CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 17-0087

Study Title:

A Phase 1, First-In-Human, Randomized, Double-Blind, Placebo Controlled, Single Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of Single Oral Doses of VT-1598 in Healthy Adult Subjects

NCT04208321

Version 1.0

DATE: 05JAN2022

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 17-0087**
Development Phase:	Phase 1
Products:	VT-1598 and Placebo
Form/Route:	Tablet/Oral
Indication Studied:	Coccidioidomycosis
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
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This study was performed in compliance with Good Clinical Practice.

TABLE OF CONTENTS

Table of Contents *(continued)*

Table of Contents *(continued)*

LIST OF ABBREVIATIONS

AE	Adverse Event
Ae_{last}	Cumulative amount of drug or metabolite excreted into the urine from time 0 to the time of the last quantifiable concentration
$Ae_{\%Dose}$	Percent of drug or metabolite excreted into urine
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area under the concentration-time curve
$AUC_{0\text{-}last}$	AUC to the last measurable concentration
$AUC_{0\text{-}inf}$	AUC extrapolated to infinity
$\%AUC_{ex}$	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation
BMI	Body Mass Index
BQL	Below the Limit of Quantification
CHEM	Chemistry
CI	Confidence Interval
CL/F	Apparent Oral Clearance
CL_R	Renal Clearance of Drug or Metabolite
C_{max}	Maximum Concentration
COAG	Coagulation
CRF	Case Report Form
CRU	Clinical Research Unit
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of Variation
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration

List of Abbreviations *(continued)*

FIH	First-In-Human
FSH	Follicle Stimulating Hormone
GGT	Gamma-Glutamyl Transferase
GM	Geometric Mean
hCG	Human Chorionic Gonadotropin
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL	High Density Lipoproteins
HEM	Hematology
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
ICH	The International Council for Harmonization
ICON BAL	ICON Bioanalytical Laboratory
ID	Identification
ISM	Independent Safety Monitor
IUD	Intrauterine Devices
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LDL	Low Density Lipoprotein
LLOQ	Lower Limit of Quantification
MedDRA®	Medical Dictionary for Regulatory Activities
Max	Maximum
Min	Minimum
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NCA	Noncompartmental Analysis
NCS	Not Clinically Significant
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
ONR	Out of Normal Range
PI	Principal Investigator

List of Abbreviations *(continued)*

PK	Pharmacokinetics
PT	Preferred Term
PTT	Partial Thromboplastin Time
QNS	Quantity not Sufficient
RBC	Red Blood Cells
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
$t_{1/2}$	Apparent terminal elimination half-life
T_{last}	Time of the last measurable concentration
T_{max}	Time to obtain maximum concentration
UA	Urinalysis
V_d/F	Apparent volume of distribution during terminal phase
VS	Vital Sign
WBC	White Blood Cell
λz	Apparent first-order terminal elimination rate constant

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 1, First-In-Human, Randomized, Double-Blind, Placebo Controlled, Single Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of Single Oral Doses of VT-1598 in Healthy Adult Subjects" (Division of Microbiology and Infectious Diseases (DMID) Protocol 17-0087) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. This SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports (CSRs)) [1], and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) [2], and Topic E9 (Statistical Principles for Clinical Trials) [3]. The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society of statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for the safety and pharmacokinetic (PK) outcomes, and (4) a list of proposed tables, figures, and listings. Within the table, figure, and listing mock-ups (Appendices1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in the CSR. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

This is a Phase 1, first-in-human (FIH), randomized, double-blind, placebo-controlled study to evaluate the safety and PK of single ascending doses (SAD) of VT-1598 administered in healthy adult subjects among 6 cohorts (5 fasted cohorts, 1 fed cohort). Each cohort contains 8 subjects (N = 8), 6 subjects will be given an oral dose of VT-1598 and 2 subjects will receive placebo.

2.1. Purpose of the Analyses

This SAP describes safety and PK analyses of 40 mg, 80 mg, 160 mg, 320 mg, and 640 mg of VT-1598 given orally under a fasted state; and of 160 mg of VT-1598 given orally under a fed state (after administration of a high-fat, high calorie meal). PK analyses include assessment of VT-1598 and its primary metabolite, VT-11134.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary:

- To determine the safety of single-ascending oral doses of VT-1598 in healthy adult subjects in a fasted state.
- To determine the safety of a single oral dose of VT-1598 in healthy adult subjects in a fed state.

Secondary:

- To determine the PK profile in plasma and urine of VT-1598 and its primary metabolite, VT-11134, in healthy adult subjects.
- To determine the effect of a high-fat, high-calorie meal on the PK profile of VT-1598 and VT-11134 when a single oral dose of VT-1598 is given.

3.2. Endpoints

Primary:

- Safety will be evaluated for single-ascending fasting oral doses of VT-1598. Safety will be assessed by adverse events (AE) from start of dosing to Day 21, clinical laboratory tests at baseline and from Day 4 to Day 21, vital signs (VS) at baseline and from Day 1 to Day 21, and electrocardiogram (ECGs) at baseline and on Day 1, Day 4, and Day 21;
- Safety will be evaluated for single oral dose of VT-1598 administered after being fed a high-fat, high-calorie meal. Safety will be assessed by adverse effects from start of dosing to Day 21, clinical laboratory tests at baseline and from Day 4 to Day 21, VS at baseline and from Day 1 to Day 21, and ECGs at baseline and on Day 1, Day 4, and Day 21.

Secondary:

- PK profiles of VT-1598 and its primary metabolite, VT-11134, will be assessed by measurement of VT-1598 and VT-11134 levels in both plasma and urine after VT-1598 administration in each cohort, when fasting. Plasma for PK analysis will be collected at planned timepoints up to 480 hours post dose and urine for PK analysis will be collected in planned intervals up to 72 hours post dose.
- PK profiles of VT-1598 and its primary metabolite, VT-1134 will be assessed by measurement of VT-1598 and VT-11134 levels in both plasma and urine after administration of VT-1598 following consumption of a high-fat, high-calorie meal. Plasma for PK analysis will be collected at planned timepoints up to 480 hours post dose and urine for PK analysis will be collected in planned intervals up to 72 hours post dose.

3.3. Study Definitions and Derived Variables

3.3.1. Cohort

Cohort in the SAP will be defined to match identically with cohort as defined in the protocol (Table 1).

Fasted cohorts:

- Cohort 1: Single 40 mg tablet of VT-1598 (6 subjects) or matching placebo (2 subjects)
- Cohort 2: Two 40 mg tablets (80 mg total) of VT-1598 (6 subjects) or matching placebo (2 subjects)
- Cohort 3: Four 40 mg tablets (160 mg total) of VT-1598 (6 subjects) or matching placebo (2 subjects)
- Cohort 4: Four 80 mg tablets (320 mg total) of VT-1598 (6 subjects) or matching placebo (2 subjects)
- Cohort 5: Eight 80 mg tablets (640 mg total) of VT-1598 (6 subjects) or matching placebo (2 subjects)

Fed cohort:

- Cohort 6: Four 40 mg tablets (160 mg total) of VT-1598 or matching placebo, following a high-fat, high-calorie meal. Cohort 6 will be comprised of the same subjects as Cohort 3 who will be assigned the same treatment arm as randomized in Cohort 3. Subjects who complete Cohort 3 but withdraw or become ineligible prior to dosing for Cohort 6 will be replaced. The Cohort 6 replacement subjects will receive the same study product as assigned to the Cohort 3 subject they are replacing.

3.3.2. Dose Group

Dose Group defines a grouping of subjects for statistical analysis, where subjects within a Dose Group receive the same study product and dose under the same fasting status. Two combined Dose Groups, the Any Dose and Placebo Dose Groups, will include all subjects who receive the same study product (VT-1598 or Placebo, respectively) regardless of the subject's fasting status. Subjects who participate in both Cohort 3 and Cohort 6 will be counted separately for each dosing period based on the study product received. Any summary tables including a column for 'All Subjects' will also count Cohort 3 and Cohort 6 subjects separately for each dosing period. 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 (Section 6.3). The Dose Groups in the order they will be presented are defined as follows:

- Any Dose: All subjects who received a complete or incomplete dose of VT-1598 regardless of fasting status. Subjects who received VT-1598 in Cohort 3 and continued to Cohort 6 will be included in the Any Dose Group separately for each dosing period.
- 40 mg Fasted: Cohort 1 subjects who received a complete dose of active drug under a fasted state.
- 80 mg Fasted: Cohort 2 subjects who received a complete dose of active drug under a fasted state.
- 160 mg Fasted: Cohort 3 subjects who received a complete dose of active drug under a fasted state.
- 160 mg Fed: Cohort 6 subjects who received a complete dose of active drug following a high-fat, high-calorie meal.
- 320 mg Fasted: Cohort 4 subjects who received a complete dose of active drug under a fasted state.
- 640 mg Fasted: Cohort 5 subjects who received a complete dose of active drug under a fasted state.
- Placebo: All subjects who received a complete or incomplete dose of placebo, regardless of fasting status. Subjects who received placebo in Cohort 3 and continued to Cohort 6 will be included in the Placebo group separately for each dosing period (unless replaced as detailed in Section 4.4.3).

Analyses by Dose Groups will be presented in the following order: Any Dose (when included), 40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted, and Placebo.

In the unlikely case that a subject is given the wrong dose, that subject may be analyzed based on actual dose received or with a different Dose Group than those described above. Reasoning for assigning the subject to a different Dose Group will be described in the CSR. The "Any Dose" group will be included in the analyses of safety endpoints only.

3.3.3. Timepoints for Safety and PK Endpoints

Table 7 shows the analysis timepoints in the order that will appear in tables and figures along with the safety and PK endpoints measured at each timepoint for all cohorts. Endpoints analyzed by timepoint include chemistry clinical laboratory results (CHEM), hematology clinical laboratory results (HEM), coagulation clinical laboratory results (COAG), and urinalysis laboratory results (UA); VS; ECG; and blood PK and urine PK samples. Serology, toxicology, and pregnancy testing at Screening will not be included in tables or figures but will be presented in listings.

3.3.4. Baseline

Baseline for clinical laboratory results and VS will be defined as the last result obtained before study product administration. If triplicate ECG measures were performed at the same visit, baseline ECG will be defined as the mean value of the last triplicate measurements before study product administration.

Baseline height, weight, and body mass index (BMI) will be the measurements obtained at Screening. Age will be based on age at the time of enrollment.

3.3.5. Study Day

Study Day will primarily be used in listings to refer to the timing of assessments and events relative to study product administration. The day that the first dose of study product is received is considered Study Day 1 for all subjects. The day prior to the first dose is considered Study Day -1, there is no Study Day 0.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 1, randomized, double-blind, placebo-controlled, SAD study in healthy adult subjects. It is designed to evaluate the safety and PK of single oral doses of VT-1598. An overall schematic of study design is shown in Figure 1. A flowchart of subject disposition will be shown in Figure 2, and a table showing all planned study cohorts and dose levels can be found in Table 1. There will be 5 fasted cohorts: 40 mg VT-1598 or matching placebo, 80 mg VT-1598 or matching placebo, 160 mg VT-1598 or matching placebo, 320 mg VT-1598 or matching placebo, 640 mg VT-1598 or matching placebo, and one fed cohort: 160 mg VT-1598 or matching placebo following a high-fat, high-calorie meal.

A maximum of 40 subjects at a single site will be enrolled in the study to one of the fasted cohorts (Cohorts 1-5). Within each fasted cohort, a total of 8 subjects will be randomized 3:1 to receive active drug (VT-1598) (6 subjects) or placebo (2 subjects). For Cohort 1 through Cohort 5, the first 2 subjects will be randomized 1:1 to receive active drug or placebo to ensure that 1 of the first 2 subjects receives active drug and the other receives placebo for sentinel dosing. The study product assignment of the remaining 6 subjects in each of the fasted cohorts (Cohorts 1-5) will be randomly assigned 5:1 active drug to placebo to maintain the 3:1 ratio for the entire cohort. All sentinel subject safety data through Day 3 will be reviewed by the Principal Investigator (PI) prior to dosing the remaining 6 subjects in each fasted cohort.

Subjects who complete Cohort 3 and do not early terminate from the study will have enrollment "rollover" to Cohort 6, the fed cohort, after a minimum of 60 days for a "wash-out" period. Cohort 3 subjects continuing to Cohort 6 will not be randomized but will receive the same study product and dose as they received in Cohort 3 (160 mg VT-1598 or matching placebo) following a high-fat, high-calorie meal. Furthermore, there will be no sentinel subjects in Cohort 6. Cohort 3 subjects that are no longer eligible for the trial after the wash-out period will be replaced (Section 4.4.3). Subjects replacing individuals from Cohort 3 who did not continue on to Cohort 6 will not be randomized and will receive the same study product assignment as the Cohort 3 subject they are replacing.

A schedule of study procedures is detailed in Table 2. Screening, baseline, and follow-up procedures will follow the same process for all cohorts. Inpatient period (Study Days 1-4) procedures will differ between the fasted (Cohorts 1-5) and fed (Cohort 6) cohorts only by the high-fat, high-calorie meal and timing of inpatient pre-dose assessments. Baseline blood PK samples, targeted physical examination, and 12-lead ECG will be conducted within 60 minutes of dosing for the fasted cohorts (Cohorts 1-5). Baseline urine PK samples will be collected within 6 hours prior to dosing for the fasted cohorts (Cohorts 1-5). For Cohort 6, these procedures will be conducted within 30 minutes prior to the start of the meal. The high-fat, high-calorie meal will be entirely consumed within 30 minutes, and Cohort 6 subjects will be dosed within 30 minutes of the start of the meal. Post-dose inpatient period procedures will be the same for all cohorts. Safety assessments will include clinical laboratory tests including CHEM, HEM, COAG, and UA; VS; and a 12-lead standard ECG. AEs and serious adverse events (SAEs) will be assessed from the time of dosing to the end of the trial.

A Safety Monitoring Committee (SMC) will be appointed to oversee the safe conduct of the trial. If criteria for halting the trial are met during the study, dosing and enrollment will be suspended, and an *ad hoc* SMC meeting will be convened to review all available safety data and to make recommendations about the dosing of all further subjects in the trial. A scheduled SMC meeting will be held after Cohort 4 for safety recommendations and confirmation of dosing before beginning Cohort 5. The SMC will also review safety data at an organizational meeting prior to the start of the study, at a scheduled meeting upon completion of dosing, final visit for all cohorts, and at the request of DMID.

There will be an interim analysis of PK data after completion of Cohort 3. The interim PK report will show PK data in aggregate and will not include any potentially unblinding information. Enrollment will not stop for the interim PK analysis. If PK is substantially different than expected, the protocol may be amended to change the timing of PK samples.

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

DMID Protocol 17-0087 is designed as a placebo-controlled double-blinded dose escalation trial with 2 subjects randomized to placebo and 6 subjects randomized to active drug per cohort. The dose escalation design is utilized to confirm the safety of low doses prior to exposing subjects to high doses. Subjects who successfully complete Cohort 3 will "rollover" to Cohort 6 after a minimum of 60 days following their first dose after completion of Cohort 3. As part of Cohort 6, subjects will be given the study product following a high-fat, high-calorie meal to study the safety and PK profiles of VT-1598 and VT-11134, its primary metabolite, under a fed state. This is intended to provide a preliminary assessment of whether there is a food effect. Comparisons of fed to fasted PK profiles will be exploratory. For comparisons of active drug Dose Groups to placebo, a pooled group of placebo subjects across multiple cohorts will be used. The same subjects assigned to placebo in Cohort 3 that continue to Cohort 6 will be counted separately within the Placebo Dose Group for each dosing period.

4.3. Selection of Study Population

Only subjects who meet all of the inclusion and none of the exclusion criteria will be eligible for enrollment into this study. No exemptions are granted on Inclusion/Exclusion Criteria in DMID-sponsored studies. Up to 48 healthy male and female subjects, ages 18-45 inclusive, will be enrolled into Cohorts 1 through 6. Neither women nor minorities will be excluded from participation in this study. Women of childbearing potential may be included as per the inclusion criteria (See inclusion criteria below). Subjects will be recruited without regard to gender or race. It is expected that race will reflect that within the community. The demographics in the local population should ensure that male and female minorities will be represented in the enrolled population.

Eligibility criteria from v5.0 of the protocol are listed below:

Inclusion Criteria:

1. Willing and able to provide written informed consent and authorization for use of protected health information;
2. Willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions (including confinement to the clinical research unit (CRU)) and is likely to complete the study as planned;
3. Male and female subjects, 18-45 years of age (inclusive);
4. Subject is in good health to be safely enrolled in this protocol as determined by medical history and physical exam;
5. BMI of 18-35 kg/m^2, inclusive, and minimum weight of 50 kg;

6. If a female participant is of childbearing potential*, she must use a highly effective contraceptive method† from 30 days before enrollment through the 3 months after dosing;

   **A woman is considered of childbearing potential unless post-menopausal (subject is at least 50 years old and has history of ≥ 2 years without menses without other known or suspected cause and has a follicle stimulating hormone (FSH) level >40 IU/L), or permanently surgically sterilized.*

   †A highly effective contraceptive method includes surgical sterilization methods such as tubal ligation, bilateral oophorectomy, salpingectomy, hysterectomy, or successful tubal obliteration (e.g., Essure®) with documented radiological confirmation test at least 90 days after the procedure, or long-acting reversible contraception (progestin-releasing subdermal implants, copper intrauterine devices (IUDs), levonorgesterel-releasing IUDs.

7. Males* having sexual intercourse with women of childbearing potential must agree to consistent use of condoms from study product administration through 3 months after dosing**;

   ** Including vasectomized men.*

   *** And must also agree to not donate sperm during this same time period.*

8. Subject has adequate venous access for blood collection.

Exclusion Criteria:

1. Has a chronic condition that may increase risk to subject or interfere with endpoint assessment (e.g., liver disease, kidney disease, immunodeficiency);
2. Chronic condition diagnosed within 90 days of the Screening visit;
3. Unstable chronic disease* within 6 months of the Screening visit;

   **As defined by need for medical intervention that lead to a change in medications and/or required hospitalization, surgery/procedure, or Emergency Department/urgent care visit.*

4. History of psychiatric condition that has required hospitalization in the last 5 years or patient is considered unstable by study investigator;
5. Any condition that is in the opinion of the Investigator could significantly impact drug absorption, distribution, or elimination;
6. Any out of normal range value* at Screening or enrollment (Section 8.1 and Appendix B of the protocol);

   **A laboratory value that is Grade 1 (with the exception of alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total bilirubin, hemoglobin or serum creatinine) will be allowed if not considered to be clinically significant by the investigator.*

7. Abnormal ECGs. See Section 7.1 of the protocol Clinical Evaluations for exceptions;
8. Electrocardiographic QTcF interval >430 msec for males and >450 msec for females at Screening;
9. Positive test for antibodies to Human Immunodeficiency Virus (HIV)-1, HIV-2, Hepatitis B Surface Antigen (HBsAg), or Hepatitis C Virus (HCV);
10. Positive urine drug test. The drugs that will be screened for includes amphetamines, barbiturates, cocaine, opiates, cannabinoids, phencyclidine, and benzodiazepines;

11. Female subject of childbearing potential who is pregnant*, lactating, or planning to become pregnant during the study period or 3 months after the final dose of study product;

    **Having a positive serum pregnancy test at the Screening Visit or any other specified timepoint prior to the dose of the study product.*

12. Received any study product in a clinical trial within 30 days prior to Screening;
13. Admitted or documented illicit drug use or alcohol abuse within 6 months prior to Screening or during their participation in the trial;
14. Consumed alcohol within 72 hours of Day -1, until after the visit to the CRU on Day 14 or have positive alcohol test at Screening or on admission to the CRU;
15. Tobacco* use within 90 days prior to the Screening Visit or while a subject is enrolled in the study OR a positive drug test for cotinine;

    **Tobacco use includes vaping, smoking tobacco, the use of snuff and chewing tobacco, and other nicotine or nicotine- containing products.*

16. Use of prescription drugs within 14 days prior to the dose of study product with the exception of hormonal contraceptives, which are permitted throughout the study;
17. Received any non-prescription medications, vitamins, or dietary supplements* within 7 days of dosing, unless prior approval is granted by both the Investigator and the Sponsor;

    **Excluded from this list is intermittent use of acetaminophen at doses of ≤2 g/day or ibuprofen ≤1200 mg/day. Herbal supplements must be discontinued 7 days prior to the dose of the study product.*

18. History of intolerance or hypersensitivity to azole antifungals;
19. Blood donation or other significant blood loss within 60 days of Screening and for the duration of the study;
20. Inability or difficulty swallowing whole capsules/tablets and/or multiple capsules/tablets;
21. Consumption of beverages and foods containing caffeine for 24 hours prior to Day -1 until discharge from the CRU on Day 4;
22. Consumption of grapefruit, or juices containing grapefruit or Seville oranges within 7 days prior to the scheduled dose of the study product until after the visit to the CRU on Day 14;
23. Subject has plans to enroll or is already enrolled in another clinical trial that could interfere with safety assessment of the investigational product at any time during the study period*;

    **Includes trials that have a study intervention such as a drug, biologic, or device.*

24. Having dietary restrictions that would preclude the subject from participating in either fed or fasted cohorts;
25. Having sensitivity or allergy to aspirin.

4.4. Treatments

4.4.1. Treatments Administered

Subject will receive either a single oral dose of VT-1598 ranging from 40 mg to 640 mg or matching placebo tablet(s) according to cohort (Table 1).

VT-1598 or placebo tablets will be administered orally with approximately 240 mL of ambient temperature water on the morning of Day 1. Subjects in fasted cohorts (Cohort 1- 5) will receive the study product after an overnight fast of at least 8 hours. Subjects in these cohorts will continue to fast for an additional 4 hours post dose. Subjects in Cohort 6 will be dosed at the same level as Cohort 3 on the morning of Day 1. This group will not fast and will be fed a high-fat, high-calorie meal which will be entirely consumed within 30 minutes. The high-fat, high-calorie test meal will be comprised of a breakfast of approximately 900-1000 calories, with approximately 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat. The dose of the study product will be administered 30 minutes after the start of the meal.

4.4.2. Identity of Investigational Product(s)

VT-1598 is a novel oral agent for the treatment of fungal infections and will be supplied as 40 mg and 80 mg tablets. VT-1598 in its physical form is a lightly colored solid formulated as a spray-dried dispersion with standard excipients including Eudragit® L100, microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and FD&C Yellow #5 aluminum lake (United States Pharmacopeia).

Placebo will be supplied as matching tablets (40 mg and 80 mg VT-1598 tablets) containing the inactive components of VT-1598. To maintain the blind, the placebo tablets will be the same size, weight, and color as the VT-1598 tablets.

Additional details of the investigational products may be found in the study protocol and Manual of Procedures (MOP).

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

Enrollment/randomization will be performed through the enrollment module in the electronic data capture system (EDC), maintained by the Statistical and Data Coordinating Center (SDCC). The randomization schedule will be generated centrally through the AdvantageEDC℠ (Electronic Data Capture System, Emmes) by the unblinded study biostatistician and a list will be transferred to the unblinded study pharmacist prior to the start of the study for the purpose of an emergency back-up. AdvantageEDC will assign each subject to a treatment arm after the demographic and eligibility data have been entered into the system. Randomization for the study is described below.

In Cohort 1 through Cohort 5, 8 subjects will be randomized in a 3:1 ratio to active drug and placebo. The first 2 subjects will be sentinel subjects and will be randomized in a 1:1 ratio to active drug and placebo, to ensure that one of the first 2 subjects receive active drug and the other receives placebo for sentinel dosing. The study product assigned to the remaining 6 subjects in Cohorts 1 through 5 will be randomly assigned in a 5:1 ratio of active drug to placebo to ensure the 3:1 ratio for the entire dosing cohort. Enrollment will occur at one site and randomization will not be stratified.

After completing the final study visit (Day 21) and at least 60 days after dosing, Cohort 3 subjects will have enrollment “rollover” to Cohort 6. Cohort 3 subjects continuing as Cohort 6 subjects will not be randomized but will receive the same assignment as they received in Cohort 3: A subject will receive placebo if he or she

received placebo as part of Cohort 3, otherwise the subject will receive 160 mg of VT-1598. There will be no sentinel subjects in Cohort 6.

An appropriate number of back-up subjects will be screened per cohort in the event that subject replacement is needed. Subjects who discontinue from study participation without receiving any amount of study product may be replaced. Subjects who experience emesis within the first 12 hours after dosing may also be replaced. The first subject in each cohort to discontinue from participation due to loss to follow up after receiving any amount of study product will not be replaced in that cohort. If more than one subject in any cohort discontinues participation, these additional subjects after the first subject will be replaced. Replacement subjects will receive the same study product as the subject they are replacing.

Subjects who complete Cohort 3 but become ineligible or withdraw prior to dosing for Cohort 6 will be replaced. Subjects in Cohort 6 who do not finish the high-fat high-calorie meal within 30 minutes will not be dosed and will be replaced. Cohort 6 replacement subjects will receive the same study product as assigned to the Cohort 3 subject they are replacing. Cohort 6 may start enrolling prior to convening the SMC meeting and prior to the start of Cohort 5.

4.4.4. Selection of Doses in the Study

See Sections 2.1 and 2.2 of the study protocol v5.0 for rationale of dose selection. Further details may be found in the Investigational Brochure [4].

4.4.5. Selection and Timing of Dose for Each Subject

Study product for each subject will be assigned by randomization and will not be further adjusted. Subjects in the fasted cohorts (Cohorts 1-5) will receive the study product in the morning by mouth after an overnight fast of at least 8 hours. Subjects will remain fasted for at least 4 hours post dose. The wash-out period for Cohort 3 subjects who continue to Cohort 6 will be a minimum of 60 days following the first dose after completion of Cohort 3 to allow for adequate time to eliminate the effect of study product prior to dosing in Cohort 6. Subjects in the fed cohort (Cohort 6) will fast overnight for at least 8 hours prior to the start of a high-fat, high-calorie meal, which will be entirely consumed in less than 30 minutes. The study product will be administered 30 minutes after the start of the meal. No other food will be ingested until after a minimum of 4 hours post dose.

4.4.6. Blinding

This is a double-blind clinical study. The VT-1598 and placebo tablets and packaging will look identical to maintain the blind for the subject and study staff administering the treatment.

Subjects, investigators, study staff administering drug, study personnel performing any study-related assessments, bioanalytical laboratory personnel, and Fisher repository personnel will be blinded to subject treatment assignments throughout the study. The DMID medical monitor and National Institute of Allergy and Infectious Diseases (NIAID) personnel will remain blinded to all subject randomization assignments. Selected individuals not involved in the conduct of the study, including members of the SMC, may have access to unblinded data as needed for safety review or other data review. The randomization scheme will be provided to the unblinded study personnel (study pharmacist preparing the study product and verifier) only for emergency unblinding purposes. Emergency unblinding of treatment assignment for a subject may be necessary due to a medical emergency or other significant medical event. Procedures for emergency unblinding are detailed in the MOP. The treatment assignment code list will be kept in a secure place at all times.

4.4.7. Prior and Concomitant Therapy

Prior drugs and medications taken, including non- prescription and herbal products, will be recorded at Screening for the previous 30 days for each subject. At each subsequent study visit, including enrollment, each new concomitant medication and changes to existing medications will be recorded in the subject's source documents and on the appropriate electronic case report form (eCRF). Prior and concomitant medications will be listed in Listing 8 and Listing 9, respectively.

See Section 7.1.2 of the study protocol v5.0 for restrictions regarding prior and concomitant therapies.

4.4.8. Treatment Compliance

Study product will be administered at the ICON Early Phase Services by site personnel in accordance with assigned randomization. Subject compliance is not anticipated to be an issue. Complete information regarding any partial or interrupted dosing will be documented. Start and end times of dosing, times of last food and fluid ingestion before dosing, and first food and fluid ingestion after dosing will be recorded on the appropriate eCRF. Within 5 minutes of product administration, study personnel will examine the oral cavity of each subject to assure that all study product was swallowed.

4.5. Safety and Pharmacokinetic Variables

The following section describes the safety and PK endpoints of the study. As this study is a Phase 1 clinical trial in healthy adult subjects, there will be no assessment of drug efficacy. For a detailed schedule of study procedures refer to Table 2. Refer to Section 3 for a list of the primary and secondary objectives and endpoints. For definitions of baseline for safety endpoints, refer to Section 3.3.4.

Incidence, relatedness, and severity of treatment-emergent AEs and SAEs will be recorded from the time of dosing to the final visit on the appropriate eCRF. All AEs will be graded for severity and the relationship to the study product by a trained and qualified member of the study team as described in Sections 8.1 and 8.2 of the study protocol v5.0. AEs and SAEs are defined in Sections 8.1 and 8.2 of the study protocol v5.0. Clinical AEs will be graded using the toxicity grading scales in Table 3.

Clinical laboratory results, VS, and ECG results will be assessed using the toxicity grading scales in Table 4, Table 5, and Table 6 , respectively**.**

In addition to AEs, the following safety endpoints will be assessed according to the study procedure listed in Table 2:

- CHEM, HEM, and COAG clinical laboratory result safety parameters:
  - The results will be graded according to the toxicity grading criteria in Table 4.
  - The following parameters will be measured:
    - CHEM parameters: albumin, glucose, blood urea nitrogen, potassium, calcium, sodium, chloride, total protein, creatinine, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), total carbon dioxide, creatine phosphokinase, phosphorus, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, magnesium, gamma-glutamyl transferase (GGT), and serum cortisol.
    - HEM parameters: hemoglobin, hematocrit, differential white blood cell count (lymphocytes, neutrophils, monocytes, eosinophils, basophils), platelet count, red blood cell count (RBC), and total white blood cell count (WBC).

  - COAG parameters: Prothrombin time, Activated partial thromboplastin time (PTT), and international normalized ratio.
  - UA parameters: specific gravity by dipstick, pH by dipstick, occult blood by dipstick, leukocyte esterase by dipstick. If dipstick urinalysis testing is abnormal, RBC by complete UA and WBC by complete UA will be assessed. Urinalysis WBC count will be measured but the results will not be graded for toxicity.

- VS parameters:
  - VS will be obtained after subjects have rested for at least 5 minutes.
  - VS parameters will be graded according to the toxicity grading criteria in Table 6.
  - Subjects with a history of sinus bradycardia will only have AEs of moderate severity or greater entered for bradycardia/decreased heart rate.
  - The following parameters will be measured:
    - Systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and temperature.
- ECG parameters:
  - ECG measurements will be conducted in triplicate, and the mean of triplicate values will be used for analysis, including analyses of change from baseline.
  - All ECG triplicate readings will be conducted at least 1 minute apart within a 15-minute period.
  - ECG results will be read by the study PI or a designated clinician and graded according to the toxicity grading criteria in Table 6. For each timepoint, overall interpretation of the ECG will be reported as Normal; Abnormal, Not Interpretable; or Abnormal, Clinically Significant (CS). Evaluation of rhythm, arrhythmia, conduction disturbance, axis, myocardial infarction, ST segment, and other abnormal findings will also be assessed.
  - If QTcF prolongation occurs after dosing then telemetry monitoring will start, and triplicate 12-lead ECGs will be captured every 30 minutes until the average for the triplicates has returned to within 60 ms of the baseline value.
  - The following parameters will be measured:
    - PR interval, QRS duration, QT interval, QTcF interval, RR interval, and mean ventricular heart rate.
    - Prior to 16NOV2020 QTc interval was included in the ECG parameters measured. Because QTc and QTcF are similar intervals, the study team determined that QTc should be removed from the eCRF so as to reduce redundant data collection. QTcF was kept as the interval as it is the parameter referenced in the Inclusion and Exclusion criteria.
- Physical exams:
  - Complete physical exams include the following parameters:
    - General appearance; head, eyes, ears, nose, and throat; neck; chest and lungs; cardiovascular system, abdomen, and musculoskeletal system, lymph nodes, extremities/skin, and neurological system.
  - Targeted physical exams include the following parameters:

- General appearance, heart, lungs, skin, abdomen.

Blood and urine samples for PK analysis will be collected according to the study procedures listed in Table 2. VT-1598 and VT-11134 concentrations will be measured from plasma and urine samples. The bioanalytical lab, ICON Bioanalytical Laboratory (ICON BAL) will analyze VT-1598 and VT-11134 concentrations using the validated liquid chromatography/tandem mass spectrometry assays (LC-MS/MS).

5. SAMPLE SIZE CONSIDERATIONS

This is a Phase 1 FIH study to assess the safety and PK of VT-1598. Since the study is primarily aimed at safety and PK evaluation, no formal power calculations based on testing a statistical hypothesis were constructed. The sample size of 8 subjects (6 subjects receiving VT-1598 and 2 subjects receiving placebo) per cohort is based on clinical experience and judgement and should provide adequate clinical information to meet the study objectives. The comparisons of PK between the fasted and fed cohorts (Cohort 3 and Cohort 6) are exploratory rather than formal analyses of fed bioequivalence. Fasted and fed PK profiles from 6 subjects are sufficient to meet the intended purpose.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Summary statistics for continuous data will include the number of subjects included in analysis (N), mean, standard deviation (SD), median, minimum value (min), and maximum value (max). Summary statistics for discrete data will include frequencies and proportions and may include confidence intervals (CIs) for the proportion. When 95% CIs are given for a proportion, exact (Clopper-Pearson) CIs will be used, unless otherwise specified. All randomized subjects will be included in the summaries of subject demographics. The Safety Population will be used for summaries of safety endpoints and the PK Analysis Population or the PK Analysis Subset will be used for summaries of PK endpoints.

Denominators for safety endpoints will be the number of subjects in the Safety Population. Denominators for clinical laboratory, VS, and ECG results at planned study timepoints will be the number of subjects with available results at the specified timepoint for that parameter. Denominators for the conceptual "Maximum Severity Post Baseline" timepoint for clinical laboratory, VS, and ECG results will be the number of subjects with an observed result for the parameter obtained post dose.

The sort order for listings is indicated in the implementation note for each listing shell (Appendix 3). The sort order of clinical laboratory tests, VS, and ECG parameters is described in Section 9.

All safety and PK analyses will be performed by Dose Group as described in Section 3.3.2.

6.2. Timing of Analyses

The final analysis will be performed after database lock.

An interim PK analysis is planned between Cohort 3 and Cohort 4. Enrollment for Cohort 4 will not depend on the PK interim analysis.

The SMC will review data at the following times:

- Between Cohort 4 and Cohort 5
- After completion of dosing and final visit for all cohorts
- *Ad hoc* meeting(s): as required in response to halting criteria (Protocol section 8.6) being met for sentinels, dose escalation, or the overall study, or at the request of DMID to review a potential safety concern identified by either the PI, medical monitor, participating investigator, or the independent safety monitor (ISM) .

