded	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)
Note: N = Number of subjects in Safety Population					

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 2: Subject Disposition by Dose Group

	SAD 1 mg (N=X)	SAD 10 mg (N=X)	Placebo (N=X)	All Subjects (N=X)
Subject Disposition	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Screened	-	-	-	x (-)
Enrolled/Randomized	x (100)	x (100)	x (100)	x (100)
Received Study Product	x (x)	x (x)	x (x)	x (x)
Completed all PK Blood Draws	x (x)	x (x)	x (x)	x (x)
Completed Final Study Visit	x (x)	x (x)	x (x)	x (x)
Early Termination	x (x)	x (x)	x (x)	x (x)
Note: N= Number of subjects randomized.				

Table 3: Analysis Populations by Dose Group

[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 will follow the order in the table.]

Analysis Populations	Reason Subjects Excluded	SAD 1 mg (N=X) n (%)	SAD 10 mg (N=X) n (%)	Placebo (N=X) n (%)	All Subjects (N=X) n (%)
Safety Population	No study product received	x (x)	x (x)	x (x)	x (x)
PK Analysis Population	Any Reason	x (x)	x (x)	x (x)	x (x)
	Subject received placebo or was enrolled in Cohort 1	x (x)	x (x)	x (x)	x (x)
	Assigned dose not received or completed	x (x)	x (x)	x (x)	x (x)
	Subject has no measurable concentration of drug	x (x)	x (x)	x (x)	x (x)
PK Analysis Subset	Any Reason	x (x)	x (x)	x (x)	x (x)
	Exclusion from PK Analysis Population	x (x)	x (x)	x (x)	x (x)
	Has protocol deviations that potentially impact PK	x (x)	x (x)	x (x)	x (x)
	PK data insufficient to estimate any PK parameters	x (x)	x (x)	x (x)	x (x)
Note: N= Number of subjects randomized.					

Table 4: Ineligibility Summary of Screen Failures

[Implementation Note: Criteria displayed in the actual table will copy verbatim from the protocol with appropriate footnotes. The final summary table will include only inclusion/exclusion criterion with at least 1 subject. Criteria that were not met by any subjects will be excluded from final table.]

		Subjects Excluded	
Inclusion/Exclusion Category	**Inclusion/Exclusion Criterion**	**n[a]**	**%[b]**
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	x
	Willing and able to provide written informed consent and authorization for use of PHI	x	x
	Willing and able to comply with protocol requirements and is likely to complete the study as planned	x	x
	Males are vasectomized or agree to use barrier contraception from first dose through 18 weeks post last dose of IP	x	x
	Females are of non-childbearing potential or agree to use specified BC for 30 days pre and post-dose	x	x
	Subject is in good health as deemed by the Investigator	x	x
	Subject has a BMI between 18.5 and 35.0 kg/m^2, inclusive and a minimum weight of 50 kg	x	x
	Subject must refrain from strenuous physical activity from screening until completion of the trial	x	x
	Subjects must refrain from OTC/Rx meds, nutrition supplements from 14 days pre-dose to final visit	x	x
	Subject has adequate venous access for blood collection	x	x
Exclusion	Any exclusion criterion	x	x
	Subjects with clinical laboratory values outside the site reference ranges prior to initial dosing	x	x
	Abnormal ECGs.	x	x
	Female subject is pregnant, lactating or planning to become pregnant	x	x
	Received any prescription medications (with exceptions) within 14 days before first dose	x	x
	Received any non-prescription medications, vitamins or supplements within 14 days of initial dose	x	x
	Current smoker or tobacco use within 90 days prior to dosing or while subject is enrolled in study	x	x
	History of illicit/illegal drug use, alcohol/substance abuse, or vaping of non-nicotine products	x	x
	Consumed alcohol <= 48 hours of xanthines/caffeine <= 24 hours before first dose until discharge	x	x
	Received any live or killed vaccines or immunoglobulins within 14 days of dosing	x	x
	Donated blood or blood products or experienced significant blood loss within 60 days of dosing	x	x
	Received a blood transfusion within 14 days of dosing	x	x

		Subjects Excluded	
Inclusion/Exclusion Category	**Inclusion/Exclusion Criterion**	**n[a]**	**%[b]**
	Previous participation in any trial within 28 days of dosing or plans to enroll in another trial	x	x
	The PI considers that the subject should not participate in the trial	x	x
Eligible but Not Enrolled	Any Reason	x	x
	[Reason 1]	x	x
	[Reason 2]	x	x

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

14.1.2 Demographic Data by Dose Group

Table 5: Summary of Categorical Demographic and Baseline Characteristics by Dose Group

Variable	Characteristic	SAD 1 mg (N=X) n (%)	SAD 10 mg (N=X) n (%)	Placebo (N=X) n (%)	All Subjects (N=X) n (%)
Sex	Male	x (x)	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)	x (x)
Ethnicity	Not Hispanic or Latino	x (x)	x (x)	x (x)	x (x)
	Hispanic or Latino	x (x)	x (x)	x (x)	x (x)
	Not Reported	x (x)	x (x)	x (x)	x (x)
	Unknown	x (x)	x (x)	x (x)	x (x)
Race	American Indian or Alaska Native	x (x)	x (x)	x (x)	x (x)
	Asian	x (x)	x (x)	x (x)	x (x)
	Native Hawaiian or Other Pacific Islander	x (x)	x (x)	x (x)	x (x)
	Black or African American	x (x)	x (x)	x (x)	x (x)
	White	x (x)	x (x)	x (x)	x (x)
	Multi-Racial	x (x)	x (x)	x (x)	x (x)
	Unknown	x (x)	x (x)	x (x)	x (x)
Note: N= Number of subjects randomized.					

Table 6: Summary of Continuous Demographic and Baseline Characteristics by Dose Group

Variable	Statistic	SAD 1 mg (N=X)	SAD 10 mg (N=X)	Placebo (N=X)	All Subjects (N=X)
Age (years)	Mean	x	x	x	x
	SD	x	x	x	x
	Median	x	x	x	x
	Min	x	x	x	x
	Max	x	x	x	x
Height (cm)	Mean	x	x	x	x
	SD	x	x	x	x
	Median	x	x	x	x
	Min	x	x	x	x
	Max	x	x	x	x
Weight (kg)	Mean	x	x	x	x
	SD	x	x	x	x
	Median	x	x	x	x
	Min	x	x	x	x
	Max	x	x	x	x
BMI (kg/m^2)	Mean	x	x	x	x
	SD	x	x	x	x
	Median	x	x	x	x
	Min	x	x	x	x
	Max	x	x	x	x
Note: N= Number of subjects randomized.					

14.1.3 Prior and Concurrent Medical Conditions

Table 7: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Dose Group

MedDRA System Organ Class	SAD 1 mg (N=X) n (%)	SAD 10 mg (N=X) n (%)	Placebo (N=X) n (%)	All Subjects (N=X) n (%)
Any SOC				
[SOC 1]				
[SOC 2]				
Note: N= Number of subjects randomized.				

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 8: Overall Summary of Adverse Events by Dose Group

[Implementation Note: Abnormal laboratory AEs assessed using the protocol toxicity tables will not be included in this summary.]

	SAD Any Dose (N=X)	SAD 1 mg (N=X)	SAD 10 mg (N=X)	Placebo (N=X)
Subjects with	**n (%)**	**n (%)**	**n (%)**	**n (%)**
At least one solicited reactogenicity event	x (x)	x (x)	x (x)	x (x)
At least one ulceration	x (x)	x (x)	x (x)	x (x)
At least one mild (or worse) solicited reactogenicity event	x (x)	x (x)	x (x)	x (x)
At least one moderate (or worse) solicited reactogenicity event	x (x)	x (x)	x (x)	x (x)
At least one severe solicited reactogenicity event	x (x)	x (x)	x (x)	x (x)
At least one adverse event	x (x)	x (x)	x (x)	x (x)
At least one related adverse event	x (x)	x (x)	x (x)	x (x)
At least one mild (or worse) related adverse event	x (x)	x (x)	x (x)	x (x)
At least one moderate (or worse) related adverse event	x (x)	x (x)	x (x)	x (x)
At least one severe related adverse event	x (x)	x (x)	x (x)	x (x)
At least one serious adverse event	x (x)	x (x)	x (x)	x (x)
At least one related, serious adverse event	x (x)	x (x)	x (x)	x (x)
At least one adverse event leading to early termination	x (x)	x (x)	x (x)	x (x)
Note: N = Number of subjects in Safety Population				

14.3.1.1 Solicited Reactogenicity Events

Table 9: Number and Percentage of Subjects Experiencing Solicited Reactogenicity Symptoms with 95% Confidence Intervals by Symptom and Dose Group

[Implementation Note: Each subject is counted once per symptom.]

Symptom	SAD Any Dose (N=X)			SAD 1 mg (N=X)			SAD 10 mg (N=X)			Placebo (N=X)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
Pain												
Tenderness												
Pruritus (Itching)												
Ecchymosis (Bruising), Functional Grade												
Ecchymosis (Bruising), Measurement Grade												
Induration (Hardness)/ Swelling, Functional Grade												
Induration (Hardness)/ Swelling, Measurement Grade												
Erythema (Redness), Functional Grade												
Erythema (Redness), Measurement Grade												
Nodule, Functional Grade												
Nodule, Measurement Grade												
Ulceration, Functional Grade												
Ulceration, Measurement Grade												
Note: N = Number of subjects in the Safety Population.												

Table 10: Number and Percentage of Subjects Experiencing Solicited Reactogenicity Symptoms with 95% Confidence Intervals by Symptom, Severity, and Dose Group

[Implementation Note: Each subject is counted once per symptom.]

Symptom	Severity	SAD Any Dose (N=X)			SAD 1 mg (N=X)			SAD 10 mg (N=X)			Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	None	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
	Mild												
	Moderate												
	Severe												
Pain	None												
	Mild												
	Moderate												
	Severe												
Tenderness	None												
	Mild												
	Moderate												
	Severe												
Pruritus (Itching)	None												
	Mild												
	Moderate												
	Severe												
Ecchymosis (Bruising), Functional Grade	None												
	…												
Ecchymosis (Bruising), Measurement Grade	None												
	…												
Induration (Hardness)/ Swelling, Functional Grade	…												

Symptom	Severity	SAD Any Dose (N=X)			SAD 1 mg (N=X)			SAD 10 mg (N=X)			Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Induration (Hardness)/ Swelling, Measurement Grade	…												
Erythema (Redness), Functional Grade	…												
Erythema (Redness), Measurement Grade	…												
Nodule, Functional Grade	…												
Nodule, Measurement Grade	…												
Ulceration, Functional Grade	…												
Ulceration, Measurement Grade	…												
Note: N = Number of subjects in Safety Population													

Table 11: Number and Percentage of Subjects Experiencing Solicited Reactogenicity Symptoms by Symptom, Severity, Time Point, and Dose Group

Dose Group	Time Point	N	None		Mild		Moderate		Severe	
			n	%	n	%	n	%	n	%
Any Symptoms										
SAD Any Dose	Max Severity Post Baseline									
	Day 1, 1 h Post-Dose									
	Day 1, 4 h Post-Dose									
	Day 2									
	Day 3									
	Day 4									
	Day 5									
	Day 6									
	Day 7									
	Max Severity Day 8 to Day 14									
	Max Severity Day 15 to Day 21									
	Max Severity Day 22 to Final Visit									
SAD 1 mg	Max Severity Post Baseline									
	…									
SAD 10 mg	Max Severity Post Baseline									
	…									
Placebo	Max Severity Post Baseline									
	…									
Pain										
SAD Any Dose	…									
SAD 1 mg	…									
SAD 10 mg	…									
Tenderness										
Ecchymosis (Bruising), Functional Grade										
Ecchymosis (Bruising), Measurement Grade										
Induration (Hardness)/ Swelling, Functional Grade										
Induration (Hardness)/ Swelling, Measurement Grade										
Erythema (Redness), Functional Grade										
Erythema (Redness), Measurement Grade										
Nodule, Functional Grade										
Nodule, Measurement Grade										
Ulceration, Functional Grade										
Ulceration, Measurement Grade										

Note: N = Number of subjects in Safety Population with solicited reactogenicity symptoms assessed at the respective time point.

14.3.1.2 Unsolicited Adverse Events

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

[Implementation Note: If there is only 1 PT for an SOC, there will be no "Any PT" row.]

Dose Group	MedDRA System Organ Class	MedDRA Preferred Term	N	n (%)	95% CI	Number of Events
SAD Any Dose	Any SOC	Any PT	x	x (x)	(x.x, x.x)	X
	[SOC 1]	Any PT	x	x (x)	(x.x, x.x)	X
		[PT 1]	x	x (x)	(x.x, x.x)	X
		[PT 2]	x	x (x)	(x.x, x.x)	X
	Any SOC	Any PT	x	x (x)	(x.x, x.x)	X
SAD 1 mg	…					
Note: N = Number of subjects in Safety Population						

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

[Implementation Note: If there is only 1 PT for an SOC, there will be no "Any PT" row.]

Dose Group	MedDRA System Organ Class	MedDRA Preferred Term	Severity	N	Related n(%)	Not Related n (%)	Total n (%)
SAD Any Dose	Any SOC	Any PT	Any Severity	x	x (x)	x (x)	x (x)
			Mild	x	x (x)	x (x)	x (x)
			Moderate	x	x (x)	x (x)	x (x)
			Severe	x	x (x)	x (x)	x (x)
	[SOC 1]	Any PT	Any Severity	x	x (x)	x (x)	x (x)
			Mild	x	x (x)	x (x)	x (x)
			Moderate	x	x (x)	x (x)	x (x)
			Severe	x	x (x)	x (x)	x (x)
		[PT 1]	Any Severity	x	x (x)	x (x)	x (x)
			Mild	x	x (x)	x (x)	x (x)
			Moderate	x	x (x)	x (x)	x (x)
			Severe	x	x (x)	x (x)	x (x)
				x	x (x)	x (x)	x (x)
SAD 1 mg	Any SOC	Any PT	Any Severity	x	x (x)	x (x)	x (x)
…	…						

Note: N = Number of subjects in Safety Population

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 14: 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 abbreviated 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 should be sorted by Dose Group, Subject ID, and AE Number.]

