CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for

DMID Protocol: 21-0013

Study Title:

A PHASE I, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF INTRAVENOUS ERTAPENEM IN COMBINATION WITH ZIDEBACTAM (WCK 6777) IN HEALTHY ADULT SUBJECTS

NCT05645757

Version 1.0

DATE: 07NOV2023

RESTRICTED

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 21-0013**
Development Phase:	Phase 1
Products:	Ertapenem PLUS Zidebactam (WCK 6777) Ertapenem Zidebactam Placebo
Form/Route:	Intravenous (IV) infusion
Indication Studied:	Bacterial Infection
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	19APR2023
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	07NOV2023
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
Ae, urine	Amount of unchanged drug excreted in urine during each collection interval
$Ae, urine_{(0-24)}$	Cumulative amount of unchanged drug excreted in urine from time zero (predose) to 24 hours after Dose 1
$Ae, urine_{(0-24),ss}$	Cumulative amount of unchanged drug excreted in urine from time zero (predose) to 24 hours after Dose 7
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Concentration – Time Curve
$AUC_{(0-24)}$	Area under the concentration – time curve from time zero to 24 h
$AUC_{(0-24),ss}$	Area under the concentration – time curve from time zero to 24 h at steady state
AUC_{0-inf}	Area under the concentration - time curve from time zero to infinity
AUC_{0-last}	Area under the concentration - time curve from time zero to the last concentration above the lower limit of quantitation
$AUC_{(0-t)}$	Area under the concentration - time curve from time zero to time t
$AUC_{(0-tau)}$	Area under the concentration – time curve to the end of the dosing interval
$AUC_{(0-tau),ss}$	Area under the concentration – time curve to the end of the dosing interval at steady state
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
C_{avg}	Calculated average concentration during the dosing interval
CHEM	Chemistry
CI	Confidence Interval
CL_{CR}	Creatinine Clearance
$CL_{R(0-24)}$	Renal clearance to 24 h following Dose 1
$CL_{R,ss}$	Renal clearance at Steady State

List of Abbreviations *(continued)*

CL_T	Total Clearance
C_{max}	Maximum Concentration
$C_{max,ss}$	Maximum Concentration at Steady State
C_{min}	Minimum Concentration
$C_{min,ss}$	Minimum Concentration at Steady State
CO_2	Carbon Dioxide
COAG	Coagulation
ConMeds	Concomitant Medications
CRF	Case Report Form
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERT	Ertapenem
F	Fahrenheit
FDA	Food and Drug Administration
fe, urine	Fraction (%) of dose excreted unchanged in urine during each collection interval following Dose 1 and Dose 7
$fe, urine_{(0-24)}$	Fraction of dose excreted unchanged in urine from time zero (predose) to 24 hours following Dose 1 and Dose 7
h	Hours
Hct	Hematocrit
HEENT	Head, Eyes, Ears, Nose, and Throat
HEM	Hematology
Hgb	Hemoglobin
HR	Heart Rate
ICH	International Council for Harmonisation
INR	International Normalized Ratio
IQR	Interquartile Range
IRB	Institutional Review Board
IV	Intravenous

List of Abbreviations *(continued)*

K_e	Terminal Phase Elimination Rate Constant
L	Liter
LDH	Lactic Dehydrogenase
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantitation
mcg	Microgram
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalent
mg	Milligram
mL	Milliliter
MM	Medical Monitor
MO	Medical Officer
MOP	Manual of Procedures
MPV	Mean Platelet Volume
N	Number (typically refers to participants)
NCE	New Chemical Entity
NIH	National Institutes of Health
NRBC CT	Nucleated Red Blood Cell Count
ONR	Outside of Normal Range
PE	Physical Exam
PI	Principal Investigator
PK	Pharmacokinetic
PT	Preferred Term
QD	Administered once per day
QTc	Corrected QT Interval of the ECG
QTcF	Corrected QT interval of the ECG using Fridericia's Formula
RAUC	Accumulation ratio for AUC
RBC	Red Blood Cell
RC_{max}	Accumulation ratio for C_{max}

List of Abbreviations *(continued)*

RDW	Red Cell Distribution Width
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
$t_{1/2}$	Terminal Half-life
TEAE	Treatment-emergent Adverse Event
T_{max}	Time to obtain maximum concentration
$T_{max,ss}$	Time to obtain maximum concentration at steady state
T_{min}	Time to obtain minimum concentration
$T_{min,ss}$	Time to obtain minimum concentration at steady state
UA	Urinalysis
ULN	Upper Limit of Normal
V_d	Volume of Distribution
$V_{d,ss}$	Volume of Distribution at Steady State
VS	Vital Signs
WBC	White Blood Cell
WHO	World Health Organization
ZID	Zidebactam

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase I, Randomized, Double-blind, Placebo-controlled, Dose Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intravenous Ertapenem in Combination with Zidebactam (WCK 6777) in Healthy Adult Subjects" (Division of Microbiology and Infectious Diseases (DMID) Protocol 21-0013) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Council for 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) [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 [4] and the Royal Statistical Society for statistical practice [5].

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for pharmacokinetic and safety outcomes, and (4) a list of proposed tables, figures, and listings. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. 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, randomized, double-blind, placebo-controlled, dose escalation study to evaluate the safety, tolerability, and pharmacokinetics (PK) of intravenous (IV) Ertapenem (ERT) in combination with Zidebactam (ZID) (WCK 6777) in healthy adult participants. Seven cohorts will be enrolled in the study. Cohorts 1, 2, 4, 5, and 7 will have 8 participants, 6 receiving the active drug and 2 receiving the placebo. All 6 participants enrolled in cohorts 3 and 6 will receive the active drug.