6.3. Analysis Populations

All analysis populations to be used in the final analysis are described in this section. A tabular listing of all randomized and enrolled subjects excluded from an analysis population (Safety Population or a PK Analysis Population) will be included in the CSR (Listing 5). In the case there are multiple reasons for exclusion from the PK Analysis Population or PK Analysis Subset, only one reason will be counted when summarizing reasons for exclusion from analysis populations in Table 10.

6.3.1. Safety Population

The Safety Population will include all subjects that received any amount of study product and will be analyzed by Dose Group. Placebo subjects will be pooled across multiple cohorts for analysis. Placebo

subjects enrolled in Cohort 3 that continued on to Cohort 6 will be counted separately for each study part, as detailed in Section 3.3.2.

6.3.2. PK Analysis Population

The PK Analysis population will consist of all subjects who received VT-1598 and have at least 1 quantifiable post dose plasma or urine sample with measurable drug or metabolite concentration. Subjects who participated in both Cohort 3 and Cohort 6 will be evaluated and included separately per dosing period for inclusion into the PK Analysis Population; i.e., subjects will be included in the PK Analysis Population once under a Fasted state and once again under a Fed state. Similarly, results from these subjects will be analyzed separately per dosing period. Subjects enrolled and randomized to receive some dose of VT-1598 who did not complete his or her dose, or otherwise received an incorrect dose will not be included in the respective Dose Group for analysis. However, listings will include concentrations and parameter estimates for those subjects. Regardless of the subject's inclusion in the PK Analysis Population, all VT-1598 and VT-11134 concentration results will be included in listings, including results from placebo subjects. The order that reasons will be considered for a PK Analysis Population will be: the subject received placebo, the assigned dose was not received or completed, the subject has no measurable drug or metabolite concentration in plasma or urine.

6.3.2.1. PK Analysis Subset

The PK Analysis Subset will be based on the PK Analysis Population and will include all subjects who completed the PK part of the trial in each dosing period without any protocol deviation that would likely affect the PK results and who have an evaluable plasma or urine concentration for either VT-1598 or VT-11134 from which at least a subset of the designated PK parameters can be determined. The order that reasons will be considered for a PK Analysis Subset will be: excluded from the PK Analysis Population, occurrence of protocol deviation(s) with potential to impact PK, PK data is insufficient to estimate any plasma or urine PK parameters.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses.

6.5. Missing Data

All attempts will be made to collect data per protocol. Any missing data or data anomalies will be communicated to the study site for clarification and resolution. Missing collection times for blood and urine PK samples may be imputed as the nominal time if the sample was confirmed to be collected within the protocol defined window. No further imputation of missing data is planned.

6.6. Interim Analyses and Data Monitoring

An SMC meeting to review safety data is planned between Cohort 4 and Cohort 5. Safety data, including AEs; SAEs; clinical laboratory results (CHEM, HEM, COAG, and UA); VS, and 12 lead ECGs will be presented by cohort. Reasons for subjects who terminate the study early or discontinue treatment will be presented for all cohorts. The SMC may also review safety data by Dose Group in the closed session or *ad hoc* meetings as requested. An interim analysis of PK data is planned following the completion of Cohort 3. The interim PK report will only show PK data in aggregate and will not include any potentially unblinding information. The interim PK analysis will be conducted on the PK Analysis Population and will present

concentration and estimated PK parameter results for both specimen types by Dose Group and analyte. Further details of the interim PK analysis are provided in the Interim Noncompartmental PK Analysis Plan for the study [6].

6.7. Multicenter Studies

This is a single-site study.

6.8. Multiple Comparisons/Multiplicity

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

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Screened subjects who were ineligible for enrollment in the study (screen failures) or eligible but not enrolled will be summarized by inclusion and exclusion criteria (Table 11). Enrolled subjects who were ineligible for inclusion in analysis populations will be summarized by reason for subject exclusion and Dose Group
(Table 10). Individual 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 9), showing the number of subjects who were screened, enrolled and randomized, received study product, completed all planned PK blood draws, completed all planned PK urine samples, completed final study visit, participated in the fast and fed cohorts (for Cohort 3 and Cohort 6), and terminated early.

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

A flowchart displaying the disposition of study subjects will be included (Figure 2). This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed by Dose Group.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by deviation category, deviation type, and Dose Group (Table 8). This table will provide both the number of subjects and the number of deviations for each deviation category and deviation type. All subject-specific protocol deviations and non-subject-specific protocol deviations will be listed in Listing 3 and Listing 4, respectively.

8. EFFICACY EVALUATION

There are no efficacy endpoints for this trial.

9. SAFETY EVALUATION

All safety analyses will be performed using the Safety Population and will be presented by Dose Group. Placebo subjects enrolled in Cohort 3 that continued on to Cohort 6 will be counted separately for each dosing period, as detailed in Section 3.3.2.

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 proportion values will be indicated within the table or table header. AEs will be summarized for the number of subjects who experienced an AE and the number of events by Dose Group and Medical Dictionary for Regulatory Activities (MedDRA®) category. Toxicity grading scales for clinical adverse events are provided in All reported AEs will be included in the summaries and analyses.

Clinical laboratory, VS, and ECG results will also be used to assess safety. Results from these assessments will be graded by severity and presented in tables and figures by Dose Group for each post baseline timepoint. The analysis timepoints that will be summarized are presented in Table 7. The most extreme severity grade observed after dosing will be summarized (Maximum Severity Post Baseline) and will include results from unscheduled visits. For tabular displays of clinical laboratory, VS, and ECG results by parameter, the maximum severity across all parameters within each category (CHEM, HEM, COAG, UA, VS, and ECG) will be included and summarized by timepoint (Any Parameter). CHEM, WBC (in COAG), and VS parameters will be displayed by event direction (increase or decrease).

9.1. Demographic and Other Baseline Characteristics

Sex, ethnicity, and race of all subjects will be summarized by Dose Group (Table 12). Ethnicity will be categorized "Hispanic or Latino," or "Not Hispanic or Latino," "Unknown," or "Not Reported." In accordance with National Institutes of Health (NIH) reporting policies, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the case report form (CRF) as "No" to each race option. Age at enrollment, height, weight and BMI at Screening will be summarized by Dose Group (Table 13). Individual subject listings will be presented for all demographic and baseline characteristics (Listing 6).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA coded using MedDRA dictionary version 23.1 or higher. Summaries of subjects' pre-existing medical conditions by MedDRA system organ class (SOC) will be presented by Dose Group (Table 14). Individual subject listings will be presented for all medical conditions (Listing 7).

9.1.2. Prior and Concomitant Medications

All medications will be coded to the Anatomical Therapeutic Classification (ATC) 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 15 for prior medications and Table 16 for concomitant medications). Individual subject listings will be presented for all prior medication (Listing 8) and concomitant medications (Listing 9).

Regardless of the certainty of the date entered, drugs will be listed and summarized as prior medications when the end date for the medication is before study product administration and listed and summarized as

concomitant medications otherwise. If a medication has no recorded end date it will be considered a concomitant medication.

9.2. Measurements of Treatment Compliance

Date and time of study product administration, along with information on whether the subject was dosed according to protocol will be included in Listing 10. Subject level drug and metabolite concentrations at each timepoint will be included in Listing 30 for plasma and Listing 31 for urine.

9.3. Adverse Events

When calculating the proportions of subjects with AEs within a given MedDRA category, subjects will be counted once for each dosing period within the same MedDRA category, and the event will be reported according to the highest severity recorded throughout the indicated time period (separately for related and unrelated AEs when both severity and relatedness are tabulated). Repeated AEs will be ignored. When calculating the number of AEs that occurred, all AEs will be summarized by Dose Group, including repetitions.

All reported adverse events will be included in the summaries and analyses.

9.3.1. Solicited Events and Symptoms

No solicited events will be collected in this trial.

9.3.2. Unsolicited Adverse Events

An overall summary of unsolicited AEs by Dose Group will be presented in Table 17 including the number of subjects with at least one AE, number of subjects with at least one related AE, and number of subjects with at least one SAE.

All AEs will be presented in Listing 11. A subject listing of non-serious AEs of moderate or greater severity will also be reported (Table 22).

Denominators for proportions are the number of subjects in the Safety Population in each Dose Group. Placebo subjects who participated in both Cohort 3 and Cohort 6 will contribute to the denominator once per each dosing period for the Placebo Dose Group. Subjects who received VT-1598 and participated in both Cohort 3 and Cohort 6 will contribute to the denominator once per each dosing period for the Any Dose Group. The following summaries for unsolicited AEs will be presented:

- The number of AEs and number and proportion of subjects reporting an AE or SAE that occurred in 5% of all subjects along with the total number of events reported will be presented by Dose Group, SOC, HLGT, and preferred term (PT) (Table 18).
- The number of AEs and number and proportion of subjects reporting an AE will be presented by Dose Group, SOC, HLGT, and PT. The 95% CI for the proportion of subjects experiencing each SOC/HLGT/PT will also be presented (Table 19).
- The number and proportion of subjects reporting a related or unrelated AE will be presented by Dose Group, SOC, HLGT, PT, severity, and relationship to study product. (Table 20)

Summaries of unsolicited AEs will be presented graphically in bar charts by Dose Group and SOC. For summaries of proportions of subjects reporting an AE, denominators will be the number of subjects in the Safety Population for each Dose Group. Placebo subjects who participated in both Cohort 3 and Cohort 6 will

contribute to the denominator once per each dosing period. Subjects who received VT-1598 and participated in both Cohort 3 and Cohort 6 will contribute to the denominator once per each dosing period for the Any Dose Group:

- The proportion of subjects reporting a related AE will be presented by the maximum severity reported per SOC (Figure 3).
- The total number of related AEs reported will be presented by Dose Group and SOC (Figure 4).

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

Individual data listings of deaths and other SAEs will be provided (Table 21). The listing will include subject ID, Dose Group, AE description, SOC, High-Level Group Term (HLGT), PT, duration of AE, reason reported as an SAE, severity, relationship to treatment, alternate etiology if not related, action taken with study treatment, whether the subject discontinued due to the AE, and AE outcome.

9.5. Pregnancies

Individual data listings of pregnancy reports will be provided if a pregnancy occurs post dosing:

- Maternal information will be presented in Listing 24.
- Gravida and para information will be presented in Listing 25.
- Live birth outcomes will be presented in Listing 26, and still birth outcomes will be presented in Listing 27.
- Spontaneous, elective, or therapeutic abortion outcomes will be presented in Listing 28.

Birth control method(s) will be listed for each subject with a start and end date (Listing 29).

9.6. Clinical Laboratory Evaluations

Toxicity grading criteria for clinical laboratory results can be found in Table 4. Unscheduled clinical laboratory evaluations will be included in listings of all clinical laboratory results, but excluded from tabular and graphical summaries by timepoint, except when calculating the maximum severity post baseline. Any pre-existing abnormal lab results at Screening and Baseline will be graded and presented in listings but will not be reported as an AE unless it is treatment-emergent (i.e. severity worsens after dosing). Clinical 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. Descriptions of each clinical laboratory summary are described below:

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

- CHEM: albumin, glucose, blood urea nitrogen, potassium, calcium, sodium, chloride, total protein, creatinine, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, total carbon dioxide, creatine phosphokinase, phosphorus, magnesium, GGT, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, and serum cortisol.
- HEM: hemoglobin, hematocrit, lymphocytes, neutrophils, monocytes, eosinophils, basophils, platelet count, RBC, and WBC.
- COAG: prothrombin time, PTT, and international normalized ratio.

- UA: specific gravity by dipstick, pH by dipstick, occult blood by dipstick, leukocyte esterase by dipstick, RBC by complete UA, and WBC by complete UA (microscopic tests to be completed if dipstick urinalysis is abnormal). If microscopic results were obtained in the absence of an abnormal dipstick result (or without dipstick tests being done), results of the complete urinalysis or microscopy will still be summarized.

All safety laboratory results, severity, and change from baseline will be listed for each subject by Dose Group and timepoint. Abnormal laboratory results (laboratory results outside the normal range defined in the MOP) will be presented. Abnormal laboratory results that do not have toxicity grading ranges defined in the protocol will not have severity indicated in tables and listings of abnormal laboratory results, except as "ONR" (out of normal range).

- All CHEM results, including unscheduled visits, will be presented in Listing 12. Abnormal results will be presented in Table 23.
- All HEM results, including unscheduled visits, will be presented in Listing 13. Abnormal results will be presented in Table 24.
- All COAG results, including unscheduled visits, will be presented in Listing 14, Abnormal results will be presented in Table 25.
- All UA results, including unscheduled visits, will be presented in Listing 15. Abnormal results will be presented in Table 26.

All Screening results will be listed for each subject by Dose Group and visit:

- Serology results (Listing 16).
- Urine toxicology and alcohol urine results (Listing 17).
- Serum human chorionic gonadotropin (hCG) and pregnancy testing results (Listing 18).

Laboratory results will be summarized in tables and figures:

- Proportion of subjects with anormal laboratory results by parameter, Dose Group, and timepoint for CHEM (Table 27), HEM (Table 30), COAG (Table 33), and UA (Table 36).
- Proportion of subjects with mild, moderate, or severe laboratory results by parameter, Dose Group, and timepoint for CHEM (Table 28), HEM (Table 31), COAG (Table 34), and UA (Table 37).
- Summary statistics of change from baseline by parameter, Dose Group, and timepoint for CHEM (Table 29), HEM (Table 32), COAG (Table 35), and UA (Table 38). UA character results (i.e. "1+") will be excluded from change from baseline summaries.
- Graphical presentation of change from baseline at scheduled visits by Dose Group, and timepoint for each parameter as a series of box plots.
  - CHEM parameters will be presented beginning at Figure 5 and continuing through Figure 28.
  - HEM parameters will be presented beginning at Figure 29 and continuing through Figure 38.
  - COAG parameters will be presented in for PTT (Figure 39**),** PT (Figure 40), and international normalized ratio (Figure 41).
  - UA parameters presented include specific gravity (Figure 42) and pH (Figure 43).

9.7. Vital Signs and Physical Evaluations

Toxicity grading criteria for VS results can be found in Table 5. Unscheduled VS measurements will be listed, but excluded from tabular and graphical summaries by timepoint, except when calculating the maximum severity post baseline. If VS measurements are repeated due to technical errors, the initial measurements made in error will not be used for analysis but will be listed. Baseline is defined as the last VS measurement taken before dosing on Day 1.

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.

The following VS parameters will be presented (in order): systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, temperature.

VS results will be summarized in tables and figures:

- Proportion of subjects with mild, moderate, or severe VS results by parameter, Dose Group, and timepoint (Table 39).
- Summary statistics of change from baseline by parameter, Dose Group, and timepoint (Table 40).
- Graphical presentation of change from baseline by parameter, Dose Group, and timepoint (beginning at Figure 44 and continuing through Figure 58).

All VS measurements, including height, weight, and BMI, will be presented in Listing 19

Abnormal physical exam findings will be presented in Listing 20.

9.8. 12-Lead Standard Electrocardiogram

ECG measurements will be conducted in triplicate; the mean of triplicate values will be used for analysis, including change from baseline analysis. Toxicity grade criteria for 12-lead standard ECG parameters (mean of triplicate QTcF interval only) can be found in Table 6. Unscheduled 12-lead standard ECG measurements will be listed but excluded from tabular and graphical summaries by timepoint, except when calculating maximum severity post baseline. Individual interval measurements and overall interpretations will be presented in Listing 21 and Listing 22, respectively. Other ECG findings will be presented in Listing 23.

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

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

- Summary of 12-lead standard ECG change in overall interpretation from baseline will be shown by Dose Group and timepoint (Table 41).
- Proportion of subjects with mild, moderate, or severe 12-lead standard ECG results will be presented for QTcF interval by Dose Group, timepoint, and severity (Table 42).
- Summary statistics of 12-lead standard ECG change from baseline results will be shown by parameter, Dose Group, and timepoint (Table 43). A categorical summary of QTcF by Dose Group and timepoint will be presented in (Table 44).
- Graphically, 12-lead standard ECG change from baseline results will be presented by parameter, Dose Group, and timepoint. PR interval will be presented in Figure 59, QRS interval will be presented in Figure 60, QT interval will be presented in Figure 61, QTcF interval will be presented in Figure 62,

RR interval will be presented in Figure 63, and mean ventricular heart rate will be presented in Figure 64.

9.9. Other Safety Measures

No additional safety measures are planned.

10. PHARMACOKINETICS

10.1. Graphical and Tabular Summaries of Pharmacokinetic Profiles

The PK Analysis Subset will be used when summarizing plasma and urine PK concentrations. For both measured analytes in each specimen type, concentrations below the limit of quantification (BQL) collected before the first measurable PK concentration above the lower limit of quantification (LLOQ) will be treated as 0 for plotting and for all calculations including noncompartmental analysis (NCA) and concentration summary statistics. All other BQL values, for each analyte within each specimen type, observed after the first measurable concentration will be treated as missing. There will be no imputation of missing concentrations. The geometric mean (GM) of concentrations will be treated as missing for sets of data points containing a BQL value.

Collection of plasma or urine samples outside of the protocol defined time window for the timepoint will not result in exclusion of the sample result from NCA. Plasma or urine samples collected out of window will be evaluated on a case by case basis. Results from PK plasma samples that were collected substantially outside of the protocol defined time window will be excluded from concentration summary statistics by nominal timepoints and plots of mean concentration by nominal timepoint. Substantially out-of-window samples are defined to be twice the size of the protocol required windows: ± 10 minutes of the nominal timepoint for the 0.5 h post dose sample; ± 20 minutes of the nominal timepoint for the remaining post dose samples on Day 1; ± 1 hour of the nominal timepoint for the remaining inpatient days, Day 2, Day 3, and Day 4; ± 2 days for the follow-up visits, Day 7 and Day 14; and ± 4 days for the final study visit, Day 21.

If the exact time of plasma PK sample collection is not recorded then the collection time will be imputed as the planned time for analysis, as long as it is not known that the sample was collected outside of the protocol defined window. If the start and/or end time of a urine PK sample is unknown then the missing time(s) will be assumed to be the planned sample collection time (start or end), as long as it is not known that the sample was collected outside of the protocol defined window. If the exact collection time is not known for either sample type, but it is known that the sample was collected outside of the protocol defined time window, then the timepoint may be excluded from analysis at the discretion of the PK analyst. Rationale for excluding results from analysis will be described in the CSR. Results from samples with imputed collection times will be indicated in listings of PK sample concentrations.

All subjects who have at least one quantifiable concentration of VT-1598 or VT-11134 measured will be included in the PK Analysis Population. The bioanalytical laboratory will report VT-1598 and VT-11134 concentrations in plasma and urine in units of ng/mL. Concentrations in plasma and urine will be reported in the same units in the CSR, while cumulative amounts excreted into urine will be reported in units of mg. Drug and metabolite concentrations in plasma and urine will be summarized by Dose Group and listed by subject:

- Subject level concentrations of VT-1598 and VT-11134 in plasma (Listing 30) and in urine (Listing 31).
- Subject specific plasma PK parameters for VT-1598 (Listing 32) and for VT-11134 (Listing 33).
- Subject specific urine inpatient PK parameters (Listing 34**)** and urine nominal collection time interval PK parameters **(**Listing 35) for VT-1598 and for VT-11134 (Listing 36 and Listing 37).

Subject level PK concentration listings will include separate columns for concentrations reported by the lab and concentrations used for analysis. The lab reported concentrations may include codes, such as: “BQL” or “QNS” (Quantity not Sufficient), while the analysis concentrations will contain numeric data only, including imputed values such as 0 for pre-dose timepoints and BQL samples prior to the first quantifiable sample.

Listings will also indicate the nominal time (i.e., the planned time) and actual post dose time in hours associated with the sample and will note sample times which were collected out of window, substantially out of window, or imputed.

Individual and PK concentrations will be presented in tables and figures by Dose Group and nominal timepoint:

- The GM and coefficient of variation (CV) of individual concentrations in plasma will be presented tabularly by Dose Groups for both VT-1598 (Table 45 for sampling times between 0 and 14 hours post dose and Table 46 for sampling times between 24 and 480 h post dose) and VT-11134 (Table 57 for sampling times between 0 and 14 hours post dose and Table 60 for sampling times between 24 and 480 hours post dose).
- Individual concentrations in plasma and summary statistics will be presented tabularly for each Dose Group for VT-1598 (beginning at Table 47 and continuing through Table 58**)** and for VT-11134 (beginning at Table 59 and continuing through Table 72).
- Individual concentrations in plasma will be presented graphically during the inpatient sampling time period (0 h, 0.5 h, 1 h, 1.5 h, 2 h, 3, h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 24 h, 36 h, 48 h, 60 h, 72 h post dose). For VT-1598, the 40 mg, 80 mg, 320 mg, and 640 mg Dose Groups will be presented in Figure 65 and the 160 mg fasted and 160 mg fed Dose Groups will be presented in Figure 66. For VT-11134, the 40 mg, 80 mg, 320 mg, and 640 mg Dose Groups will be presented in Figure 69 and the 160 mg Fasted and 160 mg Fed Dose Groups will be presented in Figure 70.
- Individual concentrations in plasma will be presented graphically over all sampling timepoints. For VT-1598, the 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups will be presented in Figure 67 and the 160 mg Fasted and Fed Dose Groups will be presented in Figure 68**.** For VT-11134, the 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups will be presented in Figure 71 and the 160 mg Fasted and Fed Dose Groups will be presented in Figure 72**.**
- Semi-log individual concentration profiles in plasma will be presented graphically during the inpatient sampling time period. For VT-1598 the 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups will be presented in Figure 77 and the 160 mg Fasted and Fed Dose Groups will be presented in Figure 78. For VT-11134 the 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups will be presented in Figure 81 and the 160 mg Fasted and Fed Dose Groups will be presented in Figure 82**.**
- Semi-log individual concentration profiles in plasma will be presented graphically over all sampling timepoints. For VT-1598 the 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups will be presented in Figure 79 and the 160 mg Fasted and Fed Dose Groups will be presented in Figure 80. For VT-11134 the 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups will be presented in Figure 83 and the 160 mg Fasted and Fed Dose Groups will be presented in Figure 84**.** Individual cumulative amounts excreted into urine and will be presented graphically for VT-1598 (40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups in Figure 73 and 160 mg Fasted and Fed Dose Groups in Figure 74) and VT-11134 (Figure 75 and Figure 76).
- Graphically, plots of mean concentration in plasma profiles will be presented with error bars representing ± 1 SD around each sample timepoint for both VT-1598 (Figure 85 for 0 h to 72 h post dose and Figure 86 for all post dose timepoints) and VT-11134 (Figure 87 for 0 h to 72 h post dose and Figure 88 for all post dose timepoints) by Dose Group.

- Semi-log mean plots will be presented for VT-1598 (Figure 91 for 0 hours to 72 hours post dose and Figure 92 for all post dose timepoints) and for VT-11134 (Figure 93 for 0 hours to 72 hours post dose and Figure 94 for all post dose timepoints) by Dose Group.
- Mean cumulative amount excreted into urine will be presented graphically by Dose Group in plots with error bars representing ± 1 SD around each sample collection time for both VT-1598 (Figure 89) and VT-11134 (Figure 90).
- Mean concentration in plasma profiles by analyte will be presented graphically for each Dose Group separately in Figure 95 for the 40 mg and 80 mg Fasted Dose Groups, in Figure 96 for the 160 mg Fasted and Fed Dose Groups, and in Figure 97 for the 320 mg and 640 mg Fasted Dose Groups.
- Mean of cumulative amounts excreted into urine by analyte will be presented graphically for each Dose Group separately in Figure 98 for the 40 mg and 80 mg Fasted Dose Groups, in Figure 99 for the 160 mg Fasted and Fed Dose Groups, and in Figure 100 for the 320 mg and 640 mg Fasted Dose Groups.

10.2. Noncompartmental Analysis

PK parameters from plasma PK data will be estimated through NCA using version 8.2 or higher of Phoenix WinNonlin®. Actual post dose time will be used for the estimation of plasma PK parameters instead of nominal time. In the case of imputed sample collection times, the imputed time will be included in NCA. PK parameters derived from urine concentration data will be calculated using a combination of Phoenix WinNonlin and SAS version 9.4 or above. Any outliers identified in the PK analysis will be discussed in the analysis report. Outliers will not be excluded from the PK analysis.

Summary statistics of PK parameter estimates by Dose Group will be presented in tables. Summary statistics will include the mean, SD, min, max, CV and GM:

- Plasma PK parameters will be summarized and presented tabularly for all Dose Groups for VT-1598 (Table 73) and VT-11134 (Table 80).
- Detailed summary statistics of each plasma PK parameter will be presented tabularly for each Dose Group for VT-1598 (beginning at Table 74 and continuing through Table 79) and VT-11134 (beginning at Table 81 and continuing through Table 86).
- Urine PK parameters will be summarized and presented tabularly for all Dose Groups for VT-1598 (Table 87) and VT-11134 (Table 94).
- Detailed summary statistics of each urine PK parameter will be presented tabularly for each Dose Group for VT-1598 (beginning at Table 88 and continuing through Table 93) and VT-11134 (beginning at Table 95 and continuing through Table 100).

The definition of CV is described below:

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

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

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

- Linear Up Log Down calculation method

- Uniform weighting
- Oral dosing
- Lambda Z Acceptance Criteria
  - Rsq_adjusted $\geq$ 0.90
  - Span $\geq$ 3 half-lives
  - Includes at least 3 timepoints after T_{max}

If an insufficient number of subjects meet the Lambda Z Acceptance Criteria for computing plasma PK parameters, then relaxed Lambda Z Acceptance Criteria may be used and will be described in the CSR.

C_{max}

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

T_{max}

Time of maximum 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 or metabolite concentration in the terminal phase (defined as the terminal region of the PK curve where drug or metabolite concentration follows first-order elimination kinetics). λz will be computed as the slope of a terminal region consisting of $\geq$ 3 successive points in the plot of log-transformed concentration data versus time. λz will be estimated using uniform weighting.

Timepoints used in the estimation of λz will be initially selected using the WinNonlin automatic algorithm. Manually chosen timepoints 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 to improve estimation of λz on a case-by-case basis. 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], and apparent volume of distribution during terminal phase [V_d/F]) will be treated as missing.

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 or metabolite 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:

$$AUC_{0\text{-inf}} = AUC_{0\text{-last}} + \frac{C_{last}}{\boldsymbol{\lambda z}}$$

Where C_{last} is the last measured concentration ≥ LLOQ. $AUC_{0\text{-inf}}$ will be obtained from the **AUCINF_obs** parameter calculated by WinNonlin®.

$\%AUC_{ex}$ is defined as percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation from time of the last measured concentration to infinity. $\%AUC_{ex}$ can be calculated by dividing AUC from time of the last measured concentration to infinity by $AUC_{0\text{-inf}}$:

$$\%AUC_{ex} = \frac{AUC_{0-inf} - AUC_{0-last}}{AUC_{0-inf}},$$

If $\%AUC_{ex}$ is >20%, the estimated $AUC_{0\text{-inf}}$ will be excluded from statistical summaries of PK parameter estimates and downstream calculations. $\%AUC_{ex}$ will be obtained from the **AUC_%Extrap_obs** parameter calculated by WinNonlin.

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

CL/F

Apparent oral clearance (CL/F) will be obtained from $Dose/AUC_{inf}$. If $\%AUC_{ex}$ is >20%, the estimated CL/F value will be excluded from statistical summaries of parameter estimates and downstream calculations. CL/F will be obtained from the **CL_F_obs** parameter calculated by WinNonlin. Clearance will be reported in units of L/h.

V_d/F

Apparent volume of distribution (V_d/F) will be calculated as (CL/F)/λz. If $\%AUC_{ex}$ is >20%, the estimated V_d/F value will be excluded from statistical summaries of parameter estimates and downstream calculations. V_d/F will be obtained from **Vz_F_obs** calculated by WinNonlin. Volume will be reported in units of L.

Ae_{last}

Ae_{last} is defined as the cumulative amount of drug or metabolite excreted into urine up to the collection time of the last measurable concentration. Amount of drug or metabolite will be reported in units of mg.

$Ae\%_{Dose}$

$Ae\%_{Dose}$ is defined as the percent of drug (VT-1598) excreted into urine up to the ending time of the last measurable concentration. $Ae\%_{Dose}$ will be obtained from $Ae_{last}/Dose*100\%$.

CL_R

CL_R is defined as the renal clearance of drug or metabolite and will be calculated as $Ae_{last}/AUC_{0\text{-}t1}$. Where $AUC_{0\text{-}t1}$ is defined as AUC from dosing (time 0) to collection time (t1) based on the last collected concentration in urine (0 h to 72 h post dose). $AUC_{0\text{-}t1}$ will be converted to mg*min/mL for calculations of CL_R. CL_R will be treated a missing if $AUC_{0\text{-}t1}$ or Ae_{last} is not estimable. Renal clearance of VT-1598 or VT-11134 will be reported in units of mL/min.

10.3. Statistical Analysis

The PK Analysis Subset will be used for statistical analyses of plasma and urine PK parameters described above.

10.3.1. Assessment of Dose Proportionality

The presence of dose proportionality in plasma in terms of exposure parameters (C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$) over the range of studied doses will be assessed among the Fasted Dose Groups using a power model approach with methods described by Smith et al. [5] The PK Analysis Subset will be used for this analysis.

The power model for the specific case of $AUC_{0\text{-}last}$ may be specified with model parameters α and β to be estimated as:

$$AUC_{0-last} = e^{\alpha} \times dose^{\beta}$$

Let ρ be the highest dose studied / lowest dose studied and let (L, U) represent the 90% CI for $\hat{\beta}$. In the presence of dose proportionality, $\rho^{\hat{\beta}}/\rho = \rho^{\hat{\beta}-1} = 1$. Note that normality of $\hat{\beta}$ is assumed, and this assumption implies that $\rho^{\hat{\beta}-1}$ has an assumed log-normal distribution. Accordingly, dose proportionality across the studied dose range is concluded using methodology analogous to that commonly used for an assessment of bioequivalence when:

$$\Theta_l = 0.8 \leq \rho^{L-1} < \rho^{U-1} \leq 1.25 = \Theta_h.$$

Or, equivalently,

$$1 + \frac{\log 0.8}{\log \rho} \leq L < U \leq 1 + \frac{\log 1.25}{\log \rho}.$$

The analysis may be inconclusive if the CI (ρ^{L-1}, ρ^{U-1}) overlaps partially with the interval (0.80, 1.25) or if the (ρ^{L-1}, ρ^{U-1}) contains the interval (0.80, 1.25).

If graphical evidence suggests dose proportionality may exist over a subset of the dose range, the above criteria of Smith et al [5]. may be applied to a subset of the data only containing values for subjects within a limited dose range. If lack of dose proportionality is evident for higher doses, other dose proportionality analyses using a subset of the full dose range studied may be explored.

Dose proportionality assessments will be presented graphically and tabularly:

- Tabular results of statistics and parameters from the plasma dose proportionality power model will be presented for both VT-1598 and VT-11134 in Table 101.
- Predicted values from a power model, including 90% pointwise prediction bands, will be overlaid on plots of the exposure parameter parameters (C_{max}, $AUC_{0\text{-}last}$, or $AUC_{0\text{-}inf}$) versus dose. Pointwise prediction bands will be defined by lower and upper limits of 90% pointwise prediction intervals

computed from the power model at each planned level dose level. Figures will be presented for all exposure parameters. For VT-1598, C_{max} will be presented in Figure 101, $AUC_{0\text{-}last}$ in Figure 102, and $AUC_{0\text{-}inf}$ in Figure 103. For VT-11134, C_{max} will be presented in Figure 104, $AUC_{0\text{-}last}$ in Figure 105, $AUC_{0\text{-}inf}$ in Figure 106.

10.3.2. Analysis of Change in T_{max} between Fasted and Fed Dose Groups

The difference in median T_{max} values and the corresponding 90% CI for the difference between the 160 mg Fasted Dose Group and Fed Dose Group will be estimated using the PK Analysis Subset. An exact Wilcoxon signed-rank test will be conducted to compare T_{max} between subjects who participated in both cohorts. This paired analysis will only be conducted if there are at least 3 individual subjects in the PK Analysis Population who are in Cohort 3 as well as Cohort 6. An exact Wilcoxon rank sum test will be used to compare the difference in median T_{max} between all subjects in the 160 mg Fasted Dose Group to the 160 mg Fed Dose Group, regardless of whether the subject participated in both dosing periods. Continuity corrections will not be used for either test. Results from the paired and unpaired comparison of changes in T_{max} will be presented in Table 102.

10.3.3. Analysis of Exposure Parameter Ratios between Fasted and Fed Dose Groups

Exposure parameters (C_{max}, $AUC_{0\text{-}last,}$ and $AUC_{0\text{-}inf}$), will be compared between the 160 mg Fasted and Fed Dose Groups using the PK Analysis Subset. The ratio of the GM of each parameter for the fed group compared to the GM of the same parameter in the corresponding fasted group will be estimated using a mixed effects model. Each exposure parameter will be estimated by fasting status with a random subject effect and a heterogeneous compound symmetry covariance structure. Because a random subject effect will be included, only one analysis will be conducted on all subjects in the 160 mg Fasted and 160 mg Fed Dose Groups for each exposure parameter, regardless of whether the subject participated in both dosing periods. In the event of nonconvergence of the model, first an unstructured covariance matrix will be specified. If the model still fails to converge the random subject effect will be removed from the model.

Table 103 will display results comparing exposure parameters in both VT-1598 and VT-11134 between the 160 mg Fasted and 160 mg Fed Dose Groups, including the ratio estimate and a 90% CI.

Pseudo code to estimate the ratio of exposure parameters between the 160 mg Fasted and 160 mg Fed Dose Groups is presented below. Variables to be used in the model are also detailed below:

- FedCondition = indicator for dose received and fasting status; 160 mg Fed = 1, 160 mg Fasted = 2
- ExposureParam_LN = log transformed values of exposure parameters for each subject.

```
proc mixed data=data;
    class Subject_ID FedCondition;
    model ExposureParam_LN= Subject_ID  FedCondition /DDFM=SATTERTH;
    random FedCondition /type=CSH sub= Subject_ID  G;
    repeated /grp= FedCondition  sub= Subject_ID;
    estimate 'Ratio of Fed to Fast' FedCondition  1 -1/CL alpha=0.1;
run;
```

Where ExposureParam_LN is the natural log of the exposure parameter being modeled (C_{max}, $AUC_{0\text{-}last,}$ and $AUC_{0\text{-}inf}$) and FedCondition is a variable indicating the fed vs fasting condition. The estimate statement will give the mean of the natural log values of each exposure parameter and the associated 90% CIs on the log scale. Exponentiating the results of the estimate statement will give the GM and associated 90% CIs for each exposure parameter.