Adverse Event	MedDRA System Organ Class	MedDRA Preferred Term	Study Day	Duration of AE in Days	Study Day the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment (Alternate Etiology)	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome
Dose Group: , Subject ID: , AE Number:											
Comments:											
Dose Group: , Subject ID: , AE Number:											
Comments:											

Table 15: 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 abbreviated 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. Listing should be sorted by Dose Group, Subject ID, and AE Number.]

Adverse Event	MedDRA System Organ Class	MedDRA Preferred Term	Study Day	Duration of AE in Days	Severity	Relationship to Study Treatment (Alternate Etiology)	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome
Dose Group: , Subject ID: , AE Number:									
Comments:									
Dose Group: , Subject ID: , AE Number:									
Comments:									

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

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

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 16: 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 abbreviated CSR. This listing includes all abnormal Chemistry results (laboratory results outside of the normal range defined in the protocol). Normal chemistry results for other parameters that occurred on the same visit as the abnormal result will not be listed. There is a separate, complete listing of all Chemistry results. In the Laboratory Parameter column, indicate the units (LB.LBSTRESU) after the parameter, e.g., Sodium (mEq/L). This listing is not color-coded. Results that are outside the normal range but not mild, moderate, or severe will have ONR listed as severity. Similarly, results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline) will be shown as ONR.

Sort order: Dose Group, Subject ID, Time Point, and Parameter.]

Dose Group	Subject ID	Sex	Time Point	Date of Assessment	Laboratory Parameter (Units)	Result	Severity

Table 17: 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 abbreviated CSR. This listing includes all abnormal Hematology results (laboratory results outside of the normal range defined in the protocol). Normal hematology results for other parameters that occurred on the same visit as the abnormal result will not be listed. There is a separate, complete listing of all Hematology results. In the Laboratory Parameter column, indicate the units (LB.LBSTRESU) after the parameter, e.g., Hemoglobin (g/dL). This listing is not color-coded. Results that are outside the normal range but not mild, moderate, or severe will have ONR listed as severity. Similarly, results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline) will be shown as ONR..

Sort order: Dose Group, Subject ID, Time Point, and Parameter.]

Dose Group	Subject ID	Sex	Time Point	Date of Assessment	Laboratory Parameter (Units)	Result	Severity

Table 18: Listing of Abnormal Laboratory Results - Coagulation

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the abbreviated CSR. This listing includes all abnormal Coagulation results (laboratory results outside of the normal range defined in the protocol). Normal coagulation results for other parameters that occurred on the same visit as the abnormal result will not be listed. There is a separate, complete listing of all Coagulation results. In the Laboratory Parameter column, indicate the units (LB.LBSTRESU) after the parameter, e.g., (seconds).This listing is not color-coded. Results that are outside the normal range but not mild, moderate, or severe will have ONR listed as severity. Similarly, results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline) will be shown as ONR.

Sort order: Dose Group, Subject ID, Time Point, and Parameter.]

Dose Group	Subject ID	Time Point	Date of Assessment	Laboratory Parameter (Units)	Result	Severity

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 abbreviated CSR. This listing includes all abnormal Urinalysis results (laboratory results outside of the normal range defined in the protocol). Normal urinalysis results for other parameters that occurred on the same visit as the abnormal result will not be listed. There is a separate, complete listing of all Urinalysis results. In the Laboratory Parameter column, indicate the units (LB.LBSTRESU) after the parameter, e.g., Leukocytes by Microscopy (/hpf). This listing is not color-coded. Results that are outside the normal range but not mild, moderate, or severe will have ONR listed as severity. Similarly, results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline) will be shown as ONR.

Sort order: Dose Group, Subject ID, Time Point, and Parameter.]

Dose Group	Subject ID	Sex	Time Point	Date of Assessment	Laboratory Parameter (Units)	Result	Severity
					Occult Blood by Dipstick	Negative	

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 20: Chemistry Toxicity Grade by Parameter, Severity, Dose Group, and Time Point

[Implementation Note: Severity will be graded based on toxicity criteria in protocol. If there is not at least 1 Mild, Moderate, or Severe Event for Max Severity Post-Baseline, then only the Max Severity Post-Baseline row will be shown for the parameter. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

Dose Group	Time Point	N	Mild	Moderate	Severe
			n (%)	n (%)	n (%)
Any Parameter					
SAD Any Dose	Baseline	x	x (x)	x (x)	x (x)
	Max Severity Post-Baseline	x	x (x)	x (x)	x (x)
	Day 2	x	x (x)	x (x)	x (x)
	Day 7	x	x (x)	x (x)	x (x)
	Final Visit	x	x (x)	x (x)	x (x)
SAD 1 mg	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
SAD 10 mg	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
Placebo	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
Sodium, Decrease					
SAD Any Dose	Baseline	x	x (x)	x (x)	x (x)
…	…	x	x (x)	x (x)	x (x)

Notes: The "Max Severity Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N=Number of subjects in the Safety Population with the laboratory result assessed at the respective time point.

Table 21: Chemistry Change from Baseline by Parameter, Dose Group, and Time Point

Dose Group	Time Point	N	Change from Baseline			
			Mean	SD	Median	Min, Max
Sodium (mEq/L)						
SAD Any Dose	Day 2	x	x	x	x	x, x
	Day 7	x	x	x	x	x, x
	Final Visit	x	x	x	x	x, x
SAD 1 mg	Day 2	x				
	…	x	x	x	x	x, x
SAD 10 mg	Day 2	x				
	…	x	x	x	x	x, x
	…	x	x	x	x	x, x
Placebo	Day 2	x	x	x	x	x, x
	…	x	x	x	x	x, x
Potassium (mEq/L)						
SAD Any Dose	Day 2	x	x	x	x	x, x
	…	x	x	x	x	x, x

Note: N=Number of subjects in the Safety Population with the laboratory result assessed at the respective time point.

14.3.5.2 Hematology Results

Table 22: Hematology Toxicity Grade by Parameter, Severity, Dose Group, and Time Point

[Implementation Note: Severity will be graded based on toxicity criteria in protocol. If there is not at least 1 Mild, Moderate, or Severe Event for Max Severity Post-Baseline, then only the Max Severity Post-Baseline row will be shown for the parameter. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

This table will repeat Table 20 for Hematology parameters.

Table 23: Hematology Change from Baseline by Parameter, Dose Group, and Time Point

This table will repeat Table 21 for Hematology parameters.

14.3.5.3 Coagulation Clinical Laboratory Results

Table 24: Coagulation Toxicity Grade by Parameter, Dose Group, and Time Point

[Implementation Note: Severity will be graded based on toxicity criteria in protocol. If there is not at least 1 Mild, Moderate, or Severe Event for Max Severity Post-Baseline, then only the Max Severity Post-Baseline row will be shown for the parameter. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

This table will repeat Table 20 for Coagulation parameters.

Table 25: Coagulation Change from Baseline by Parameter, Dose Group, and Time Point

This table will repeat Table 21 for Coagulation parameters.

14.3.5.4 Urinalysis Results

Table 26: Urinalysis Toxicity Grade by Parameter, Severity, Dose Group, and Time Point

[Implementation Note: Severity will be graded based on toxicity criteria in protocol. If there is not at least 1 Mild, Moderate, or Severe Event for Max Severity Post-Baseline, then only the Max Severity Post-Baseline row will be shown for the parameter. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

This table will repeat Table 20 for Urinalysis parameters.

14.3.6 Displays of Vital Signs

Table 27: Vital Sign Toxicity Grade by Parameter, Severity, Dose Group, and Time Point

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

Dose Group	Time Point	N	Mild n (%)	Moderate n (%)	Severe n (%)
Any Parameter					
SAD Any Dose	Baseline	x	x (x)	x (x)	x (x)
	Max Severity Post Baseline				
	Day 1, 15 minutes Post-Dose	x	x (x)	x (x)	x (x)
	Day 1, 1 h Post-Dose	x	x (x)	x (x)	x (x)
	Day 1, 2 h Post-Dose	x	x (x)	x (x)	x (x)
	Day 2	x	x (x)	x (x)	x (x)
	Day 4	x	x (x)	x (x)	x (x)
	Day 7	x	x (x)	x (x)	x (x)
	Day 14	x	x (x)	x (x)	x (x)
	Final Visit	x	x (x)	x (x)	x (x)
SAD 1 mg	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
SAD 10 mg	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
Placebo	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
Systolic Blood Pressure, Decrease					
SAD Any Dose	Baseline	x	x (x)	x (x)	x (x)
…	…	x	x (x)	x (x)	x (x)

Notes: The "Max Severity Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N = Number of subjects in Safety Population with the vital sign assessed for the respective time point.

Table 28: Vital Sign Change from Baseline by Parameter, Dose Group, and Time Point

Dose Group	Time Point	N	Change from Baseline			
			Mean	SD	Median	Min, Max
Systolic Blood Pressure (mmHg)						
SAD Any Dose	Day 1, 15 minutes Post-Dose	x	x	x	x	x, x
	Day 1, 1 h Post-Dose	x	x	x	x	x, x
	Day 1, 2 h Post-Dose	x	x	x	x	x, x
	Day 2	x	x	x	x	x, x
	Day 4	x	x	x	x	x, x
	Day 7	x	x	x	x	x, x
	Day 14	x	x	x	x	x, x
	Final Visit	x	x	x	x	x, x
SAD 1 mg	Day 1, 15 minutes Post-Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
SAD 10 mg	Day 1, 15 minutes Post-Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
Placebo	Day 1, 30 minutes Post-Dose	x	x	x	x	x, x
			x	x	x	x, x
Diastolic Blood Pressure (mmHg)						
SAD Any Dose	Day 1, 15 minutes Post-Dose	x	x	x	x	x, x
..	…	x	x	x	x	x, x
Note: N=Number of subjects in the Safety Population with the laboratory result assessed at the respective time point.						

14.3.7 Displays of ECG Measurements

Table 29: ECG Overall Interpretations, Post Dose Compared to Baseline by Dose Group and Time Point

ECG Interpretation	SAD Any Dose n (%)	SAD 1 mg n (%)	SAD 10 mg n (%)	Placebo n (%)
Day 1, 4 h Post-Dose				
N	x	x	x	x
Normal at Both Times	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, NCS	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, CS				
Abnormal, NCS at Both Times	x (x)	x (x)	x (x)	x (x)
Abnormal, NCS to Abnormal, CS				
Abnormal, NCS to Normal	x (x)	x (x)	x (x)	x (x)
Day 7				
N	x	x	x	x
Normal at Both Times	x (x)	x (x)	x (x)	x (x)
…	x (x)	x (x)	x (x)	x (x)
Final Visit				
N	x	x	x	x
Normal at Both Times	x (x)	x (x)	x (x)	x (x)
…	x (x)	x (x)	x (x)	x (x)

Notes: N = Number of subjects in Safety Population with the ECG results assessed at the respective time point.
CS= clinically significant; NCS= not clinically significant.

Table 30: ECG Toxicity Grade by Parameter, Severity, Dose Group, and Time Point

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

Dose Group	Time Point	N	Mild n (%)	Moderate n (%)	Severe n (%)
PR Interval					
SAD Any Dose	Baseline	x	x (x)	x (x)	x (x)
	Max Severity Post Baseline				
	Day 1, 4 h Post-Dose	x	x (x)	x (x)	x (x)
	Day 7	x	x (x)	x (x)	x (x)
	Final Visit	x	x (x)	x (x)	x (x)
SAD 1 mg	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
SAD 10 mg	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
Placebo	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
QTcF Interval					
SAD Any Dose	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)

Notes: The "Max Severity Post Baseline" rows indicate the maximum severity of ECG Results Related to study treatment experienced by each subject at any time point post baseline, including unscheduled assessments.
N = Number of subjects in Safety Population with the ECG results assessed at the respective time point.

Table 31: ECG Change from Baseline by Parameter, Dose Group, and Time Point

Dose Group	Time Point	N	Change from Baseline			
			Mean	SD	Median	Min, Max
PR Interval (msec)						
SAD Any Dose	Day 1, 4 h Post-Dose	x	x	x	x	x, x
	Day 7	x	x	x	x	x, x
	Final Visit	x	x	x	x	x, x
SAD 1 mg	Day 1, 4 h Post-Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
SAD 10 mg	Day 1, 4 h Post-Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
Placebo	Day 1, 4 h Post-Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
QRS Duration (msec)						
SAD Any Dose	Day 1, 4 h Post-Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x

Note: N = Number of subjects in Safety Population with the ECG results assessed at the respective time point.

Table 32: Summary of QTcF by Dose Group and Time Point

[Implementation Note: For all QTcF categories that specified gender, N based on gender should be used for calculating proportions]

QTcF Category	Time Point	SAD Any Dose	SAD 1 mg	SAD 10 mg	Placebo
		n / N (%)	n / N (%)	n / N (%)	n / N (%)
QTcF >450 ms, Male	Day 1, 4 h Post-Dose	x / x (x)	x / x (x)	x / x (x)	x / x (x)
	Day 7	x / x (x)	x / x (x)	x / x (x)	x / x (x)
	Final Visit	x / x (x)	x / x (x)	x / x (x)	x / x (x)
QTcF >470 ms, Female	Day 1, 4 h Post-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)
QTcF >480 ms	Day 1, 4 h Post-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)
QTcF >500 ms	Day 1, 4 h Post-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)
30 ms ≤ QTcF increases from baseline < 60 ms	Day 1, 4 h Post-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)
QTcF increases from baseline ≥ 60 ms	Day 1, 4 h Post-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)

N= Number of subjects in Safety Population with the ECG results assessed at the respective time point. N is calculated based on specified sex for "QTcF >450 ms, Male" and "QTcF >470 ms, Female" categories.