2.1. Purpose of the Analyses

These analyses will assess the safety, tolerability, and PK of WCK 6777 in comparison with placebo and will be included in the CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary

- Assess the safety and tolerability of three dose-escalating regimens of WCK 6777 (ERT and ZID combination) and two dose-escalating regimens of standalone ERT or ZID following single daily doses for 7 days in healthy adult participants

Secondary

- Characterize the PK profiles in plasma (total and free) and in urine of three dose-escalating regimens of WCK 6777 (ERT and ZID combination) and the two dose-escalating regimens of standalone ERT or ZID following single daily doses for 7 days in healthy adult participants

3.2. Endpoints

Primary

- Type, incidence, severity, and relatedness to study drug of all treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in each treatment cohort from the first dose through the follow-up period.

Secondary

- PK parameter estimates and calculated exposures in plasma (total and free) and urine for ERT and ZID, when given alone and in combination following the single initial dosing on Day 1 and after daily dose administration for 7 days.

3.3. Study Definitions and Derived Variables

Baseline

Any systemic medical condition and the last vital sign (VS), electrocardiogram (ECG) and clinical safety laboratory test value that are recorded prior to dosing on Day 1 will be considered a baseline finding for the purpose of data analysis.

Treatment Group

Results of safety and PK analyses will be presented by study product. All participants assigned to the placebo group will be presented as pooled together for the purposes of these analyses. Treatment groups will be presented in the following order: WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo. Results from placebo participants will not appear in the PK analyses.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a phase 1, randomized, double-blind, placebo-controlled, dose escalation study to evaluate the safety, tolerability, and pharmacokinetics of IV ERT in combination with Zidebactam (WCK 6777) in healthy adult participants. An overall schematic of study design is shown in Figure 1. This study will enroll 52 participants into 7 cohorts.

WCK 6777 (ERT+ZID) will be evaluated in three cohorts - Cohorts 1, 4, and 7 will have 8 participants each (6 study drug combination and 2 placebos); ERT will be evaluated in two cohorts - Cohorts 2 and 5 will have 8 participants each (6 ERT and 2 placebo); and ZID will be evaluated in two cohorts - Cohorts 3 and 6 will have 6 participants each (all 6 ZID). The study will be placebo-controlled and double-blinded in all cohorts except Cohorts 3 and 6. No placebo participants are included in standalone ZID cohorts since adequate safety data for higher doses of ZID are available.

Study enrollment will proceed from Cohort 1 to Cohort 7 starting with the lowest dose and escalating to the next higher dose. Individual dose Cohorts 2 and 3, as well as Cohorts 5 and 6 will run in parallel. For each combination treatment cohort (Cohorts 1, 4 and 7), two sentinel participants will receive study treatments (one WCK 6777 and one placebo; drug/placebo ratio 1:1) and followed for safety for approximately 24 hours (h) prior to dosing of the remaining 6 participants in the cohort. If no halting rules have been met 24 h after start of dosing, dosing of sentinel participants will continue for the remainder of the study and the additional 6 participants in the cohort will be dosed (5 will receive WCK 6777 and 1 will receive placebo; drug/placebo ratio 5:1). Sentinels will not be employed in the single treatment cohorts.

Blood (plasma) and urine samples will be collected for measuring drug concentrations for PK analysis for 24 h after starting the first IV infusion on Day 1, and for 24 h after starting the last IV infusion on Day 7. Plasma concentrations will also be measured before and 12 h after dosing on Days 2 to 6. Total and free drug concentrations of ERT and ZID will be measured in plasma and total drug concentration of ERT and ZID in the urine by validated LC-MS/MS assays.

Safety data will be monitored from the time of infusion on Day 1 through Day 8, and at the last visit (Day 11+3 days) and will consist of: daily assessments of TEAEs, vital signs and symptom-directed physical examination (PE); clinical laboratory safety tests (Day -1, Days 2, 4, 6, and Day 8 [prior to the discharge from the study site]), and 12-lead ECGs (Day-1, Day 8 and Day 11 [+3 days]), and a complete PE on the last visit (Day 11 +3 days). AEs will be assessed by the study clinicians for severity or seriousness, and relatedness to study drug(s) and include outcome and duration.

Dose escalation from combination Cohort 1 (1 g ERT + 1 g ZID) to higher single dose Cohorts 2 (2 g ERT) and 3 (2 g ZID), and from combination Cohort 4 (2 g ERT + 2 g ZID) to higher single dose Cohorts 5 (3 g ERT) and 6 (3 g ZID) will be based on the safety monitoring committee (SMC) review of unblinded cumulative interim safety data collected through study Day 11 (+3 days) in each combination treatment cohort (See Protocol Section 9.6.1). The recommendation to continue to the next planned combination cohorts (i.e., Cohort 4 and Cohort 7), will be made by the study team (DMID medical officer (MO) and medical monitor (MM) and the site principal investigator (PI)) after review of blinded safety data in Cohorts 2 and 3 and Cohorts 5 and 6, respectively. The statistical and data coordinating center (SDCC) will provide a report of number of participants meeting dose escalation halting criteria. The decision to continue dose escalation to the next single or combination dose cohorts will be made by DMID after review of the SMC or the study team recommendation. If the decision is to continue dose escalation, the next in line cohort(s) will enroll.