The resulting estimate from the mixed effects model will give the difference in log transformed values of the mean for each exposure parameter and the associated 90% CI on the log scale. These values will be exponentiated in order to present the ratio of the GM of exposure parameters and corresponding CIs on the original scale. This model and subsequent exponential transformation will be repeated for each exposure parameter (C_{max}, $AUC_{0\text{-}last,}$ and $AUC_{0\text{-}inf}$). An absence of food effect will be indicated by the 90% CI being contained in the equivalence limits of 80-125 percent for C_{max}, $AUC_{0\text{-}last,}$ and $AUC_{0\text{-}inf}$, per FDA guidance on the assessment of food effect [7].

11. IMMUNOGENICITY

There are no immunogenicity endpoints in this trial.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

P-values >0.001 and <0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as ">0.999". 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 values, will use the same number of decimal places as the original data. Proportions will be presented as 2 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". Estimated parameters not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

For PK parameters, AUCs will be reported using 3 significant digits. $t_{1/2}$, T_{max}, CL/F, and V_d/F values will be reported using 2 significant digits. λz values will be reported to 3 significant digits. C_{max} will be reported with the same number of significant digits as the measurement.

Listings of individual subject data will 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 platforms. Any data sharing activities will include the USUBJID and not the subject identifiers assigned at the study site.

14. TECHNICAL DETAILS

SAS version 9.4 or above and R versions 3.2 or above will be used to generate tables, figures, and listings. PK parameters will be estimated through NCA using Phoenix® WinNonlin version 8.2 or later.

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

Only one subject from the fasted 160 mg cohort (Cohort 3) returned for the fed 160 mg cohort (Cohort 6). This impacts the planned analysis of change in T_{max} between fasted and fed Dose Groups. Previously, an exact Wilcoxon-signed rank test had been proposed to compare subjects who had participated in both cohorts, however since fewer than 3 subjects were present in both cohorts, this analysis was not completed. Instead, only an exact Wilcoxon rank sum test was performed to compare the change in T_{max} between fasted and fed Dose Groups.

16. REFERENCES

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7. A Phase 1, First-In-Human, Randomized, Double-Blind, Placebo Controlled, Single Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of Single Oral Doses of VT-1598 in Healthy Adult Subjects v5.0 for DMID Protocol 17-0087. Emmes Corporation; June 2021.

17. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.1 Overall Study Design and Plan Description

Table 1: Study Design

Cohort	Dose[a] (mg)	Fasting Status	VT-1598		Placebo		Cohort Comments
			Number of Subjects[b]	Study Product	Number of Subjects[b]	Study Product	
1	40	Fasted	6	Single 40 mg VT-1598 tablet	2	Single 40 mg matching Placebo	Safety data for Cohort 1 subjects through Day 7 will be confirmed by reviewing objective pre-defined criteria before continuing to Cohort 2.
2	80	Fasted	6	Two 40 mg VT-1598 tablets	2	Two 40 mg matching Placebo	Safety data for Cohort 2 subjects through Day 7 will be confirmed by reviewing objective pre-defined criteria before continuing to Cohort 3.
3	160	Fasted	6	Four 40 mg VT-1598 tablets	2	Four 40 mg matching Placebo	Safety data for Cohort 3 subjects through Day 7 will be confirmed by reviewing objective pre-defined criteria before continuing to Cohorts 4 and 6. Interim analysis of PK data (Cohorts 1-3) [c].
4	320	Fasted	6	Four 80 mg VT-1598 tablets	2	Four 80 mg matching Placebo	Cumulative safety data for all subjects in Cohorts 1-4 through Day 21 will be reviewed by the SMC for recommendation/confirmation of dosing before continuing to Cohort 5.
5	640	Fasted	6	Eight 80 mg VT-1598 tablets	2	Eight 80 mg matching Placebo	
6	160	Fed	6	Four 40 mg VT-1598 tablets	2	Four 40 mg matching Placebo	Cohort 6 is comprised of the same subjects as Cohort 3.[d] These subjects will receive the same study product in Cohort 6 as Cohort 3, following a high-fat, high-calorie meal. Cohort 6 may start enrolling prior to convening the SMC meeting and prior to the start of Cohort 5.

[a] Dose refers to the free base equivalent of the drug.
[b] Within each fasted cohort, two sentinel subjects will be admitted initially, and the randomization scheme will be designed to ensure that one subject will receive VT-1598 and the other will receive placebo. All sentinel subject safety data through Day 3 is reviewed by PI prior to dosing the remainder of the cohort.
[c] PK data only. Enrollment for Cohort 4 will not stop for the PK interim analysis.
[d] The Cohort 6 replacement subjects will receive the same treatment as assigned to the Cohort 3 subject they are replacing.

9.5.1 Pharmacokinetics and Safety Measurements Assessed and Flow Chart

Table 2: Schedule of Study Procedures

Activity	Screening	Baseline	Inpatient (Treatment) Period			Follow-up Period			Unscheduled
Study Visit	**Visit 1**	**Visit 2**	**Visit 3**			**Visit 4**	**Visit 5**	**Visit 6**	
Study Day	**Day -28 to -2**	**Day -1**	**Day 1**	**Days 2 & 3**	**Day 4**	**Day 7 (±1 day)**	**Day 14 (± 1 day)**	**Day 21/ End of Study[s] (±2 days)**	
Informed Consent	X								
Demographics	X								
Inclusion/Exclusion Criteria	X	X							
Height, Weight, BMI	X	X[a]							
Medical History[b]	X	X[c]				X[c]	X[c]	X[c]	
Physical Examination	X[d]	X[e]	X[e]		X[e]			X[e]	X[e]
Vital Signs[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]
ECG[g]	X[g]		X[g]		X[g]			X[g]	X[g]
Clinical Laboratory Tests[h]	X	X			X	X	X	X	X
Pregnancy Test[i]	X	X						X	
FSH[j]	X								
Drug Screen[k]	X	X							
Immunology Screen[l]	X								
PK Blood Samples[m]			X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
PK Urine Samples[n]			X[n]	X[n]	X[n]				
Future Use Specimen Collection			X						
Prior/Concomitant Medications/Treatments	X	X	X[o]	X	X	X	X	X	X

Activity	Screening	Baseline	Inpatient (Treatment) Period			Follow-up Period			Unscheduled
Study Visit	**Visit 1**	**Visit 2**	**Visit 3**			**Visit 4**	**Visit 5**	**Visit 6**	
Study Day	**Day -28 to -2**	**Day -1**	**Day 1**	**Days 2 & 3**	**Day 4**	**Day 7 (±1 day)**	**Day 14 (± 1 day)**	**Day 21/ End of Study[s] (±2 days)**	
Review/confirm adherence to dietary restrictions/birth control methods[p]	X	X			X	X	X	X	
Admit to CRU		X							
Discharge from CRU					X				
Receive study product[q,r]			X						
Collect and Record AEs			X	X	X	X	X	X	X

*Cohort 6 may enroll prior to the SMC meeting or prior to the start of Cohort 5 (but no less than 60 days after completion of Cohort 3).

Abbreviations: AE: adverse event; BMI: body mass index; ECG: electrocardiogram; EW: early withdrawal; FSH: follicle-stimulating hormone; HIV-1: Human Immunodeficiency Virus-1; HIV-2: Human Immunodeficiency Virus-2; HBsAg: Hepatitis B surface antigen; Anti-HCV: anti-Hepatitis C virus; IMP: investigational medicinal product; PK, pharmacokinetics.

[a] Weight and BMI only.

[b] Including alcohol and tobacco use history.

[c] Update medical history as appropriate from previous visit.

[d] Complete physical examination (general appearance; head, eyes, ears, nose, and throat; neck; chest and lungs; cardiovascular system, abdomen, musculoskeletal system, lymph nodes, extremities/skin, and neurological system).

[e] Targeted physical examination (general appearance, heart, lungs, skin, and abdomen). On Day 4, targeted PE will be performed at 72 hours (±30 min).

[f] Vital signs (hear rate, blood pressure, temperature, and respiratory rate) at Screening, Day -1, pre-dose on Day 1 and approximately 1,2,4,8,24 (Day 2), 48 (Day 3), 72 (Day 4), 144 (Day 7 outpatient visit), 312 (Day 14 outpatient visit) and 480 (Day 21 outpatient visit) hours after dosing. The pre-dose Day 1 vital signs measurements should be taken within 60 minutes of dosing. Day 1 post dose vital sign measurements should be taken ± 10 minutes of the nominal timepoint. All other vital sign measurements during the inpatient stay should be taken within ± 30 minutes of the nominal timepoint. For outpatient visits, vital sign measurements should be taken within the visit window. All vital signs are taken after a subject is at rest for at least 5 minutes.

[g] ECGs will be performed at Screening; pre-dose taken within 60 minutes of dosing and post dose, taken 4 hours after dosing on Day 1; at 72 hours (± 30 minutes) prior to discharge from the CRU on Day 4 (±12 min), and on Day 21. All ECG readings are triplicate readings, at least 1 minute apart within a 15-minute period and are taken after at least 5 minutes in the supine position. For the Day 21 outpatient visit, the ECG should be taken within the visit window.

[h] Clinical laboratory tests include: clinical chemistry panel (albumin, glucose, blood urea nitrogen or urea potassium, calcium, sodium, chloride, total protein, creatinine, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total carbon dioxide, creatine phosphokinase, phosphorus, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, magnesium, gamma-glutamyl transferase (GGT) and serum cortisol), hematology (red blood cell count, total and white differential white blood cell count, hemoglobin, hematocrit, and platelet count), coagulation parameters (activated partial thromboplastin time, prothrombin time, and international normalized ratio), and urinalysis (leukocyte esterase, blood, pH, and specific gravity [microscopic tests to be completed if dipstick urinalysis is abnormal]). Subjects must fast at least 8 hours before blood collection for the clinical chemistry panel. Cortisol must be fasting and drawn before 10 a.m.

[i] Serum pregnancy test for women of childbearing potential at Screening, Day -1, and Day 21 (Final Study Visit).

[j] Follicle-stimulating hormone on all post-menopausal women at Screening.

Activity	Screening	Baseline	Inpatient (Treatment) Period			Follow-up Period			Unscheduled
Study Visit	**Visit 1**	**Visit 2**	**Visit 3**			**Visit 4**	**Visit 5**	**Visit 6**	
Study Day	**Day -28 to -2**	**Day -1**	**Day 1**	**Days 2 & 3**	**Day 4**	**Day 7 (±1 day)**	**Day 14 (± 1 day)**	**Day 21/ End of Study[s] (±2 days)**	

[k] Urine drug test at Screening and on Day -1 to include cotinine, opiates, cocaine, cannabinoids, phencyclidine, benzodiazepines, barbiturates, amphetamines, and cotinine. Alcohol screen is performed by urine test.

[l] Immunology screen to include test for the detection of antibodies to HIV-1 and HIV-2, HBsAg, and antibodies to HCV.

[m] PK blood samples will be collected on the following schedule following study product administration on Day 1: pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36, 48, 60, 72, 144 (Day 7 outpatient visit), 312 (Day 13 outpatient visit) and 480 (Day 21 outpatient visit) hours post dose. The pre-dose Day 1 PK blood sample should be taken within 60 minutes of before dosing for the fasted cohorts and within 30 minutes of the start of the pre-dose meal for the fed cohort; the Day 1 0.5-hour post dose blood sample should be taken within ± 5 minutes of the nominal timepoint. Remaining post dose Day 1 PK blood sample should be taken within ± 10 minutes of the nominal timepoint. An additional 6 mL blood for future use is collected at 6 hours (+/10 minutes) post dose. day 2, 3, and 4 PK blood samples should be taken within ± 30 minutes of the nominal timepoint. For outpatient visits, PK blood samples should be taken within the visit window. PK blood samples take precedence; however vital signs and ECGs should be completed before the blood draw, when possible.

[n] PK urine samples will be collected in the following intervals, following study product administration on Day 1: -6 to 0 hours before dose, and 0-6, 6-12, 12-24, 24-36, 36-48, 48-60-, and 60-72-hours post dose.

[o] A review for concomitant medication will be performed before and after dosing on Day 1.

[p] Screening: review birth control methods, permitted/non-permitted medications, non-medications, dietary and activity restrictions; Day -1; confirm that subject adhered to dietary restrictions (no food/beverage containing alcohol for previous 72 hours or caffeine for the previous 24 hours; no grapefruit, no grapefruit juice, or juices containing grapefruit, or Seville oranges for the previous 7 days); Days 7 and 14 - confirm that the subject adhered to post-discharge dietary restrictions (no consumption of grapefruit, or juices containing grapefruit or Seville oranges, no alcohol consumption) until after the visit to the CRU on Day 14; Review post-discharge instructions (including birth control methods, permitted/non-permitted medications, non-medications, dietary and activity restrictions).

[q] Cohorts 1-5 will receive study product when fasted and subjects will remain fasted for at least 4 hours post dose; Cohort 6 will receive study product following a high-fat, high-calorie meal, which is consumed within 30 minutes and dosing is administered at 30 minutes after the start of the meal.

[r] For the nominal dose escalations, the study product will be administered in a fasted state and the subjects will remain fasted for 4 hours post dose. Cohort 6 will be dosed with 160 mg of study product after ingestion of a high-fat, high-calorie meal.

[s] For unscheduled visits, Safety assessments including updated history and the following onsite evaluations will be obtained: AE, PE, and any other study procedures deemed necessary by the PI. Early termination assessments will be the same day as the Day 21 procedures.

Table 3: Clinical Adverse Event Toxicity Grading Scale

System	Toxicity	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Gastrointestinal	Nausea/vomiting	No to mild interference with activity or 1 to 2 episodes/24 hours	Moderate interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration
	Diarrhea	2 - 4 loose stools or <400 gm/24 hours	5-6 stools or 400 – 800gm/24 hours	7 or more watery stools or >800gms/24 hours or requires outpatient IV hydration
Systemic Reactions	Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
	Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Other Conditions	Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity, not requiring medical intervention	Prevents daily activity and requires medical intervention

Table 4: Clinical Laboratory Reference Ranges and Toxicity Grading Scales

Parameter[a]	Direction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Sodium (hyponatremia) - mEq/L	Decrease	131-132	129-130	<129
Sodium (hypernatremia) - mEq/L	Increase	144-145	146-147	>147
Potassium (hypokalemia) - mEq/L	Decrease	3.2-3.4	3.0 – 3.1	<3.0
Potassium (hyperkalemia) - mEq/L	Increase	5.2 – 5.4	5.5 – 5.6	>5.6
Phosphorus - mg/dL	Decrease	2.3 – 2.4	2.1 – 2.2	≤2.0
Phosphorous - mg/dL	Increase	N/A	N/A	N/A
Magnesium - mg/dL	Decrease	1.3-1.5	1.1-1.2	<1.1
Gamma- Glutamyl Transferase (GGT) (Male) - U/L	N/A	N/A	N/A	N/A
Gamma- Glutamyl Transferase (GGT) (Female) - U/L	N/A	N/A	N/A	N/A
Glucose (hypoglycemia) - mg/dL	Decrease	65 – 69	55 – 64	<55
Glucose (hyperglycemia) (Fasting) - mg/dL	Increase	106 – 125	126 – 200	>200
Blood Urea Nitrogen - mg/dL	Increase	21-26	27 – 31	> 31
Creatinine (Male) - mg/dL	Increase	1.3 – 2.0	2.1-2.3	>2.3
Creatinine (Female) - mg/dL	Increase	1.0 – 1.7	1.8 – 2.0	>2.0
Calcium (hypocalcemia) - mg/dL	Decrease	8.0-8.7	7.5 – 7.9	<7.5
Calcium (hypercalcemia) - mg/dL	Increase	10.4-10.8	10.9-11.4	>11.4
Chloride - mEq/L	N/A	N/A	N/A	N/A
CPKt (Male) - U/L	Increase	338.8-462	462.1-924	> 924.1
CPKt (Female) - U/L	Increase	211.2-288	288.1-576	> 576.1
A.M. Cortisol (serum, drawn prior to 10 a.m.) - ug/dL	Decrease	3.60-3.96	3.00-3.59	< 3.00
Albumin (hypoalbuminemia) - g/dL	Decrease	2.8 – 3.4	2.5 – 2.7	< 2.5
AST (Males) - U/L	Increase	44-100	100.1-200	> 200
AST (Females) - U/L	Increase	35.2-80.0	80.1-160.0	> 160.0
ALT (Males) - U/L	Increase	45.1-102.5	102.51-205.0	> 205.0
ALT (Females) - U/L	Increase	36.3-82.5	82.51-165.0	> 165.0
Total Bilirubin (serum) - mg/dL	Increase	1.32-1.50	1.60-1.80	> 1.80
Direct Bilirubin - mg/dL	Increase	0.22-0.25	0.26-0.30	> 0.30
Indirect Bilirubin - mg/dL	Increase	1.31-1.49	1.491-1.79	>1.79
Amylase - U/L	Increase	162.8 -222.0	222.1-296	>296
Lipase - U/L	Increase	73.7-100.5	100.6-134	>134
Hemoglobin (Male) - g/dL	Decrease	11.2 - 12.2	10.0 – 11.1	<10.0
Hemoglobin (Female) - g/dL	Decrease	9.8 - 10.8	8.5 - 9.7	<8.5
WBC - cell/mm^3	Increase	10,001– 15,000	15,001 – 20,000	> 20,000
WBC (African American Males) - cell/mm^3	Increase	9,001 – 14, 000	14,001 – 19, 000	>19,000

Parameter[a]	Direction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
WBC (African American Females) - cell/mm^3	Increase	11,001 – 15,000	15,001 – 20,000	>20,000
WBC - cell/mm^3	Decrease	2,500– 3,999	1,500 – 2,499	< 1,500
WBC (African American Males) - cell/mm^3	Decrease	2,200 – 2,499	1,200 – 2,199	<1,200
WBC (African American Females) - cell/mm^3	Decrease	2,200 – 2,499	1,500 – 2,199	<1,500
Neutrophils - cell/mm^3	Decrease	1,300 – <1,699	1,000 – 1,299	< 1,000
Neutrophils (African American Males) - cell/mm^3	Decrease	1,000 – 1,299	800 - 999	<800
Neutrophils (African American Females) - cell/mm^3	Decrease	1,100 – 1,299	1,000 – 1,099	<1,000
Platelets - cell/mm^3	Decrease	120,000 – <150,000	100,000 – 119,999	<100,000
Prothrombin time - seconds	Increase	11.6 – 12.6	12.7 – 13.7	>13.7
Prothrombin INR	Increase	1.2-1.4	1.5-1.9	2.0 or higher
PTT (partial thromboplastin time) - seconds	Increase	30.1 – 36.8	36.9 – 43.6	>43.6
Total Protein - g/dL	Decrease	5.5 - 5.9	5.0 - 5.4	<5.0
Alkaline phosphatase (Male) - IU/L	Increase	131-260	264-390	> 390.1
Alkaline phosphatase (Female) - IU/L	Increase	106-210	211-315	> 315.1
Hematocrit (Male) - %	Decrease	33.0 -36.1	29.8 - 32.9	< 29.8
Hematocrit (Female) - %	Decrease	29.5 - 32.6	26.0 – 29.4	< 26.0
RBC (Male) - 10^6/uL	Decrease	3.9 - 4.1	3.4 - 3.8	< 3.4
RBC (Female) - 10^6/uL	Decrease	3.5 - 3.7	3.0 - 3.4	< 3.0
Lymphocytes - cell/mm^3	Decrease	600- 799	500 – 599	< 500
Monocytes - cell/mm^3	Increase	1001-2000	2001-3000	>3000
Eosinophils - cell/mm^3	Increase	871 - 950	951 - 1700	>1700
Basophils - cell/mm^3	Increase	101 - 300	301 - 800	> 800
High Density Lipoproteins (HDL) (Male) - mg/dL	N/A	N/A	N/A	N/A
High Density Lipoproteins (HDL) (Female) - mg/dL	N/A	N/A	N/A	N/A
Total Carbon Dioxide - mEq/L	N/A	N/A	N/A	N/A
Total Cholesterol - mg/dL	N/A	N/A	N/A	N/A
Low Density Lipoprotein Cholesterol, Direct - mg/dL	N/A	N/A	N/A	N/A
Triglycerides - mg/dL	N/A	N/A	N/A	N/A
Protein*	Increase	1+	2+	>2+
Glucose*	Increase	1+	2+	>2+
Blood (microscopic) - red blood cells per high power field - rbc/hpf* °	Increase	3-10	11-50	>50 and/or gross blood

[a] Laboratory tests without toxicity grading defined in the protocol have N/A in this table for grading ranges.

*Abnormal laboratory values, performed as part of hematology, chemistry panel, or urinalysis but not listed in Table 4, VT-1598 TOXICITYGRADING CRITERIA FOR NORMAL HUMAN SUBJECTS, will be evaluated by the study clinicians, recorded in the source document and, if clinically significant, considered AEs and graded according to the criterion described in version 5.0 of the study Protocol Section 8.1.

° Hematuria during active menses is considered not clinically significant.

Table 5: Vital Signs Toxicity Grading Scale

Parameter	Direction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C)	Increase	38.0-38.4	38.5-38.9	39.0-40
Fever (°F)	Increase	100.4-101.1	101.2-102.0	102.1-104
Tachycardia (bpm)	Increase	101-115	116-130	>130
Bradycardia (bpm), if baseline > 60	Decrease	50-54	45-49	<45
Bradycardia (bpm), if baseline ≤ 60	Decrease	45-50	40-44	<40
Hypertension (systolic) (mmHg)	Increase	141-150	151-155	>155
Hypotension (systolic) (mmHg)	Decrease	85-89	80-84	<80
Hypertension (diastolic) (mmHg)	Increase	91-95	96-100	>100
Respiratory Rate (breaths/minute)	Increase	17-20	21-25	>25

Table 6: ECG Toxicity Grading Scale

Parameter	Direction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
QTcF (ms)	Increase	> 30 but ≤ 60 above baseline	> 60 above baseline to ≤ 500	>500

Table 7: Analysis Timepoints for Safety and PK Endpoints

Parameter	Analysis Timepoint	Abbreviated Label	Endpoint
CHEM, HEM, COAG, UA VS ECG	Screening	N/A	CHEM, HEM, COAG, UA, VS, ECG
	Admission (Baseline)/ Admission	d-1	CHEM, HEM, COAG, UA/ VS, ECG
	Day 1, Pre-Dose (Baseline)	0 h	VS, ECG
	Maximum Severity Post baseline	N/A	CHEM, HEM, COAG, UA, VS, ECG
	Day 1, 1 h Post Dose	1 h	VS
	Day 1, 2 h Post Dose	2 h	VS
	Day 1, 4 h Post Dose	4 h	VS
	Day 1, 8 h Post Dose	8 h	VS
	Day 2	d2	VS
	Day 3	d3	VS
	Day 4	d4	CHEM, HEM, COAG, UA, VS, ECG
	Day 7	d7	CHEM, HEM, COAG, UA, VS
	Day 14	d14	CHEM, HEM, COAG, UA, VS
	Day 21	d21	CHEM, HEM, COAG, UA, VS, ECG
PK	Day 1, Pre-Dose	0 h	Plasma
	Day 1, Pre-Dose	-6-0 h	Urine
	Day 1, 0.5 h Post Dose	0.5 h	Plasma
	Day 1, 1 h Post Dose	1 h	Plasma
	Day 1, 1.5 h Post Dose	1.5 h	Plasma
	Day 1, 2 h Post Dose	2 h	Plasma
	Day 1, 3 h Post Dose	3 h	Plasma
	Day 1, 4 h Post Dose	4 h	Plasma
	Day 1, 6 h Post Dose	6 h	Plasma
	Day 1, 0-6 h Post Dose	0-6 h	Urine
	Day 1, 8 h Post Dose	8 h	Plasma
	Day 1, 10 h Post Dose	10 h	Plasma
	Day 1, 12 h Post Dose	12 h	Plasma
	Day 1, 6-12 h Post Dose	6-12 h	Urine
	Day 1, 14 h Post Dose	14 h	Plasma
	Day 2, 24 h Post Dose	24 h	Plasma
	Day 1, 12-24 h Post Dose	12-24 h	Urine
	Day 2, 36 h Post Dose	36 h	Plasma
	Day 2, 24-36 h Post Dose	24-36 h	Urine
	Day 3, 48 h Post Dose	48 h	Plasma

Parameter	Analysis Timepoint	Abbreviated Label	Endpoint
	Day 2, 36-48 h Post Dose	36-48 h	Urine
	Day 3, 60 h Post Dose	60 h	Plasma
	Day 4, 72 h Post Dose	72 h	Plasma
	Day 3, 60-72 h Post Dose	60-72 h	Urine
	Day 7, 144 h Post Dose	144 h	Plasma
	Day 14, 312 h Post Dose	312 h	Plasma
	Day 21, 480 h Post Dose	480 h	Plasma

10.2 Protocol Deviations

Table 8: Distribution of Protocol Deviations by Category, Deviation Type, and Dose Group

[Implementation Note: N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the All Subjects group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.]

Category	Deviation Type	Number of Subjects (Number of Deviations)							
		40 mg Fasted (N=X)	80 mg Fasted (N=X)	160 mg Fasted (N=X)	160 mg Fed (N=X)	320 mg Fasted (N=X)	640 mg Fasted (N=X)	Placebo (N=X)	All Subjects (N=X)
Eligibility/Enrollment	Any type	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Did not meet inclusion criterion	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Met exclusion criterion	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	ICF not signed prior to study procedures	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Treatment Administration Schedule	Any type	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Out of window visit	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Missed visit/visit not conducted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Missed treatment administration	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Delayed treatment administration	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Follow-Up Visit Schedule	Any type	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Out of window visit	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Missed visit/visit not conducted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Protocol Procedure/Assessment	Any type	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Incorrect version of ICF signed	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Blood not collected	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Category	Deviation Type	Number of Subjects (Number of Deviations)							
		40 mg Fasted (N=X)	80 mg Fasted (N=X)	160 mg Fasted (N=X)	160 mg Fed (N=X)	320 mg Fasted (N=X)	640 mg Fasted (N=X)	Placebo (N=X)	All Subjects (N=X)
	Urine not collected	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Other specimen not collected	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Too few aliquots obtained	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Specimen result not obtained	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Required procedure not conducted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Required procedure done incorrectly	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Study product temperature excursion	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Specimen temperature excursion	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Required specimen collected out of window	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Required procedure done out of window	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Treatment Administration	Any type	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Required procedure done incorrectly	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Study product temperature excursion	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Blinding Policy/Procedure	Any type	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Treatment unblinded	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Other	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Notes: N=The number of subjects enrolled/randomized.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the All Subjects and Placebo columns.

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 9: Subject Disposition by Dose Group

[Implementation Note: N for the Placebo column will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the All Subjects column will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.

The "Participated in Fast (Cohort 3) and Fed (Cohort 6) Cohorts" is the number of Cohort 3 subjects in each Dose Group who continued to Cohort 6. It will be "-" for the Dose Groups to which it does not apply: 40 mg Fasted, 80 mg Fasted, 160 mg Fed, 320 mg Fasted, and 640 mg Fasted]

Subject Disposition	40 mg Fasted (N=X) n (%)	80 mg Fasted (N=X) n (%)	160 mg Fasted (N=X) n (%)	160 mg Fed (N=X) n (%)	320 mg Fasted (N=X) n (%)	640 mg Fasted (N=X) n (%)	Placebo (N=X) n (%)	All Subjects (N=X) n (%)
Screened	--	--	--	--	--	--	--	xx
Enrolled/Randomized	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)
Received Study Product	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Completed all PK Blood Draws	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Completed all PK Urine Samples	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Completed Final Study Visit (Study Day 21)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Participated in Fast (Cohort 3) and Fed (Cohort 6) Cohorts	-	-	x (x)	-	-	-	x (x)	x (x)
Early Termination	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Notes: N=Number of subjects enrolled/randomized.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the All Subjects and Placebo columns.

Table 10: Analysis Population Exclusions by Dose Group

[Implementation Notes: Although subjects may meet multiple criteria for exclusion, each subject randomized to VT-1598 or Placebo in Cohorts 1,2,4, or 5 will only be counted under one reason for exclusion in this table. Cohort 3 subjects randomized to Placebo who continued on to Cohort 6 will be counted once per reason for exclusion. Priority for assigning reasons for exclusions is consistent with the order in the table. N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6.]

Analysis Populations	Reason Subjects Excluded	40 mg Fasted (N=X) n (%)	80 mg Fasted (N=X) n (%)	160 mg Fasted (N=X) n (%)	160 mg Fed (N=X) n (%)	320 mg Fasted (N=X) n (%)	640 mg Fasted (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)	x (x)	x (x)	x (x)	x (x)
PK Analysis Population	Any reason	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Subject received placebo	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Assigned dose not received or completed	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Subject has no measurable concentration in plasma or urine at any timepoint	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
PK Analysis Subset	Any reason	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Excluded from PK Analysis Population	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Protocol deviation(s) with potential to impact PK	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	PK data insufficient to estimate any PK parameters	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Notes: N=Number of subjects enrolled/randomized.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the All Subjects and Placebo columns.

Table 11: Ineligibility Summary of Screen Failures

[Implementation Note: Although subjects may meet multiple criteria for exclusion, each subject will only be counted under one reason for exclusion in this table. 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. If any of the criteria footnotes change in subsequent versions of the study protocol, the updated text should be used instead.]

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Subjects Excluded	
		n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	xx
	Willing and able to provide written informed consent and authorization for use of protected health information	x	xx
	Willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions (including confinement to the CRU) and is likely to complete the study as planned	x	xx
	Male and female subjects, 18-45 years of age (inclusive)	x	xx
	Subject is in good health to be safely enrolled in this protocol and determined by medical history and physical exam		
	BMI of 18-35 kg/m^2, inclusive, and minimum weight of 50 kg		
	If a female participant is of childbearing potential[c], she must use a highly effective contraceptive method[d] from 30 days before enrollment through the 3 months after dosing.		
	Males[e] having sexual intercourse with women of childbearing potential must agree to consistent use of condoms from study product administration through 3 months after dosing[f]		
	Subject has adequate venous access for blood collection		
Exclusion	Any exclusion criterion	x	xx
	Has a chronic condition that may increase risk to subject or interfere with endpoint assessment (e.g., liver disease, kidney disease, immunodeficiency)	x	xx
	Chronic condition diagnosed within 90 days of the Screening visit	x	xx
	Unstable chronic disease[g] within 6 months of the Screening visit	x	xx
	History of psychiatric condition that has required hospitalization in the last 5 years or patient is considered unstable by study investigator		
	Any condition that is in the opinion of the Investigator could significantly impact drug absorption, distribution, or elimination		
	Any out of normal range value[h] at screening or enrollment (Section 8.1 and Appendix B of the protocol)		

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Subjects Excluded	
		n[a]	%[b]
	Abnormal ECGs. See Section 7.1 of the protocol Clinical Evaluations for exceptions		
	Electrocardiographic QTcF interval >430 msec for males and >450 msec for females at Screening		
	Positive test for antibodies to HIV-1, HIV-2, HBsAg, or HCV		
	Positive urine drug test. The drugs that will be screened for includes amphetamines, barbiturates, cocaine, opiates, cannabinoids, phencyclidine, and benzodiazepines		
	Female subject of childbearing potential who is pregnant[i], lactating, or planning to become pregnant during the study period or 3 months after the final dose of study product		
	Received any study product in a clinical trial within 30 days prior to Screening		
	Admitted or documented illicit drug use or alcohol abuse within 6 months prior to Screening or during their participation in the trial		
	Consumed alcohol within 72 hours of Day -1, until after the visit to the CRU on Day 14 or have positive alcohol test at Screening or on admission to the CRU		
	Tobacco[j] use within 90 days prior to the Screening Visit or while a subject is enrolled in the study OR a positive drug test for cotinine		
	Use of prescription drugs within 14 days prior to the dose of study product with the exception of hormonal contraceptives, which are permitted throughout the study		
	Received any non-prescription medications, vitamins, or dietary supplements [k] within 7 days of dosing, unless prior approval is granted by both the Investigator and the Sponsor		
	History of intolerance or hypersensitivity to azole antifungals		
	Blood donation or other significant blood loss within 60 days of screening and for the duration of the study		
	Inability or difficulty swallowing whole capsules/tablets and/or multiple capsules/tablets		
	Consumption of beverages and foods containing caffeine for 24 hours prior to Day -1 until discharge from the CRU on Day 4		
	Consumption of grapefruit, or juices containing grapefruit or Seville oranges within 7 days prior to the scheduled dose of the study product until after the visit to the CRU on Day 14		
	Subject has plans to enroll or is already enrolled in another clinical trial that could interfere with safety assessment of the investigational product at any time during the study period[l]		
	Having dietary restrictions that would preclude the subject from participating in either fed or fasting cohorts		

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Subjects Excluded	
		n[a]	%[b]
	Having sensitivity or allergy to aspirin		
Eligible but Not Enrolled	Any Reason		
	[Reason 1]		
	[Reason 2]		

[a] More than one criterion may be marked per subject.
[b] Denominator for proportions is the total number of screen failures.
[c] A woman is considered of childbearing potential unless post-menopausal (subject is at least 50 years old and has history of > 2 years without menses without other known or suspected cause and has a FSH level >40 IU/L), or permanently surgically sterilized.
[d] A highly effective contraceptive method includes surgical sterilization methods such as tubal ligation, bilateral oophorectomy, salpingectomy, hysterectomy, or successful tubal obliteration (e.g., Essure®) with documented radiological confirmation test at least 90 days after the procedure, or long-acting reversible contraception (progestin-releasing subdermal implants, copper intrauterine devices (IUDs), levonorgesterel-releasing IUDs.
[e] Including vasectomized men.
[f] And must also agree to not donate sperm during this same time period.
[g] As defined by need for medical intervention that lead to a change in medications and/or required hospitalization, surgery/procedure, or ED/urgent care visit.
[h] A laboratory value that is Grade 1 (with the exception of ALT, AST, Total bilirubin, hemoglobin or serum creatinine) will be allowed if not considered to be clinically significant by the investigator.
[i] Having a positive serum pregnancy test at the Screening Visit or any other specified timepoint prior to the dose of the study product.
[j] Tobacco use includes vaping, smoking tobacco, the use of snuff and chewing tobacco, and other nicotine or nicotine- containing products.
[k] Excluded from this list is intermittent use of acetaminophen at doses of <2 g/day or ibuprofen <1200 mg/day. Herbal supplements must be discontinued 7 days prior to the dose of the study product.
[l] Includes trials that have a study intervention such as a drug, biologic, or device.

14.1.2 Demographic Data by Study Group

Table 12: Summary of Categorical Demographic and Baseline Characteristics by Dose Group

[Implementation Note: N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the All Subjects group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.]