14.4 Summary of Concomitant Medications

Table 33: Number and Percentage of Subjects with Prior Medications by WHO Drug Classification and Dose Group

[Implementation Note: 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	SAD 1 mg (N=X)	SAD 10 mg (N=X)	Placebo (N=X)	All Subjects (N=X)
		n (%)	n (%)	n (%)	n (%)
Any Level 1 Codes	Any Level 2 Codes				
[ATC Level 1 - 1]	Any [ATC 1 – 1]				
	[ATC 2 - 1]				
	[ATC 2 - 2]				
	[ATC 2 - 3]				
[ATC Level 1 – 2]	[ATC 2 - 1]				
	[ATC 2 - 2]				
	[ATC 2 - 3]				
Note: N = Number of subjects in Safety Population					

Table 34: Number and Percentage of Subjects with Concomitant Medications by WHO Drug Classification and Dose Group

[Implementation Note: Include concomitant medications (medications that are ongoing or that have an end date after first dose) only]

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	SAD 1 mg (N=X)	SAD 10 mg (N=X)	Placebo (N=X)	All Subjects (N=X)
		n (%)	n (%)	n (%)	n (%)
Any Level 1 Codes	Any Level 2 Codes				
[ATC Level 1 - 1]	Any [ATC 1 – 1]				
	[ATC 2 - 1]				
	[ATC 2 - 2]				
	[ATC 2 - 3]				
[ATC Level 1 – 2]	[ATC 2 - 1]				
	[ATC 2 - 2]				
	[ATC 2 - 3]				
Note: N = Number of subjects in Safety Population					

14.5 Pharmacokinetics

Table 35: Rezafungin Concentrations in Plasma, SAD 10 mg Dose Group

	Nominal Time[a] (h)													
Subject ID	**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**96**	**144**	**312 (Day 14)**	**696 (Day 30)**
PHU.00123	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PHU.00124	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PHU.00125	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	x	x
Statistics														
N[b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SD	x	x	x	x	x	x	x	x	x	x	x	x	x	x
GM	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CV %	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Min	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Max	x	x	x	x	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.
Note: Samples that were collected substantially outside of the protocol-defined window are excluded from summary statistics (but not from NCA) and are indicated by an asterisks (*).

Table 36: Summary Statistics for Rezafungin PK Parameters in Plasma – SAD 10 mg Dose Group

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

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram

[Implementation Note: CONSORT diagram will show numbers of subjects screened and enrolled, and by Dose Group will show number randomized, treated, and completed per protocol. Additionally, it will show the number of subjects excluded from analysis populations by reason for exclusion.]

This is a place holder for Figure 1. The specifications for Figure 1 are in the implementation note.

14.3.1.1 Solicited Reactogenicity Symptoms

Figure 2: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group and Severity

[Implementation Note: All local reactogenicity symptoms will be listed using consistent symptom names as the solicited reactogenicity table shells, including "Any Symptoms"]

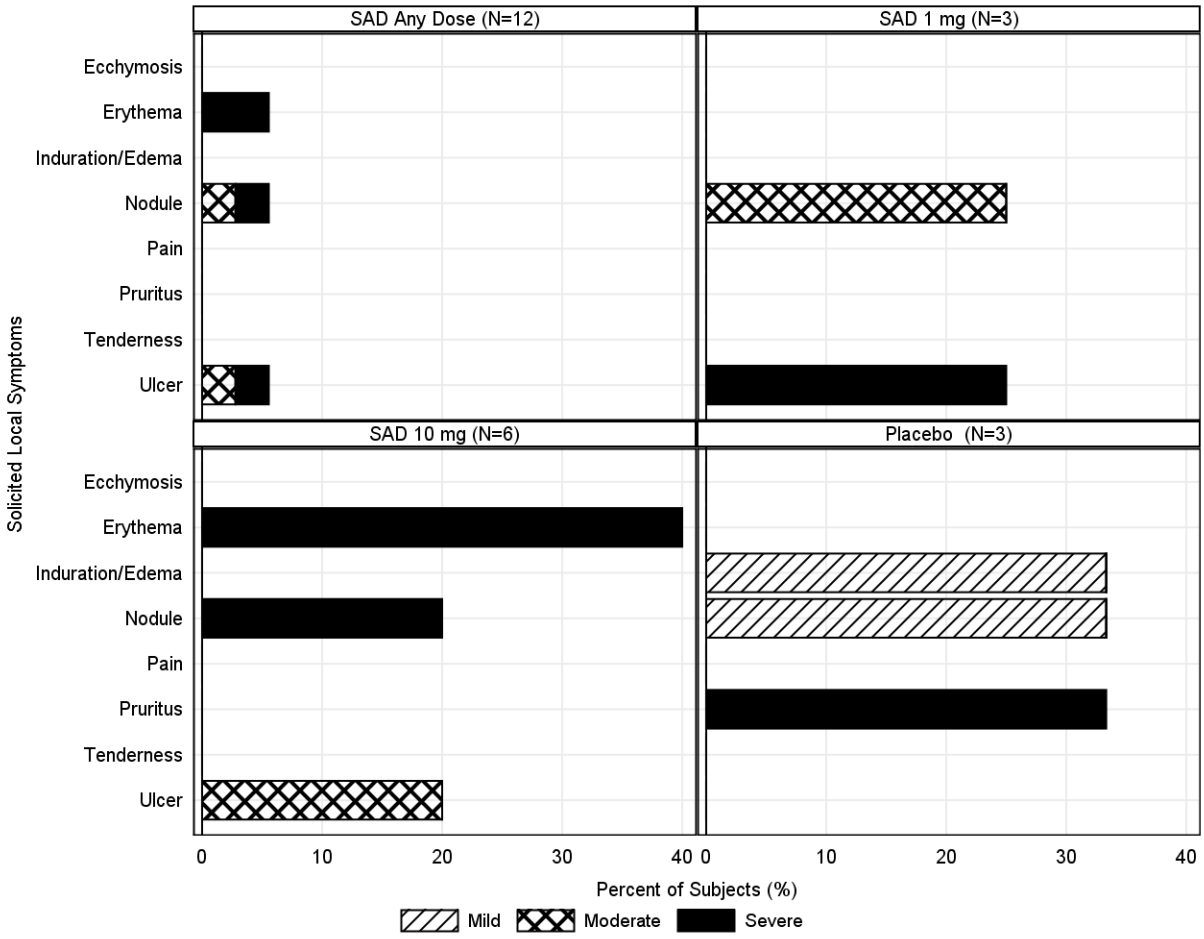


Figure 3: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Any Symptoms

[Implementation Note: Maximum severity on Day 1 will be calculated based on all time points collected on Day 1 (Day 1, 1 h Post-Dose and Day 1, 4 h Post-Dose). Maximum severity on Day 14 and Final Visit will be calculated based on records in memory aid and in clinic assessments.]

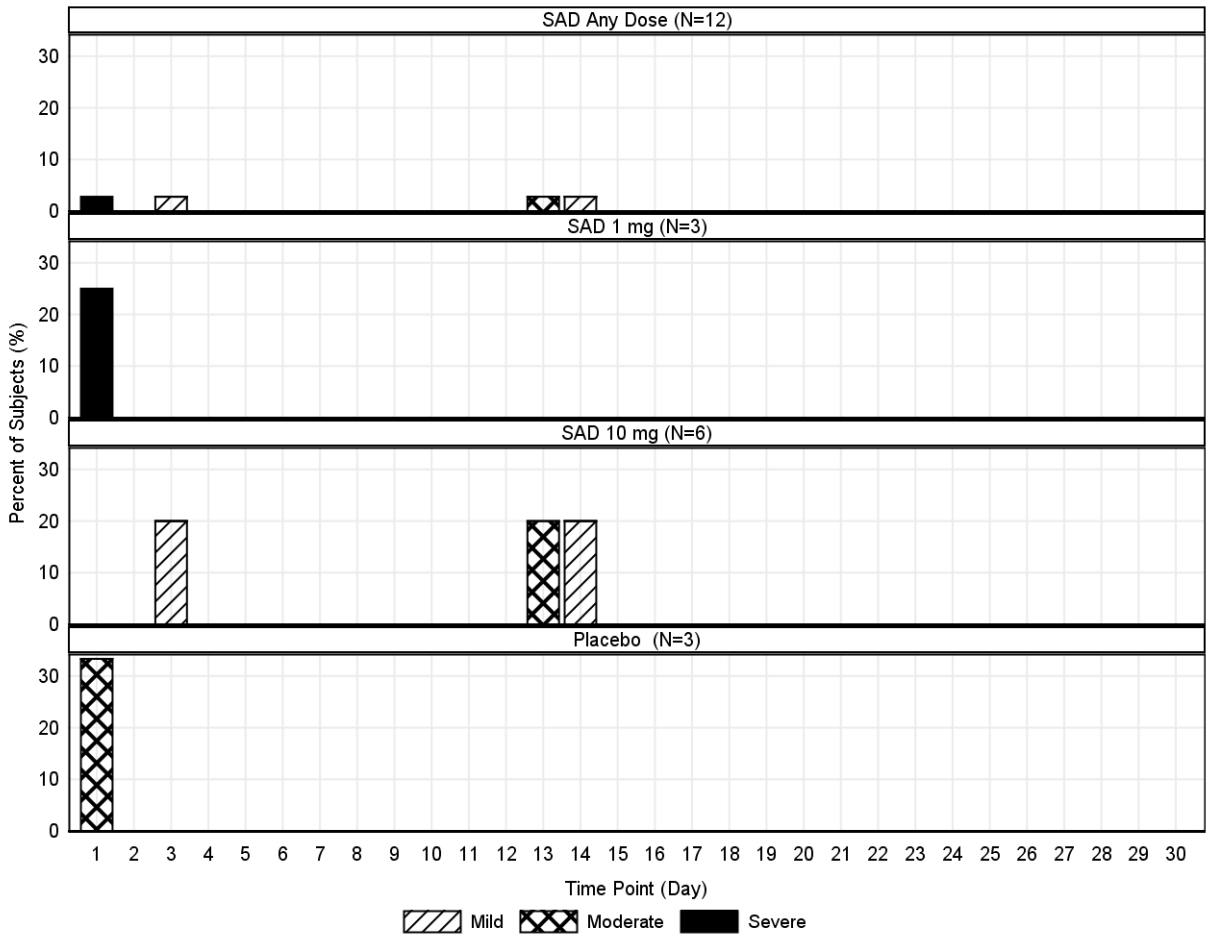


Figure 4: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Pain

This figure will repeat Figure 3 for Pain

Figure 5: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Tenderness

This figure will repeat Figure 3 for Tenderness

Figure 6: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Pruritus (Itching)

This figure will repeat Figure 3 for Pruritus (Itching)

Figure 7: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Ecchymosis (Bruising), Functional Grade

This figure will repeat Figure 3 for Ecchymosis (Bruising), Functional Grade

Figure 8: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Ecchymosis (Bruising), Measurement Grade

This figure will repeat Figure 3 for Ecchymosis (Bruising), Measurement Grade

Figure 9: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Induration (Hardness)/ Swelling, Functional Grade

This figure will repeat Figure 3 for Induration (Hardness)/ Swelling, Functional Grade

Figure 10: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Induration (Hardness)/ Swelling, Measurement Grade

This figure will repeat Figure 3 for Induration (Hardness)/ Swelling, Measurement Grade

Figure 11: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Erythema (Redness), Functional Grade

This figure will repeat Figure 3 for Erythema (Redness), Functional Grade

Figure 12: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Erythema (Redness), Measurement Grade

This figure will repeat Figure 3 for Erythema (Redness), Measurement Grade

Figure 13: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Nodule, Functional Grade

This figure will repeat Figure 3 for Nodule, Functional Grade

Figure 14: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Nodule, Measurement Grade

This figure will repeat Figure 3 for Nodule, Measurement Grade

Figure 15: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Ulceration, Functional Grade

This figure will repeat Figure 3 for Ulceration, Functional Grade

Figure 16: Proportions of Subjects with Solicited Reactogenicity Symptoms by Dose Group, Time Point, and Severity – Ulceration, Measurement Grade

This figure will repeat Figure 3 for Ulceration, Measurement Grade

14.3.1.2 Unsolicited Adverse Events

Figure 17: Proportions of Subjects with Related Adverse Events by Dose Group, MedDRA SOC, and Severity

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events deemed related to study product. 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. Each figure panel will show counts for all SOCs observed in any Dose Group during the study (as a related AE). If the number of SOCs is too large to fit if using 2 rows of panels, then this figure will be split into multiple figures in the CSR, with 1 row of 2 panels in each figure. SOCs will be ordered alphabetically.]