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

The treatment regimen for the first combination cohort (Cohort 1), WCK 6777 2 g (ERT 1 g with ZID 1 g daily; 30-minute infusion), was selected because there are no human safety and PK data available with these agents in combination. The second combination cohort (Cohort 4) will evaluate the safety and PK of the anticipated therapeutic combination regimen of WCK 6777 4 g (ERT 2 g with ZID 2 g daily; 1-h infusion). The third combination-treatment cohort (Cohort 7) will evaluate the safety and PK of higher daily doses of WCK 6777 6 g (ERT 3 g + ZID 3 g daily; 2-h infusion). The primary purpose of the ERT 3 g with ZID 3 g combination treatment cohort is to ensure maximal flexibility in the clinical development program in the event there is a need to evaluate more intensive combination daily dosing regimens and different infusion strategies in future clinical trials. Moreover, 3 + 3 g/daily combination regimen will provide critical information on dose proportionality, PK linearity, and plasma protein binding linearity. As it is well-established that healthy participants do not fully reflect the real-world inter-participant variability observed in patients [6], the higher daily dosing regimen will also provide data on the safety, tolerability, and PK of upper range exposures likely to be encountered in clinical practice with ERT 2 g + ZID 2 g. To mitigate the risk of higher osmolality-linked infusion reactions, the volume of each infusion in the 2-g and 3-g dose standalone and combined groups (Cohorts 2-7) will be increased to 250 mL. The duration of infusions in the 2 g and 3-g cohorts were chosen to mitigate infusion duration-related AEs (nausea, vomiting) with ERT doses >2 g [7]. In four of the seven cohorts (Cohorts 2, 3, 5 and 6) single 2-g and 3 g ERT or ZID infusions will be administered. ERT 1 g daily and ZID 1 g daily will not be evaluated as single drug treatment cohorts as there are sufficient safety, tolerability, and PK data with these standalone regimens [7, 8, 9].

In all cohorts, 6 participants will receive study drug product. Two additional participants will receive placebo in the 2 g/daily and 3 g/daily ERT single treatment cohorts to maximize interpretation of the safety and tolerability of the observed results. The single drug treatment cohorts are being conducted to collect the baseline safety and pharmacokinetic data. Specifically, the single treatment arms of ERT and ZID are necessary to assess for the presence of any PK interactions between the two constituents and to deduce the role of each, in the event of any safety or tolerability signals in the combination cohorts. In conjunction with the escalating dose combination regimens, the single treatment drug cohorts will also provide information on dose PK proportionality, which is necessary for building robust individual population PK models for ERT and ZID, which, supplemented with PK/PD studies, will help justify the dose regimen for advanced clinical trials.

4.3. Selection of Study Population

Only participants who meet all inclusion criteria and no exclusion criteria will be eligible for enrollment into the trial. Eligibility criteria can be found in v5.0 of the Protocol.

4.3.1. Inclusion Criteria

For a list of inclusion criteria, see Section 5.1 of Protocol v5.0.

4.3.2. Exclusion Criteria

For a list of exclusion criteria, see Section 5.2 of Protocol v5.0.

4.4. Treatments

4.4.1. Treatments Administered

In each cohort, either study drug alone or in combination will be administered as an intravenous infusion (IV) of 100 mL daily for 7 consecutive days in Cohort 1 or 250 mL daily for 7 consecutive days in Cohorts 2 to 7. For each successive treatment cohort, however, the dose will be progressively escalated from 1 g/daily to 2 g/daily and to 3 g/daily, and the duration of infusion time increased from 30 min to 1 h and to 2 h over the course of the study. In Cohort 1, WCK 6777 2 g (ERT 1 g/daily combined with ZID 1 g/daily) will be administered in 30 (±5) minutes (min); in Cohort 2 (ERT 2 g/daily), Cohort 3 (ZID 2 g/daily), and Cohort 4 (WCK 6777 4 g [ERT 2 g/daily combined with ZID 2 g/daily] the study drug(s) will be administered in 60 (±10) min, and in Cohort 5 (ERT 3 g/daily), Cohort 6 (ZID 3 g daily) and Cohort 7 (WCK 6777 6 g [ERT 3 g/daily combined with ZID 3g/daily]), the study drug(s) will be administered in 120 (±10) min.

4.4.2. Identity of Investigational Product(s)

Zidebactam for Injection, 1 g/vial
Zidebactam dihydrate (CAS No. 1996664-59-5) is a proprietary New Chemical Entity (NCE) of Wockhardt coded as WCK 5107. It is a bicyclo-acyl-hydrazide (DBO pharmacophore) chemically identified as (2S, 5R)-7-Oxo-6-sulphooxy-2-[N'-(©-piperidin-3-carbonyl)-hydrazinocarbonyl]-1, 6-diaza-bicyclo [3.2.1] octane dihydrate. ZID has a molecular formula of $C_{13}H_{21}N_5O_7S \cdot 2H_2O$ and a molecular weight of 427.45 daltons (includes two water molecules). ZID exists as pale yellow to white crystalline powder. It is slightly hygroscopic and is freely soluble in water and insoluble in dichloromethane [9].

Ertapenem Sodium for Injection, 1 g/vial (ERT)
ERT is generally available as ertapenem sodium (CAS No. 153773-82-1), and chemically identified as [4R-[3(3S*,5S*),4α,5β,6β(R*)]]-3-[[5-[[(3-carboxyphenyl)amino] carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylic acid monosodium salt. It has a molecular formula $C_{22}H_{24}N_3O_7SNa$ and a molecular weight of 497.50 daltons. ERT sodium is a white to off-white hygroscopic, weakly crystalline powder. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol, and insoluble in isopropyl acetate and tetrahydrofuran [8].

WCK 6777 (ERT-ZID)
WCK 6777 is a combination of equal amounts of ERT, a carbapenem antibiotic, and ZID, a non-β-lactam entity which acts as a β-lactam enhancer. It is being developed as once-a day parenteral therapy for the treatment of Gram-negative infections. The indications described for ERT would be targeted for WCK 6777 in clinical settings.

Placebo
0.9% Sodium Chloride Injection, USP will be used as the placebo for this study.

Sterile Water for Injection, USP is sterile, nonpyrogenic, distilled water for intravenous administration after addition of a suitable solute. No antimicrobial or other substance has been added. The pH is 5.5 (5.0 to 7.0). The osmolarity is 0 mOsmol/L. It will be used for reconstituting ERT and ZID separately or combined (for WCK 6777) prior to dilution with sterile 0.9% Sodium Chloride Injection, USP.

0.9% Sodium Chloride Injection, USP is a sterile, nonpyrogenic solution. Each 100 mL contains 900 mg sodium chloride in water for injection. It contains sodium (Na^+) 154 mEq/L and chloride (Cl^-) 154 mEq/L. The osmolarity is 308 mOsmol/L (calc.). The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.6, range 4.5 to 7.0). This solution contains no bacteriostatic, antimicrobial agent or added buffer. It will be used as the diluent for ERT and ZID and as the placebo in this study.