Variable	Characteristic	40 mg Fasted (N=X)	80 mg Fasted (N=X)	160 mg Fasted (N=X)	160 mg Fed (N=X)	320 mg Fasted (N=X)	640 mg Fasted (N=X)	Placebo (N=X)	All Subjects (N=X)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex	Male	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Female	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Ethnicity	Not Hispanic or Latino	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Hispanic or Latino	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Not Reported	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Unknown	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Race	American Indian or Alaska Native	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Asian	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Native Hawaiian or Other Pacific Islander	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Black or African American	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	White	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Multi-Racial	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Unknown	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Not Reported	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)

Notes: N=Number of subjects enrolled/randomized.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the All Subjects and Placebo columns.

Table 13: Summary of Continuous Demographic and Baseline Characteristics by Dose Group

[Implementation Note: N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the All Subjects group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.]

Variable	Statistic	40 mg Fasted (N=X)	80 mg Fasted (N=X)	160 mg Fasted (N=X)	160 mg Fed (N=X)	320 mg Fasted (N=X)	640 mg Fasted (N=X)	Placebo (N=X)	All Subjects (N=X)
Age (years)	Mean	xx	xx	xx	xx	xx	xx	xx	xx
	SD	xx	xx	xx	xx	xx	xx	xx	xx
	Median	xx	xx	xx	xx	xx	xx	xx	xx
	Min	x	x	x	x	x	x	x	x
	Max	x	x	x	x	x	x	x	x
Height (cm)	Mean	xx	xx	xx	xx	xx	xx	xx	xx
	SD	xx	xx	xx	xx	xx	xx	xx	xx
	Median	xx	xx	xx	xx	xx	xx	xx	xx
	Min	x	x	x	x	x	x	x	x
	Max	x	x	x	x	x	x	x	x
Weight (kg)	Mean	xx	xx	xx	xx	xx	xx	xx	xx
	SD	xx	xx	xx	xx	xx	xx	xx	xx
	Median	xx	xx	xx	xx	xx	xx	xx	xx
	Min	x	x	x	x	x	x	x	x
	Max	x	x	x	x	x	x	x	x
BMI (kg/m^2)	Mean	xx	xx	xx	xx	xx	xx	xx	xx
	SD	xx	xx	xx	xx	xx	xx	xx	xx
	Median	xx	xx	xx	xx	xx	xx	xx	xx
	Min	x	x	x	x	x	x	x	x
	Max	x	x	x	x	x	x	x	x

Notes: N=Number of subjects enrolled/randomized.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the All Subjects and Placebo columns.

14.1.3 Prior and Concurrent Medical Conditions

Table 14: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Dose Group

[Implementation Note: N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the All Subjects group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.]

MedDRA System Organ Class	40 mg Fasted (N=X) n (%)	80 mg Fasted (N=X) n (%)	160 mg Fasted (N=X) n (%)	160 mg Fed (N=X) n (%)	320 mg Fasted (N=X) n (%)	640 mg Fasted (N=X) n (%)	Placebo (N=X) n (%)	All Subjects (N=X) n (%)
Any SOC	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
[SOC 1]	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
[SOC 2]	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)

Notes: N=Number of subjects enrolled/randomized.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the All Subjects and Placebo columns.

14.4 Summary of Concomitant Medications

Table 15: Number and Percentage of Subjects with Prior Medications by WHO Drug Classification and Dose Group

[Implementation Note: Only include prior medications, medications with an end date prior to the first dose.

N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the All Subjects group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.]

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	40 mg Fasted (N=X)	80 mg Fasted (N=X)	160 mg Fasted (N=X)	160 mg Fed (N=X)	320 mg Fasted (N=X)	640 mg Fasted (N=X)	Placebo (N=X)	All Subjects (N=X)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Level 1 Codes	Any Level 2 Codes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
[ATC Level 1 - 1]	Any [ATC 1 - 1]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 1]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 2]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 3]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
[ATC Level 1 - 2]	[ATC 2 - 1]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 2]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 3]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Notes: N=Number of subjects enrolled/randomized.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the Placebo and All Subjects columns.

Table 16: Number and Percentage of Subjects with Concurrent Medications by WHO Drug Classification and Dose Group

[Implementation Note: Only include concomitant medications, medications that are ongoing or that have an end date after the dosing.

N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the All Subjects group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.]

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	40 mg Fasted (N=X)	80 mg Fasted (N=X)	160 mg Fasted (N=X)	160 mg Fed (N=X)	320 mg Fasted (N=X)	640 mg Fasted (N=X)	Placebo (N=X)	All Subjects (N=X)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Level 1 Codes	Any Level 2 Codes	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
[ATC Level 1 - 1]	Any [ATC 1 - 1]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 1]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 2]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 3]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
[ATC Level 1 - 2]	[ATC 2 - 1]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 2]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	[ATC 2 - 3]	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Notes: N=Number of subjects enrolled/randomized.
Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each study part in the Placebo Dose Group.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 17: Overall Summary of Adverse Events by Dose Group

[Implementation Note: N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the Any Dose group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.]

	Any Dose (N=X)	40 mg Fasted (N=X)	80 mg Fasted (N=X)	160 mg Fasted (N=X)	160 mg Fed (N=X)	320 mg Fasted (N=X)	640 mg Fasted (N=X)	Placebo (N=X)
Subjects meeting at least one of the below conditions	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
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 (%)

Notes: N=Number of subjects in the Safety Population in each Dose Group.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the Any Dose and Placebo columns.
Subjects are only counted once for each category, Dose Group, and study part, regardless of the number of events.

Table 18: Adverse Events Occurring in 5% of Subjects in Any Dose Group by MedDRA System Organ Class, Preferred Term, and Dose Group - Safety Population

[Implementation Note: If there is only 1 PT for an SOC, there will be no "Any PT" row. Abnormal laboratory AEs assessed using the protocol toxicity tables will not be included in this summary.

N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the Any Dose group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.]

MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Any Dose (N=X)		40 mg Fasted (N=X)		80 mg Fasted (N=X)		160 mg Fasted (N=X)		160 mg Fed (N=X)		320 mg Fasted (N=X)		640 mg Fasted (N=X)		Placebo (N=X)	
			n (%)	Num. of Events	n (%)	Num. of Events	n (%)	Num. of Events	n (%)	Num. of Events	n (%)	Num. of Events	n (%)	Num. of Events	n (%)	Num. of Events	n (%)	Num. of Events
Serious Adverse Events																		
Any SOC	Any HLGT	Any PT	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x
SOC1	Any HLGT	Any PT	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x
SOC1	HLGT1	Any PT	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x
SOC1	HLGT1	PT1	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	
Etc.		Etc.	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x
Other (Non-serious) Adverse Events																		
Any SOC	Any HLGT	Any PT	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x
SOC1	Any HLGT	Any PT	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x
SOC1	HLGT1	Any PT	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x
SOC1	HLGT1	PT1	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x
Etc.		Etc.	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x	x (x)	x

Notes: N=Number of subjects in the Safety Population in each Dose Group.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the Any Dose and Placebo columns.
n=number of subjects reporting adverse events.

14.3.1.2 Unsolicited Adverse Events

Table 19: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Dose Number, and Dose Group

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

N for the Any Dose Group will be the number of subjects who received VT-1598 for each cohort, counting the same subjects who received VT-1598 in Cohort 3 separately from the subjects who received VT-1598 in Cohort 6. Similarly, N for the Placebo group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.

Dose Group order: Any Dose, 40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted, Placebo]

Dose Group	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	n (%)	95% CI[a]	Number of Events
Any Dose (N=X)	Any SOC	Any HLGT	Any PT	x (x)	xx, xx	x
	[SOC 1]	Any HLGT	Any PT	x (x)	xx, xx	x
		HLGT1	Any PT	x (x)	xx, xx	x
			[PT 1]	x (x)	xx, xx	x
	[SOC 2]	Any HLGT	Any PT	x (x)	xx, xx	x
		HLGT1	Any PT	x (x)	xx, xx	x
			[PT 1]	x (x)	xx, xx	x
40 mg Fasted (N=X)	…		…	x (x)	xx, xx	x
…	…		…	x (x)	xx, xx	x
Placebo (N=X)	…		…	x (x)	xx, xx	x

Notes: N=Number of subjects in the Safety Population in the specified Dose Group.
Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each dosing period in the Any Dose Group and the Placebo Dose Group.
n=number of subjects reporting adverse events within each SOC/PT.
A subject is only counted once per PT per Dose Group and dosing period.
[a] Exact Clopper-Pearson Confidence Interval.

Table 20: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Dose Group

[Implementation Note: N for the Placebo group will be the number of subjects who received Placebo for each cohort, counting the same subjects who received Placebo in Cohort 3 separately from the subjects who received Placebo in Cohort 6. Similarly, N for the Any Dose group will count the same subjects in Cohort 3 who continued on to Cohort 6 separately.

Dose Group order: Any Dose, 40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted, Placebo]

Dose Group	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Severity	Related n (%)	Not Related n (%)	Total n (%)
Any Dose (N=X)	Any SOC	Any HLGT	Any PT	Any Severity	x (%)	x (%)	x (%)
				Mild	x (%)	x (%)	x (%)
				Moderate	x (%)	x (%)	x (%)
				Severe	x (%)	x (%)	x (%)
	[SOC 1]	Any HLGT	Any PT	Any Severity	x (%)	x (%)	x (%)
				…	x (%)	x (%)	x (%)
		HLGT1	Any PT	Any Severity	x (%)	x (%)	x (%)
				…	x (%)	x (%)	x (%)
		HLGT1	[PT1]	Any Severity	x (%)	x (%)	x (%)
				…	x (%)	x (%)	x (%)
40 mg Fasted (N=X)	Any SOC		Any PT	Any Severity	x (%)	x (%)	x (%)
…	…		…	…	x (%)	x (%)	x (%)
Placebo (N=X)	…		…	…	x (%)	x (%)	x (%)

Notes: N=Number of subjects in the Safety Population in each Dose Group.
Results from subjects in Cohort 3 that continued on to Cohort 6 are summarized separately for each dosing period in the Any Dose Group and the Placebo Dose Group.
Subjects who only participated in one study part are only counted once per PT and Dose Group, in the highest reported severity.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 21: Listing of Serious Adverse Events

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. If the event is ongoing (no stop date), indicate "ongoing" for the "Duration of AE in Days". 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.

Dose Group order: 40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted, Placebo]

Adverse Event	MedDRA System Organ Class	MedDRA Higher Level Group Term	MedDRA Preferred Term	No. of Days Post Dose	Duration of AE in Days	No. of Days Post Dose 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 22: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. If the event is ongoing (no stop date), indicate "ongoing" for the "Duration of AE in Days". . Listing should be sorted by Dose Group, Subject ID, and AE Number.

Dose Group order: 40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted, Placebo]

Adverse Event	MedDRA System Organ Class	MedDRA Higher Level Group Term	MedDRA Preferred Term	No. of Days Post Dose	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 23: Listing of Abnormal Laboratory Results – Chemistry

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing 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 Appendix 3. In the Laboratory Parameter column, indicate the units in parentheses after the parameter, e.g., Sodium (mEq/L). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 133 (Mild). Results that are outside the normal range but not mild, moderate, or severe will have (ONR) as the severity included after the result. Results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline, as described in Section 9.6) will be shown as "ONR".

Sort order: Dose Group, Subject ID, Timepoint, and Parameter.

Dose Group order: 40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted, Placebo.

Parameter order: albumin, glucose, blood urea nitrogen, potassium, calcium, sodium, chloride, total protein, creatinine, triglycerides, total cholesterol, low-density lipoprotein, high-density lipoprotein, total carbon dioxide, creatine phosphokinase, phosphorus, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, magnesium, gamma-glutamyl transferase (GGT), serum cortisol]

Dose Group	Subject ID	Sex	Age (years)	Timepoint	Date of Assessment	Laboratory Parameter (Units)	Result (Severity)

Table 24: Listing of Abnormal Laboratory Results – Hematology

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing 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 Appendix 3. In the Laboratory Parameter column, indicate the units in parentheses after the parameter, e.g., Hemoglobin (g/dL). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 10.5 (Moderate). Results that are outside the normal range but not mild, moderate, or severe will have (ONR) as the severity included after the result. Results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline, as described in Section 9.6) will be shown as "ONR".

Sort order: Dose Group, Subject ID, Timepoint, and Parameter

Dose Group order: 40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted, Placebo.

Parameter order: hemoglobin, hematocrit, lymphocytes, neutrophils, monocytes, eosinophils, basophils, platelet, red blood cell count, and white blood cell count.]

Dose Group	Subject ID	Sex	Age (years)	Timepoint	Date of Assessment	Laboratory Parameter (Units)	Result (Severity)

Table 25: 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 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 Appendix 3. In the Laboratory Parameter column, indicate the units in parentheses after the parameter, e.g., Prothrombin Time (s). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 10.5 (Moderate). Results that are outside the normal range but not mild, moderate, or severe will have (ONR) as the severity included after the result. Results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline, as described in Section 9.6) will be shown as "ONR".

Sort order: Dose Group, Subject ID, Timepoint, and Parameter.

Dose Group order: 40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted, Placebo.

Parameter order: aPTT, PT, INR.]

Dose Group	Subject ID	Sex	Age (years)	Timepoint	Date of Assessment	Laboratory Parameter (Units)	Result (Severity)

Table 26: Listing of Abnormal Laboratory Results - Urinalysis

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing 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 in parentheses after the parameter, e.g., Red Blood Cells (/HPF). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 10.5 (Moderate). Results that are outside the normal range but not mild, moderate, or severe will have (ONR) as the severity included after the result. Results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline, as described in Section 9.6) will be shown as "ONR". Method should describe the type of urinalysis done, dipstick or microscopic test.

Sort order: Dose Group, Subject ID, Timepoint, Parameter, and Method.

Dose Group order: 40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted, Placebo.

Parameter order: specific gravity, pH, occult blood, leukocyte esterase, RBC, WBC]

Dose Group	Subject ID	Sex	Age (years)	Timepoint	Date of Assessment	Laboratory Parameter (Units)	Result (Severity)

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 27: Chemistry Abnormal Results by Parameter, Dose Group, and Timepoint

[Implementation Note: Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dosing period in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dosing period in the Placebo Dose Group.

Parameter order: albumin, glucose, blood urea nitrogen, potassium, calcium, sodium, chloride, total protein, creatinine, triglycerides, total cholesterol, low-density lipoprotein, high-density lipoprotein, total carbon dioxide, creatine phosphokinase, phosphorus, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, magnesium, gamma-glutamyl transferase (GGT), serum cortisol]

Dose Group	Timepoint	N	Abnormal, Low		Abnormal, High	
			n	%	n	%
Chemistry - Any Parameter						
Any Dose	Baseline	x	x (x)	x (x)	x (x)	x (x)
	Day 4	x	x (x)	x (x)	x (x)	x (x)
	Day 7	x	x (x)	x (x)	x (x)	x (x)
	Day 14	x	x (x)	x (x)	x (x)	x (x)
	Day 21	x	x (x)	x (x)	x (x)	x (x)
40 mg Fasted	Baseline	x	x (x)	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)	x (x)
80 mg Fasted	Baseline	x	x (x)	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)	x (x)
160 mg Fasted	Baseline	x	x (x)	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)	x (x)
160 mg Fed	Baseline	x	x (x)	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)	x (x)
320 mg Fasted	Baseline	x	x (x)	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)	x (x)
640 mg Fasted	Baseline	x	x (x)	x (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)	x (x)	x (x)
Albumin						
Any Dose	Baseline	x	x (x)	x (x)	x (x)	x (x)
…	…	x	x (x)	x (x)	x (x)	x (x)

Note: N=Number of subjects in the Safety Population with the laboratory result assessed at the respective timepoint.
Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each dosing period in both the Any Dose Group and the Placebo Dose Group.

Table 28: Chemistry Laboratory Toxicity Grade by Parameter, Dose Group, Timepoint, and Severity

[Implementation Note: If there is not at least one Mild, Moderate, or Severe event for a Dose Group within a parameter, then only the Maximum Severity Post Baseline row will be shown for that parameter. Only include chemistry parameters with grading criteria in the protocol. Toxicities representing an increase in the laboratory result will be summarized separately from decreases. For example, there will be one row for "Sodium, Decrease" and another for "Sodium, Increase". Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dosing period in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dosing period in the Placebo Dose Group.

Parameter order: albumin, glucose, blood urea nitrogen, potassium, calcium, sodium, chloride, total protein, creatinine, triglycerides, total cholesterol, low-density lipoprotein, high-density lipoprotein, total carbon dioxide, creatine phosphokinase, phosphorus, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, magnesium, gamma-glutamyl transferase (GGT), serum cortisol. Decrease parameters will always be listed before increase parameters, if applicable]

Dose Group	Timepoint	N	Mild	Moderate	Severe
			n (%)	n (%)	n (%)
Chemistry - Any Parameter					
Any Dose	Baseline	x	x (x)	x (x)	x (x)
	Maximum Severity Post Baseline	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)
	Day 21	x	x (x)	x (x)	x (x)
40 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
80 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
160 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
160 mg Fed	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
320 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
640 mg Fasted	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)
Albumin, Decrease					
Any Dose	Baseline	x	x (x)	x (x)	x (x)
…	…	x	x (x)	x (x)	x (x)

Notes: The "Maximum Severity Post Baseline" rows indicate the maximum severity experienced by each subject at any timepoint post baseline, including unscheduled assessments.

N=Number of subjects in the Safety Population with the laboratory result assessed at the respective timepoint. Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each study part in both the Any Dose Group and the Placebo Dose Group.

Table 29: Chemistry Summary Statistics Change from Baseline by Parameter, Dose Group, and Timepoint

[Implementation Note: Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dosing period in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dosing period in the Placebo Dose Group.

Mean, SD, and median will be reported to one decimal place greater than the original data. Min and max values will be reported with the same number of decimal places as the original data.

Parameter order: albumin, glucose, blood urea nitrogen, potassium, calcium, sodium, chloride, total protein, creatinine, triglycerides, total cholesterol, low-density lipoprotein, high-density lipoprotein, total carbon dioxide, creatine phosphokinase, phosphorus, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, magnesium, gamma-glutamyl transferase (GGT), serum cortisol]

Dose Group	Timepoint	N	Change from Baseline			
			Mean	SD	Median	Min, Max
Albumin (g/dL)						
Any Dose	Day 4	x	x	x	x	x, x
	Day 7	x	x	x	x	x, x
	Day 14	x	x	x	x	x, x
	Day 21	x	x	x	x	x, x
40 mg Fasted	Day 4	x	x	x	x	x, x
	…	x	x	x	x	x, x
80 mg Fasted	Day 4	x	x	x	x	x, x
	…	x	x	x	x	x, x
160 mg Fasted	Day 4	x	x	x	x	x, x
	…	x	x	x	x	x, x
160 mg Fed	Day 4	x	x	x	x	x, x
	…	x	x	x	x	x, x
320 mg Fasted	Day 4	x	x	x	x	x, x
	…	x	x	x	x	x, x
640 mg Fasted	Day 4	x	x	x	x	x, x
	…	x	x	x	x	x, x
Placebo	Day 4	x	x	x	x	x, x
	…	x	x	x	x	x, x
Glucose (mg/dL)						
Any Dose	Day 4	x	x	x	x	x, x
…	…	x	x (x)	x (x)	x (x)	x (x)
…						

Notes: N=Number of subjects in the Safety Population with the laboratory result assessed at the respective timepoint. Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each study part in both the Any Dose Group and the Placebo Dose Group.

14.3.5.2 Hematology Results

Table 30: Hematology Abnormal Results by Parameter, Dose Group, and Timepoint

[Parameter order: hemoglobin, hematocrit, lymphocytes, neutrophils, monocytes, eosinophils, basophils, platelet, red blood cell count, white blood cell count]

This table will repeat Table 27 for Hematology Parameters

Table 31: Hematology Laboratory Toxicity Grade by Parameter, Dose Group, Timepoint, and Severity

[Parameter order: hemoglobin, hematocrit, lymphocytes, neutrophils, monocytes, eosinophils, basophils, platelet, red blood cell count, white blood cell count.]

This table will repeat Table 28 for Hematology Parameters

Table 32: Hematology Summary Statistics Change from Baseline by Parameter, Dose Group, and Timepoint

[Parameter order: hemoglobin, hematocrit, lymphocytes, neutrophils, monocytes, eosinophils, basophils, platelet, red blood cell count, white blood cell count.]

This table will repeat Table 29 for Hematology Parameters

14.3.5.3 Coagulation Results

Table 33: Coagulation Abnormal Results by Parameter, Dose Group, and Timepoint

[Parameter order: activated partial thromboplastin time, prothrombin time, international normalized ratio.]

This table will repeat Table 27 for Coagulation Parameters

Table 34: Coagulation Laboratory Toxicity Grade by Parameter, Dose Group, Timepoint, and Severity

[Parameter order: activated partial thromboplastin time, prothrombin time, international normalized ratio.]

This table will repeat Table 28 for Coagulation Parameters

Table 35: Coagulation Summary Statistics Change from Baseline by Parameter, Dose Group, and Timepoint

[Parameter order: activated partial thromboplastin time, prothrombin time, international normalized ratio.]

This table will repeat Table 29 for Coagulation Parameters

14.3.5.4 Urinalysis Results

Table 36: Urinalysis Abnormal Results by Parameter, Dose Group, and Timepoint

[Parameter order: specific gravity, pH, occult blood, leukocyte esterase, urine RBC, and urine WBC]

This table will repeat Table 27 for Urinalysis Parameters

Table 37: Urinalysis Laboratory Toxicity Grade by Parameter, Dose Group, Timepoint, and Severity

[Parameter order: specific gravity, pH, leukocyte esterase, urine RBC, and urine WBC]

This table will repeat Table 28 for Urinalysis Parameters

Table 38: Urinalysis Summary Statistics Change from Baseline by Parameter, Dose Group, and Timepoint

[Parameter order: specific gravity and pH.]

This table will repeat Table 29 for Urinalysis Parameters (specific gravity and pH only)

14.3.6 Displays of Vital Signs

Table 39: Vital Sign Toxicity Grade by Parameter, Dose Group, Timepoint, and Severity

[Implementation Note: If there is not at least one Mild, Moderate, or Severe event for a Dose Group within a parameter, then only the Maximum Severity Post Baseline row will be shown for that parameter. Summarize increase results separately from decrease results. For example, there will be one row for "Pulse, Decrease" and another for "Pulse, Increase". Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dosing period in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dosing period in the Placebo Dose Group.

Parameter order: systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, temperature]

Dose Group	Timepoint	N	Mild	Moderate	Severe
			n (%)	n (%)	n (%)
Any Parameter					
Any Dose	Baseline	x	x (x)	x (x)	x (x)
	Maximum Severity Post Baseline	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 1, 4 h Post Dose	x	x (x)	x (x)	x (x)
	Day 1, 8 h Post Dose	x	x (x)	x (x)	x (x)
	Day 2	x	x (x)	x (x)	x (x)
	Day 3	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)
	Day 21	x	x (x)	x (x)	x (x)
40 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
80 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
160 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
160 mg Fed	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
320 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
640 mg Fasted	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)
Pulse, Decrease (bpm)					
Any Dose	Baseline	x	x (x)	x (x)	x (x)
…	…	x	x (x)	x (x)	x (x)
…					

Notes: The "Maximum Severity Post Baseline" rows indicate the maximum severity experienced by each subject at any timepoint post baseline, including unscheduled assessments.
N=Number of subjects in the Safety Population with the vital sign assessed at the respective timepoint.
Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each study part in both the Any Dose Group and the Placebo Dose Group.

Table 40: Vital Sign Change from Baseline by Parameter, Dose Group, and Timepoint

[Implementation Note: Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dosing period in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dosing period in the Placebo Dose Group.

Mean, SD, and median will be reported to one decimal place greater than the original data. Min and max values will be reported with the same number of decimal places as the original data.

Parameter order: systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, temperature]

Dose Group	Timepoint	N	Change from Baseline			
			Mean	SD	Median	Min, Max
Systolic Blood Pressure						
Any Dose	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 1, 4 h Post Dose	x	x	x	x	x, x
	Day 1, 8 h Post Dose	x	x	x	x	x, x
	Day 2	x	x	x	x	x, x
	Day 3	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
	Day 21	x	x	x	x	x, x
40 mg Fasted	Day 1, 1 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
80 mg Fasted	Day 1, 1 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
160 mg Fasted	Day 1, 1 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
160 mg Fed	Day 1, 1 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
320 mg Fasted	Day 1, 1 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
640 mg Fasted	Day 1, 1 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
Placebo	Day 1, 1 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
Pulse, Increase (bpm)						
Any Dose	Day 1, 1 h Post Dose	x	x	x	x	x, x
…	…	x	x	x	x	x, x
…						

Notes: N=Number of subjects in the Safety Population with the vital sign assessed at the respective timepoint. Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each study part in both the Any Dose Group and the Placebo Dose Group.

14.3.7 Displays of ECG Measurements

Table 41: Summary of Post Dose ECG Change in Overall Interpretations from Baseline by Dose Group and Timepoint

[Implementation Note: Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dose received in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dose received in the Placebo Dose Group.]

Change from Baseline in ECG Interpretation	Any Dose n (%)	40 mg Fasted n (%)	80 mg Fasted n (%)	160 mg Fasted n (%)	160 mg Fed n (%)	320 mg Fasted n (%)	640 mg Fasted n (%)	Placebo n (%)
Day 1, 4 h Post Dose								
N	x	x	x	x	x	x	x	x
Normal at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, NCS	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Normal to Abnormal, CS	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Day 4								
N	x	x	x	x	x	x	x	x
Normal at Both Times	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
…								
Day 21								
N	x	x	x	x	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 the Safety Population with ECG measurements at the timepoints indicated.
Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each study part in both the Any Dose Group and the Placebo Dose Group.
NCS = Not clinically significant, CS = Clinically significant.

Table 42: ECG Toxicity Grade by Parameter, Severity, Dose Group, and Timepoint

[Implementation Note: If there is not at least one Mild, Moderate, or Severe event for a Dose Group within a parameter, then only the Maximum Severity Post Baseline row will be shown for that parameter. Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dosing period in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dosing period in the Placebo Dose Group.]

Dose Group	Timepoint	N	Mild	Moderate	Severe
			n (%)	n (%)	n (%)
QTcF Interval (msec)					
Any Dose	Baseline	x	x (x)	x (x)	x (x)
	Maximum Severity Post Baseline	x	x (x)	x (x)	x (x)
	Day 1, 4h Post Dose	x	x (x)	x (x)	x (x)
	Day 4	x	x (x)	x (x)	x (x)
	Day 21	x	x (x)	x (x)	x (x)
40 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
80 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
160 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
160 mg Fed	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
320 mg Fasted	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
640 mg Fasted	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)

Notes: The "Maximum Severity Post Baseline" row indicates the maximum severity of ECG results experienced across all subjects at any timepoint post baseline, including unscheduled assessments.
N=Number of subjects in the Safety Population with ECG results assessed at the respective timepoint.
Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each study part in both the Any Dose Group and the Placebo Dose Group.

Table 43: ECG Change from Baseline by Parameter, Severity, Dose Group, and Timepoint

[Implementation Note: Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dosing period in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dosing period in the Placebo Dose Group.

Parameter order: PR Interval, QRS Duration, QT Interval, QTcF Interval, RR Interval, Mean Ventricular Heart Rate.]

Dose Group	Timepoint	N	Change from Baseline			
			Mean	SD	Median	Min, Max
PR Interval (msec)						
Any Dose	Day 1, 4 h Post Dose	x	x	x	x	x, x
	Day 4	x	x	x	x	x, x
	Day 21	x	x	x	x	x, x
40 mg Fasted	Day 1, 4 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
80 mg Fasted	Day 1, 4 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
160 mg Fasted	Day 1, 4 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
160 mg Fed	Day 1, 4 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
320 mg Fasted	Day 1, 4 h Post Dose	x	x	x	x	x, x
	…	x	x	x	x	x, x
640 mg Fasted	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)						
Any Dose	Day 1, 4 h Post Dose	x	x	x	x	x, x
…	…	x	x	x	x	x, x
…						

Notes: N=Number of subjects in the Safety Population with ECG measurements at the respective timepoint.
Results from subjects in Cohort 3 that continued on to Cohort 6 are counted separately for each study part in both the Any Dose Group and the Placebo Dose Group.

Table 44: Categorical Summary of QTcF by Dose Group and Timepoint

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

QTcF Category	Timepoint	N	Any Dose	40 mg Fasted	80 mg Fasted	160 mg Fasted	160 mg Fed	320 mg Fasted	640 mg Fasted	Placebo
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
QTcF >450 ms, Male	Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
		x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
		x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Day 7	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
		x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
		x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Day 21	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
		x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
		x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
QTcF >470 ms, Female	Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	…	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
QTcF >480 ms	Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	…	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
QTcF >500 ms	Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	…	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
30 ms ≤ QTcF increases from baseline < 60 ms	Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	…	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
QTcF increases from baseline ≥ 60 ms	Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	…	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)

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

Table 45: VT-1598 Concentrations in Plasma by Dose Group – 0 h to 14 h Post Dose

	Nominal Time[a] (h)										
Dose Group	**0**	**0.5**	**1.5**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**
40 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
80 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
160 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
160 mg Fed	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
320 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
640 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Notes: Concentrations are reported in units of ng/mL.
Values of GM (CV %) are shown.
[a] Times are relative to time of dosing.

Table 46: VT-1598 Concentrations in Plasma by Dose Group – 24 h to 480 h Post Dose

	Nominal Time[a] (h)							
Dose Group	**24**	**36**	**48**	**60**	**72**	**144**	**312**	**480**
40 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
80 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
160 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
160 mg Fed	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
320 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
640 mg Fasted	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Notes: Concentrations are reported in units of ng/mL.
Values of GM (CV %) are shown.
[a] Times are relative to time of dosing.

Table 47: VT-1598 Concentrations in Plasma, SAD 40 mg Fasted Dose Group – 0 h to 14 h Post Dose

[Implementation Note: Mark concentrations collected out of window with an asterisk (*) next to the concentration and include a footnote before the

Samples collected out of window are noted by an asterisk (*).

Mark concentrations collected substantially out of window with two asterisks (**) next to the concentration and include a footnote:

Samples collected substantially out of window are noted by two asterisks (**).

Mark imputed concentration times with three asterisks (***) next to the concentration and include a footnote:

Samples with imputed collection times are noted by three asterisks (***).]

	Nominal Time[a] (h)										
Subject ID	**0**	**0.5**	**1.5**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**
PHU.00123	x	x	x	x	x	x	x	x	x	x	x
PHU.00124	x	x	x	x	x	x	x	x	x	x	x
PHU.00125	x	x	x	x	x	x	x	x	x	x	x
…											
Statistics	x	x	x	x	x	x	x	x	x	x	x
N[b]	x	x	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x	x	x
SD	x	x	x	x	x	x	x	x	x	x	x
GM	x	x	x	x	x	x	x	x	x	x	x
CV %	x	x	x	x	x	x	x	x	x	x	x
Min	x	x	x	x	x	x	x	x	x	x	x
Max	x	x	x	x	x	x	x	x	x	x	x

Notes: Concentrations are reported in units of ng/ml.
[Out of window footnotes here, if applicable]
[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 the sample was taken before the first measurable PK sample with a concentration above the LLOQ. BQL values were treated as missing otherwise.

Table 48: VT-1598 Concentrations in Plasma, SAD 40 mg Fasted Dose Group – 24 h to 480 h Post Dose

	Nominal Time[a] (h)							
Subject ID	**24**	**36**	**48**	**60**	**72**	**144**	**312**	**480**
PHU.00123	x	x	x	x	x	x	x	x
PHU.00124	x	x	x	x	x	x	x	x
PHU.00125	x	x	x	x	x	x	x	x
…								
Statistics	x	x	x	x	x	x	x	x
N[b]	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
GM	x	x	x	x	x	x	x	x
CV %	x	x	x	x	x	x	x	x
Min	x	x	x	x	x	x	x	x
Max	x	x	x	x	x	x	x	x

Note: Concentrations are reported in units of ng/mL.
[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 the sample was taken before the first measurable PK sample with a concentration above the LLOQ. BQL values were treated as missing otherwise.

Table 49: VT-1598 Concentrations in Plasma, 80 mg Fasted Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for the 80 mg Fasted Dose Group

Table 50: VT-1598 Concentrations in Plasma, 80 mg Fasted Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for the 80 mg Fasted Dose Group

Table 51: VT-1598 Concentrations in Plasma, 160 mg Fasted Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for the 160 mg Fasted Dose Group

Table 52: VT-1598 Concentrations in Plasma, 160 mg Fasted Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for the 160 mg Fasted Dose Group

Table 53: VT-1598 Concentrations in Plasma, 160 mg Fed Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for the 160 mg Fed Dose Group

Table 54: VT-1598 Concentrations in Plasma, 160 mg Fed Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for the 160 mg Fed Dose Group

Table 55: VT-1598 Concentrations in Plasma, 320 mg Fasted Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for the 320 mg Fasted Dose Group

Table 56: VT-1598 Concentrations in Plasma, 320 mg Fasted Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for the 320 mg Fasted Dose Group

Table 57: VT-1598 Concentrations in Plasma, 640 mg Fasted Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for the 640 mg Fasted Dose Group

Table 58: VT-1598 Concentrations in Plasma, 640 mg Fasted Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for the 640 mg Fasted Dose Group

Table 59: VT-11134 Concentrations in Plasma by Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 45 for VT-11134 concentrations in plasma, by Dose Group

Table 60: VT-11134 Concentrations in Plasma by Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 46 for VT-11134 concentrations in plasma, by Dose Group

Table 61: VT-11134 Concentrations in Plasma, 40 mg Fasted Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for VT-11134 concentrations in plasma for the 40 mg Fasted Dose Group

Table 62: VT-11134 Concentrations in Plasma, 40 mg Fasted Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for VT-11134 concentrations in plasma for the 40 mg Fasted Dose Group

Table 63: VT-11134 Concentrations in Plasma, 80 mg Fasted Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for VT-11134 concentrations in plasma for the 80 mg Fasted Dose Group

Table 64: VT-11134 Concentrations in Plasma, 80 mg Fasted Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for VT-11134 concentrations in plasma for the 80 mg Fasted Dose Group

Table 65: VT-11134 Concentrations in Plasma, 160 mg Fasted Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for VT-11134 concentrations in plasma for the 160 mg Fasted Dose Group

Table 66: VT-11134 Concentrations in Plasma, 160 mg Fasted Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for VT-11134 concentrations in plasma for the 160 mg Fasted Dose Group

Table 67: VT-11134 Concentrations in Plasma, 160 mg Fed Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for VT-11134 concentrations in plasma for the 160 mg Fed Dose Group

Table 68: VT-11134 Concentrations in Plasma, 160 mg Fed Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for VT-11134 concentrations in plasma for the 160 mg Fed Dose Group

Table 69: VT-11134 Concentrations in Plasma, 320 mg Fasted Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for VT-11134 concentrations in plasma for the 320 mg Fasted Dose Group

Table 70: VT-11134 Concentrations in Plasma, 320 mg Fasted Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for VT-11134 concentrations in plasma for the 320 mg Fasted Dose Group

Table 71: VT-11134 Concentrations in Plasma, 640 mg Fasted Dose Group – 0 h to 14 h Post Dose

This table will repeat Table 47 for VT-11134 concentrations in plasma for the 640 mg Fasted Dose Group

Table 72: VT-11134 Concentrations in Plasma, 640 mg Fasted Dose Group – 24 h to 480 h Post Dose

This table will repeat Table 48 for VT-11134 concentrations in plasma for the 640 mg Fasted Dose Group

Table 73: Summary Statistics for VT-1598 PK Parameters in Plasma by Dose Group

PK Parameter (Units)	40 mg Fasted	80 mg Fasted	160 mg Fasted	160 mg Fed	320 mg Fasted	640 mg Fasted
C_{max}, (ng/mL)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
C_{max}/Dose, ((ng/mL)/mg)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
T_{max}, (h)	x (x - x)	x (x - x)	x (x - x)	x (x - x)	x (x - x)	x (x - x)
$AUC_{(0\text{-}last)}$, (ng*h/mL)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0\text{-}last)}$, Dose ((ng*h/mL)/mg)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0\text{-}inf)}$,(ng*h/mL)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0\text{-}inf)}$/Dose, ((ng*h/mL)/mg)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
λz, (1/h)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
$t_{1/2}$, (h)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
CL/F, (L/h)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
V_d/F, (L)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Note: Values of GM (CV %) are shown, except for T_{max} for which values of median (min-max) are shown.