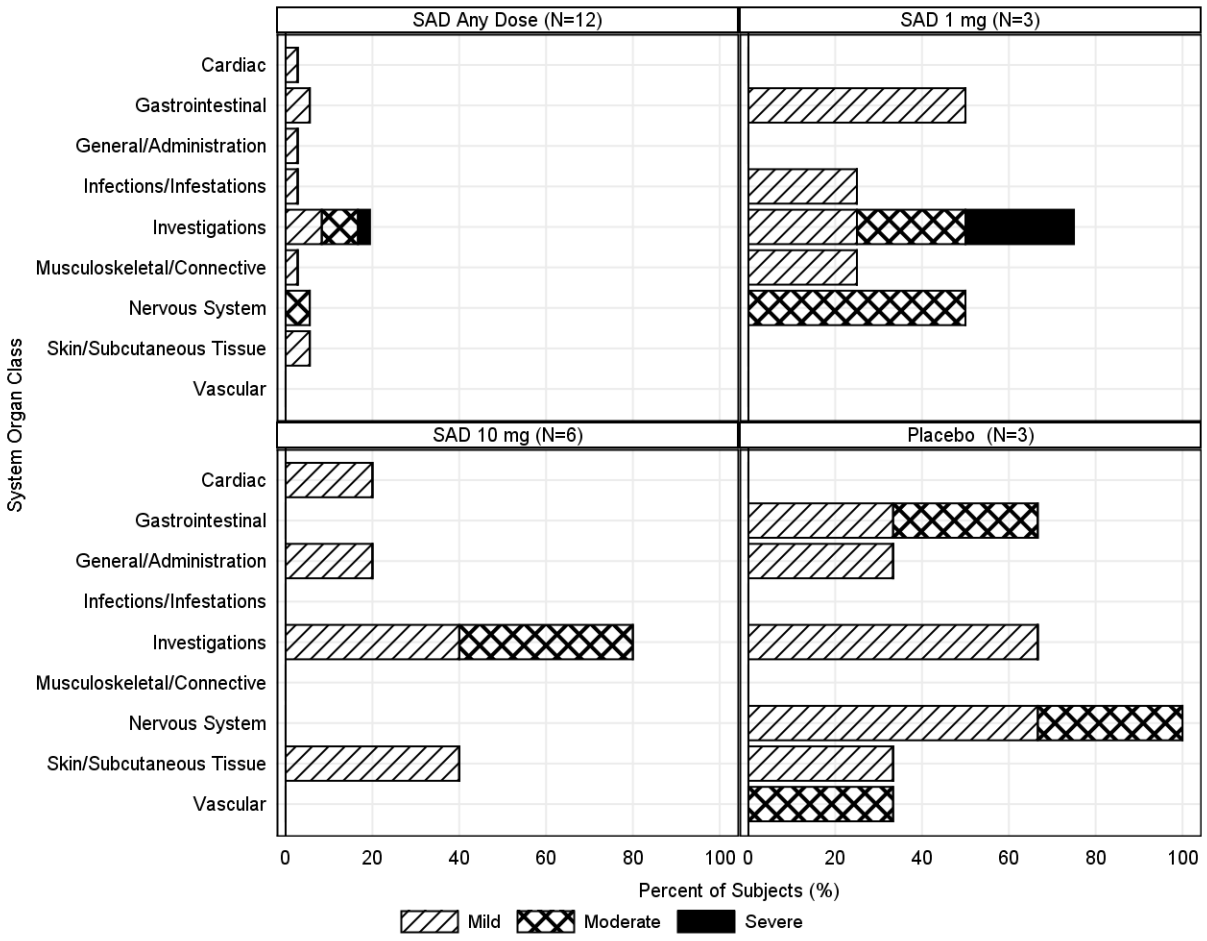
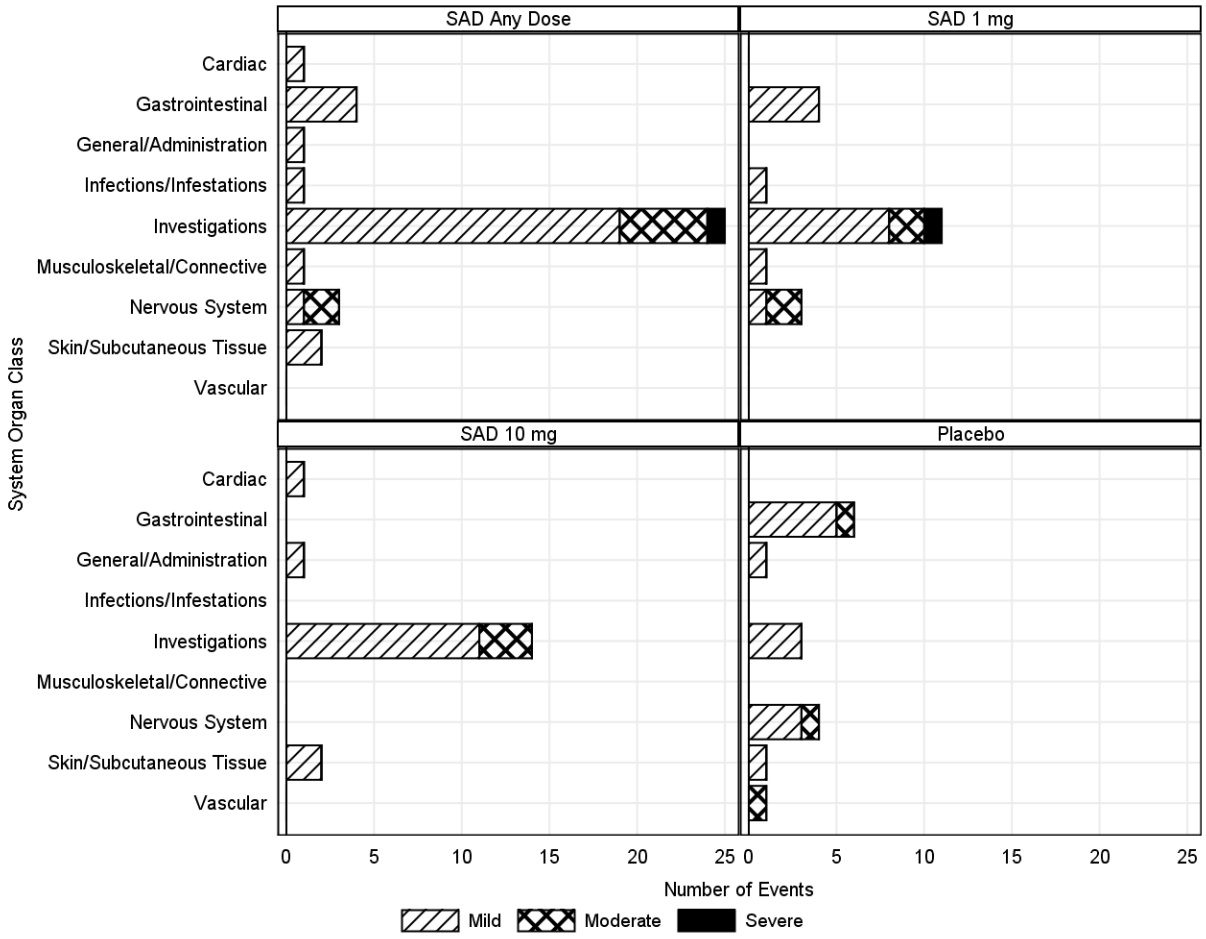


Figure 18: Number of Related Adverse Events by Dose Group, MedDRA SOC, and Severity

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events deemed related to study product. 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. Each figure panel will show counts for all SOCs observed in any Dose Group during the study (as a related AE). If the number of SOCs is too large to fit if using 2 rows of panels, then this figure will be split into multiple figures in the CSR, with 1 row of 2 panels in each figure. SOCs will be ordered alphabetically.]



14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Figure 19: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Dose Group – Sodium

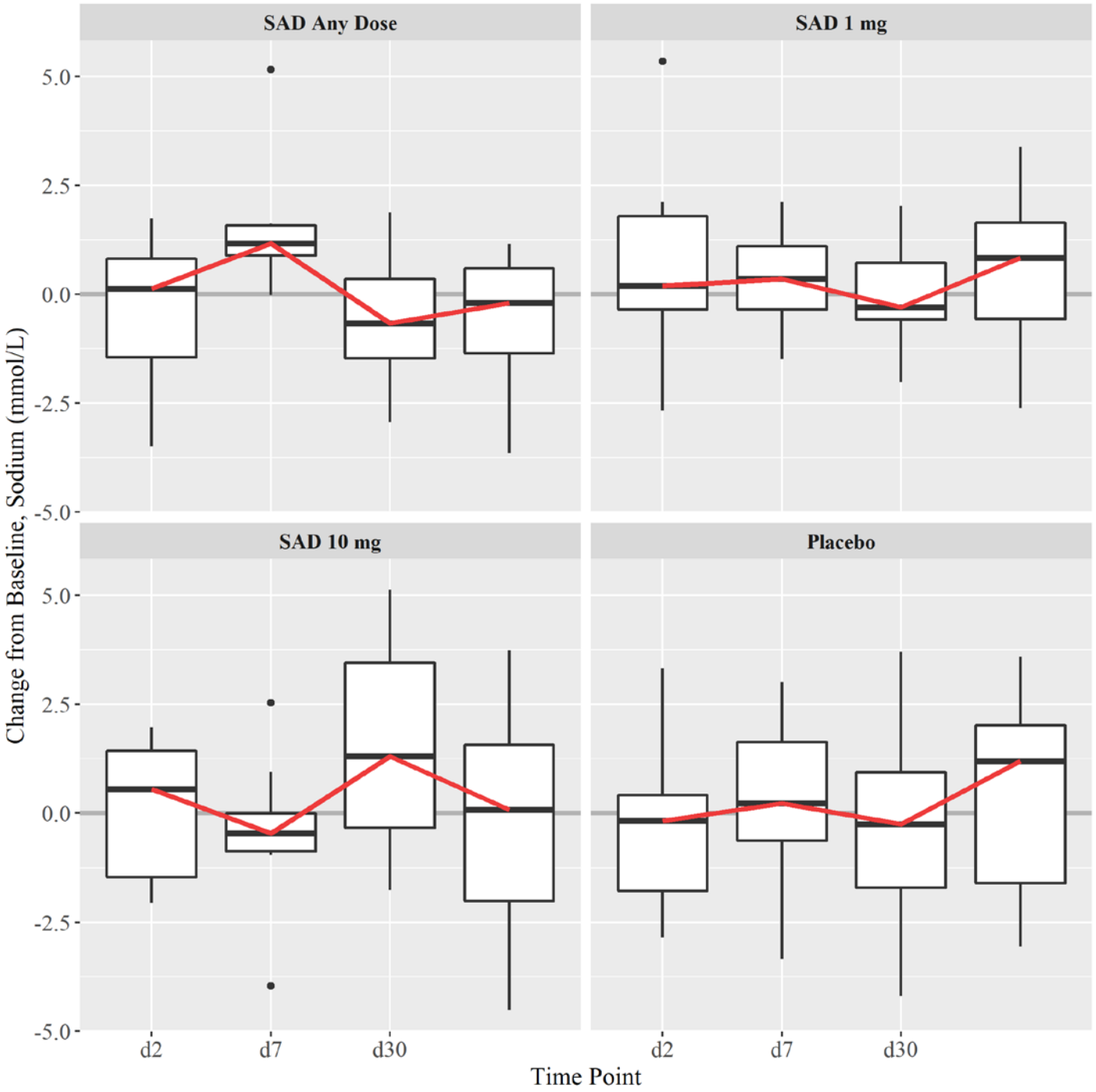


Figure 20: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Potassium

This figure will repeat Figure 19 for Potassium.

Figure 21: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Calcium

This figure will repeat Figure 19 for Calcium.

Figure 22: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Phosphorus

This figure will repeat Figure 19 for Phosphorus.

Figure 23: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Chloride

This figure will repeat Figure 19 for Chloride.

Figure 24: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Total Carbon Dioxide

This figure will repeat Figure 19 for Total Carbon Dioxide.

Figure 25: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Glucose

This figure will repeat Figure 19 for Glucose.

Figure 26: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Blood Urea Nitrogen

This figure will repeat Figure 19 for Blood Urea Nitrogen.

Figure 27: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Creatinine

This figure will repeat Figure 19 for Creatinine.

Figure 28: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Protein

This figure will repeat Figure 19 for Protein.

Figure 29: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Albumin

This figure will repeat Figure 19 for Albumin.

Figure 30: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Creatine Phosphokinase

This figure will repeat Figure 19 for Creatine Phosphokinase.

Figure 31: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Aspartate Aminotransferase

This figure will repeat Figure 19 for Aspartate Aminotransferase.

Figure 32: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Alanine Aminotransferase

This figure will repeat Figure 19 for Alanine Aminotransferase.

Figure 33: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Alkaline Phosphatase

This figure will repeat Figure 19 for Alkaline Phosphatase.

Figure 34: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Total Bilirubin

This figure will repeat Figure 19 for Total Bilirubin.

Figure 35: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Direct Bilirubin

This figure will repeat Figure 19 for Direct Bilirubin.

14.3.5.2 Hematology Results

Figure 36: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Hemoglobin

This figure will repeat Figure 19 for Hemoglobin.

Figure 37: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Hematocrit

This figure will repeat Figure 19 for Hematocrit.

Figure 38: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group, – Red Blood Cell Count

This figure will repeat Figure 19 for Red Blood Cell Count.

Figure 39: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group –White Blood Cell Count

This figure will repeat Figure 19 for White Blood Cell Count.

Figure 40: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Neutrophil Count

This figure will repeat Figure 19 for Neutrophil Count.

Figure 41: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Lymphocyte Count

This figure will repeat Figure 19 for Lymphocyte Count.

Figure 42: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Monocyte Count

This figure will repeat Figure 19 for Monocyte Count.

Figure 43: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Eosinophil Count

This figure will repeat Figure 19 for Eosinophil Count.

Figure 44: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Basophil Count

This figure will repeat Figure 19 for Basophil Count.

Figure 45: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Platelets

This figure will repeat Figure 19 for Platelets.

14.3.5.3 Coagulation Results

Figure 46: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Prothrombin Time

This figure will repeat Figure 19 for Prothrombin Time.

Figure 47: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Activated Partial Thromboplastin Time

This figure will repeat Figure 19 for Activated Partial Thromboplastin Time.

Figure 48: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter and Dose Group – Prothrombin International Normalized Ratio

This figure will repeat Figure 19 for Prothrombin International Normalized Ratio.