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

For the drug combination cohorts (Cohorts 1, 4, and 7) and standalone ERT cohorts (Cohorts 2 and 5), the trial will be double-blinded, placebo controlled, with eight participants randomized to receive either active drug(s) or placebo (normal saline) in an overall 3:1 ratio (6 participants study drug and 2 participants placebo). For each drug combination dosing cohort, two sentinel participants will be randomized in a 1:1 fashion to active drug and placebo and will be followed for 24 h. If there are no safety events, the remaining six participants in each cohort will be randomized in a 5:1 ratio to active drug and placebo. Sentinel participants will not be used for the randomized, standalone ERT cohorts and for the ZID cohorts.

Randomized treatment assignments for these cohorts will be generated centrally at the SDCC through the Advantage eClinical® application by the unblinded study biostatistician, and a list will be transferred to the unblinded study personnel (i.e., research pharmacists and a verifier) at the research site prior to start of the study for the purpose of an emergency back-up, which will be kept up in a secure place. The research pharmacists will perform dose preparation; the unblinded verifier is a member of the pharmacy team who will not participate in dose preparation.

4.4.4. Selection of Doses in the Study

In vivo pharmacokinetic/pharmacodynamic (PK/PD) studies involving neutropenic mouse lung infection models have demonstrated that the ERT-ZID combination exerts significant bactericidal action against KPC, OXA-48-like and MBL-expressing Enterobacterales at mouse exposures that correspond to 2 g q24h clinical exposures of ERT and 2 g q24h exposures of ZID obtained when dosed individually [9].

The IV No Observed Adverse Effect Level (NOAEL) doses, based on a 28-day repeat dose toxicity study for ZID in rat and dog, are 800 and 750 mg/kg/day, respectively, and the corresponding exposure in terms of 24-hour (h) area under the plasma drug concentration-time curves (AUCs) are 1950 and 1962 µg·h/mL, respectively. On the basis of ZID NOAEL dose exposures in dog (750 mg/kg/day) and rat (800 mg/kg/day) and anticipated ZID clinical exposure of 300 µg·h/mL at 2 g/day, a safety window of approximately six times is estimated [9].

Extrapolation of the dog IV NOAEL dose of 750 mg/kg to a human dose (based on body surface area) would lead to a human equivalent dose for ZID of 416 mg/kg, corresponding to 29 g for a 70- kg human. Likewise, considering the NOAEL dose (800 mg/kg) in rat, the human equivalent dose for ZID would be 64 mg/kg, corresponding to 9 g for a 70 kg human [9].

4.4.5. Selection and Timing of Dose for Each Participant

Study product for each participant will be assigned by randomization and will not be further adjusted. A list of study products by cohort is available in Table 1.

A Phase 1 study is required given that human safety and PK data are not available for ERT and ZID administered in combination. The following observations support conduct of this study: (a) Non-clinical mechanism of action (MOA) and PK/PD studies establish ERT/ZID 2 g/2 g QD as a potential treatment of patients with CRE infections; (b) Multiple Phase 1 studies conducted for ZID alone or in combination with FEP demonstrated safety and tolerability of ZID at multiple daily doses up to 6 g (2 g q8h) administered over 7 to 10 days; (c) Higher IV ERT doses of 2 g and 3 g QD have been studied in previous phase 1 and 2 studies (n = 101) [7, 8]; (d) The preclinical toxicity studies of WCK 6777 in rats and dogs employing doses that generated exposures higher than the clinical exposures reported for ERT 2 g and ZID 2 g suggest that the combination would be safe and tolerable.

4.4.6. Blinding

All investigative site personnel, study volunteers, DMID, Wockhardt and DVC personnel will remain blinded through database lock, with the exception of an unblinded pharmacist/verifier at the research site, an unblinded SDCC biostatistician, and a DMID/CMS manager responsible for PK sample storage. The randomization scheme will be provided to the unblinded research pharmacist at the site, who will perform dose preparation, and a pharmacy verifier who will not participate in dose preparation. These pharmacy personnel at the site will not be involved in study-related assessments or have participant contact for data collection following study drug administration. The study staff participating in the administration of study product and assessment of the participants will not be aware of the administered contents of the IV infusion in the randomized arms of the study. Study drugs will be diluted in normal saline, and they will look identical to placebo in the IV infusion bag so the study staff and the participant will not be able to determine whether placebo or active drug are being administered. The label on the IV infusion bag will not have information that can identify the contents. Only plasma and urine PK samples collected from participants who received active drug(s) will be sent to the bioanalytical laboratory, KCAS, for testing. To select these samples, an SDCC Unblinded Biostatistics Team will determine which volunteers received active drug and will provide the list of samples from those volunteers to DMID-CMS. DMID-CMS repository employees will identify those samples and ship to KCAS. KCAS personnel are blinded regarding participant, study day, and timepoint sequence within a study day. Individual samples are barcoded, and the barcode includes information that can match the sample to the volunteer identification number, aliquot number, treatment cohort and collection timepoint. Data from KCAS will be received by the SDCC Unblinded Biostatistics Team and entered into the database after the safety analysis was completed by the SDCC Blinded Biostatistics team. The SMC will receive blinded data in aggregate and presented by cohort. The SMC may review unblinded data prepared by an unblinded biostatistician in the closed session only.

4.4.7. Prior and Concomitant Therapy

Medications include the following: prescription drugs, birth control hormonal preparations, nonprescription medication, herbs, vitamins, nutritional supplements, and illicit and recreational substances. Medications taken before or after dosing will be reported as Prior Medications or Concomitant Medications (ConMeds), respectively.

Prior prescription medications will be recorded at Screening Visit. All prior medications are not allowed during the study period with the exception of oral contraceptives, which are permitted throughout the study if already used.