Table 74: Summary Statistics for VT-1598 PK Parameters in Plasma, 40 mg Fasted Dose Group

Statistics	C_{max} (ng/mL)	C_{max}/Dose ((ng/mL)/mg)	T_{max} (h)	$AUC_{0\text{-}last}$ (ng*h/mL)	$AUC_{0\text{-}last}$/Dose ((ng*h/mL)/)/mg)	$AUC_{0\text{-}inf}$ (ng*h/mL)	$AUC_{0\text{-}inf}$/Dose ((ng*h/mL)/mg)	Λz (1/h)	CL/F (L/h)	V_d/F (L)
N	x	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x	x
SD	x	x	x	x	x	x	x	x	x	x
Min	x	x	x	x	x	x	x	x	x	x
Max	x	x	x	x	x	x	x	x	x	x
CV %	x	x	x	x	x	x	x	x	x	x
GM	x	x	x	x	x	x	x	x	x	x

Table 75: Summary Statistics for VT-1598 PK Parameters in Plasma, 80 mg Fasted Dose Group

This table will repeat Table 74 for VT-1598 PK parameters in Plasma for the 80 mg Fasted Dose Group

Table 76: Summary Statistics for VT-1598 PK Parameters in Plasma, 160 mg Fasted Dose Group

This table will repeat Table 74 for VT-1598 PK parameters in Plasma for the 160 mg Fasted Dose Group

Table 77: Summary Statistics for VT-1598 PK Parameters in Plasma, 160 mg Fed Dose Group

This table will repeat Table 74 for VT-1598 PK parameters in Plasma for the 160 mg Fed Dose Group

Table 78: Summary Statistics for VT-1598 PK Parameters in Plasma, 320 mg Fasted Dose Group

This table will repeat Table 74 for VT-1598 PK parameters in Plasma for the 320 mg Fasted Dose Group

Table 79: Summary Statistics for VT-1598 PK Parameters in Plasma, 640 mg Fasted Dose Group

This table will repeat Table 74 for VT-1598 PK parameters in Plasma for the 640 mg Fasted Dose Group

Table 80: Summary Statistics for VT-11134 PK Parameters in Plasma by Dose Group

This table will repeat Table 73 for VT-11134 PK parameters in plasma, by Dose Group

Table 81: Summary Statistics for VT-11134 PK Parameters in Plasma, 40 mg Fasted Dose Group

This table will repeat Table 74 for VT-11134 PK parameters in plasma for the 40 mg Fasted Dose Group

Table 82: Summary Statistics for VT-11134 PK Parameters in Plasma, 80 mg Fasted Dose Group

This table will repeat Table 74 for VT-11134 PK parameters in Plasma for the 80 mg Fasted Dose Group

Table 83: Summary Statistics for VT-11134 PK Parameters in Plasma, 160 mg Fasted Dose Group

This table will repeat Table 74 for VT-11134 PK parameters in Plasma for the 160 mg Fasted Dose Group

Table 84: Summary Statistics for VT-11134 PK Parameters in Plasma, 160 mg Fed Dose Group

This table will repeat Table 74 for VT-11134 PK parameters in Plasma for the 160 mg Fed Dose Group

Table 85: Summary Statistics for VT-11134 PK Parameters in Plasma, 320 mg Fasted Dose Group

This table will repeat Table 74 for VT-11134 PK parameters in Plasma for the 320 mg Fasted Dose Group

Table 86: Summary Statistics for VT-11134 PK Parameters in Plasma, 640 mg Fasted Dose Group

This table will repeat Table 74 for VT-11134 PK parameters in Plasma for the 640 mg Fasted Dose Group

Table 87: Summary Statistics for VT-1598 PK Parameters in Urine by Dose Group

	40 mg Fasted	80 mg Fasted	160 mg Fasted	160 mg Fed	320 mg Fasted	640 mg Fasted
Inpatient Period (0-72 h)[a]						
Ae_{last} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
$Ae_{\%Dose}$ (%)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
CL_R (mL/min)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Nominal Collection Time Interval[a]						
Ae_{0-6} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{6-12} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{12-24} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{24-36} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{36-48} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{48-60} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{60-72} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)

Note: Values of Mean (Min, Max) are shown, except for CL_R, for which values of GM (CV %) are shown.
[a] Times are relative to time of dosing.

Table 88: Summary Statistics for VT-1598 PK Parameters in Urine, 40 mg Fasted Dose Group

Statistics	Inpatient Period (0-72 h)[a]			Nominal Collection Time Interval[a]						
	Ae_{last} (mg)	$Ae_{\%Dose}$ (%)	CL_R (mL/min)	Ae_{0-6} (mg)	Ae_{6-12} (mg)	Ae_{12-24} (mg)	Ae_{24-36} (mg)	Ae_{36-48} (mg)	Ae_{48-60} (mg)	Ae_{60-72} (mg)
N	x	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x	x
SD	x	x	x	x	x	x	x	x	x	x
Min	x	x	x	x	x	x	x	x	x	x
Max	x	x	x	x	x	x	x	x	x	x
CV %	x	x	x	x	x	x	x	x	x	x
GM	x	x	x	x	x	x	x	x	x	x

[a] Times are relative to time of dosing.

Table 89: Summary Statistics for VT-1598 PK Parameters in Urine, 80 mg Fasted Dose Group

This table will repeat Table 88 for VT-1598 PK parameters in Urine for the 80 mg Fasted Dose Group

Table 90: Summary Statistics for VT-1598 PK Parameters in Urine, 160 mg Fasted Dose Group

This table will repeat Table 88 for VT-1598 PK parameters in Urine for the 160 mg Fasted Dose Group

Table 91: Summary Statistics for VT-1598 PK Parameters in Urine, 160 mg Fed Dose Group

This table will repeat Table 88 for VT-1598 PK parameters in Urine for the 160 mg Fed Dose Group

Table 92: Summary Statistics for VT-1598 PK Parameters in Urine, 320 mg Fasted Dose Group

This table will repeat Table 88 for VT-1598 PK parameters in Urine for the 320 mg Fasted Dose Group

Table 93: Summary Statistics for VT-1598 PK Parameters in Urine, 640 mg Fasted Dose Group

This table will repeat Table 88 for VT-1598 PK parameters in Urine for the 640 mg Fasted Dose Group

Table 94: Summary Statistics for VT-11134 PK Parameters in Urine by Dose Group

	40 mg Fasted	80 mg Fasted	160 mg Fasted	160 mg Fed	320 mg Fasted	640 mg Fasted
Inpatient Period (0-72 h)[a]						
Ae_{last} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
CL_R (mL/min)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Nominal Collection Time Interval[a]						
Ae_{0-6} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{6-12} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{12-24} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{24-36} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{36-48} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{48-60} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae_{60-72} (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)

Note: Values of Mean (Min, Max) are shown, except for CL_R for which values of GM (CV %) are shown.
[a] Times are relative to time of dosing.

Table 95: Summary Statistics for VT-11134 PK Parameters in Urine, 40 mg Fasted Dose Group

	Inpatient Period (0-72 h) [a]		Nominal Collection Time Interval[a]						
Statistics	**Ae_{last} (mg)**	**CL_R (mL/min)**	**Ae_{0-6} (mg)**	**Ae_{6-12} (mg)**	**Ae_{12-24} (mg)**	**Ae_{24-36} (mg)**	**Ae_{36-48} (mg)**	**Ae_{48-60} (mg)**	**Ae_{60-72} (mg)**
N	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x
SD	x	x	x	x	x	x	x	x	x
Min	x	x	x	x	x	x	x	x	x
Max	x	x	x	x	x	x	x	x	x
CV %	x	x	x	x	x	x	x	x	x
GM	x	x	x	x	x	x	x	x	X

[a] Times are relative to time of dosing.

Table 96: Summary Statistics for VT-11134 PK Parameters in Urine, 80 mg Fasted Dose Group

This table will repeat Table 95 for VT-11134 PK parameters in Urine for the 80 mg Fasted Dose Group

Table 97: Summary Statistics for VT-11134 PK Parameters in Urine, 160 mg Fasted Dose Group

This table will repeat Table 95 for VT-11134 PK parameters in Urine for the 160 mg Fasted Dose Group

Table 98: Summary Statistics for VT-11134 PK Parameters in Urine, 160 mg Fed Dose Group

This table will repeat Table 95 for VT-11134 PK parameters in Urine for the 160 mg Fed Dose Group

Table 99: Summary Statistics for VT-11134 PK Parameters in Urine, 320 mg Fasted Dose Group

This table will repeat Table 95 for VT-11134 PK parameters in Urine for the 320 mg Fasted Dose Group

Table 100: Summary Statistics for VT-11134 PK Parameters in Urine, 640 mg Fasted Dose Group

This table will repeat Table 95 for VT-11134 PK parameters in Urine for the 640 mg Fasted Dose Group

Table 101: Assessment of Dose Proportionality Among Fasted Dose Groups

Statistic	VT-1598			VT-11134		
	C_{max}	$AUC_{0\text{-}last}$	$AUC_{0\text{-}inf}$	C_{max}	$AUC_{0\text{-}last}$	$AUC_{0\text{-}inf}$
	(ng/mL)	(ng*h/mL)	(ng*h/mL)	(ng/mL)	(ng*h/mL)	(ng*h/mL)
Lowest Dose Included (mg)	x	x	x	x	x	x
Highest Dose Included (mg)	x	x	x	x	x	x
ρ	x	x	x	x	x	x
β-hat	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Standard Error (β-hat)	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
$\rho^{\beta\text{-hat-}1}$ 90% CI	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
Conclude parameter shows dose proportionality?	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No

Note: β-hat is an estimate obtained using the linear model log(Param) = α + dose × β, where Param is $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, or C_{max}. Perfect dose proportionality is equivalent to β = 1. The value ρ is equivalent to the ratio of the highest dose included in the analysis divided by the lowest dose included in the analysis. Presence of dose proportionality is concluded when the 90% confidence interval for $\rho^{\beta\text{-hat-}1}$ is contained within the interval (0.80,1.25).

Table 102: Comparison of T_{max} between Fasted and Fed 160 mg Dose Groups

[Implementation Note: Since fewer than 3 subjects in the PK Analysis Population were in both Cohort 3 and Cohort 6 then the Wilcoxon signed-rank test comparing T_{max} (Paired) between the cohorts will not be conducted. The N, Estimate, and 90% CI cells should be "-" and a footnote should be added to explain why they are missing.]

Parameter	Estimand	Subjects Included	VT-1598			VT-11134		
			N[a]	Estimate	90% CI[b]	N[a]	Estimate	90% CI[b]
T_{max} (Paired)	Median of (160 mg Fed T_{max}) - (160 mg Fasted T_{max})	Subjects who received 160 mg of VT-1598 in both Cohort 3 (Fast) and Cohort 6 (Fed).	x	x	(x, x)	x	x	(x, x)
T_{max} (Independent)	(160 mg Fed T_{max} Median) - (160 mg Fasted T_{max} Median)	Any subject who received 160 mg of VT-1598 in either Cohort 3 (Fast) or Cohort 6 (Fed)	x	x	(x, x)	x	x	(x, x)

[a] N=Number of subjects with data used to compute T_{max}. In the paired comparison, data was used from any subject in the PK Analysis Subset who received 160 mf VT-1598 under both a fasted and fed state. In the independent comparison, data was used from any subject in the PK Analysis Subset who received 160 mg VT-1598 under either a fasted or fed state, regardless of whether or not the subject participated in both study parts.

[b] The 90% CI for subjects who receive VT-1598 and participated in both cohorts was calculated using Wilcoxon signed-rank test. The 90% CI for all subjects who received VT-1598 in either cohort was calculated using a Wilcoxon rank sum test.

Table 103: Comparison of Plasma PK Exposure Parameters between Fasted and Fed 160 mg Dose Groups – VT-1598

Exposure Parameter Comparison	VT-1598			VT-11134		
	N[a]	Estimate	90% CI[b]	N[a]	Estimate	90% CI[b]
C_{max} Ratio (Fed/Fast)	x	x	(x, x)	x	x	(x, x)
$AUC_{(0\text{-}last)}$ Ratio (Fed/Fast)	x	x	(x, x)	x	x	(x, x)
$AUC_{(0\text{-}inf)}$ Ratio (Fed/Fast)	x	x	(x, x)	x	x	(x, x)

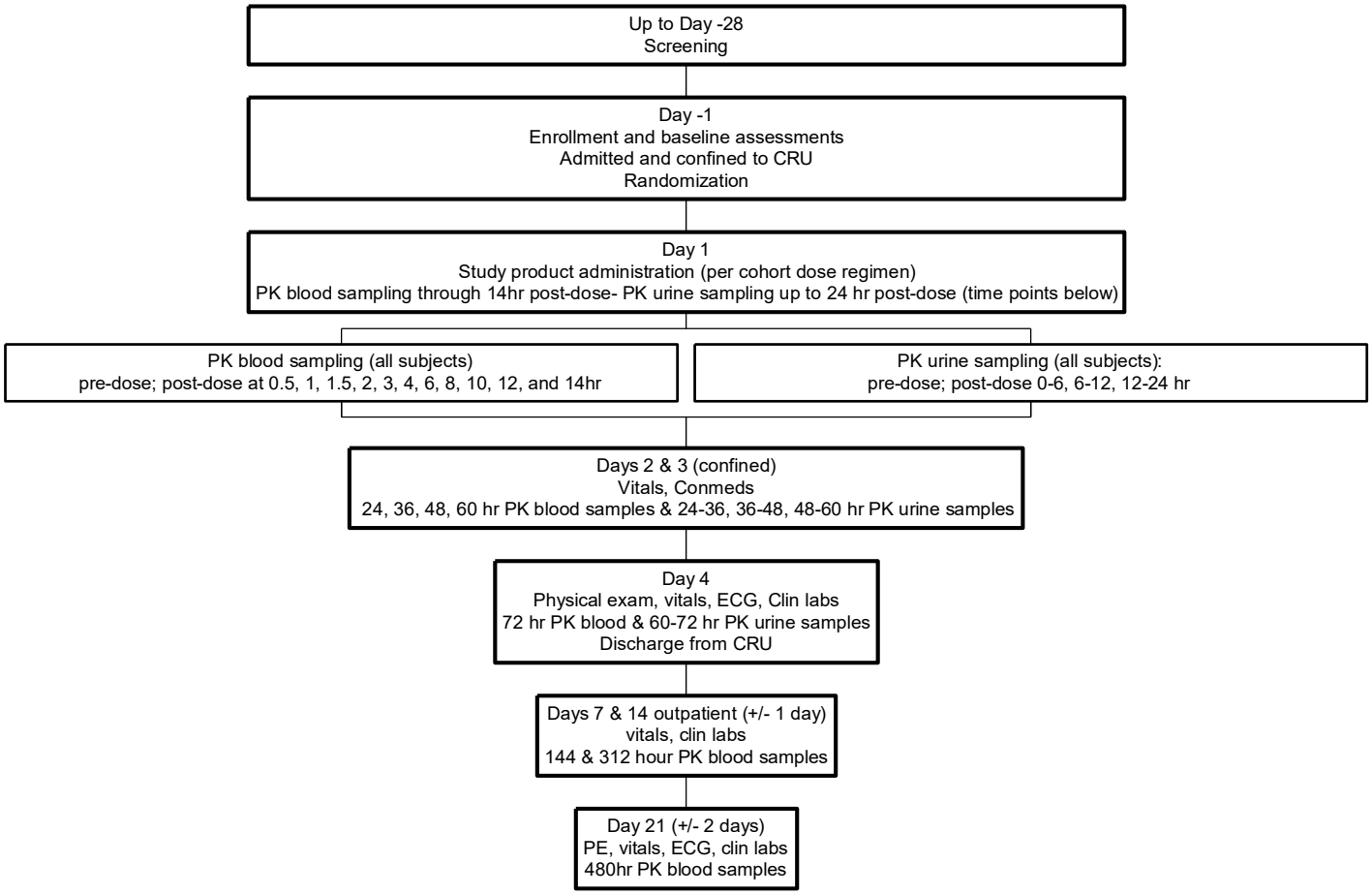
[a] N=Number of subjects with data used to compute the exposure parameters. Data was used from any subject in the PK Analysis Subset who received 160 mg VT-1598 under either a fasted or fed state, regardless of whether or not the subject participated in both study parts. BQL values were imputed as 0 if the sample was taken before the first measurable PK sample with a concentration above the LLOQ. BQL values were treated as missing otherwise.

[b] 90% CI estimated using a mixed effects model for the geometric mean of each parameter by fasting status with a random subject effect. Individual parameter estimates were log transformed before inclusion in the model.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

Figure 1: Schematic of Study Design



10.1 Disposition of Subjects

Figure 2: CONSORT Flow Diagram

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

Placeholder for Figure 2 – CONSORT Flow Diagram

14.3.1.2 Unsolicited Adverse Events

Figure 3: Proportion of Subjects with Related Adverse Events by MedDRA SOC and Maximum Severity – All Dose Groups

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events related to the study product. Note that this figure will present the number of subjects with each type of SOC. A subject will only be counted once for the same SOC for the maximum severity reported. Each figure panel will show counts for all SOCs observed in the Any Dose Group during the study (as a related AE). If the number of SOCs is too large to fit using 2 rows of panels, then the figure can be split with one row of 3 panels in each figure.

Subjects who received VT-1598 in both Cohorts 3 and 6 will be summarized separately for each dose received in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be summarized separately for each dose received in the Placebo Dose Group.

Order SOCs alphabetically.]

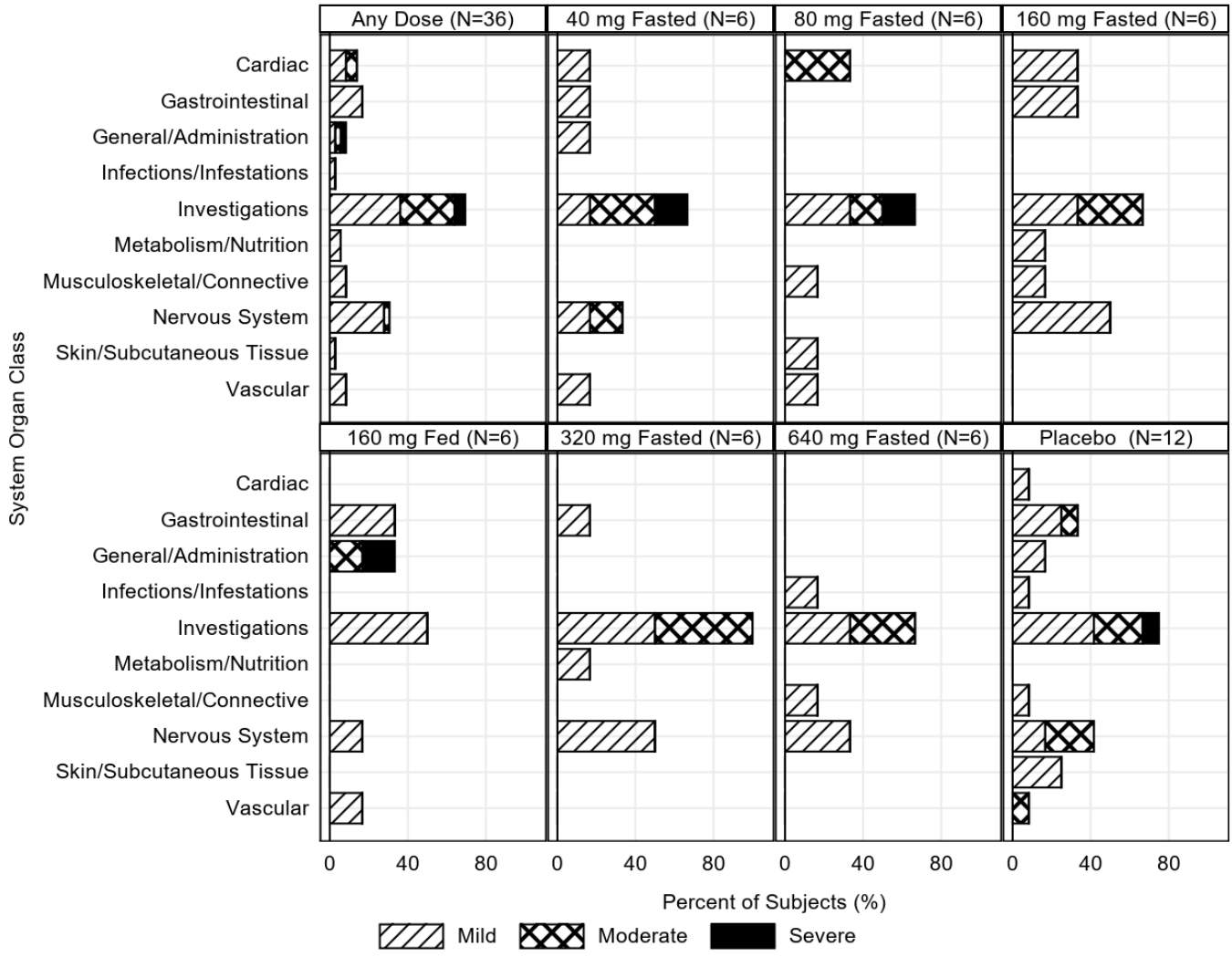
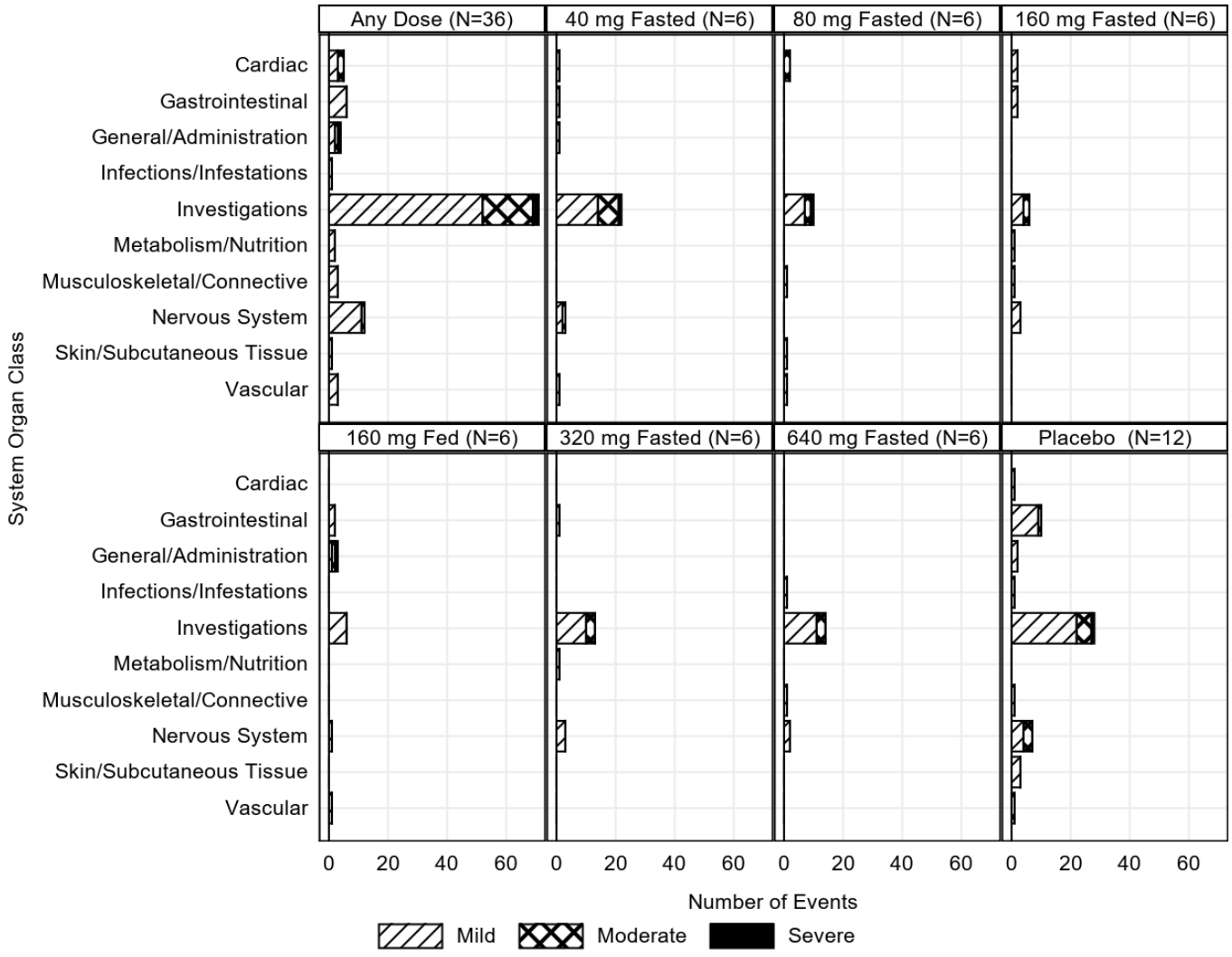


Figure 4: Number of Related Adverse Events by MedDRA SOC and Severity – All Dose Groups

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events related to the study product. Note that this figure will present the total counts of adverse events, a subject may contribute 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 using 2 rows of panels, then the figure can be split with one row of 3 panels in each figure.

Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dose received in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dose received in the Placebo Dose Group.

Order SOCs alphabetically.]



14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Figure 5: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Albumin

[Implementation Note: Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dose received in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dose received in the Placebo Dose Group.]

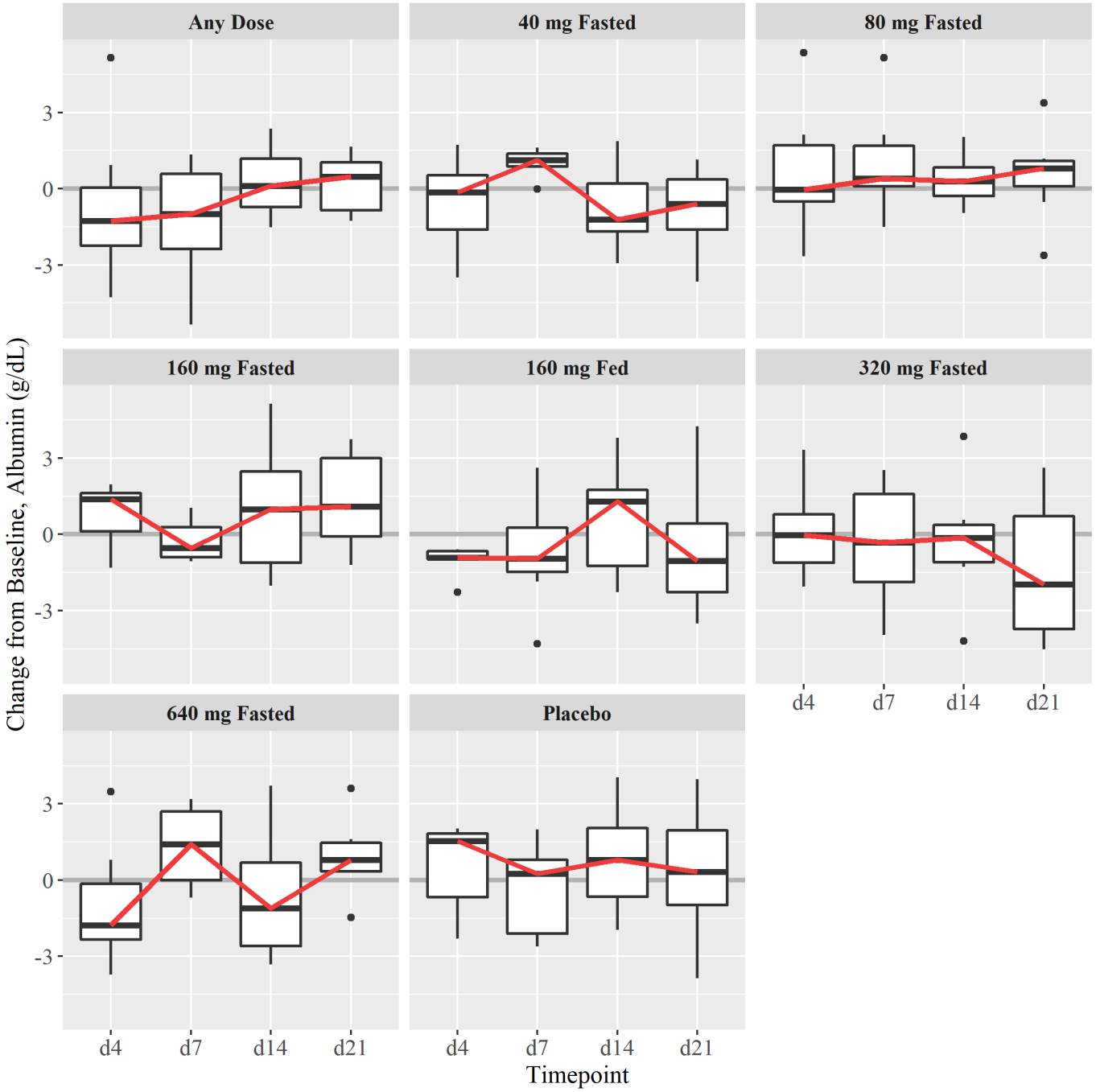


Figure 6: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Glucose

This figure will repeat Figure 5 for Glucose

Figure 7: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Blood Urea Nitrogen

This figure will repeat Figure 5 for Blood Urea Nitrogen

Figure 8: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Potassium

This figure will repeat Figure 5 for Potassium

Figure 9: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Calcium

This figure will repeat Figure 5 for Calcium

Figure 10: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Sodium

This figure will repeat Figure 5 for Sodium

Figure 11: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Chloride

This figure will repeat Figure 5 for Chloride

Figure 12: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Total Protein

This figure will repeat Figure 5 for Total Protein

Figure 13: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Creatinine

This figure will repeat Figure 5 for Creatinine

Figure 14: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Triglycerides

This figure will repeat Figure 5 for Triglycerides

Figure 15: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Total Cholesterol

This figure will repeat Figure 5 for Total Cholesterol

Figure 16: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Low-Density Lipoprotein

This figure will repeat Figure 5 for Low-Density Lipoprotein

Figure 17: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – High-Density Lipoprotein

This figure will repeat Figure 5 for High-Density Lipoprotein

Figure 18: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Total Carbon Dioxide

This figure will repeat Figure 5 for Total Carbon Dioxide

Figure 19: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Creatine Phosphokinase

This figure will repeat Figure 5 for Creatine Phosphokinase

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

This figure will repeat Figure 5 for Phosphorus

Figure 21: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Alkaline Phosphatase

This figure will repeat Figure 5 for Alkaline Phosphatase

Figure 22: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Aspartate Aminotransferase

This figure will repeat Figure 5 for Aspartate Aminotransferase

Figure 23: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Alanine Aminotransferase

This figure will repeat Figure 5 for Alanine Aminotransferase

Figure 24: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Total Bilirubin

This figure will repeat Figure 5 for Total Bilirubin

Figure 25: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Direct Bilirubin

This figure will repeat Figure 5 for Direct Bilirubin

Figure 26: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Magnesium

This figure will repeat Figure 5 for Magnesium

Figure 27: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Gamma-Glutamyl Transferase

This figure will repeat Figure 5 for Gamma-Glutamyl Transferase

Figure 28: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Serum Cortisol

This figure will repeat Figure 5 for Serum Cortisol

14.3.5.2 Hematology Results

Figure 29: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Hemoglobin

This figure will repeat Figure 5 for Hemoglobin

Figure 30: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Hematocrit

This figure will repeat Figure 5 for Hematocrit

Figure 31: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Lymphocytes

This figure will repeat Figure 5 for Lymphocytes

Figure 32: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Neutrophils

This figure will repeat Figure 5 for Neutrophils

Figure 33: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Monocytes

This figure will repeat Figure 5 for Monocytes

Figure 34: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Eosinophils

This figure will repeat Figure 5 for Eosinophils

Figure 35: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Basophils

This figure will repeat Figure 5 for Basophils

Figure 36: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Platelet Count

This figure will repeat Figure 5 for Platelets

Figure 37: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Red Blood Cell Count

This figure will repeat Figure 5 for Red Blood Cell Count

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

This figure will repeat Figure 5 for White Blood Cell Count

14.3.5.3 Coagulation Results

Figure 39: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Activated Partial Thromboplastin Time

This figure will repeat Figure 5 for Activated Partial Thromboplastin Time

Figure 40: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Prothrombin Time

This figure will repeat Figure 5 for Prothrombin Time

Figure 41: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – International Normalized Ratio

This figure will repeat Figure 5 for International Normalized Ratio

14.3.5.4 Urinalysis Results

Figure 42: Urinalysis Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – Specific Gravity

This figure will repeat Figure 5 for Specific Gravity

Figure 43: Urinalysis Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Dose Group, and Timepoint – pH

This figure will repeat Figure 5 for pH

14.3.5.6 Displays of Vital Signs

Figure 44: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 40 mg Fasted, 80 mg Fasted, and 320 mg Fasted Dose Groups– Systolic Blood Pressure

[Implementation note: the presented order of dose groups in this figure contradicts the specified order of section 3.3.2 due to constraints on the number of graphs that can be presented per page. The 160 mg Fasted and Fed and the Any Dose/Placebo graphs are kept together for ease of viewing.]