14.3.6 Displays of Vital Signs

Figure 49: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Dose Groups – Systolic Blood Pressure

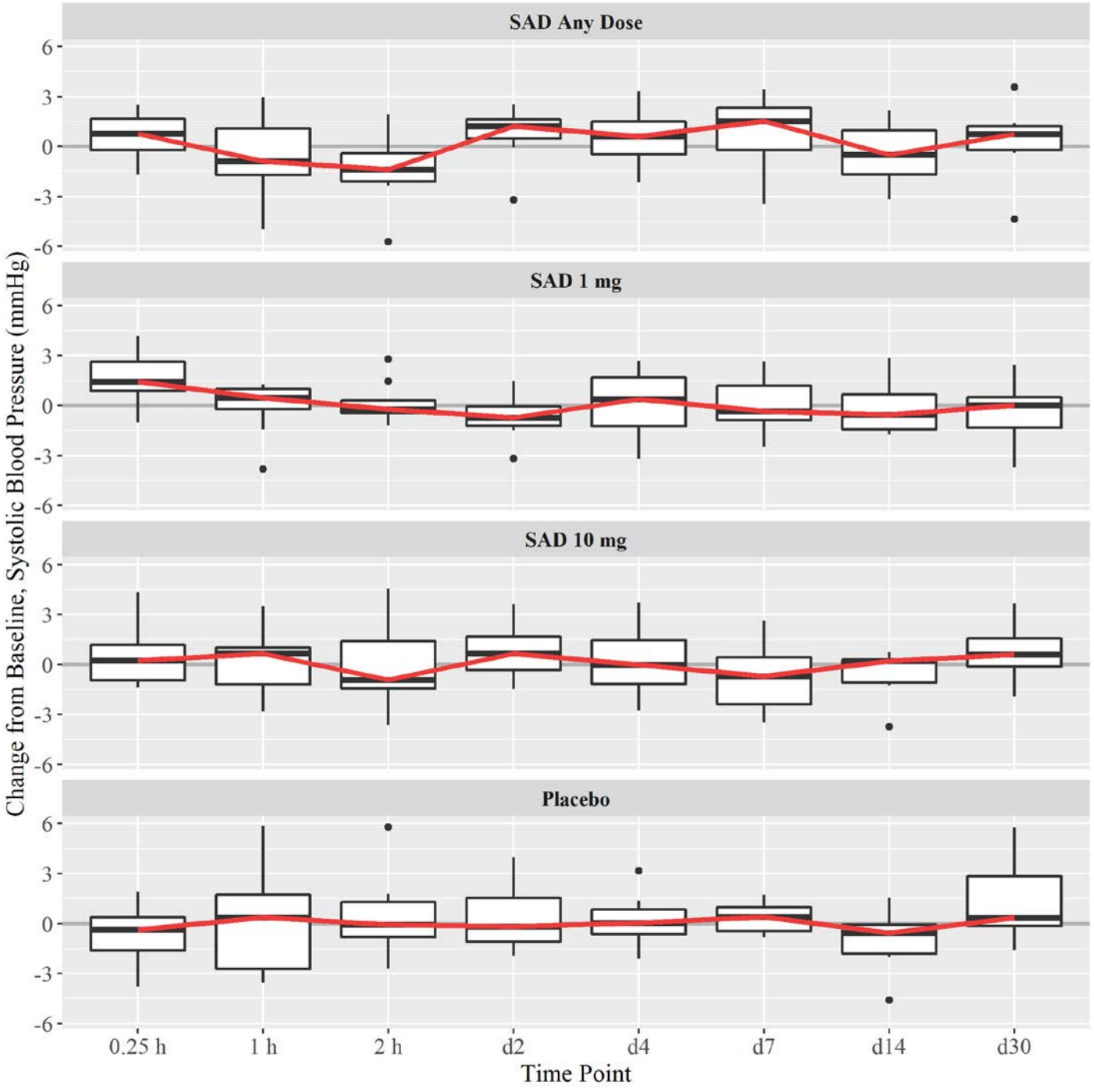


Figure 50: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Dose Groups – Diastolic Blood Pressure

This figure will repeat Figure 49 for Diastolic Blood Pressure.

Figure 51: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Dose Groups – Heart Rate

This figure will repeat Figure 49 for Heart Rate.

Figure 52: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Dose Groups – Respiration Rate

This figure will repeat Figure 49 for Respiration Rate.

Figure 53: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Dose Groups – Temperature

This figure will repeat Figure 49 for Temperature.

14.3.7 Displays of ECG Measurements

Figure 54: ECG by Scheduled Visits: Change from Baseline by Parameter – PR Interval

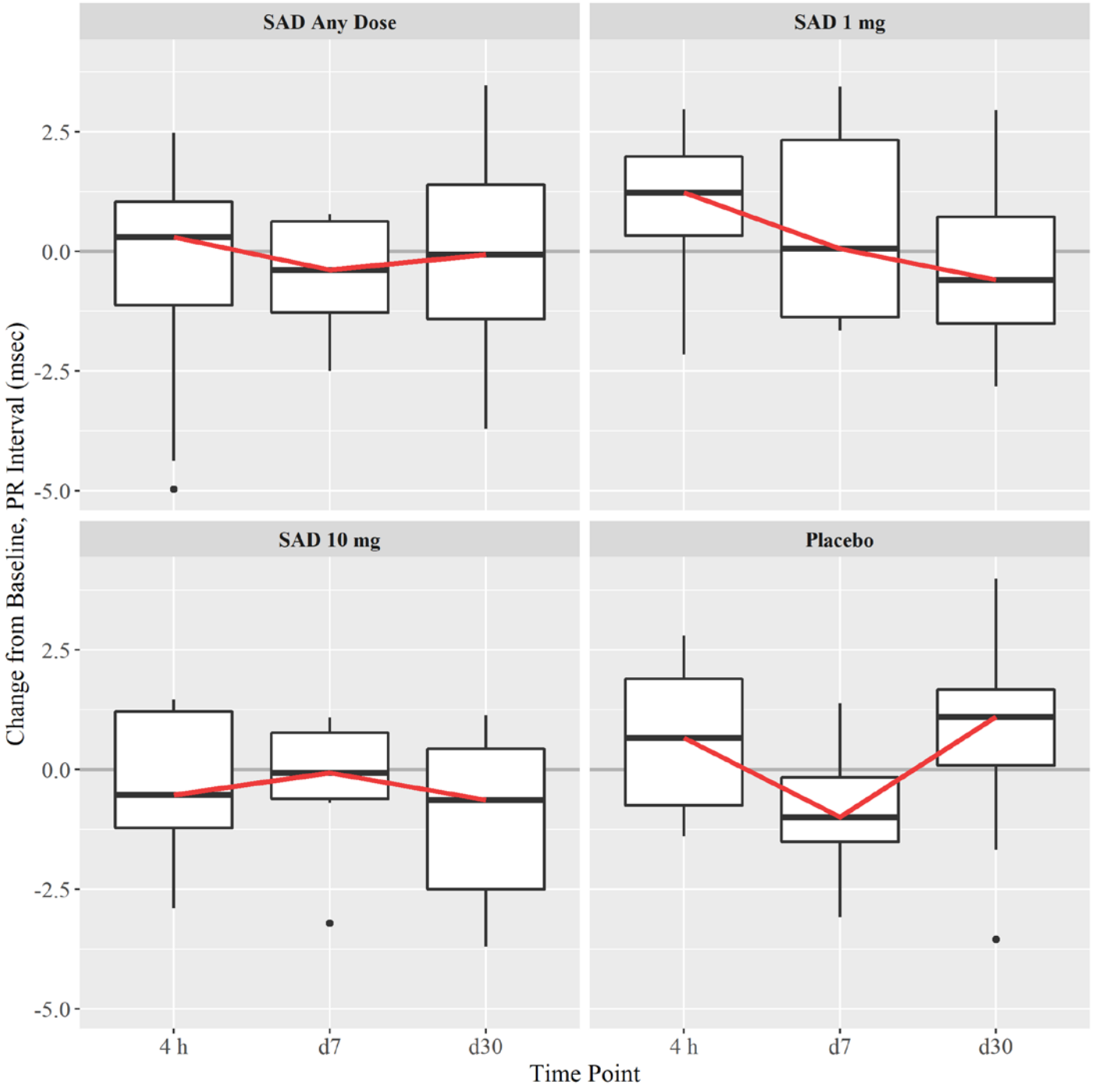


Figure 55: ECG by Scheduled Visits: Change from Baseline by Parameter – QRS Duration

This figure will repeat Figure 54 for QRS Duration.

Figure 56: ECG by Scheduled Visits: Change from Baseline by Parameter – QT Interval

This figure will repeat Figure 54 for QT Interval.

Figure 57: ECG by Scheduled Visits: Change from Baseline by Parameter – QTcF Interval

This figure will repeat Figure 54 for QTcF Interval.

Figure 58: ECG by Scheduled Visits: Change from Baseline by Parameter – RR Interval

This figure will repeat Figure 54 for RR Interval.

Figure 59: ECG by Scheduled Visits: Change from Baseline by Parameter –Ventricular Rate

This figure will repeat Figure 54 for Ventricular Rate.

Figure 60: Individual Rezafungin Concentration within 144 h Post-Dose in Plasma Profiles – SAD 10 mg Dose Group

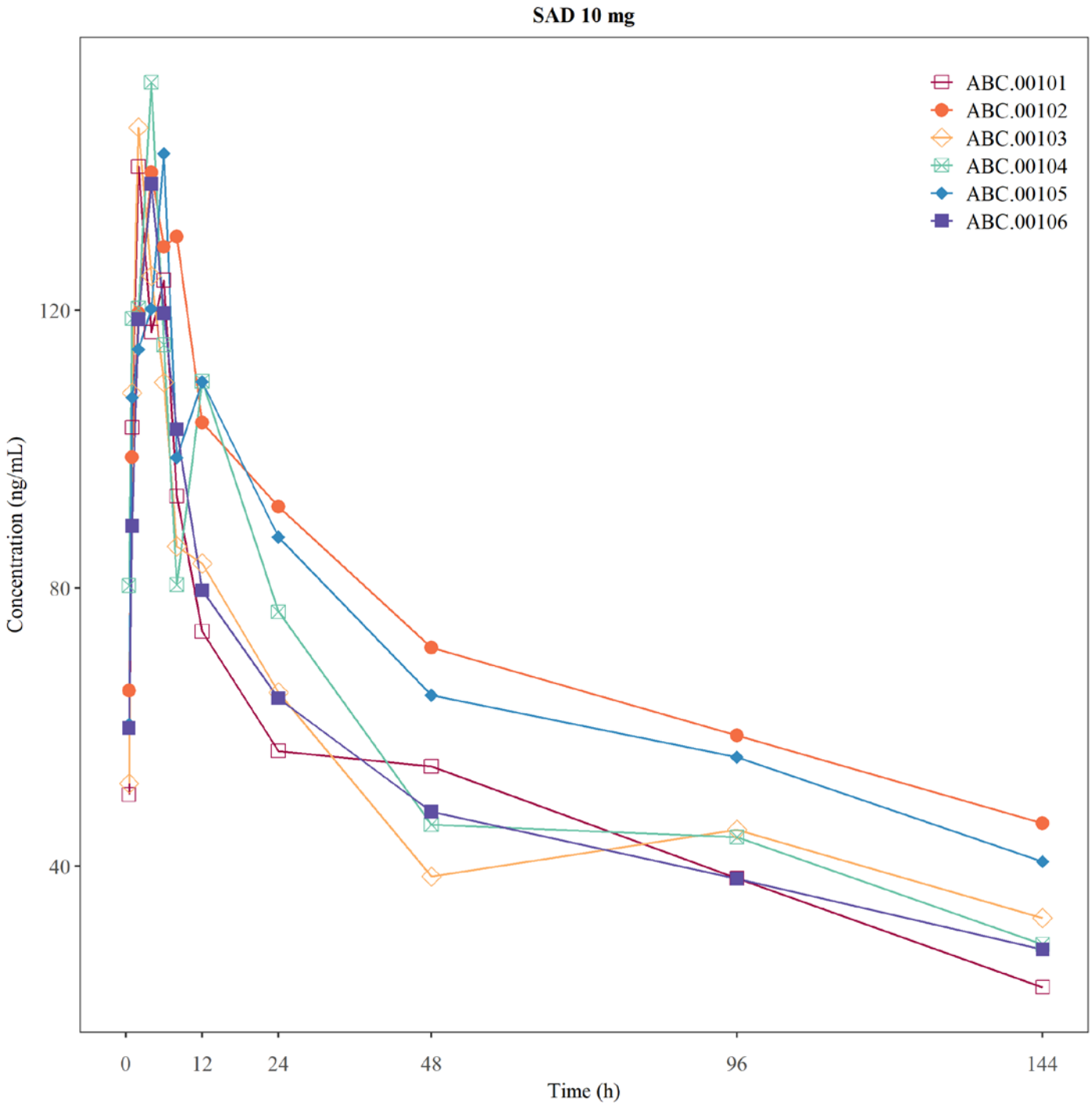


Figure 61: Semi-Log Individual Rezafungin Concentration within 144 h Post-Dose in Plasma Profiles – SAD 10 mg Dose Group