The following medications are prohibited for the indicated periods prior to dosing:

- Receipt of probenecid or furosemide within 14 days prior to study enrollment.
- Receipt of any antibiotics within 14 days prior to study enrollment.
- Receipt of prescription medications (except birth control pills or hormone replacement in females) within 14 days prior to study enrollment, unless in the opinion of site investigator the medication will not interfere with the study procedures or impact participant safety).
- Receipt of the following medications that interact with human OAT3 within 14 days prior to study enrollment: Adefovir, Anagliptin, Baricitinib, Cefaclor, Cimetidine, Ciprofloxacin (Systemic), Clofarabine, Eluxadoline, Empagliflozin, Furosemide, Ketoprofen, Methotrexate, Mycophenolate, PEMEtrexed, Penicillin G (Parenteral/Aqueous), Penicillin G Benzathine, Penicillin G Procaine, Penicillin V Benzathine, Penicillin V Potassium, Zidovudine.
- Receipt of herbal and dietary supplements (including St. John's Wort) within 14 days prior to study

enrollment.
• Receipt of valproic acid within 14 days prior to study enrollment.

Non-prescription medications, herbs, vitamins, and nutritional supplements will not be taken within 14 days before dosing and during the trial. Exceptions: vitamins and OTC medications, taken for <48 h for the treatment of common symptoms (e.g., headache, indigestion, muscle pain), including solitary doses of up to 1,000 mg acetaminophen (paracetamol), may be allowed if approved by the Site PI or authorized clinician(s).

Blood/blood products (RBCs, WBCs, platelets, and plasma) donation of 500 mL within 3 months or more than 100 mL within 30 days before signing informed consent to this trial is not allowed, and it is prohibited during the course of this trial.

Following dosing, each new ConMed and changes to existing medications will be recorded. Participants will be required not to utilize non-study medications during the trial except those deemed necessary by the Site PI or authorized clinician(s).

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

4.4.8. Treatment Compliance

Since each dose of study drug(s) will be administered by site personnel, participant compliance is not anticipated to be an issue. Complete information regarding any partial or interrupted dosing will be documented. Participants withdrawn prior to dosing or without at least one PK blood draw will be excluded from PK data analysis. All PK samples prior to participant withdrawal or treatment discontinuation will be included in summaries of drug concentrations. Participants who receive any amount of study product will be followed up with their consent for safety assessments until Final Visit (Day 11+3) and for completion of scheduled plasma PK sample collection following the last dose of study drug they received.

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 participants, there will be no assessment of drug efficacy. For a detailed schedule of study procedures refer to Table 2.

4.5.1. Safety Variables

The following safety endpoints will be assessed:

- Chemistry (CHEM), Hematology (HEM), Urinalysis (UA), and Coagulation (COAG) clinical laboratory result safety parameters will be collected according to the schedule of study procedures in Table 2:
  - The following parameters will be measured:
    - CHEM parameters: electrolytes (sodium, potassium, chloride, total carbon dioxide [CO_2]), creatinine with estimation of creatinine clearance (CL_{CR}) by the Cockcroft-Gault method, blood urea nitrogen (BUN), glucose (fasting), total bilirubin, direct bilirubin, alanine

aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), lactic dehydrogenase (LDH), total protein, and albumin.

- HEM parameters: Hemoglobin (Hgb), Hematocrit (Hct), red blood cell (RBC), platelet count, and white blood cell (WBC) count with absolute differential count.
- COAG parameters: international normalized ratio (INR) with prothrombin time (PT), activated partial thromboplastin time (APTT).
- UA parameters: Routine dipstick testing of clean-catch urine for occult blood, protein, glucose, ketones, nitrate, bilirubin, leucocyte esterase, specific gravity, and pH.
  - If urine dipstick is abnormal for blood, protein, glucose and leukocyte esterase, urine microscopy will be performed (for WBC, RBC, bacteria, and other cell counts), and the results will supersede those of the dipstick UA.

- VS parameters will be collected according to the schedule in Table 2:
  - The following parameters will be measured:
    - resting (measured after supine for at least 5 min) systolic blood pressure (SBP) and diastolic BP (DBP), heart rate (HR), respiratory rate (RR), and oral temperature (T).
- ECG parameters will be collected according to the schedule in Table 2:
  - ECG measurements will be conducted in triplicate, and the mean of triplicate values will be used for analysis, including analyses of change from baseline.
  - The following parameters will be measured:
    - PR interval, QRS duration, QT interval, QTcF interval, RR interval, and ventricular rate
- Physical exams:
  - Complete physical exams will be collected according to the schedule in Table 2 and include the following parameters:
    - General appearance, HEENT, heart, lungs, abdomen, skin, musculoskeletal system, lymph nodes, and a standard neurological exam.
  - A symptom-directed physical exam may be performed before dosing on Day 1, at any time after dosing on Days 1 to 7, and at Unscheduled visit for evaluation of TEAEs.

Incidence, relatedness, and severity of TEAEs 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 9.2.2 and 9.2.3 of the study protocol v5.0. AEs and SAEs are defined in Section 9 of the protocol. Clinical VS and systemic AEs will be graded using the toxicity grading scales in Protocol Appendix B, Table 2. Clinical laboratory, and ECG results will be assessed using the toxicity grading scales in Protocol Appendix B, Table 3 and Table 4, respectively.

4.5.2. Pharmacokinetics Variables

Blood (plasma) samples and urine samples for PK analysis will be collected according to the schedule of study procedures listed in Table 2. Total and free ERT and ZID concentrations will be measured in plasma samples, and total ERT and ZID concentrations will be measured in urine samples. Plasma and urine

concentrations of ERT and ZID will be quantitated using validated Study drug concentration data in plasma and urine will be transferred to SDCC (Emmes) from the bioanalytical lab, KCAS, for reporting and pharmacokinetic analysis.

PK parameters to be estimated for single dose and multiple dose plasma samples and urine samples are detailed in Section 10.1.