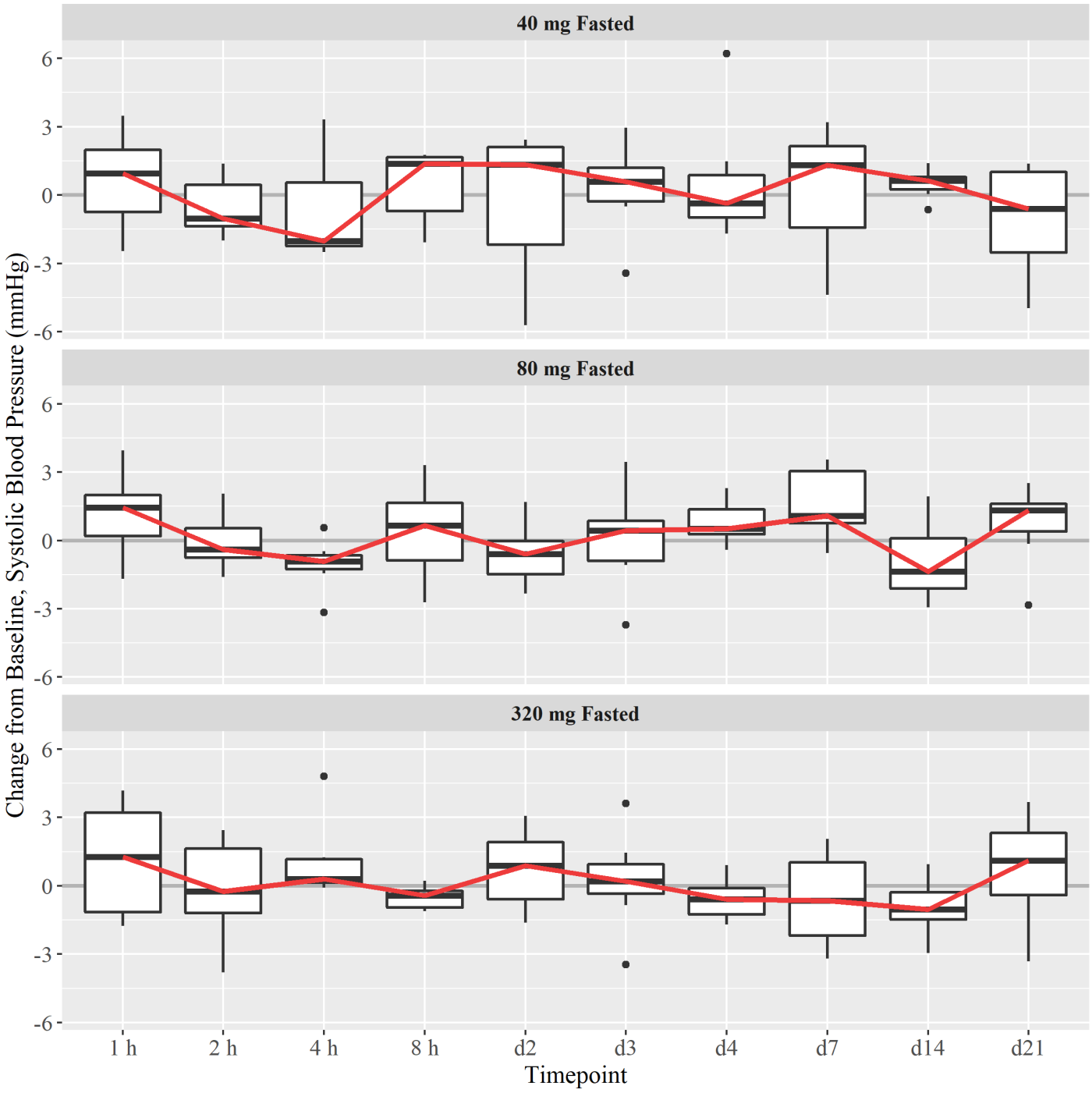


Figure 45: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 160 mg Fasted, 160 mg Fed, and 640 mg Fasted Dose Groups– Systolic Blood Pressure

[Implementation note: the presented order of dose groups in this figure contradicts the specified order of section 3.3.2 due to constraints on the number of graphs that can be presented per page. The 160 mg Fasted and Fed and the Any Dose/Placebo graphs are kept together for ease of viewing.]

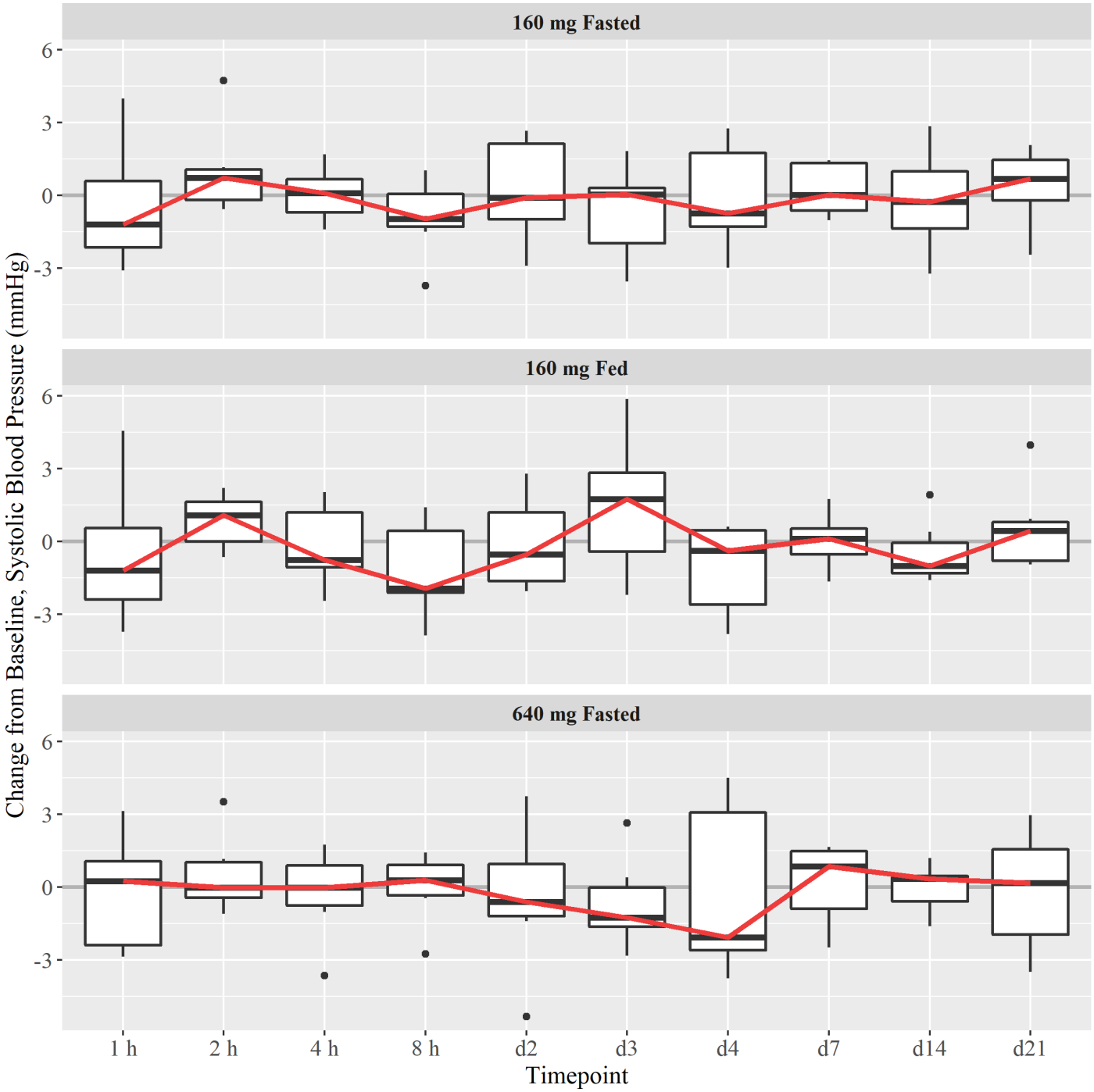


Figure 46: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, Any Dose and Placebo Dose Groups– Systolic Blood Pressure

[Implementation Note: Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dose received in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dose received in the Placebo Dose Group. The presented order of dose groups in this figure contradicts the specified order of section 3.3.2 due to constraints on the number of graphs that can be presented per page. The 160 mg Fasted and Fed and the Any Dose/Placebo graphs are kept together for ease of viewing.]

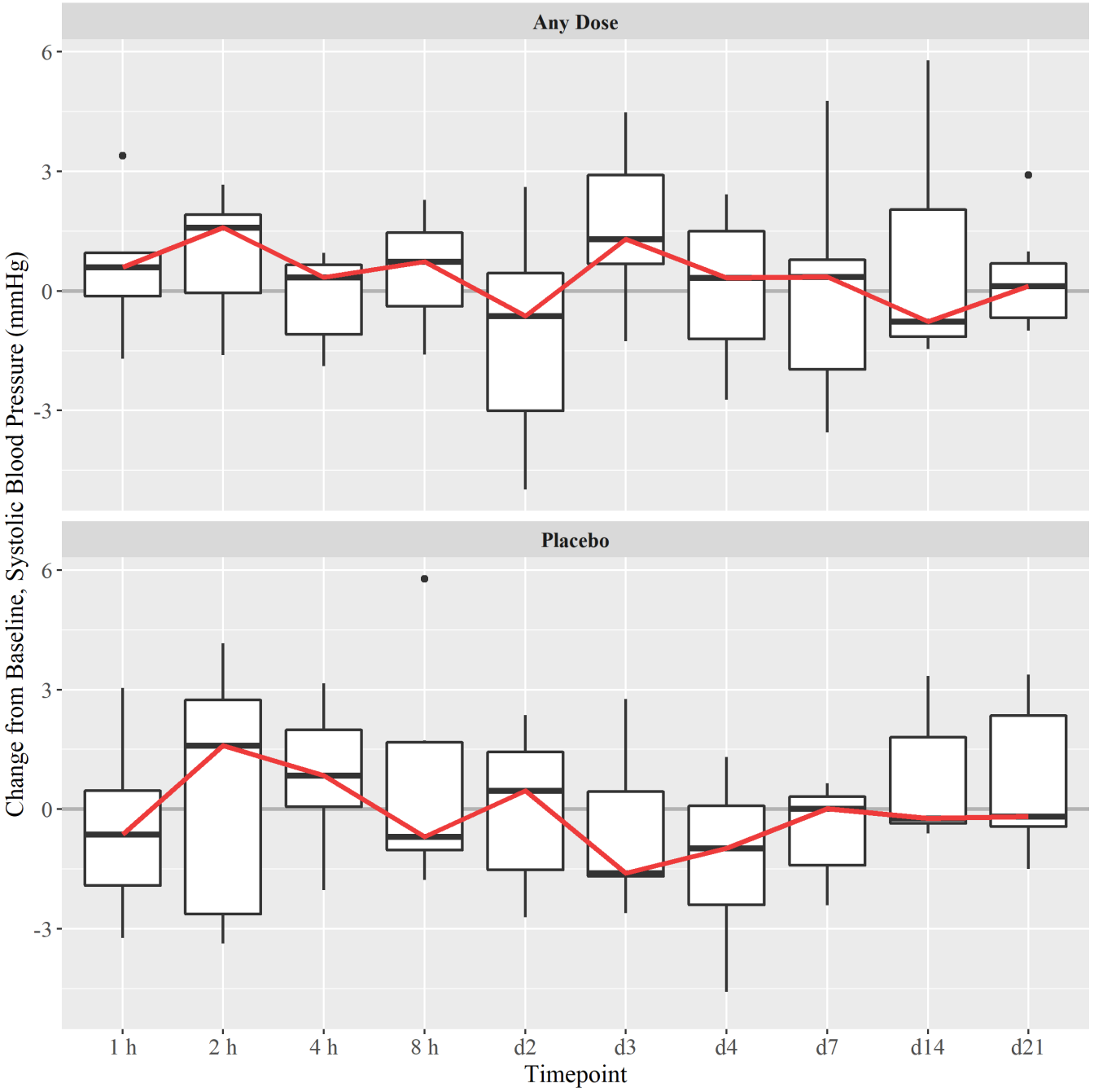


Figure 47: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 40 mg Fasted, 80 mg Fasted, and 320 mg Fasted Dose Groups– Diastolic Blood Pressure

This figure will repeat Figure 43 for Diastolic Blood Pressure

Figure 48: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 160 mg Fasted, 160 mg Fed, and 640 mg Fasted Dose Groups– Diastolic Blood Pressure

This figure will repeat Figure 44 for Diastolic Blood Pressure in 160 mg Fasted, 160 mg Fed, and 640 mg Fasted Dose Groups

Figure 49: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, Any Dose and Placebo Dose Groups– Diastolic Blood Pressure

This figure will repeat Figure 45 for Diastolic Blood Pressure in the Any Dose Group and Placebo Dose Group

Figure 50: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 40 mg Fasted, 80 mg Fasted, and 320 mg Fasted Dose Groups– Pulse

This figure will repeat Figure 43 for Pulse

Figure 51: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 160 mg Fasted, SAD 160 mg Fed, and 640 mg Fasted Dose Groups – Pulse

This figure will repeat Figure 44 for Pulse in 160 mg Fasted, 160 mg Fed, and 640 mg Fasted Dose Groups

Figure 52: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, Any Dose and Placebo Dose Groups– Pulse

This figure will repeat Figure 45 for Pulse in the Any Dose Group and Placebo Dose Group

Figure 53: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 40 mg Fasted, 80 mg Fasted, and 320 mg Fasted Dose Groups– Respiratory Rate

This figure will repeat Figure 43 for Respiratory Rate

Figure 54: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 160 mg Fasted, 160 mg Fed, and 640 mg Fasted Dose Groups – Respiratory Rate

This figure will repeat Figure 44 for Respiratory Rate in 160 mg Fasted, 160 mg Fed, and 640 mg Fasted Dose Groups

Figure 55: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, Any Dose and Placebo Dose Groups– Respiratory Rate

This figure will repeat Figure 45 for Respiratory Rate in the Any Dose Group and Placebo Dose Group

Figure 56: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 40 mg Fasted, 80 mg Fasted, and 320 mg Fasted Dose Groups– Temperature

This figure will repeat Figure 43 for Temperature

Figure 57: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, 160 mg Fasted, 160 mg Fed, and 640 mg Fasted Dose Groups– Temperature

This figure will repeat Figure 44 for Temperature in 160 mg Fasted, 160 mg Fed, and 640 mg Fasted Dose Groups

Figure 58: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint, Any Dose and Placebo Dose Groups– Temperature

This figure will repeat Figure 45 for Temperature in the Any Dose Group and Placebo Dose Group

14.3.5.7 Displays of ECG Measurements

Figure 59: ECG by Scheduled Visits: Change from Baseline by Parameter and Dose Group – PR Interval

[Implementation Note: Subjects who received VT-1598 in both Cohorts 3 and 6 will be included separately for each dose received in the Any Dose Group. Similarly, subjects who received placebo in both Cohorts 3 and 6 will be included separately for each dose received in the Placebo Dose Group.]

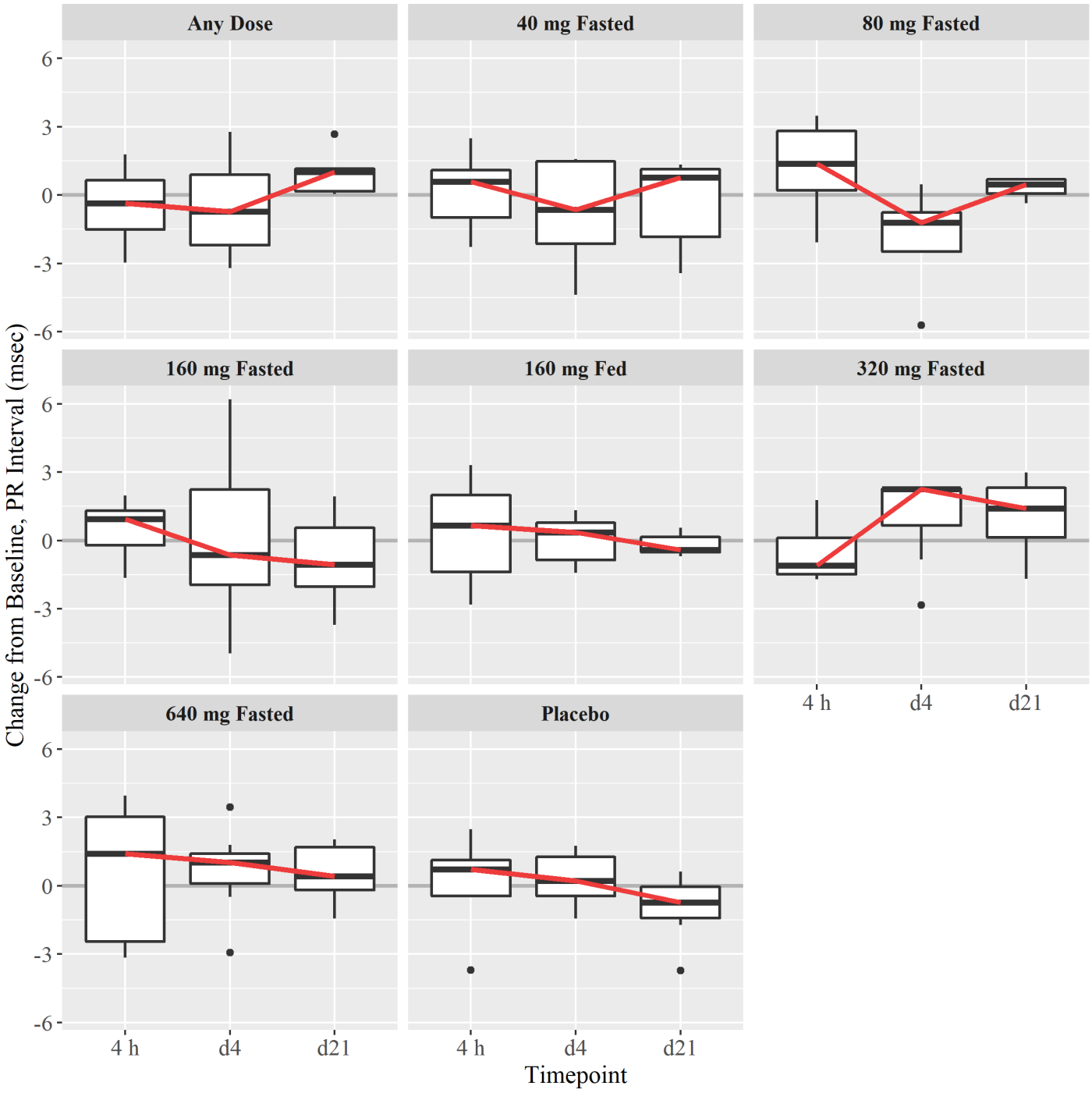


Figure 60: ECG by Scheduled Visits: Change from Baseline by Parameter and Dose Group – QRS Duration

This figure will repeat Figure 58 for QRS Duration

Figure 61: ECG by Scheduled Visits: Change from Baseline by Parameter and Dose Group – QT Interval

This figure will repeat Figure 58 for QT Interval

Figure 62: ECG by Scheduled Visits: Change from Baseline by Parameter and Dose Group – QTcF Interval

This figure will repeat Figure 58 for QTcF Interval

Figure 63: ECG by Scheduled Visits: Change from Baseline by Parameter and Dose Group – RR Interval

This figure will repeat Figure 58 for RR Interval

Figure 64: ECG by Scheduled Visits: Change from Baseline by Parameter and Dose Group –Mean Ventricular Heart Rate

This figure will repeat Figure 58 for Mean Ventricular Heart Rate

14.3.5.6 Displays of PK Results and Parameters

Figure 65: Individual VT-1598 Concentration in Plasma Profiles, 0 h to 72 h Post Dose – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

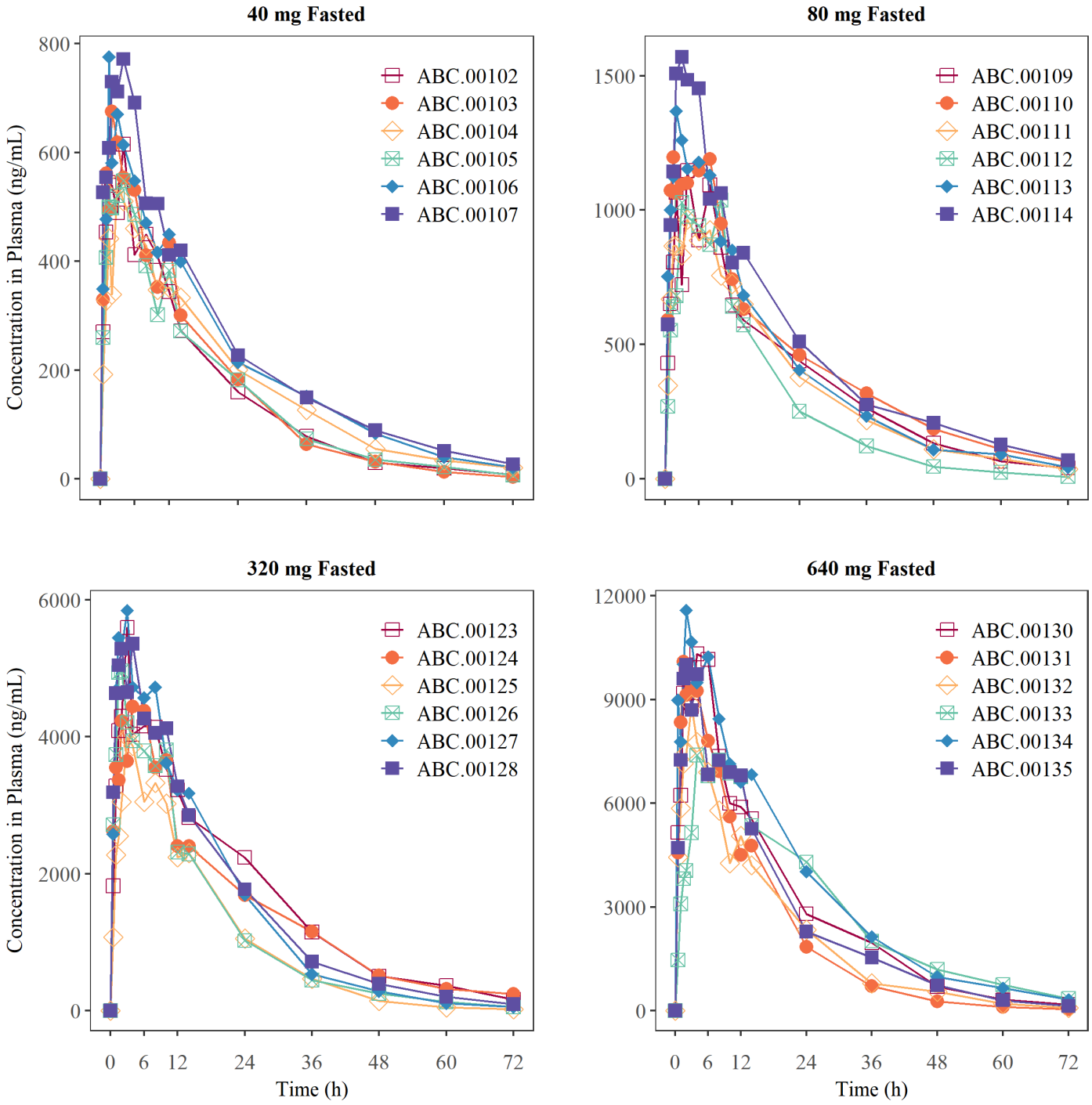


Figure 66: Individual VT-1598 Concentration in Plasma Profiles, 0 h to 72 h Post Dose – 160 mg Fasted and 160 mg Fed Dose Groups

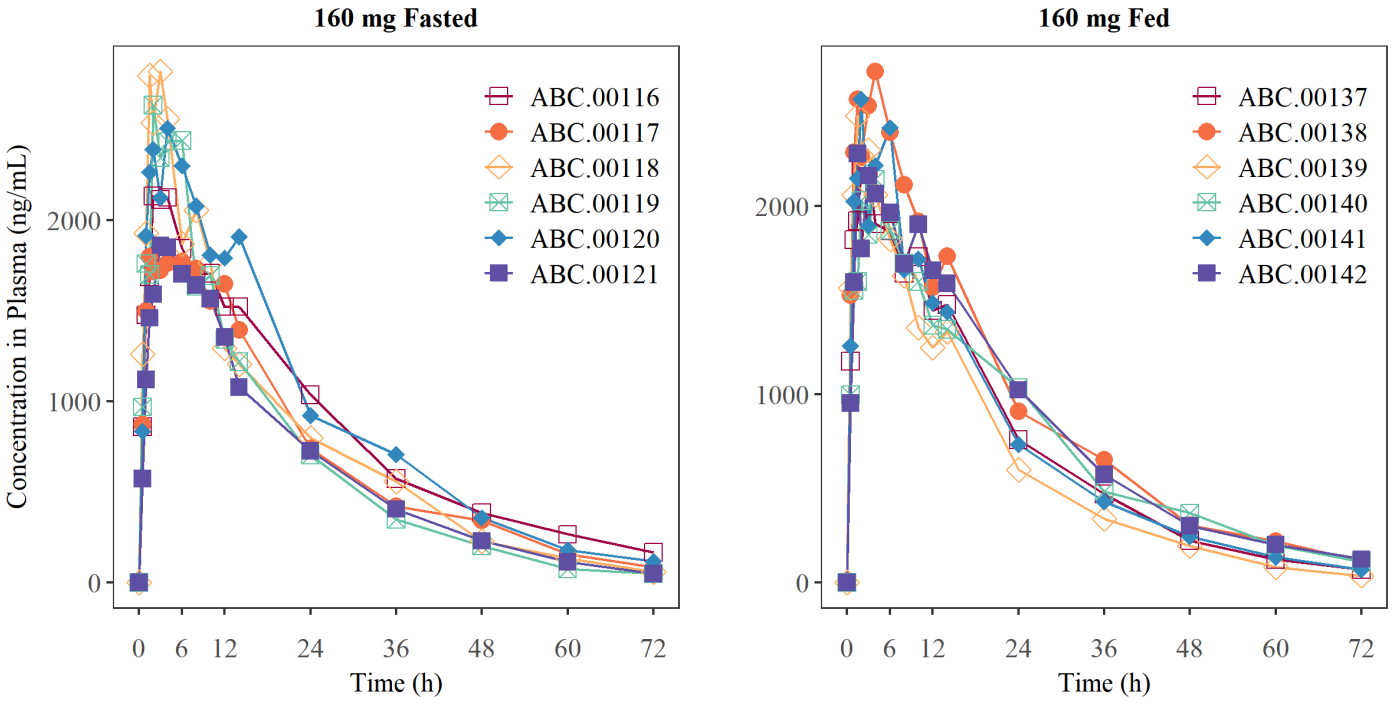


Figure 67: Individual VT-1598 Concentration in Plasma Profiles, All Timepoints Post Dose – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

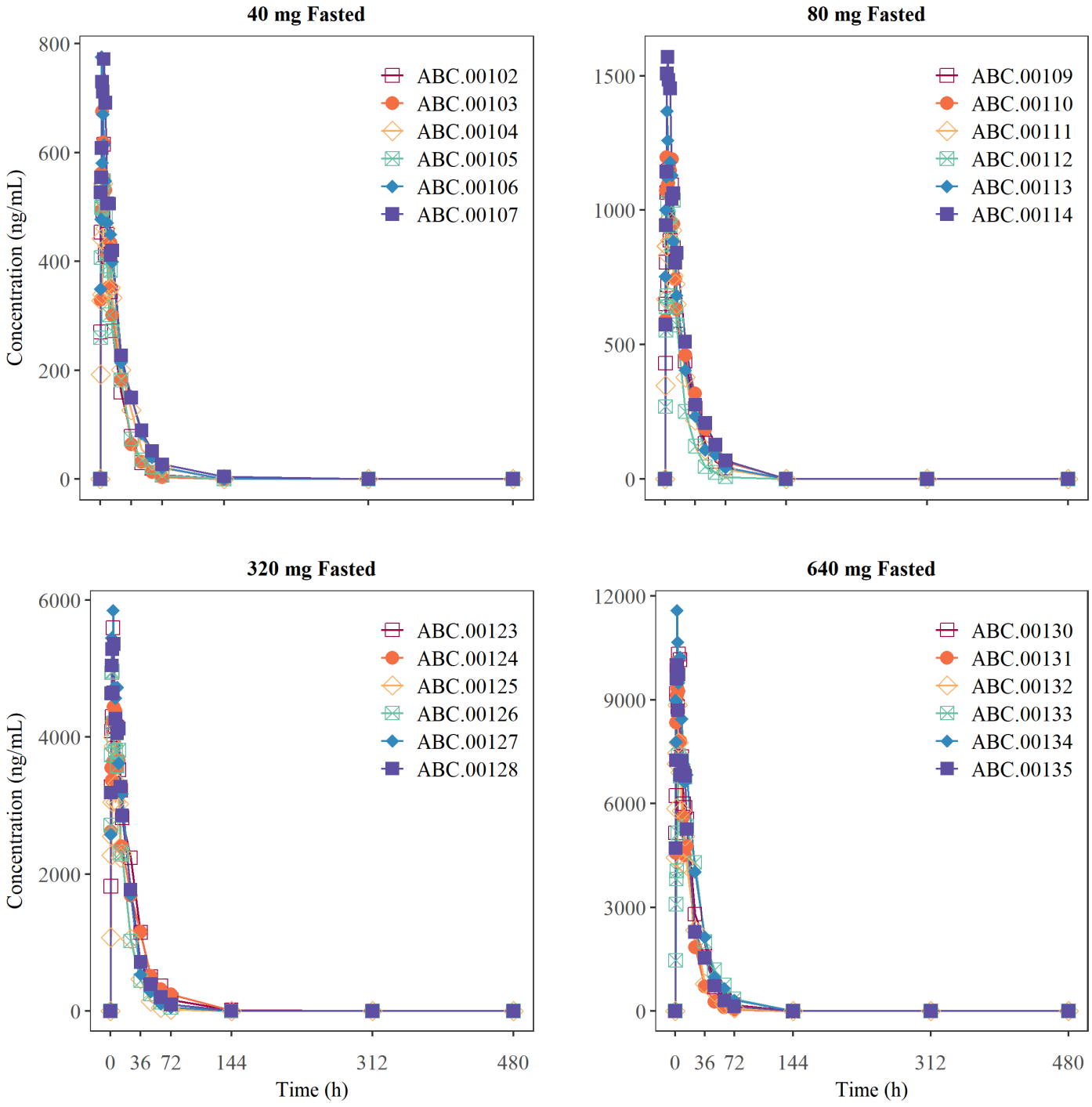


Figure 68: Individual VT-1598 Concentration in Plasma Profiles, All Timepoints Post Dose – 160 mg Fasted and 160 mg Fed Dose Groups

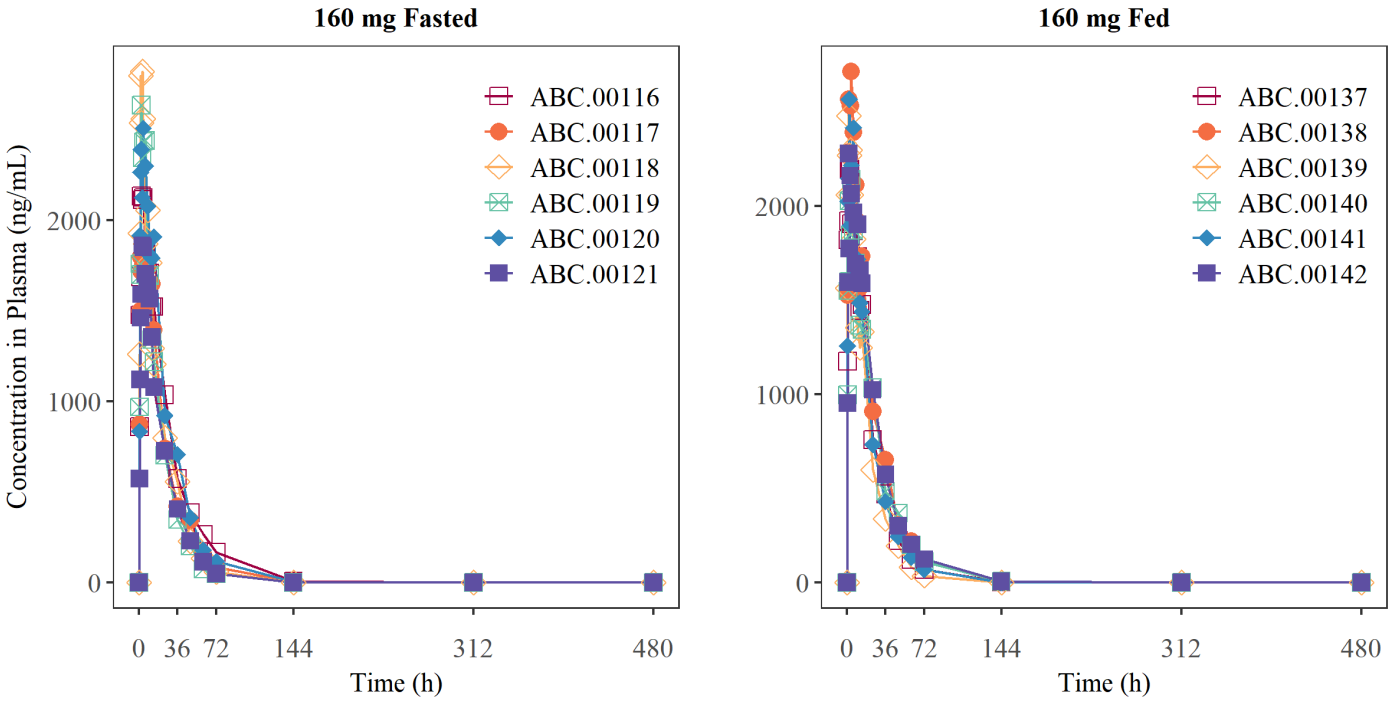


Figure 69: Individual VT-11134 Concentration in Plasma Profiles by Dose Group, 0 h to 72 h Post Dose – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

This figure will repeat Figure 64 for VT-11134 in Plasma

Figure 70: Individual VT-11134 Concentration in Plasma Profiles by Dose Group, 0 h to 72 h Post Dose – 160 mg Fasted and 160 mg Fed Dose Groups

This figure will repeat Figure 65 for VT-11134 in Plasma

Figure 71: Individual VT-11134 Concentration in Plasma Profiles by Dose Group, All Timepoints Post Dose – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