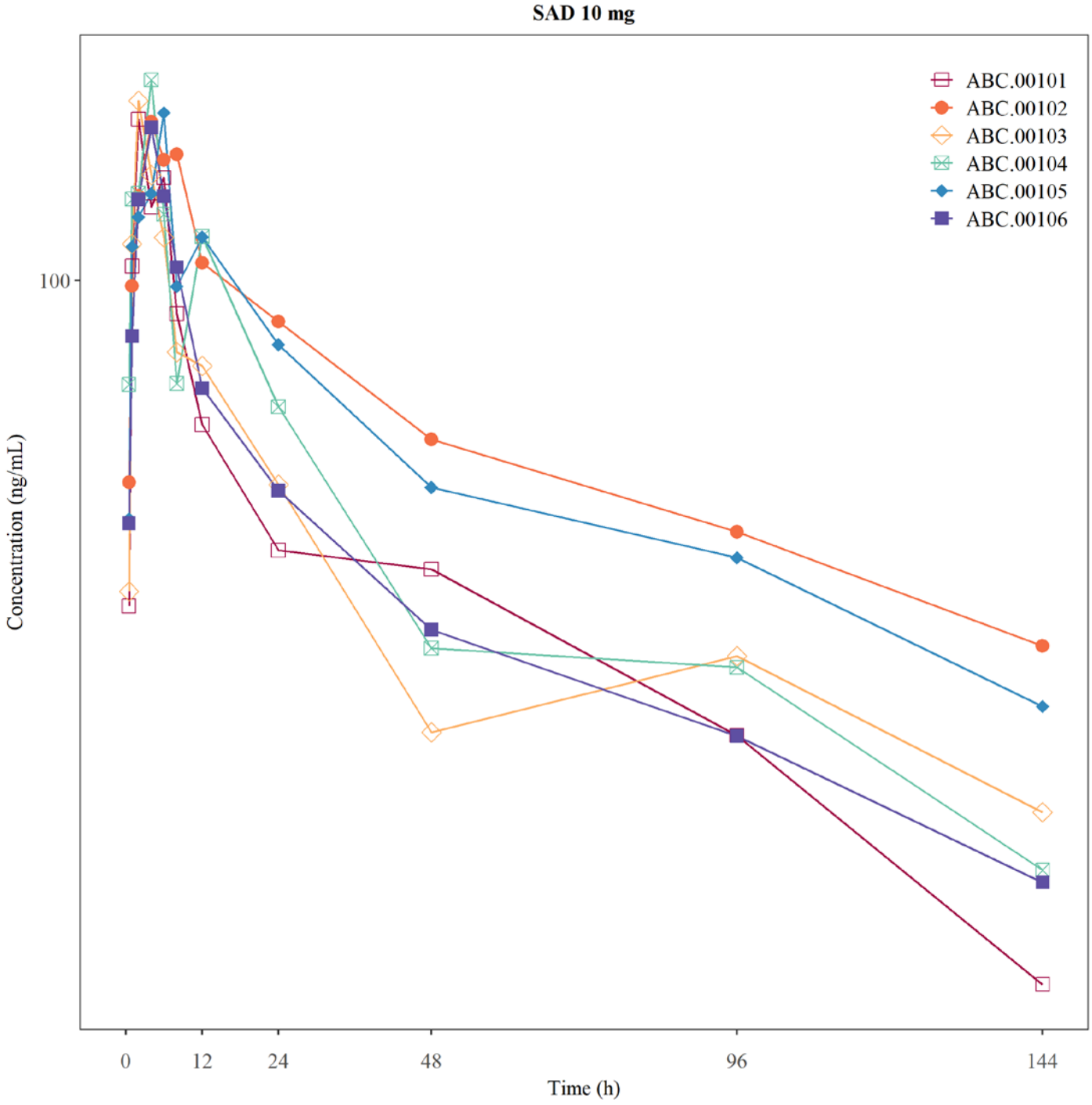


Figure 62: Individual Rezafungin Concentration for All Time Points in Plasma Profiles – SAD 10 mg Dose Group

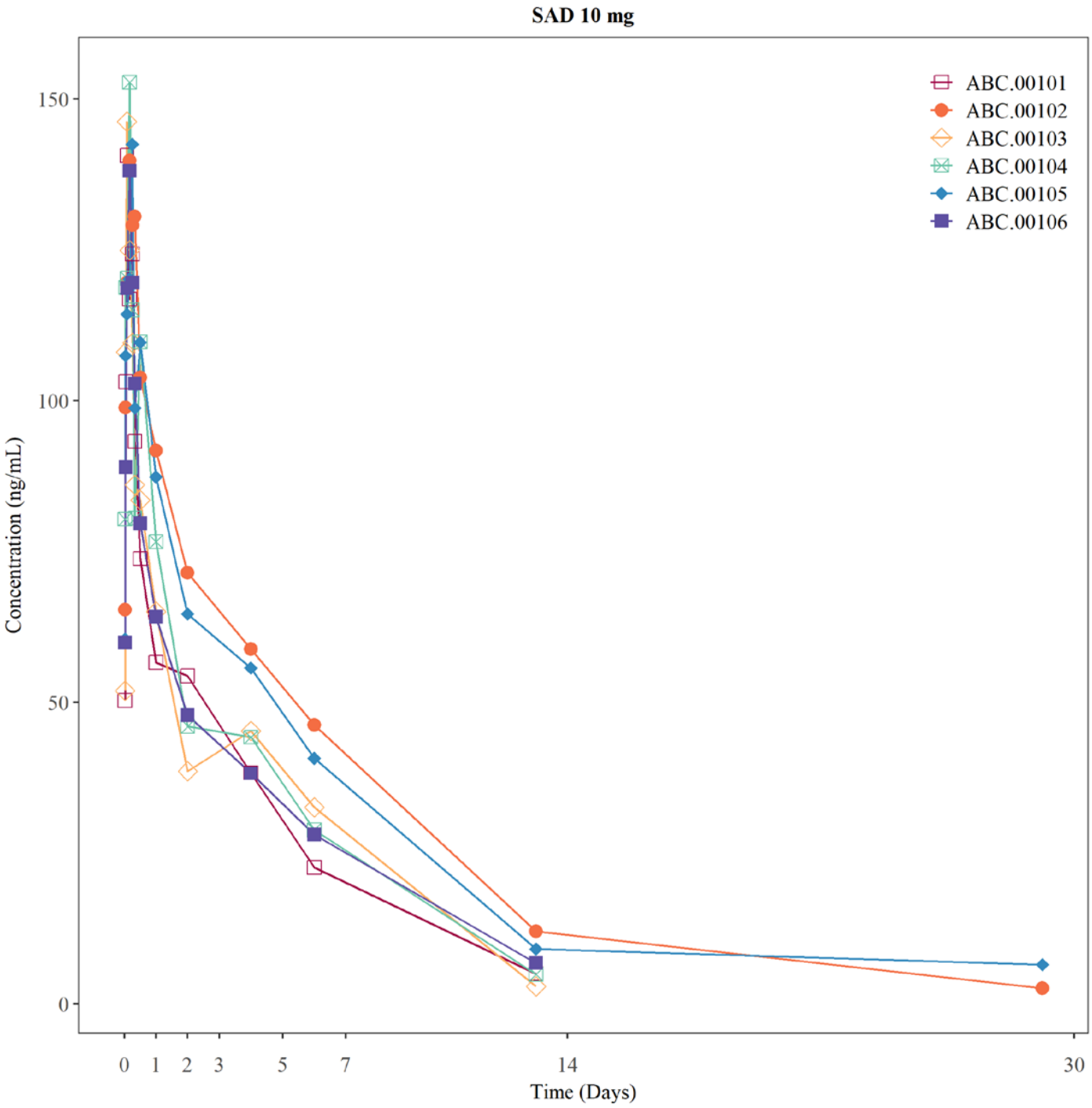


Figure 63: Semi-Log Individual Rezafungin Concentration for All Time Points in Plasma Profiles – SAD 10 mg Dose Group

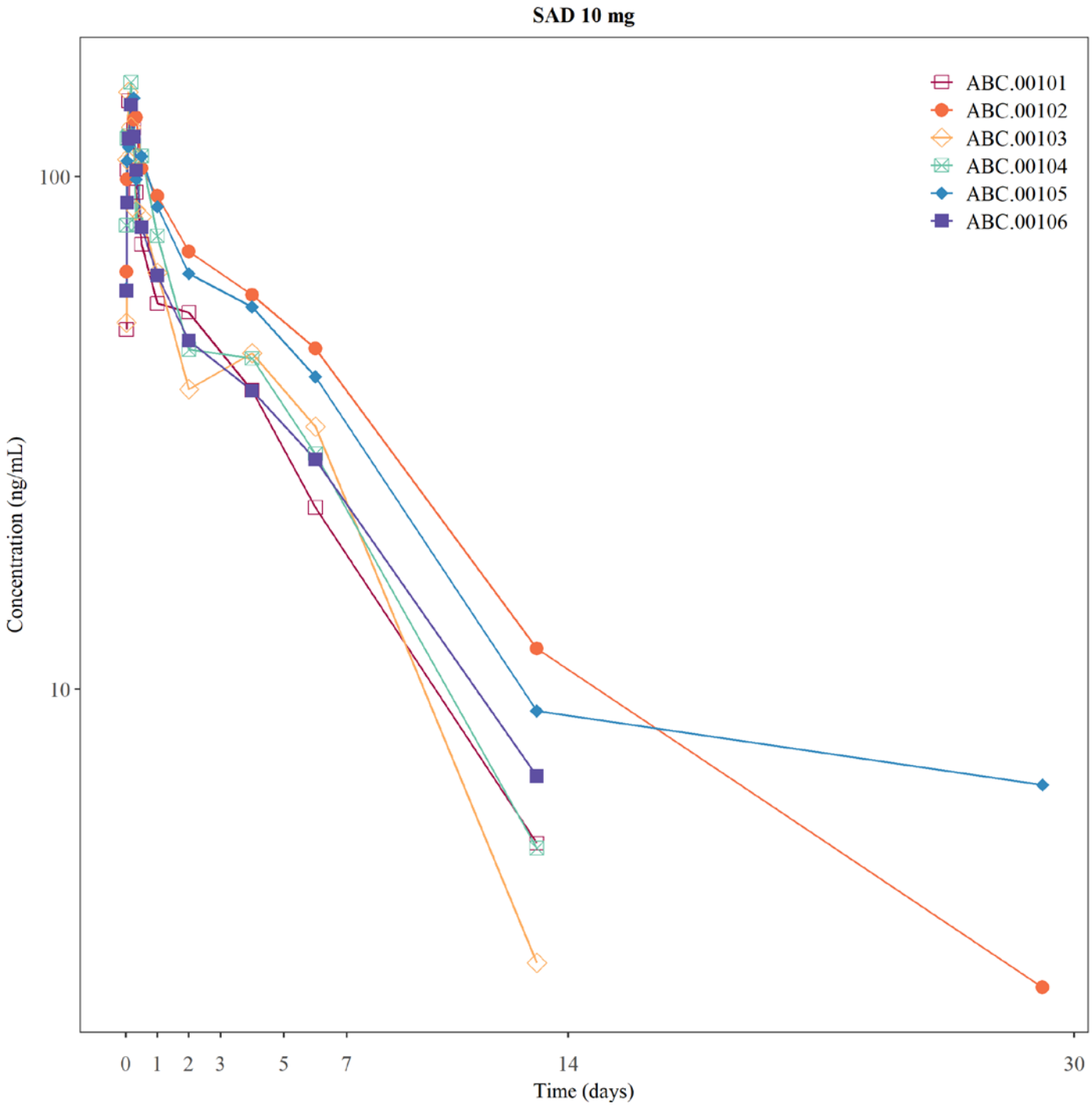


Figure 64: Mean Rezafungin Concentration within 144 h Post-Dose in Plasma Profiles – SAD 10 mg Dose Group

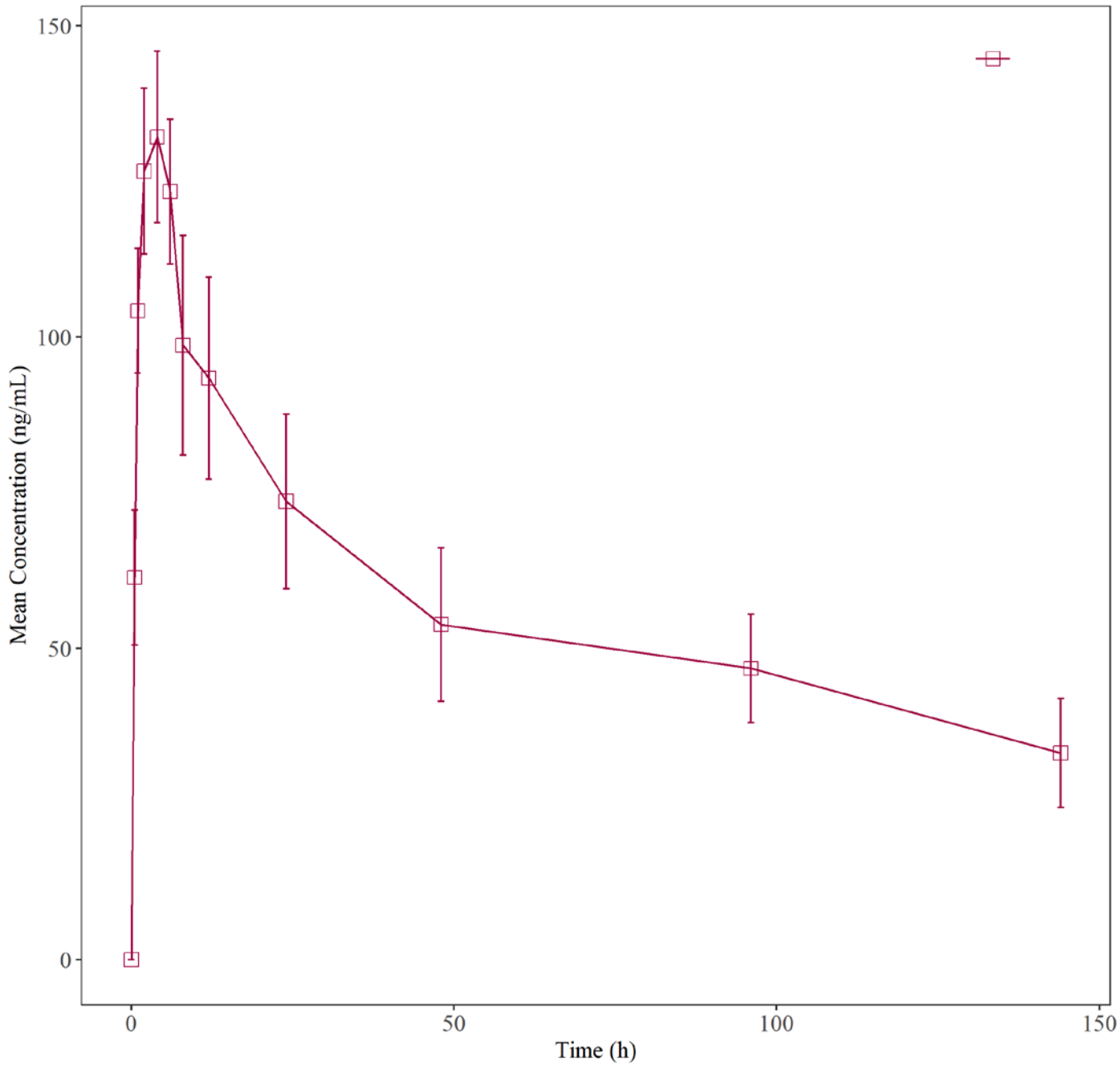


Figure 65: Semi-Log Mean Rezafungin Concentration within 144 h Post-Dose in Plasma Profiles – SAD 10 mg Dose Group