5. SAMPLE SIZE CONSIDERATIONS

The sample size of 52 participants assigned into 7 treatment cohorts with 8 participants per cohort (6 participants randomized to receive active drug(s) and 2 placebo), with the exception of Cohorts 3 and 6, where 6 participants will receive active ZID only, was chosen to obtain reasonable evidence of safety without exposing undue numbers of healthy participants to ERT combined with ZID, ERT alone, and ZID alone at this phase of clinical evaluation. Previous experience in Phase 1 studies has shown that the sample size being proposed is sufficient to fulfill the primary and secondary objectives of the study. Power calculations have not been performed.

Participants who are withdrawn before dosing or who do not have at least 1 PK blood draw will be replaced with a participant assigned to the same treatment cohort. Additionally, participants will be replaced in each cohort to ensure there are at least 7 participants with complete PK profiles in each cohort with 8 participants each and at least 5 participants in each standalone ZID cohort. A participant will be considered to have a complete PK profile if at least 70% of planned plasma PK samples are collected.

The SDCC (Emmes) will monitor the number of participants in each cohort with a complete PK profile. Due to the potential for 2 of the 7 participants in each cohort with complete PK profiles to be placebo participants it is expected there will be at least 5 participants with evaluable PK data in each cohort with 8 participants (Cohorts 1, 2, 4, 5, and 7). It is expected that 5 participants in each cohort with 6 participants (Cohorts 3 and 6) will have evaluable PK data since this cohort enrolls no placebo participants.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Summary statistics for continuous data will include the number of participants 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 participants will be included in the summaries of participant 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 participants in the Safety Population. Denominators for clinical, clinical laboratory, VS, and ECG results at planned study timepoints will be the number of participants in the Safety Population with available results at the specified timepoint for that parameter. Denominators for the conceptual "Maximum Severity Post Baseline" timepoint for clinical, clinical laboratory, VS, and ECG results will be the number of participants 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. The sort order of clinical, clinical laboratory tests, VS, and ECG parameters is described in Section 9.

6.2. Timing of Analyses

A final CSR will be prepared after all safety, 12-lead standard ECG, and plasma and urine PK data are available.

Interim cumulative safety data to determine escalation to higher dose will be presented to the SMC after completion of Cohort 1 and Cohort 4.

Blinded safety and tolerability data will be periodically reviewed by the DMID medical team (medical monitor and medical officer) and the site PI or authorized study clinician (listed on FDA Form 1572) to assess whether rules for halting progression to the next study cohort have been met (see Protocol Section 9.5 for a list of halting criteria) and specifically to recommend dose escalation to Cohort 4 following Cohorts 2 and 3, and to Cohort 7 following Cohorts 5 and 6. SMC meetings are scheduled to review cumulative interim safety data after completion of all participants in Cohort 1 before dose escalation to Cohorts 2 and 3, and after completion of all participants in Cohorts 1 through 4 before dose escalation to Cohorts 5 and 6. An *ad hoc* SMC meeting will review safety data if halting criteria have been met for dose escalation to Cohorts 4 and 7. The SMC will receive data in aggregate. The SMC may request to receive data by study product vs. placebo in a closed session. The SMC may also request that the blind be broken for individual participants, as needed, to assess safety issues.

The SMC will review final safety data in all cohorts when available after database lock.

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 participants excluded from an analysis population (Safety Population, PK Analysis Population, or PK Analysis Subset) will be included in the CSR (Listing 5). Reasons for exclusion from analysis populations will be summarized in Table 9.

6.3.1. Safety Population

The *safety population* will include all participants who received any amount of study drug(s).

6.3.2. PK Analysis Population

The *PK analysis population* will consist of all participants who received at least a single dose of study drug and have at least one quantifiable post-dosing plasma drug concentration measured.

6.3.3. PK Analysis Subset Population

The *PK Analysis Subset* is defined as the subset of the PK Analysis Population that received the intended doses of study drug(s) and have sufficient data that permit estimation of PK parameters. Any participant with at least one estimable PK parameter will be included in this subset, however, only estimable parameters will be summarized. Participants will be analyzed by dose as treated.

To assess the impact of missing data, a sensitivity analysis will be conducted using the *PK Analysis Subset Subgroup*. PK data from participants that were compliant with dosing and had all planned PK samples collected on either Day 1 or Day 7 will be included from the respective complete day(s) for this subset.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses; however, a sensitivity analysis of the PK Analysis Subset will be conducted using the PK Analysis Subset Subgroup.

6.5. Missing Data

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values.

Outliers will not be excluded from the safety and PK analyses. Outliers identified during the PK analysis will be discussed in the CSR text. Outliers will be defined as any values of plasma or urine concentration for a given Treatment Group that fall outside the interquartile fences of their respective distribution. Given an interquartile range (IQR) of Q3-Q1, where Q3 is the 75^{th} percentile and Q1 is the 25^{th} percentile, outliers will be those that are greater than Q3 + (1.5 x IQR) or those that are less than Q1 - (1.5 x IQR).

6.6. Interim Analyses and Data Monitoring

An SMC meeting to review safety data is planned after the completion of Cohort 1 before dose escalation to Cohorts 2 and 3, and after the completion of Cohort 4 before dose escalation to Cohorts 5 and 6. Safety data, including AEs; SAEs; clinical assessments; VS; clinical laboratory results (CHEM, HEM, COAG, and UA); and 12 lead ECGs will be presented by cohort. Reasons for participants who terminate the study early or discontinue treatment will be presented for all cohorts. The SMC may also review safety data by Treatment Group in the closed session or ad hoc meetings as requested.

6.7. Multicenter Studies

This is a single-site study.

6.8. Multiple Comparisons/Multiplicity

The analysis of the primary endpoint in this study is descriptive rather than a hypothesis test, therefore no adjustments for multiple testing are planned.