This figure will repeat Figure 66 for VT-11134 in Plasma

Figure 72: Individual VT-11134 Concentration in Plasma Profiles by Dose Group, All Timepoints Post Dose – 160 mg Fasted and 160 mg Fed Dose Groups

This figure will repeat Figure 67 for VT-11134 in Plasma

Figure 73: Individual Cumulative Amount of VT-1598 Excreted into Urine – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

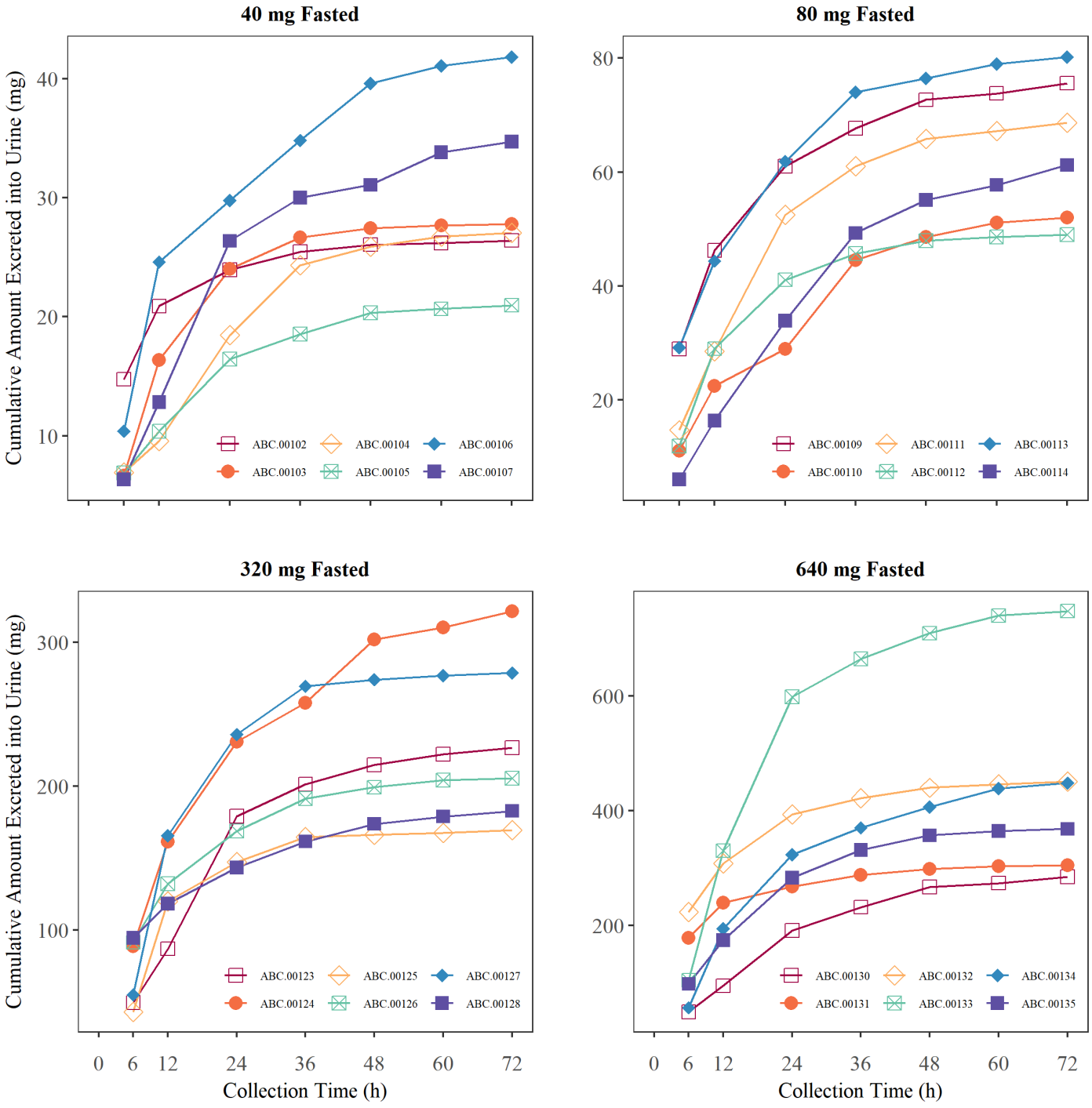


Figure 74: Individual Cumulative Amount of VT-1598 Excreted into Urine – 160 mg Fasted and 160 mg Fed Dose Groups

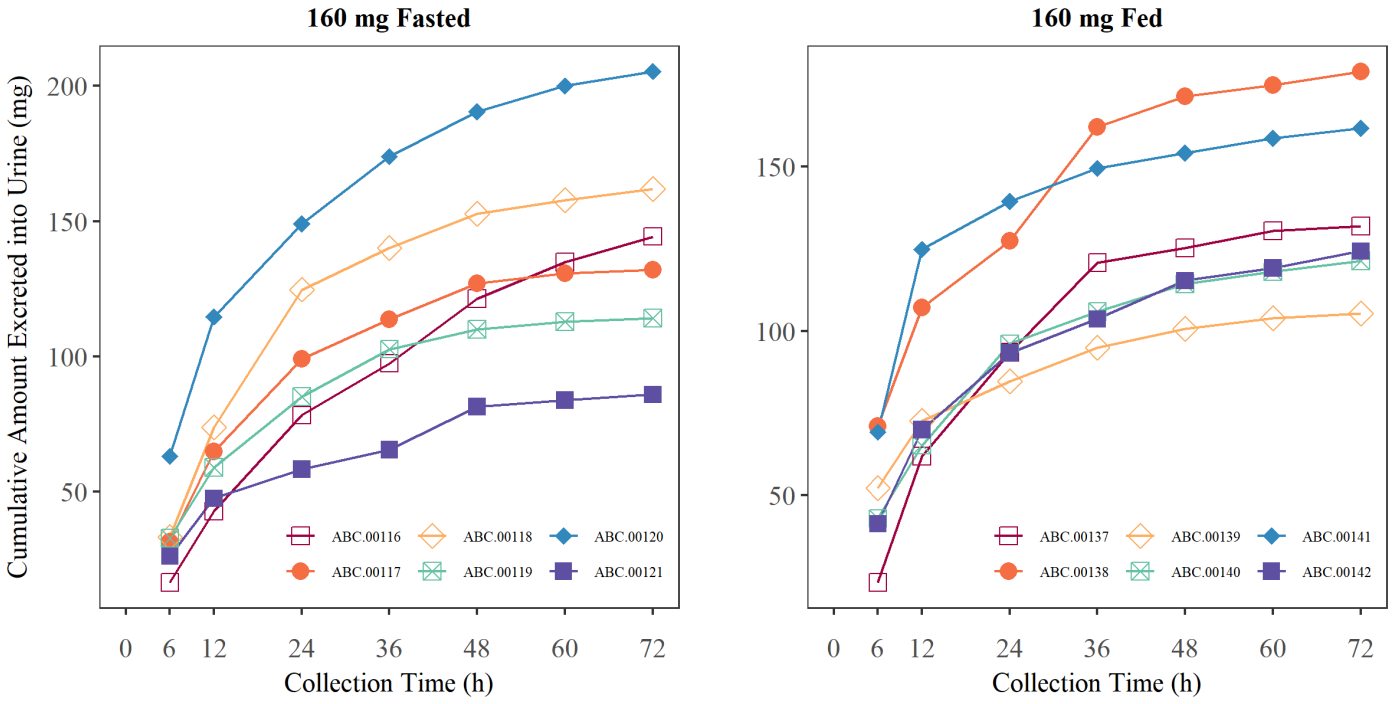


Figure 75: Individual Cumulative Amount of VT-11134 Excreted into Urine by Dose Group – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

This figure will repeat Figure 72 for VT-11134 in Urine

Figure 76: Individual Cumulative Amount of VT-11134 Excreted into Urine by Dose Group – 160 mg Fasted and 160 mg Fed Dose Groups

This figure will repeat Figure 73 for VT-11134 in Urine

Figure 77: Semi-Log Individual VT-1598 Concentration Profiles in Plasma, 0 h to 72 h Post Dose – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

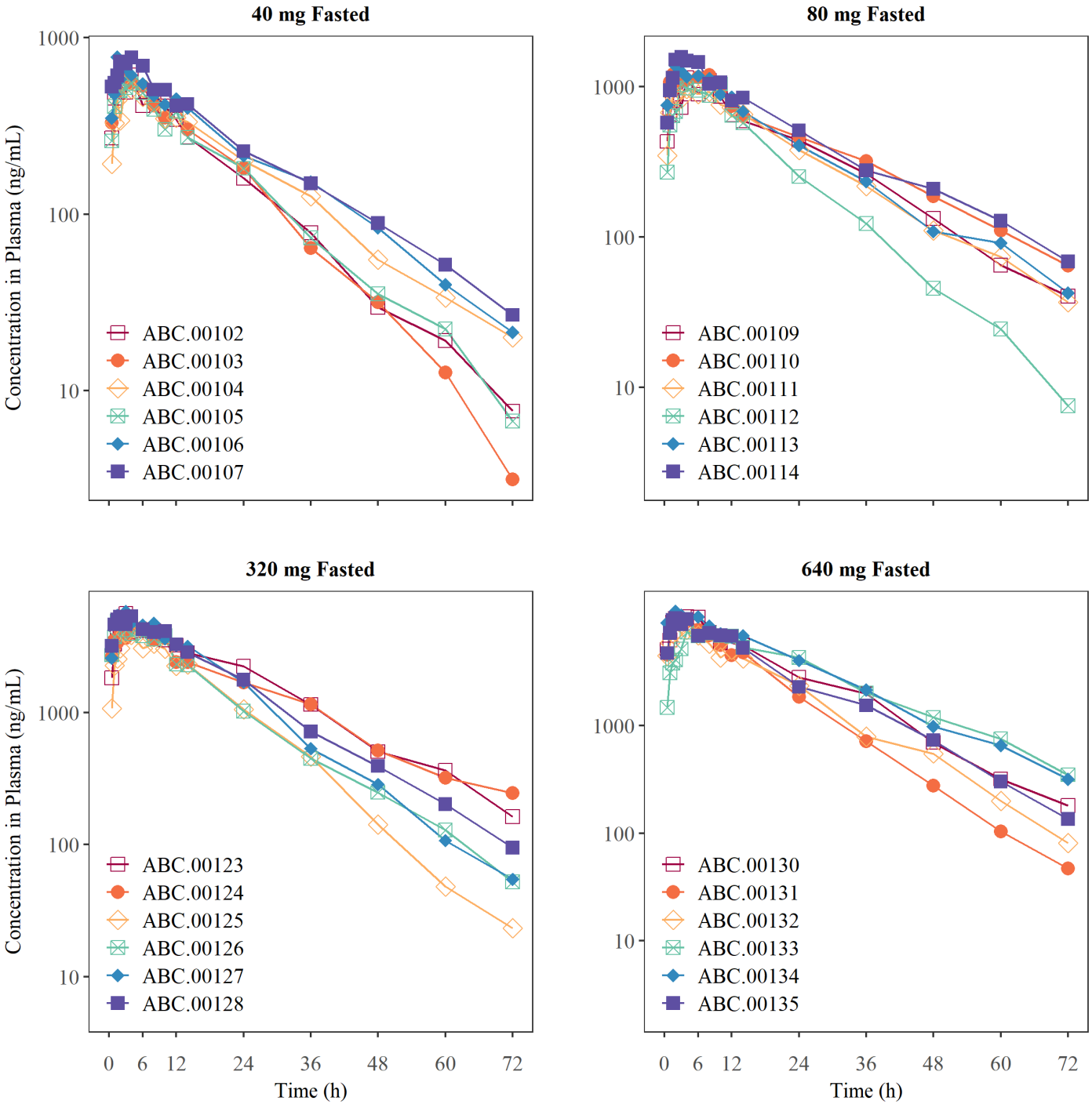


Figure 78: Semi-Log Individual VT-1598 Concentration Profiles in Plasma, 0 h to 72 h Post Dose – 160 mg Fasted and 160 mg Fed Dose Groups

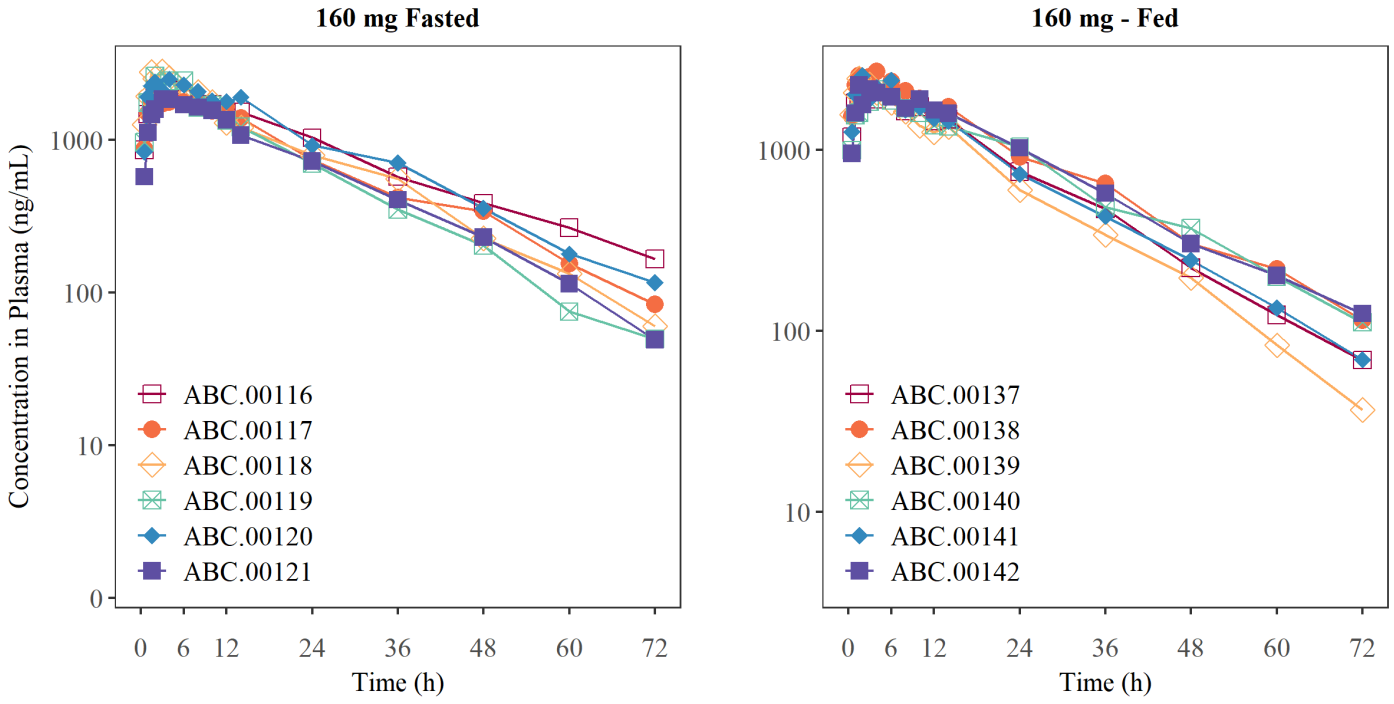


Figure 79: Semi-Log Individual VT-1598 Concentration Profiles in Plasma, All Timepoints – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

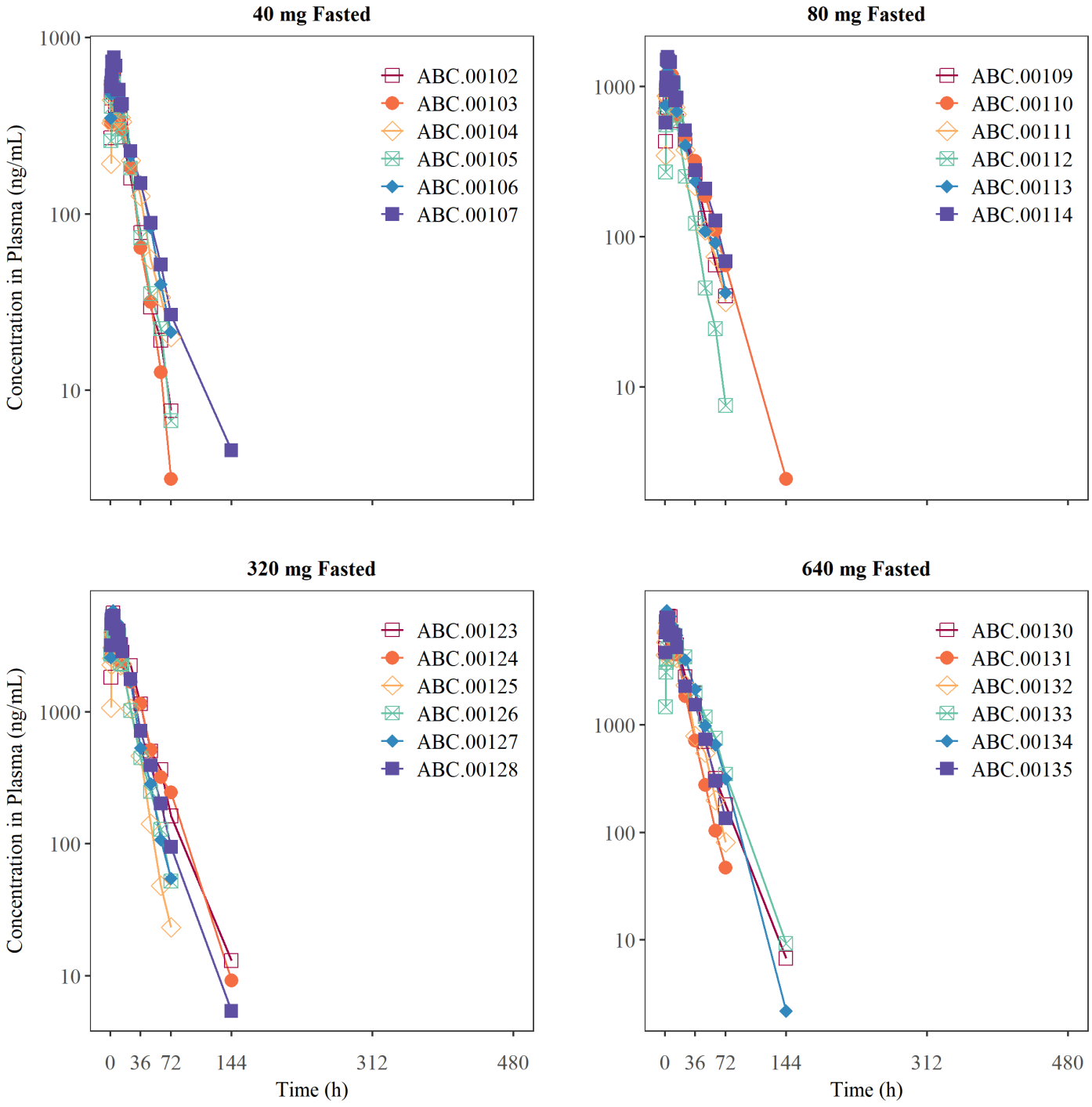


Figure 80: Semi-Log Individual VT-1598 Concentration Profiles in Plasma, All Timepoints – 160 mg Fasted and 160 mg Fed Dose Groups

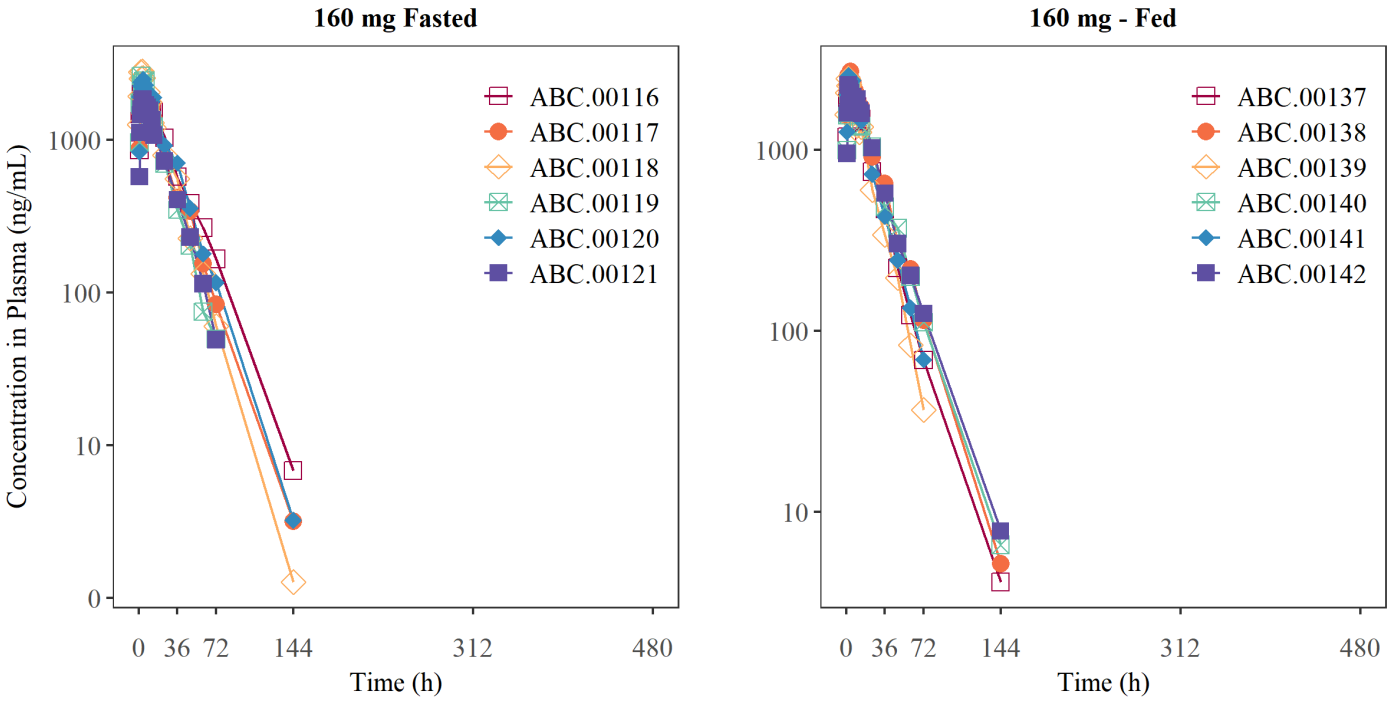


Figure 81: Semi-Log Individual VT-11134 Concentration Profiles in Plasma, 0 h to 72 h Post Dose – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

This figure will repeat Figure 76 for VT-11134 in plasma

Figure 82: Semi-Log Individual VT-11134 Concentration Profiles in Plasma, 0 h to 72 h Post Dose – 160 mg Fasted and 160 mg Fed Dose Groups

This figure will repeat Figure 77 for VT-11134 in plasma

Figure 83: Semi-Log Individual VT-11134 Concentration Profiles in Plasma, All Timepoints Post Dose – 40 mg, 80 mg, 320 mg, and 640 mg Fasted Dose Groups

This figure will repeat Figure 78 for VT-11134 in plasma

Figure 84: Semi-Log Individual VT-11134 Concentration Profiles in Plasma, All Timepoints Post Dose – 160 mg Fasted and 160 mg Fed Dose Groups

This figure will repeat Figure 79 for VT-11134 in plasma

Figure 85: Mean VT-1598 Concentration in Plasma Profiles by Dose Group – 0 h to 72 h Post Dose

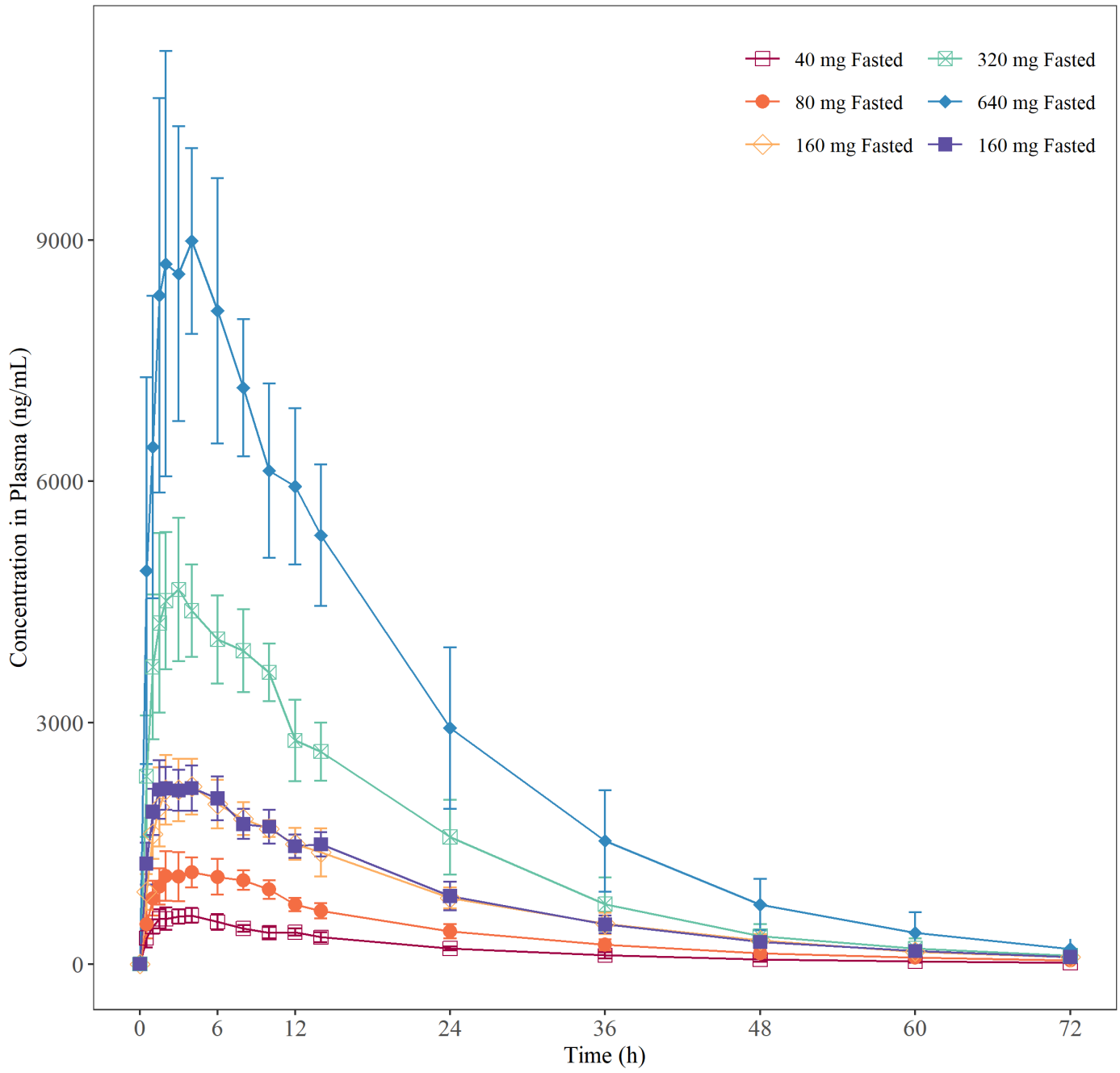


Figure 86: Mean VT-1598 Concentration in Plasma Profiles by Dose Group – All Timepoints Post Dose

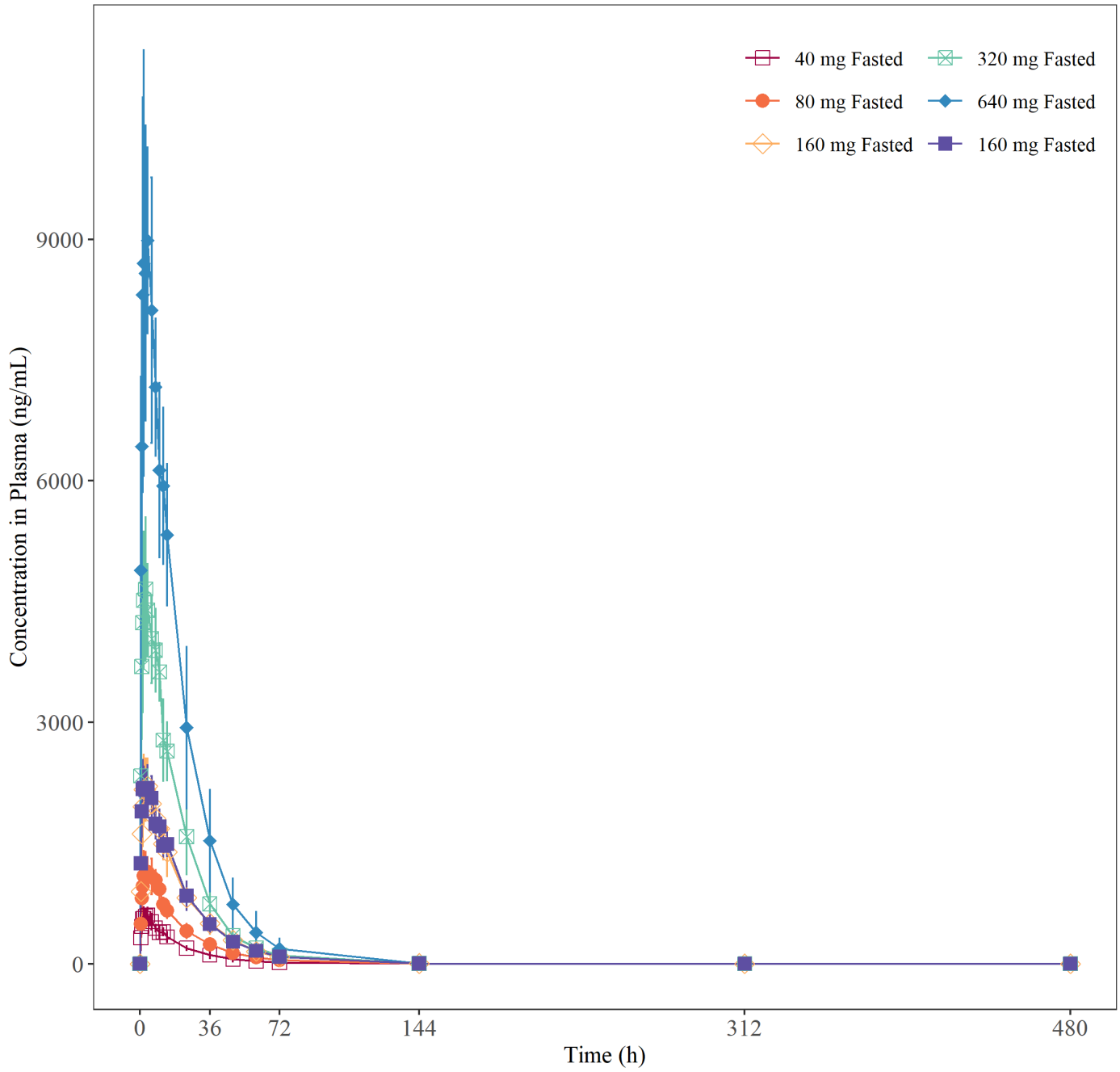


Figure 87: Mean VT-11134 Concentration in Plasma Profiles by Dose Group – 0 h to 72 h Post Dose

This figure will repeat Figure 84 for VT-11134 in plasma

Figure 88: Mean VT-11134 Concentration in Plasma Profiles by Dose Group – All Timepoints Post Dose

This figure will repeat Figure 85 for VT-11134 in plasma

Figure 89: Mean Cumulative Amount of VT-1598 Excreted into Urine by Dose Group

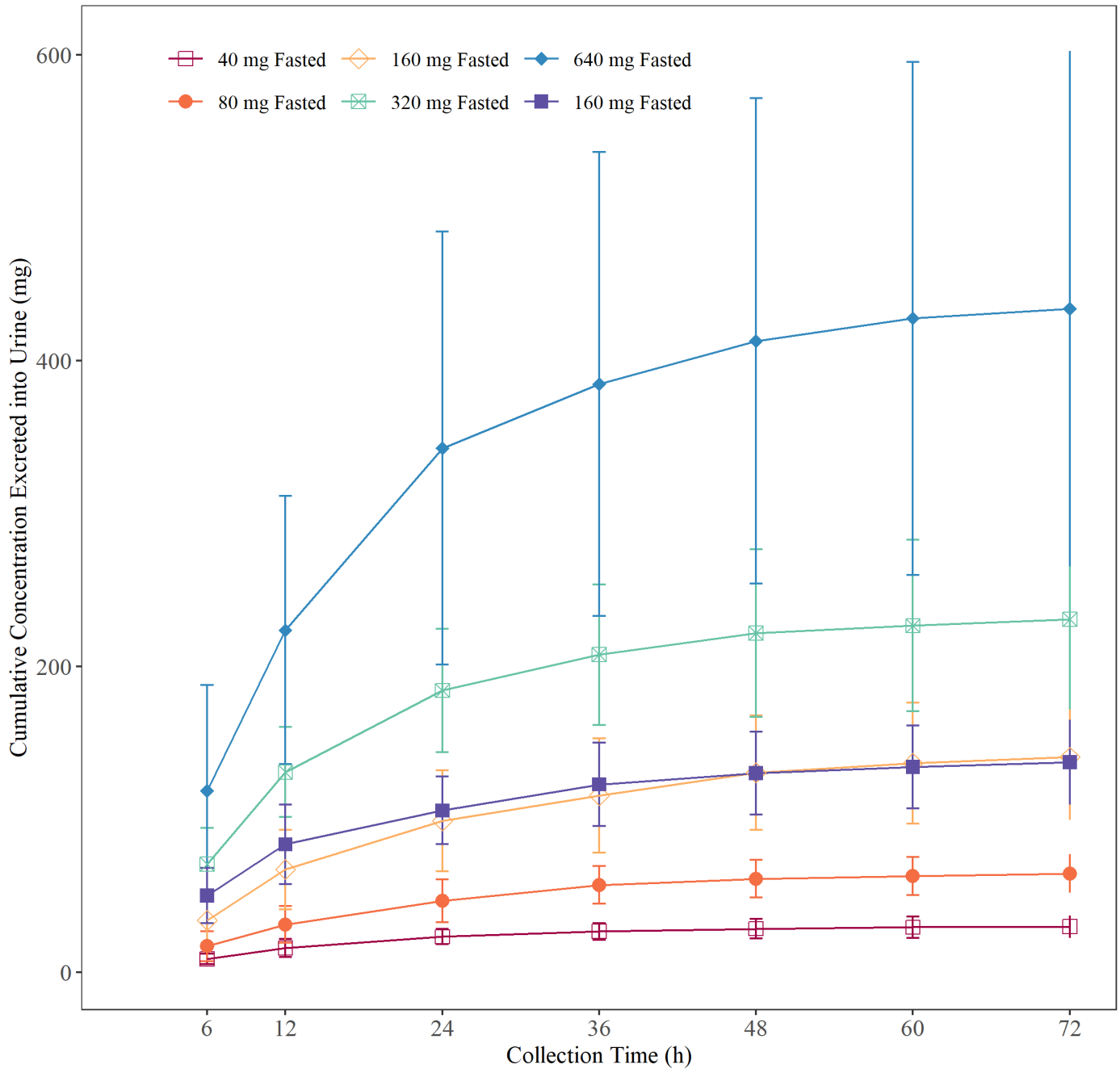


Figure 90: Mean Cumulative Amount of VT-11134 Excreted into Urine by Dose Group

This figure will repeat Figure 88 for VT-11134 in urine

Figure 91: Mean Semi-Log VT-1598 Concentration in Plasma Profiles by Dose Group – 0 h to 72 h Post Dose