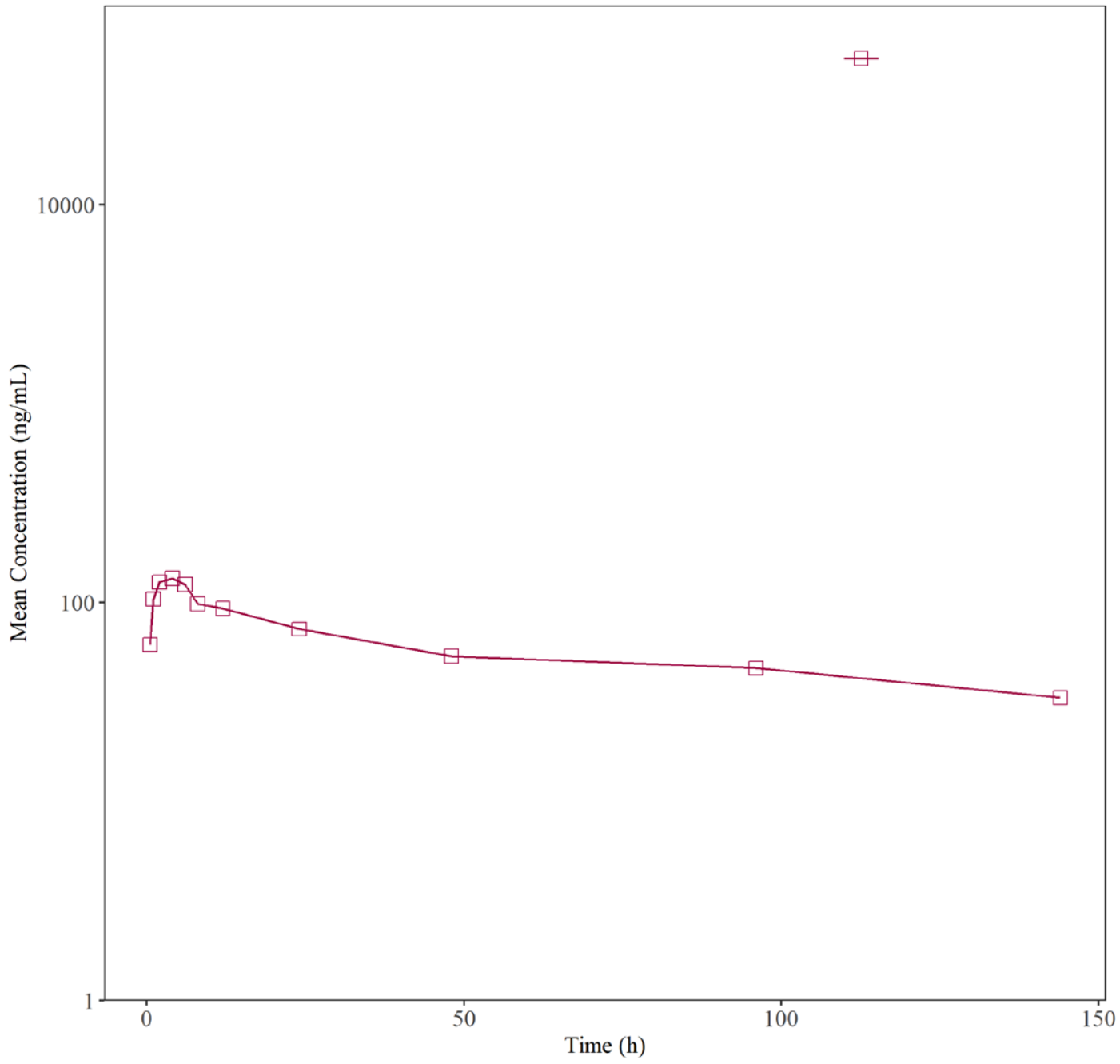


Figure 66: Mean Rezafungin Concentration for All Time Points in Plasma Profiles – SAD 10 mg Dose Group

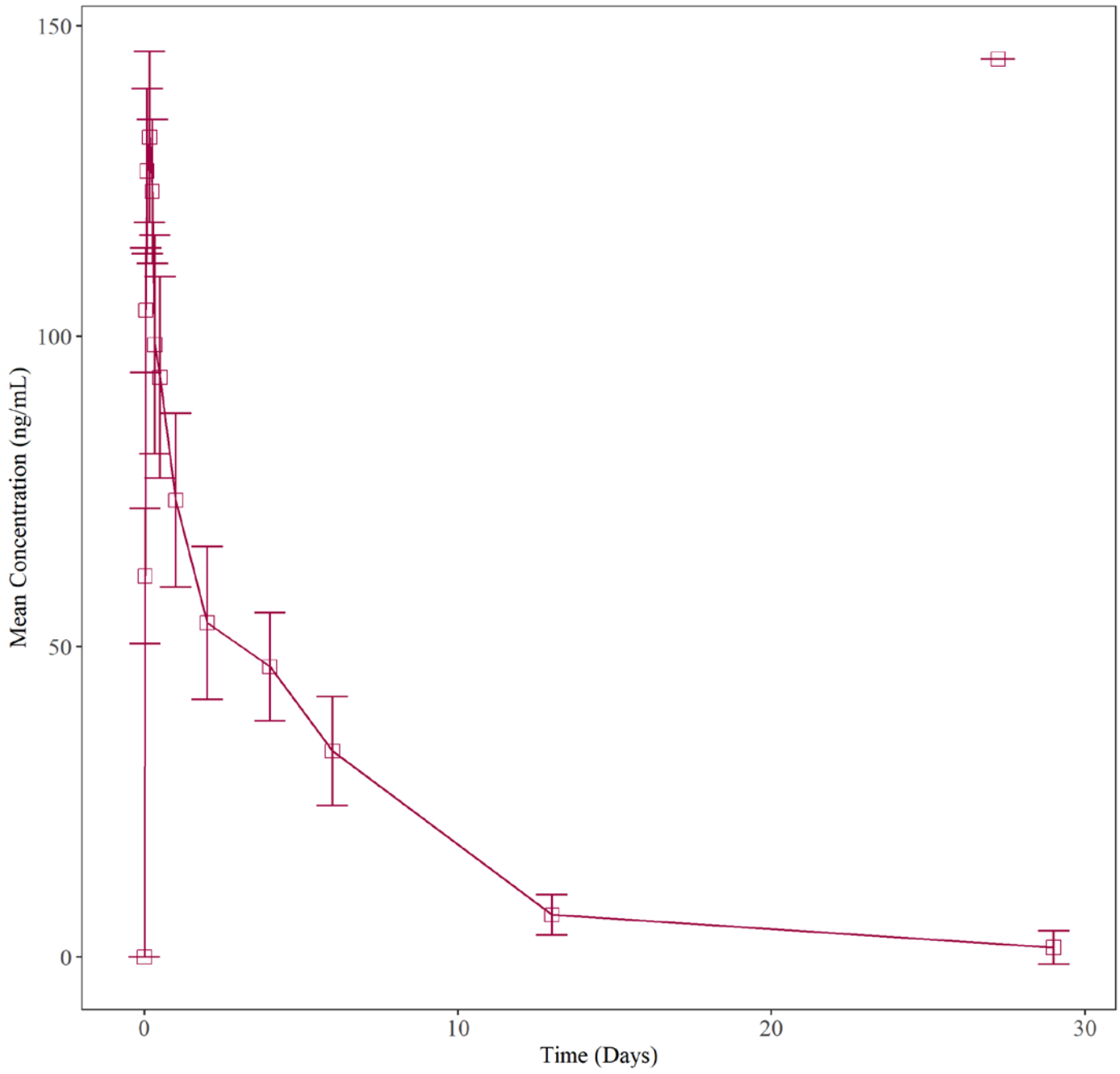
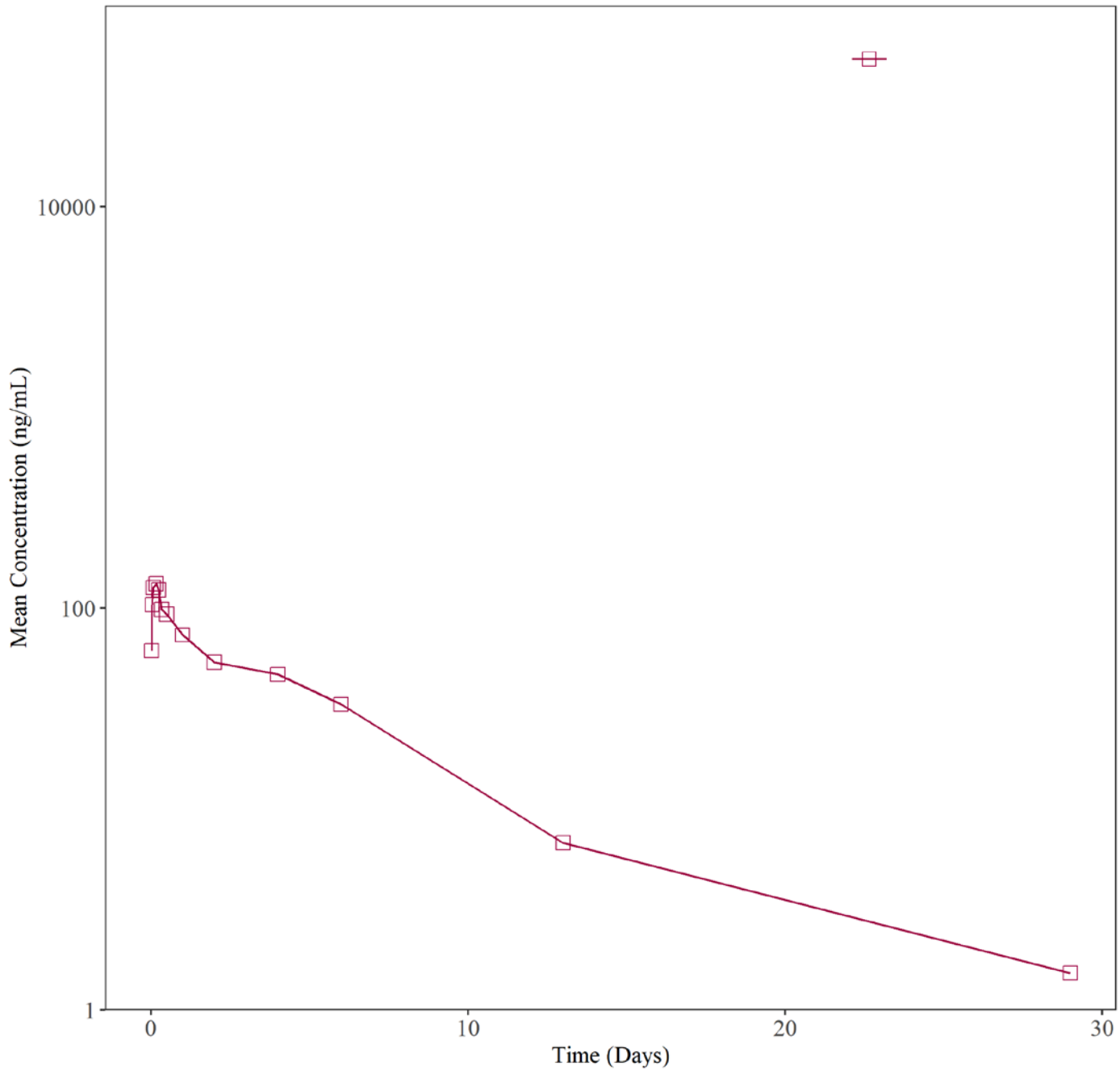


Figure 67: Semi-Log Mean Rezafungin Concentration for All Time Points in Plasma Profiles – SAD 10 mg Dose Group



APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

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

(This is a placeholder for the abbreviated CSR)

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 2: 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. Sort order: Dose Group, Subject ID, Category (in the case a subject both terminates early and discontinues treatment).]

Dose Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day
SAD 1 mg	PHU.00123	Early Termination	Lost to Follow-up	7

16.2.2 Protocol Deviations

Listing 3: 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." Sort order: Dose Group, Subject ID, DV Number. If deviation resulted in AE or subject termination, or affected product stability, indicate which of those events occurred in the listing row, since columns for those 3 events were concatenated to save space.]