7. STUDY PARTICIPANTS

7.1. Disposition of Participants

Screened participants who were ineligible for enrollment in the study (screen failures) or eligible but not enrolled will be summarized by inclusion and exclusion criteria (Table 10). Enrolled participants who were ineligible for inclusion in analysis populations will be summarized by reason for participant exclusion and Treatment Group (Table 9). Individual listings of participants who were excluded from the Safety Population, the PK Analysis Population, or the PK Analysis Subset will be listed (Listing 5).

Participant disposition will be summarized (Table 8), showing the number of participants who were screened, enrolled and randomized, received study product, had at least one quantifiable post-dosing plasma drug concentration measured, completed all planned PK blood draws, completed all planned PK urine samples, have complete PK profiles, completed final study visit, and terminated early. Participants who discontinued dosing or terminated early from the study will be listed (Listing 2). A flowchart displaying the disposition of study participants will be included (Figure 2). This figure will present the number of participants screened, enrolled, lost to follow-up, and analyzed by Treatment Group.

7.2. Protocol Deviations

A summary of participant-specific protocol deviations will be presented by deviation category, deviation type, and Treatment Group (Table 7). This table will provide both the number of participants and the number of deviations for each deviation category and deviation type. All participant-specific protocol deviations and non-participant-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 Treatment Group. Placebo participants from each cohort that enrolled placebos (Cohorts 1, 2, 4, 5, and 7) will be pooled together for the purposes of the safety analyses.

TEAEs and SAEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities® (MedDRA). All AEs occurring after study drug dosing will be summarized using frequency counts and percentages. The following summaries will be presented for TEAEs and SAEs:

- Overall (i.e., regardless of severity or relationship to treatment).
- By severity grade (mild, moderate, or severe).
- By relationship to study drug.
- By MedDRA level hierarchy (system organ class [SOC], higher level group term [HLGT] and preferred term [PT]).

Unless otherwise specified, at each level of participant summarization in reporting the incidence of TEAEs, a participant will be counted once if the participant reported one or more TEAEs. If more than one occurrence of a TEAE is reported, the TEAE of the worst severity or the worst-case relationship assessment will be summarized.

If a participant was accepted into the trial with a laboratory value of an analyte that overlaps with values used for grading Grade 1 laboratory abnormalities, a TEAE will be reported if the on-study value of the same analyte is graded Grade 2 or higher.

9.1. Demographic and Other Baseline Characteristics

Sex, ethnicity, and race of all participants will be summarized by Treatment Group (Table 11). 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, participants 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 body mass index (BMI) at Screening will be summarized by Treatment Group (Table 12). Individual participant 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 24.1 or higher. Summaries of participants’ pre-existing medical conditions by MedDRA SOC will be presented by Treatment Group (Table 13). Individual participant 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 215 for prior medications and Table 216 for ConMeds). Individual participant listings will be presented for all prior medication (Listing 37) and ConMeds (Listing 38).

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 participant was dosed according to protocol will be included in Listing 8. A listing of infusion interruptions will be presented in Listing 9. Participant level ERT/ZID concentrations at each timepoint will be included in Listing 10 for total ERT and/or ZID concentrations in plasma, Listing 11 for free ERT and/or ZID concentrations in plasma, and Listing 20 for total ERT and/or ZID concentrations in urine.

9.3. Adverse Events

An overall summary of adverse events by Treatment Group will be presented in Table 192 including the number of participants with at least one AE, number of participants with at least one related AE, and number of participants with at least one SAE.

All AEs will be presented in Listing 25. A participant listing of non-serious AEs of moderate or greater severity will also be reported (Table 196).

The following summaries for AEs will be presented by Treatment Group, SOC, HLGT, and PT:

- The number of AEs and number and proportion of participants reporting an AE or SAE that occurred in 5% of participants in any treatment group will be presented (Table 193).
- The number of AEs and number and proportion of participants reporting an AE will be presented. The 95% CI for the proportion of participants experiencing each SOC/HLGT/PT will also be presented (Table 194).
- The number and proportion of participants reporting a related or unrelated AE will be presented by severity and relationship to study product (Table 195).

Summaries of AEs will be presented graphically in bar charts by Treatment Group and SOC. For summaries of proportions of participants reporting an AE, denominators will be the number of participants in the Safety Population for each Treatment Group:

- The total number of related AEs reported will be presented (Figure 65).
- The proportion of participants reporting a related AE will be presented by the maximum severity reported per SOC (Figure 66).

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

Individual data listings of deaths and other SAEs will be provided (Table 197). The listing will include participant ID, Treatment Group, AE description, SOC, 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 participant 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 39.
- Gravida and para information will be presented in Listing 40.
- Live birth outcomes will be presented in Listing 41, and still birth outcomes will be presented in Listing 42.
- Spontaneous, elective, or therapeutic abortion outcomes will be presented in Listing 43.

9.6. Clinical Laboratory Evaluations

Toxicity grading criteria for clinical laboratory results can be found in Table 5. 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. All clinical laboratory results will be listed for each participant from time of screening to last study visit. Any abnormal lab results at Screening or Baseline with values in the Grade 1 range but deemed acceptable for enrollment per protocol Section 5.1, inclusion criterion #5, will be presented in listings but will only be reported as TEAEs if the severity increases to Grade 2 or higher. 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.

All safety laboratory results, severity, and change from baseline will be listed for each participant by Treatment Group and timepoint. Abnormal laboratory results (laboratory results outside the normal range defined in the protocol) 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). Results that have toxicity grading ranges defined in the protocol and are outside the normal range, but not mild, moderate, or severe, will have (ONR) as the severity included after the result.

The sort order for chemistry parameters will be as follows: sodium, potassium, calcium, chloride, CO_2, creatinine, CL_{CR}, BUN, glucose (fasting), total bilirubin, direct bilirubin, ALT, AST, AP, LDH, total protein, and albumin.

The sort order for hematology parameters will be as follows: Hgb, Hct, RBC, platelet count, Total WBC count, and absolute counts for neutrophils, monocytes, lymphocytes, eosinophils, and basophils.