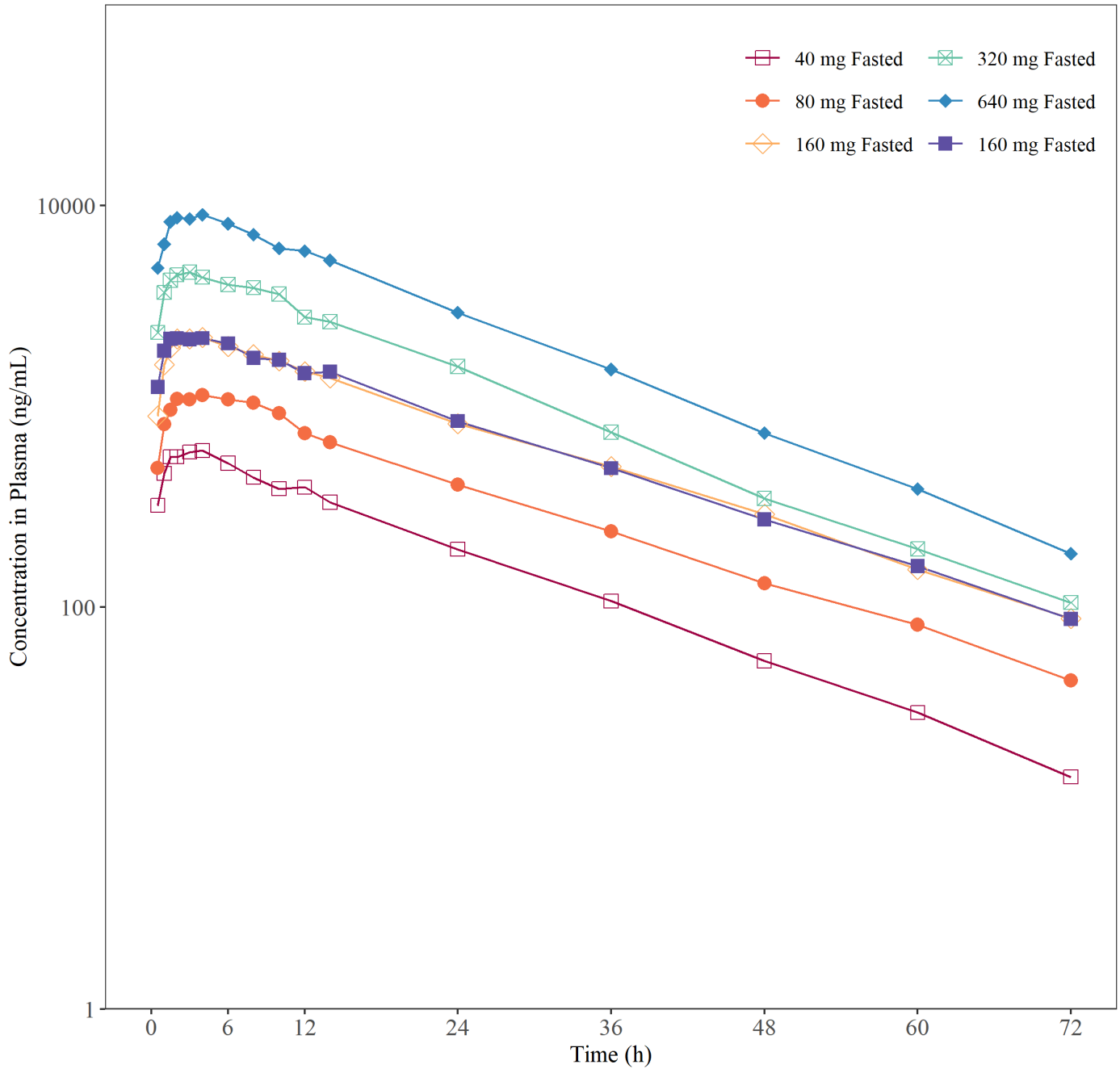


Figure 92: Mean Semi-Log VT-1598 Concentration in Plasma Profiles by Dose Group – All Timepoints Post Dose

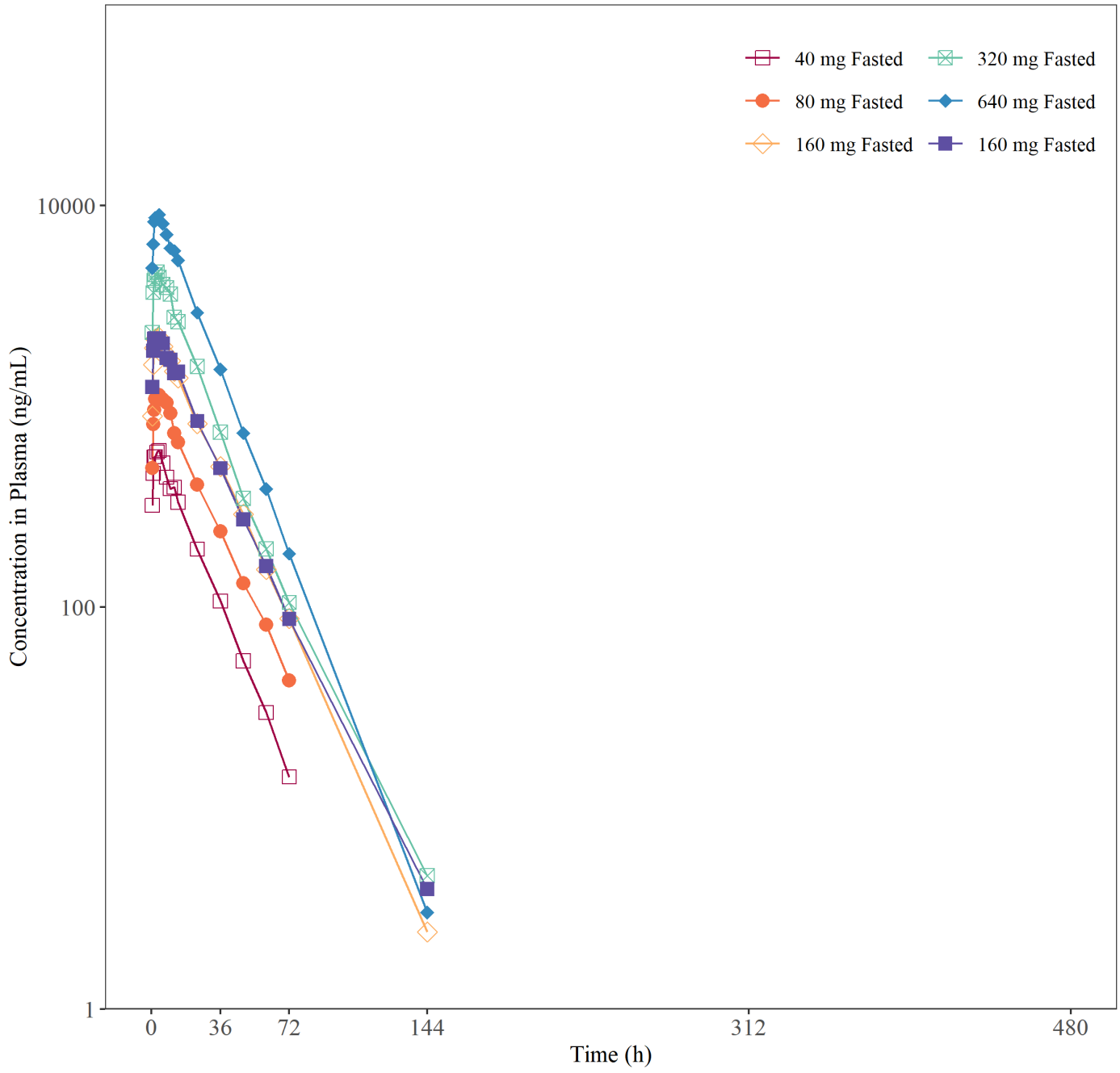


Figure 93: Mean Semi-Log VT-11134 Concentration in Plasma Profiles, by Dose Group – 0 h to 72 h Post Dose

This figure will repeat Figure 90 for VT-11134 in plasma

Figure 94: Mean Semi-Log VT-11134 Concentration in Plasma Profiles, by Dose Group – All Timepoints Post Dose

This figure will repeat Figure 91 for VT-11134 in plasma

Figure 95: Mean Concentration in Plasma by Analyte – 40 mg and 80 mg Fasted Dose Groups

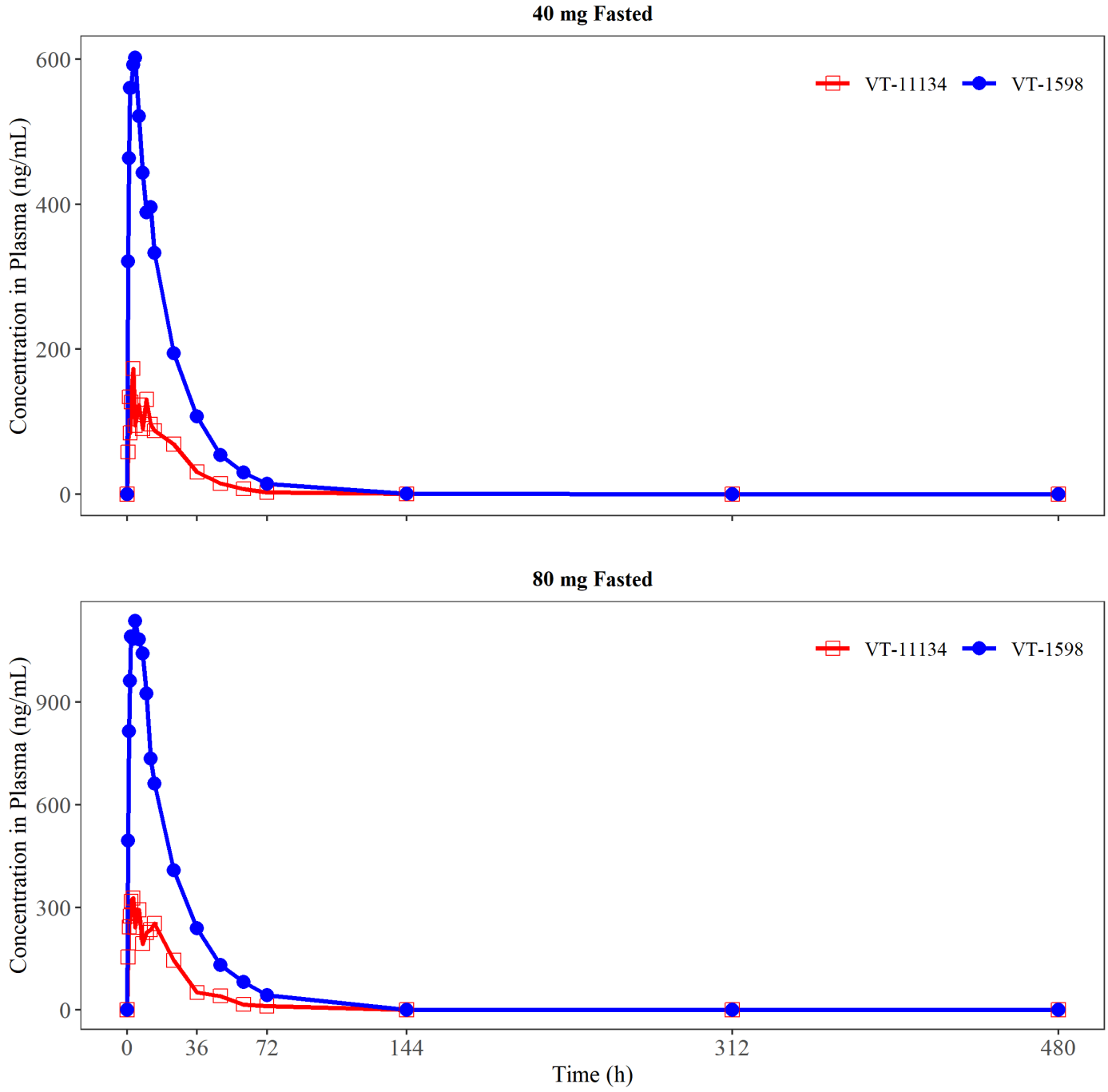


Figure 96: Mean Concentration in Plasma by Analyte – 160 mg Fasted and Fed Dose Groups

This figure will repeat Figure 94 for the 160 mg Fasted and Fed Dose Groups

Figure 97: Mean Concentration in Plasma by Analyte – 320 mg and 640 mg Fasted Dose Groups

This figure will repeat Figure 94 for the 320 and 640 mg Dose Groups

Figure 98: Mean of Cumulative Amount Excreted into Urine by Analyte – 40 mg and 80 mg Fasted Dose Groups

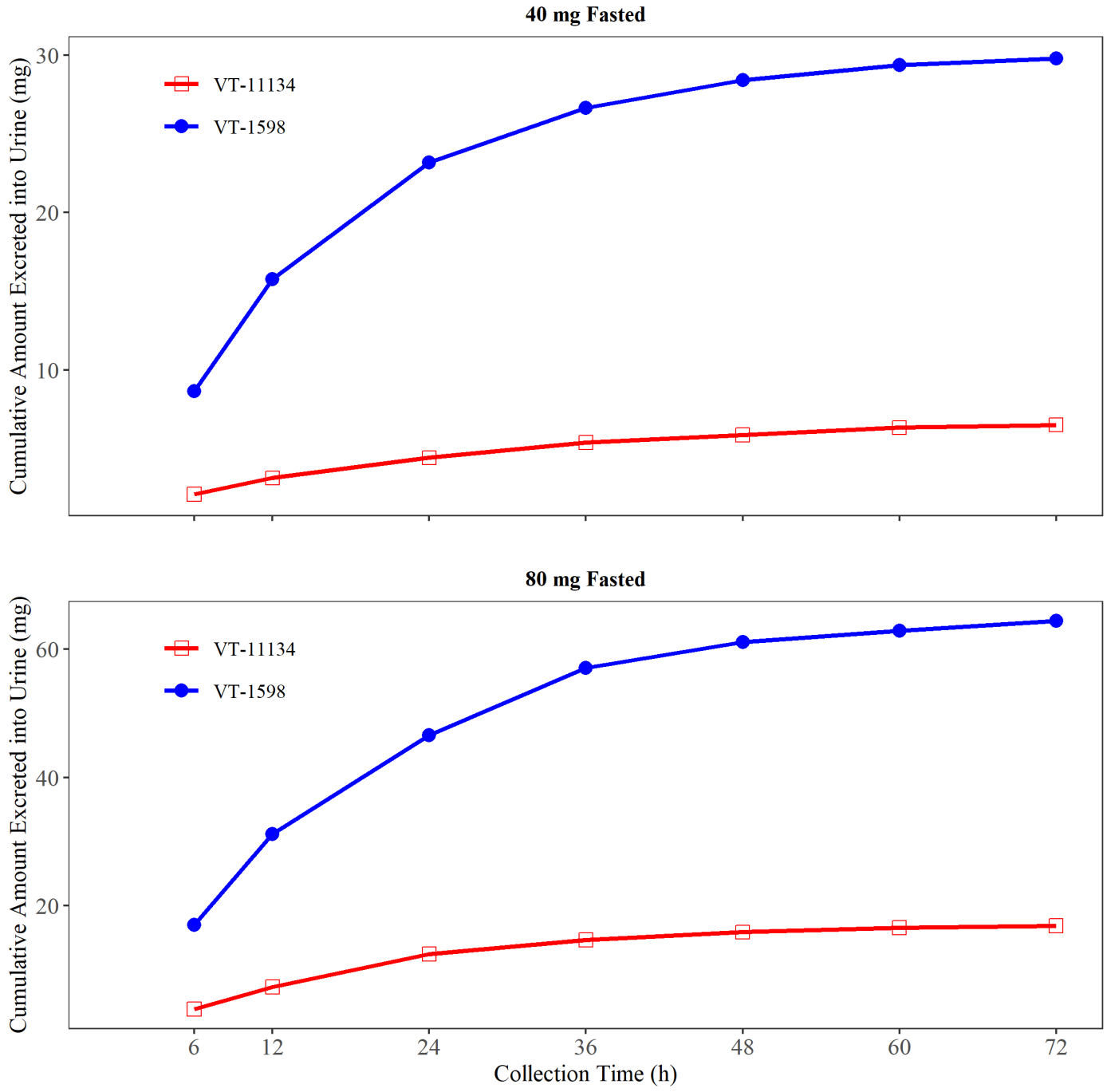


Figure 99: Mean of Cumulative Amount Excreted into Urine by Analyte – 160 mg Fasted and Fed Dose Groups

This figure will repeat Figure 97 for the 160 mg Fasted and Fed Dose Groups

Figure 100: Mean of Cumulative Amount Excreted into Urine by Analyte – 320 and 640 mg Fasted Dose Groups

This figure will repeat Figure 97 for the 320 mg and 640 mg Fasted Dose Groups

Figure 101: Dose Proportionality, Fasted C_{max}, VT-1598 in Plasma

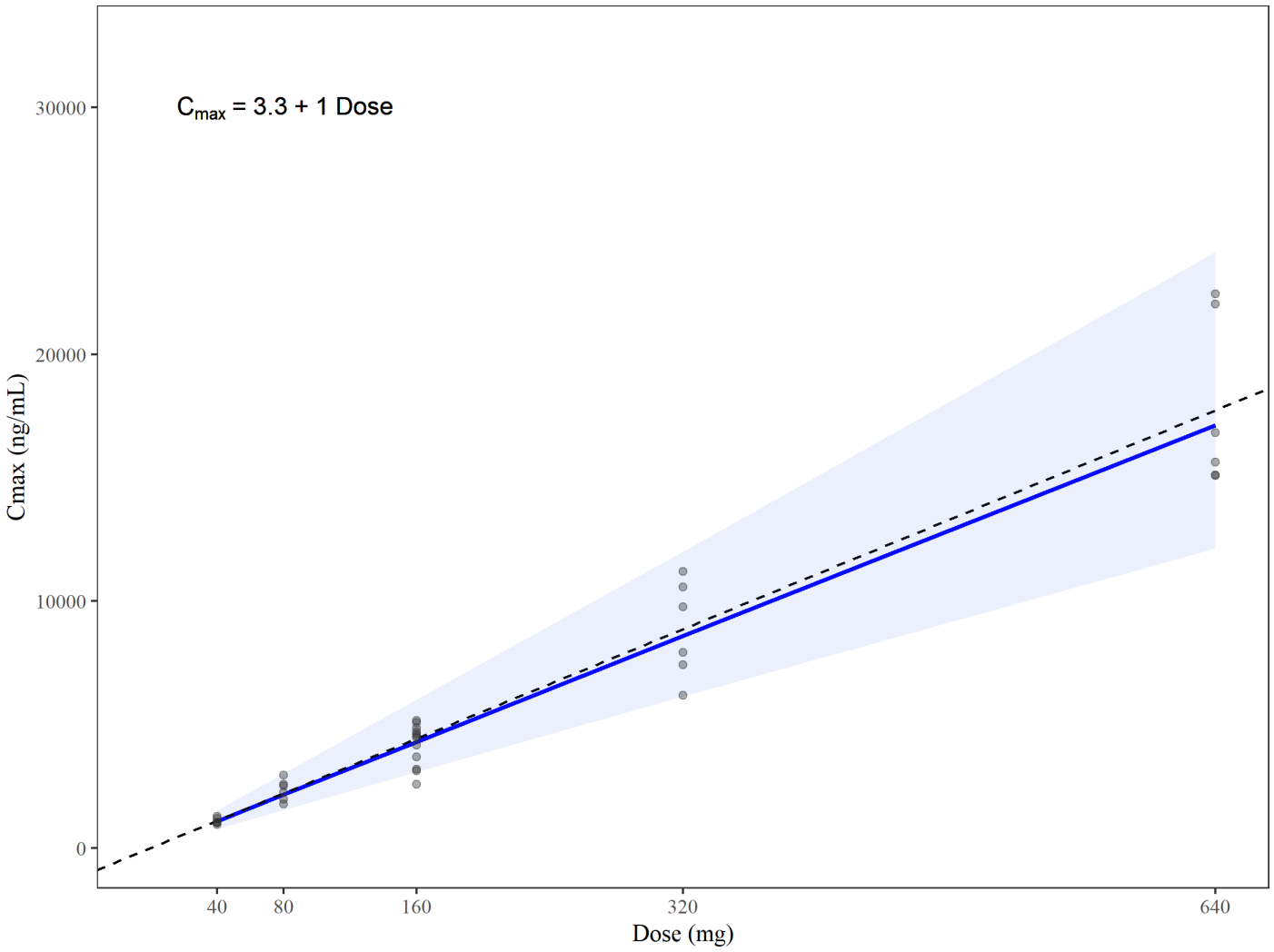


Figure 102: Dose Proportionality, Fasted $AUC_{0\text{-}last}$, VT-1598 in Plasma

This figure will repeat Figure 100 from for $AUC_{0\text{-}last}$ for VT-1598 in plasma

Figure 103: Dose Proportionality, Fasted $AUC_{0\text{-}inf}$, VT-1598 in Plasma

This figure will repeat Figure 100 from for $AUC_{0\text{-}inf}$ for VT-1598 in plasma

Figure 104: Dose Proportionality, Fasted C_{max}, VT-11134 in Plasma

This figure will repeat Figure 100 from for C_{max} for VT-11134 in plasma

Figure 105: Dose Proportionality, Fasted $AUC_{0\text{-}last}$, VT-11134 in Plasma

This figure will repeat Figure 100 from for $AUC_{0\text{-}last}$ for VT-11134 in plasma

Figure 106: Dose Proportionality, Fasted $AUC_{0\text{-}inf}$, VT-11134 in Plasma

This figure will repeat Figure 100 from for AUC0-inf for VT-11134 in plasma

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

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

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

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 2: 16.2.1: Early Terminations or Discontinued Subjects

[Implementation Note: Category will either be “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 that a subject both terminates early and discontinues treatment).]

Dose Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day
40 mg Fasted	PH2.00123	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 the "specify" fields, separated by a colon, e.g., "Other: Subject refusal." If deviation resulted in AE or subject termination, or affected product stability, indicate which of those events occurred in the listing row since those 3 columns were concatenated.

Review the site comments carefully. Replace any occurrences of the PATID in the comments with the USUBJID.

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

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."

Review the site comments carefully. Replace any occurrences of the PATID in the comments with the USUBJID.

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 a subject was not excluded from any analysis population, the subject will not appear in the listing. If the subject was excluded from multiple analysis populations, they will have one row per analysis population excluded from in the listing.

If no specifications are required for a reason for exclusion, then exclude the last column "Reason Subject Excluded Specification".

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
40 mg Fasted	PH2.00123	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)

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

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	MH Number	Medical History Term	MedDRA System Organ Class	MedDRA Preferred Term	Condition Start Day	Condition End Day
40 mg Fasted	PHU.00123	1	NUT ALLERGY	IMMUNE SYSTEM DISORDERS	FOOD ALLERGY	>5 years prior to enrollment	Ongoing

16.2.10 Concomitant Medications

Listing 8: Prior Medications

[Implementation Note: Include prior medications (medications with an end date prior to dosing) only. If the medication was taken for a Medical History condition, then include the MH description and the MH number in parentheses in the "Taken for a condition on the Medical History" column. If the start date is more than 30 days before enrollment, then categorize as follows:

- 5 years prior to enrollment
- 1-5 years prior to enrollment
- 1-12 months 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; MH Number)	ATC Level 1 (ATC Level 2)
40 mg Fasted	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 9: 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 description and number in parentheses, e.g., "Yes (AE/MH Description; 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)
40 mg Fasted	PHU.00123	001	BENADRYL	2	2	ITCHING	Yes (MACULAR RASH; 001)	No	DERMATOLOGICALS (ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.)

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

Listing 10: 16.2.5: Compliance Data

[Implementation Note: If not dosed according to protocol, details will be given in the Comments column (manually written, not programmed). If dose is not applicable for the subject, the date and time columns for those doses will be N/A. 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 Group	Subject ID	Dosed According to Protocol?	Dose Date	Dose Time	Vomited After Receiving Study Product?	Comments
40 mg Fasted	PHU.0123	Yes/No	ddMMMyyyy	hh:mm	Yes/No	
…						

16.2.6 Adverse Events

Listing 11: 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 "Relationship to Study Treatment (Alternate Etiology)" column, merge the data fields for relationship to study treatment and alternate etiology, separated 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 Higher Level Group Term	MedDRA Preferred Term	Number of Days Post Dose	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:											

16.2.7 Individual Laboratory Measurements

Listing 12: 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). The "extra" fields that are completed for abnormal results are not included in this listing; they are included in the listing of abnormal laboratory results that is included in the table shells document. Results outside of the reference range but not graded as Mild, Moderate, or Severe, should have ONR shown as the Severity Grade. Change from Baseline column will be blank for parameters that are not numeric.

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

Dose Group	Subject ID	Timepoint	Date of Assessment	Sex	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range
40 mg Fasted	PHU.00123	Day 4		Female	Sodium (mEq/L)	132 (Mild)	-7	131-132

Listing 13: 16.2.8.2: Clinical Laboratory Results – Hematology

[Implementation Note:

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

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

Listing 14: 16.2.8.3: Clinical Laboratory Results – Coagulation

[Implementation Note:

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

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

Listing 15: 16.2.8.3: Clinical Laboratory Results – Urinalysis

[Implementation Note: Change from baseline will not be calculated for character results. The change from baseline cell should be "-" for those rows.

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

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

16.2.9 Individual Screening Measurements

Listing 16: 16.2.9.1: Screening Laboratory Results – Serology

[Sort Order: Dose Group, Subject ID, Visit (visit order: Screening, Admission, Unscheduled).]

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

Listing 17: 16.2.9.1: Screening Laboratory Results – Urine Toxicology

[Implementation Note: If there are results for urine toxicology or alcohol breathalyzer tests on an Unscheduled visit, then the Study Day will be included in parentheses for the Visit.

Sort order: Dose Group, Subject ID, Visit (visit order: Screening, Admission, Unscheduled).]

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

Listing 18: 16.2.9.1: Screening Laboratory Results – Serum hCG and FSH Tests

[Implementation Note: If there are results for serum hCG on an Unscheduled visit, then the Study Day will be included in parentheses for the Visit. If obtained, FSH testing results will be shown in this listing.]

Sort order: Dose Group, Subject ID, Visit (visit order: Screening, Admission, Unscheduled).]

Dose Group	Subject ID	Visit	Serum HCG Result	FSH Test Result
40 mg Fasted	PHU.00123	Screening	Negative	ND

Note: ND=Test not performed

16.2.9 Vital Signs and Physical Exam Findings

Listing 19: 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 also be included in this listing. 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 (order: Height, Weight, BMI, Systolic Blood Pressure, Diastolic Blood Pressure, Pulse, Respiratory Rate, Temperature), Timepoint, Date of Assessment, Time of Assessment.]

Dose Group	Subject ID	Parameter (units)	Timepoint	Date of Assessment	Time of Assessment	Result (Severity)	Change from Baseline	Reason for Repeat
40 mg Fasted	PHU.00123	Systolic Blood Pressure (mmHg)	Day 1, 1 h Post Dose	ddMMMyyy	hh:mm	142 (Mild)	10	

Listing 20: 16.2.9.2: Abnormal 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 description and number in parentheses, e.g., "Yes (AE Description; 007)".

Sort order: Dose Group, Subject ID, Timepoint, Date of Assessment, Time of Assessment, Body System, and Finding.]

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

16.2.9 Individual ECG Results

Listing 21: 16.2.9.1: 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 the mean of triplicate readings, no assessment time should be presented and the replicate number should specify "Mean".

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

Dose Group	Subject ID	Sex	Parameter	Timepoint	Assessment Date	Assessment Time	Result (Severity)	Change from Baseline	Replicate Number	Reason for Repeat
40 mg Fasted	PHU.00123	Male	PR Interval	Day 4	ddMMMyyy	hh:mm	450 (Mild)	25	1	

Listing 22: 16.2.9.1: 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, Time of Assessment.]

Dose Group	Subject ID	Sex	Timepoint	Assessment Date	Interpretation	Comments	Reason for Repeat
40 mg Fasted	PHU.00123	Male	Day 4	ddMMMyyy	Abnormal NCS	Sinus Bradycardia	

Listing 23: 16.2.9.1: Listing of ECG Findings

[Implementation Note: This listing will contain observations of the EG domain, subset to contain observations where EGCAT="FINDING" and EGTESTCD^="INTP". The Category column will be based on EG.EGTEST and the Finding column will be based on EG.EGORRES.

Sort order: Dose Group, Subject ID, Date of Assessment, Time of Assessment, Category (EGTEST), and Finding (EGSTRESC).]

Dose Group	Subject ID	Timepoint	Date of Assessment	Category	Finding
40 mg Fasted	PHU.00123	Day 4	ddMMMyyy	Sinus Node Rhythms and Arrhythmias	SINUS ARRHYTHMIA

16.2.11 Pregnancy Reports

Listing 24: 16.2.11.1: Pregnancy Reports – Maternal Information

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

Dose 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 25: 16.2.11.2: Pregnancy Reports – Gravida and Para

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

Note: Gravida includes the current pregnancy, para events do not.
[a] Preterm Birth
[b] Term Birth
Extremely PB: <25 weeks
Very Early PB: 25 0/7-31 6/7 weeks
Early PB: 32 0/7-33 6/7 weeks
Late PB: 34 0/7-36 6/7 weeks
Early TB: 37 0/7-38 6/7 weeks
Full TB: 39 0/7-40 6/7 weeks
Late TB: 41 0/7-41 6/7 weeks
Post TB: ≥42 0/7 weeks

Listing 26: 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 27: 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 28: 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 29: 16.2.11.6: Birth Control Listing

[Implementation Note: If subject is not of childbearing potential, indicate the reason that the subject is not of childbearing potential in parentheses in the "Childbearing Potential" column.

Sort order: Dose Group, Subject ID, and Birth Control Start Day.]

Dose Group	Subject ID	Sex	Childbearing Potential	Birth Control Method	Birth Control Start Day	Birth Control End Day
40 mg Fasted	PHU.00123	Female	Yes	Hormonal Injections	-100	Ongoing

16.2.10 Subject Level PK Concentrations

Listing 30: 16.2.10: Subject Level VT-1598 and VT-11134 Concentrations – Plasma

[Implementation Note: Units of nominal time and actual timepoint vary by timepoint and will be provided for each time rather than in the column heading. Laboratory Reported Concentration will give verbatim value reported by lab (with minimal formatting, as needed) and will use a character value such as PC.PCORRES. Analysis Concentration will report the value actually used for analysis and will use a numeric variable such as ADNCA.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.

In the actual time column, mark out of window times with one asterisk (*), mark substantially out of window times with two asterisks (**), and mark imputed times with three asterisks (***)

Sort order: Dose Group, Subject ID, Analyte (VT-1598 then VT-11134), and Actual Time.]

Dose Group	Analyte	Subject ID	Nominal Time[a]	Actual Time[a]	Laboratory Reported Concentration (ng/mL)	Analysis Concentrations (ng/mL)	Used in λz Calculations
40 mg Fasted	VT-1598	PHU.00123	0 h	0 h	0	0	No

[a] Times are relative to time of dosing. For actual time, out of window times are indicated by an asterisk (*), substantially out of window times are indicated by two asterisks (**) and imputed times are indicated by three asterisks (***).
BQL=Below the Limit of Quantification

Listing 31: 16.2.10: Subject Level VT-1598 and VT-11134 Concentrations – Urine

[Implementation Note: Units of nominal time and actual timepoint vary by timepoint and will be provided for each time rather than in the column heading. Laboratory Reported Concentration will give verbatim value reported by lab (with minimal formatting, as needed) and will use a character value such as PC.PCORRES. Analysis Drug Concentration will report the value actually used for analysis and will use a numeric variable such as ADNCA.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.

In the actual time column, mark out of window times with one asterisk (*) and mark imputed times with three asterisks (***).

Sort order: Dose Group, Analyte (VT-1598 then VT-11134), Subject ID, and Actual Time.]

Dose Group	Analyte	Subject ID	Nominal Collection Interval[a]	Actual Collection Interval[a]	Laboratory Reported Concentration (ng/mL)	Urine Volume (mL)	Analysis Concentrations (ng/mL)	Total Amount Excreted From Urine (mg)
40 mg Fasted	VT-1598	PHU.00123	0-6 h	0-6 h	0	100	0	No

[a]Times are relative to time of dose. For actual time, out of window times are indicated by an asterisk (*) and imputed times are indicated by three asterisks (***).
BQL=Below Quantitative Limit

Listing 32: Subject Specific VT-1598 Plasma PK Parameters

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

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

Listing 33: Subject Specific VT-11134 Plasma PK Parameters

This listing will repeat Listing 32 for VT-11134 PK parameters in plasma.

Listing 34: Subject Specific VT-1598 Urine Inpatient Period PK Parameters

[Sort Order: Dose Group (40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted), Subject ID.]

Dose Group	Subject ID	Ae_{last} (mg)	$Ae_{\%Dose}$ (%)	CL_R (mL/min)
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	x	x
x	x	x	x	x

Listing 35: Subject Specific VT-1598 Urine Nominal Collection Time Interval PK Parameters

[Sort Order: Dose Group (40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted), Subject ID.]

Dose Group	Subject ID	Ae_{0-6} (mg)	Ae_{6-12} (mg)	Ae_{12-24} (mg)	Ae_{24-36} (mg)	Ae_{36-48} (mg)	Ae_{48-60} (mg)	Ae_{60-72} (mg)
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	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	x	x	x	x	x	x	x

Listing 36: Subject Specific VT-11134 Urine Inpatient Period PK Parameters

[Sort Order: Dose Group (40 mg Fasted, 80 mg Fasted, 160 mg Fasted, 160 mg Fed, 320 mg Fasted, 640 mg Fasted), Subject ID.]

Dose Group	Subject ID	Ae_{last} (mg)	CL_R (mL/min)
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

Listing 37: Subject Specific VT-11134 Urine Nominal Collection Time Interval PK Parameters

This table will repeat Listing 35 for VT-11134 in urine.