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

Listing 4: 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: Start Date, Deviation.]

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

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 5: 16.2.3: Subjects Excluded from Analysis Populations

[Implementation Note: This data in this listing should be congruent with the "Analysis Populations by Dose Group" table. If subject not excluded from any analysis population, the subject will not appear in the listing. If the subject is excluded from multiple analysis populations, they will have one row per analysis population excluded from in the listing.

Sort order: Dose Group, Subject ID, Analysis from which Subject is Excluded (order: Safety, PK Analysis Population, PK Analysis Subset).]

Dose Group	Subject ID	Analysis from which Subject is Excluded	Results Available?	Reason Subject Excluded	Reason Subject Excluded Specification
SAD 1 mg	PHU.00123	PK Analysis Subset	Yes	Has protocol deviations that potentially impact PK	Subject consumed food 1 hour prior to dosing
Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.					

16.2.4 Demographic Data

Listing 6: 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)."

Sort order: Dose Group, Subject ID.]

Dose Group	Subject ID	Sex	Age at Enrollment (years)	Ethnicity	Race	Weight at Screening (kg)	Height at Screening (cm)	BMI at Screening (kg/m^2)
SAD 1 mg	PHU.00123	Female	24	Not Hispanic	Black or African American	xx	xxx	xx

Listing 7: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

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

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

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

Sort order: Dose Group, Subject ID, MH Number.]

Dose Group	Subject ID	Medical History Number	Medical History Term	MedDRA System Organ Class	MedDRA Preferred Term	Condition Start Day	Condition End Day
SAD 1 mg	PHU.00123	1	NUT ALLERGY	IMMUNE SYSTEM DISORDERS	FOOD ALLERGY	>5 years prior to enrollment	Ongoing

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

Listing 8: 16.2.5: Compliance and/or Drug Concentration Data

[Implementation Note: If not dosed according to protocol, details will be given in the Comments column (manually written, not programmed). If Dose is inapplicable for subject, the date and time columns for those doses will be "N/A" and for planned doses that did not occur the date and time columns for those doses will be "not dosed."

Sort order: Dose Group, Subject ID, Dose Date, Dose Time]

Dose Group	Subject ID	Dosed According to Protocol?	Dose Date	Dose Time	Comments
SAD 1 mg	PHU.00123	Yes	ddMMMyyyy	hh:mm	
…					

16.2.7 Adverse Events

Listing 9: 16.2.7.2: Solicited Reactogenicity Events – Local Symptoms

[Implementation Note: Functional grade will be displayed under "Functional Grade" column and measurement and measurement grade will be displayed together in "Measurement (Grade)" column ex: 30 (Mild)

Sort order: Dose Group, Subject ID, Time Point]

Dose Group	Subject ID	Time Point	Assessment[a]	Location	Symptom	Functional Grade	Measurement (Grade)
			Clinic	Upper Left	Pain	Mild	30 (Mild)
			MA				

[a] MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Reactogenicity Events eCRF. Clinic = Data collected by clinic staff during symptom assessment.

Listing 10: 16.2.7.3: Unsolicited Adverse Events

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. This listing includes all unsolicited adverse events. Sort order: Dose Group, Subject ID, AE Number.]

Adverse Event	MedDRA System Organ Class	MedDRA Preferred Term	Study Day	Duration of AE in Days	Severity	SAE?	Relationship to Study Treatment (Alternate Etiology)	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome
Dose Group: , Subject ID: , AE Number:										
Comments:										
Dose Group: , Subject ID: , AE Number:										
Comments:										

16.2.8 Individual Laboratory Measurements

Listing 11: 16.2.8.1: Clinical Laboratory Results – Chemistry

[Implementation Note: These listings (for hematology, chemistry, coagulation, and urinalysis) include all laboratory results, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., 16.2 (Mild). Results not in the reference range, but not graded as Mild, Moderate, or Severe, should have ONR shown as the Severity Grade.

Sort order: Parameter, Dose Group, Subject ID, and Time Point. Change from Baseline column will be blank for parameters that are not numerical.]

Dose Group	Subject ID	Time Point	Date of Assessment	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range
SAD 1 mg	PHU.00123	Day 2	ddMMMyyyy	Male	Sodium (mmol/L)	132 (Mild)	-7	135 -145

Listing 12: 16.2.8.2: Clinical Laboratory Results – Hematology

Dose Group	Subject ID	Time Point	Date of Assessment	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range
			ddMMMyyyy					

Listing 13: Clinical Laboratory Results – Coagulation

Dose Group	Subject ID	Time Point	Date of Assessment	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range
			ddMMMyyyy				

Listing 14: 16.2.8.3: Clinical Laboratory Results – Urinalysis

[Implementation Notes: If parameter is determined using multiple methods, present the result from each method as a separate row, with Dipstick results preceding Complete UA results.]

Dose Group	Subject ID	Time Point	Date of Assessment	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range
SAD 1 mg	PHU.00123	Day 2	ddMMMyyyy	Male	Total Protein by Dipstick	Positive (ONR)	Negative
SAD 1 mg	PHU.00123	Day 2		Male	RBC Count by Microscopic Evaluation (/HPF)	5 (Mild)	<5

Listing 15: Clinical Laboratory Results – Serology

[Implementation Note: Listing will be sorted by Dose Group, Subject ID, then by Visit (order: Screening, then Unscheduled). If there are results for urine toxicology tests on an Unscheduled visit, the Study Day will be included in parentheses for the Visit.]

Dose Group	Subject ID	Visit	HIV Antibodies	HCV Antibodies	HBsAg
SAD 1 mg	PHU.00123	Screening	Negative	Negative	Negative
SAD 1 mg	PHU.00123	Unscheduled (Day 4)	Negative	Negative	Negative

Listing 16: Screening Laboratory Results – Urine Toxicology

[Implementation Note: Listing will be sorted by Dose Group, Subject ID, then by Visit (order: Screening, then Unscheduled). If there are results for urine toxicology tests on an Unscheduled visit, the Study Day will be included in parentheses for the Visit.]

Dose Group	Subject ID	Visit	Cannabinoids	Amphetamines	Barbiturates	Cocaine	Opiates	Benzodiazepines	Phencyclidine	Alcohol	Cotinine
SAD 1 mg	PHU.00123	Screening	Negative	Negative	Negative	Negative	Negative	Negative	Negative		
SAD 1 mg	PHU.00123	Admission	Negative	Negative	Negative	Negative	Negative	Negative	Negative		
SAD 1 mg	PHU.00123	Unscheduled (Day 4)	Negative	Negative	Negative	Negative	Negative	Negative	Negative		

Listing 17: Laboratory Results – Serum hCG and Pregnancy Tests

[Implementation Note: Listing will be sorted by Dose Group, Subject ID, then by Visit (order: Screening, then Admission, then Unscheduled). If there are results for serum hCG or serum/urine pregnancy tests on an Unscheduled visit, the Study Day will be included in parentheses for the Visit. FSH testing results, if obtained, will be shown in this listing.]

Dose Group	Subject ID	Visit	Serum HCG Result	FSH Test Result
SAD 1 mg	PHU.00123	Screening	Negative	ND
Note: ND = Test not performed				

16.2.9 Vital Signs and Physical Exam Findings

Listing 18: 16.2.9.1: Vital Signs

[Implementation Note: This listing includes all vital sign assessments, scheduled and unscheduled. All height, weight, and BMI measurements will be included in this listing as well. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal assessments, e.g., 100.7 (Mild). Sort order: Dose Group, Subject ID, Parameter, Date of Assessment, and Time of Assessment.]

Dose Group	Subject ID	Parameter (units)	Time Point	Date of Assessment	Time of Assessment	Result (Severity Grade)	Change from Baseline	Reason for Repeat
SAD 1 mg	PHU.00123	Systolic Blood Pressure (mmHg)	Day 1, 30 minutes Post-Dose	ddMMMyyyy	hh:mm	142 (Mild)	+10	

Listing 19: 16.2.9.2: 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 (RASH, 007)". In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Dose Group, Subject ID, Date of Assessment, Time of Assessment, Body System, and Finding.]

Dose Group	Subject ID	Time Point	Date of Assessment	Time of Assessment	Body System	Abnormal Findings	Reported as an AE? (AE Description; Number)

16.2.10 ECG Results and Findings

Listing 20: Listing of ECG Interval Measurements

[Implementation Note: This listing includes all ECG assessments, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal assessments, e.g., 100.7 (Mild). For all change from baseline, show "+" or "-" next to the change from baseline results if an increase or decrease.

Sort order: Dose Group, Subject ID, Parameter, Date of Assessment, and Time of Assessment.]

Dose Group	Subject ID	Sex	Parameter (units)	Time Point	Date of Assessment	Time of Assessment	Result (Severity Grade)	Change from Baseline	Replicate Number	Reason for Repeat
				Pre-Dose	ddMMMyyyy				1	
				Pre-Dose					2	
				Pre-Dose					3	
SAD 1 mg	PHU.00123	Male	QTcF (msec)	Pre-Dose (Baseline)		MEDIAN	147			
SAD 1 mg	PHU.00123	Male	QTcF (msec)	Day 1, 2 h Post-Dose	ddMMMyyyy	hh:mm	450 (Mild)	+25		

Listing 21: Listing of ECG Overall Interpretation and Comments

[Implementation Note: This listing includes all ECG assessments, scheduled and unscheduled.

Sort order: Dose Group, Subject ID, Date of Assessment, and Time of Assessment.]

Dose Group	Subject ID	Time Point	Date of Assessment	Time of Assessment	Interpretation	Comments
SAD 1 mg	PHU.00123	Day 1, 2 h Post-Dose	ddMMMyyyy	hh:mm	Abnormal, NCS	Sinus Bradycardia
					Abnormal, CS	

Listing 22: Listing of ECG Findings

[Implementation Note: Sort order: Dose Group, Subject ID, Date of Assessment, Time of Assessment, Category, and Finding.]

Dose Group	Subject ID	Time Point	Date of Assessment	Time of Assessment	Category	Finding
SAD 1 mg	PHU.00123	Day 1, 2 h Post-Dose	ddMMMyyyy	hh:mm	Arrhythmia	Sinus arrhythmia

16.2.10 Concomitant Medications

Listing 23: Prior Medications

[Implementation Note: Include prior medications (medications with an end date prior to dosing) only. 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.

Sort order: Dose Group, Subject ID, and CM Number.]

Dose Group	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)
SAD 1 mg	PHU.00123	001	BENADRYL	1-12 months prior to enrollment	1-12 months prior to enrollment	ITCHING	No	DERMATOLOGICALS (ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.)

Listing 24: 16.2.10: Concomitant Medications

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

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

If ongoing, display "Ongoing" in the "Medication End Day" column. If taken for an AE or MH, display "Yes" with the AE or MH Number in parentheses, e.g., "Yes (RASH, 007)". In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.

Sort order: Dose Group, Subject ID, and CM Number.]

Dose Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)
SAD 1 mg	PHU.00123	001	BENADRYL	2	2	ITCHING	Yes (MACULAR RASH; 001)	No	DERMATOLOGICALS (ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.)

16.2.11 Pregnancy Reports

Listing 25: 16.2.11.1: Pregnancy Reports – Maternal Information

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

Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.

Listing 26: 16.2.11.2: Pregnancy Reports – Gravida and Para

			Live Births												
Subject ID	Pregnancy Number	Gravida	Extremely PB[a]	Very Early PB[a]	Early PB[a]	Late PB[a]	Early TB[b]	Full TB[b]	Late TB[b]	Post TB[b]	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?

Note: Gravida includes the current pregnancy, para events do not.
a Preterm Birth
b Preterm Birth

Listing 27: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

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

Note: Congenital Anomalies are included in the Adverse Event listing.

Listing 28: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

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

Listing 29: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

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

Listing 30: Birth Control Listing

[Implementation Note: If subject not of child bearing potential, indicate reason subject is not of child bearing potential in parentheses in the column Child Bearing Potential. If start date is more than 30 days before enrollment then categorize, rather than use exact study days, categorize as follows: 1-12 months prior to enrollment, 1-5 years prior to enrollment, or 5 years prior to enrollment.

Sort Order: Dose Group, Subject ID, and then by Start Day.]

Dose Group	Subject ID	Sex	Child Bearing Potential	Birth Control Method	Birth Control Start Day	Birth Control End Day
SAD 1 mg	PHU.00123	Female	Yes	Hormonal Injections	-2	Ongoing

Listing 31: Subject Level Drug Concentrations

[Implementation Note: Units of nominal time and actual time vary by time point and will be provided for each time rather than in the column heading. Laboratory Reported Drug Concentration will give verbatim value reported by lab (with minimal formatting, as needed) and will use a character variable such as PC.PCORRES. Analysis Drug Concentration will report the value actually used for analysis and will use a numeric variable such as ADPC.AVAL. If one or more samples are excluded from NCA, two additional columns will be provided in the PK report listing: Excluded from NCA (Yes/No) and Reason for Exclusion from NCA.

Sort order: Dose Group, Subject ID, and Actual Time.]

Dose Group	Subject ID	Nominal Time[a]	Actual Time[a]	Laboratory Reported Drug Concentration (ng/mL)	Analysis Drug Concentration (ng/mL)	Used in λz Calculations
SAD 1 mg	PHU.00123	0	0	0	0	No

[a]Times are relative to time of previous dose.
Note: Actual Times that were outside of protocol-defined time windows are indicated by an asterisk (*). Samples that were collected substantially outside of the protocol-defined window are excluded from summary statistics (but not from NCA) and are indicated by two asterisks (**).

Listing 32: Subject-Specific PK Parameters

[Implementation Note: Sort order: Dose Group and Subject ID.]

Dose Group	Subject ID	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}last}$ (h*ng/mL)	$AUC_{0\text{-}inf}$ (h*ng/mL)	λz (1/h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)