The sort order for coagulation parameters will be as follows: INR, PT, and APTT.

The sort order for urinalysis parameters will be as follows: occult blood, protein, glucose, bilirubin, ketones, nitrate, leucocyte esterase, specific gravity, and pH.

- All CHEM results, including at unscheduled visits, will be presented in Listing 26. Abnormal results will be presented in Table 198.
- All HEM results, including at unscheduled visits, will be presented in Listing 27. Abnormal results will be presented in Table 199.
- All COAG results, including at unscheduled visits, will be presented in Listing 28. Abnormal results will be presented in Table 200.
- All UA results (dipstick and microscopic), including at unscheduled visits, will be presented in Listing 29. Abnormal results will be presented in Table 201.

All Screening results will be listed for each participant by Treatment Group and visit:

- Serology results (Listing 30).
- Serum human chorionic gonadotropin (hCG) and FSH pregnancy testing results (Listing 31).
- Urine toxicology and alcohol urine results (Listing 32).

Laboratory results will be summarized in tables and figures:

- Proportion of participants with mild, moderate, or severe laboratory results by parameter, Treatment Group, and timepoint for CHEM (Table 202), HEM (Table 204), COAG (Table 206), and UA (Table 208).
- Summary statistics of measurements and change from baseline are presented by parameter, Treatment Group, and timepoint for CHEM (Table 203), HEM (Table 205), COAG (Table 207), and UA (Table 209).
- Graphical presentation of change from baseline at scheduled visits by Treatment Group, and timepoint for each parameter as a series of box plots.
  - CHEM parameters will be presented beginning at Figure 66 and continuing through Figure 82.
  - HEM parameters will be presented beginning at Figure 83 and continuing through Figure 91.
  - COAG parameters will be presented for INR (Figure 92), PT (Figure 93) and APTT (Figure 94).
  - UA parameters presented include specific gravity (Figure 95) and pH (Figure 96).

9.7. Vital Signs and Physical Evaluations

Toxicity grading criteria for VS results can be found in Table 3. Unscheduled VS measurements will be listed, but excluded from tabular and graphical summaries by timepoint, except when calculating the maximum severity post baseline. Baseline is defined as the VS measurement taken 30min before dosing on Day 1. 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. The following rules will be used to determine which VS measurement to use for analyses if repeat measurements occur:

1. If the first replicate is normal, then it will be used for analysis.
2. If the first and second replicates are both abnormal, then the replicate with the higher severity will be used for analysis.
3. If the first replicate is abnormal, the second replicate is normal, and the third replicate was not performed, then the first replicate will be used in the analysis.
4. If the first replicate is abnormal, the second replicate is normal, and the third replicate is normal, then the second replicate will be used in the analysis.
5. If the first replicate is abnormal, the second replicate is normal, and the third replicate is abnormal, then the abnormal replicate with the higher severity will be used for analysis.

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 sort order for VS parameters will be as follows: SBP, DBP, HR, RR, and T.

VS results will be summarized in tables and figures:

- Proportion of participants with mild, moderate, or severe VS results by parameter, Treatment Group, and timepoint (Table 210).
- Summary statistics of measurements and change from baseline are presented by parameter, Treatment Group, and timepoint (Table 211).
- Graphical presentation of change from baseline by parameter, Treatment Group, and timepoint (beginning at Figure 97 and continuing through Figure 101).

All VS measurements, including height, weight, and BMI, will be presented in Listing 33.

Abnormal physical exam findings will be presented in Listing 34.

9.8. 12-Lead Standard Electrocardiogram

Toxicity grade criteria for 12-lead standard ECG parameters (mean of PR and QTcF intervals only from single ECG recordings on Day 8 and Day 11 (+3 days)) 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 35 and Listing 36, respectively**.** The parameter order will be as follows: PR Interval, QRS Duration, QT Interval, QTcF Interval, RR Interval, Mean Ventricular Heart Rate (based on RR interval).

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 Treatment Group and timepoint (Table 212)
- Proportion of participants with mild, moderate, or severe 12-lead standard ECG results will be presented for QTcF interval by Treatment Group, timepoint, and severity **(**Table 213**).**
- Summary statistics of 12-lead standard ECG change from baseline results will be shown by parameter, Treatment Group, and timepoint **(**Table 214).
- Graphically, 12-lead standard ECG change from baseline results will be presented by parameter, Treatment Group, and timepoint. PR interval will be presented in Figure 102, QRS interval will be presented in Figure 103**,** QT interval will be presented in Figure 104**,** QTcF interval will be presented in Figure 105**,** RR interval will be presented in Figure 106**,** and mean ventricular heart rate (based on RR interval) will be presented in Figure 107.

9.9. Tolerability

Tolerability to study product will be summarized by Treatment Group in Table 14 and include number and incidence of participants who: 1) discontinued study drug due to an AE, 2) chose to withdraw from the study due to an AE at any time from start of dosing until end of study, or 3) were withdrawn from the study by the investigator due to an AE at any time from start of dosing until end of study.

10. PHARMACOKINETICS

The PK Analysis Population will be used when summarizing plasma and urine drug concentrations, and the PK Analysis Subset will be used to conduct noncompartmental analysis (NCA). 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 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, determined by exact rather than nominal time of collection, 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. For plasma samples these substantially out-of-window samples will be defined as those collected:

- Greater than ± 10 minutes outside of the nominal timepoint for the 0.25 h, 0.5 h, 1 h, and 2 h post-dose samples for Dose 1 and Dose 7 as well as the 12 h post-dose samples for Dose 2 through Dose 6
- greater than ± 20 minutes outside of the nominal timepoint for the 3 h and 4 h post-dose samples for Dose 1 and Dose 7
- greater than ± 30 minutes outside of the nominal timepoint for the 8 h, 12 h, and 18 h post-dose samples for Dose 1 and Dose 7
- greater than ± 1 h for the 24 h post-dose sample for Dose 1 and Dose 7

For urine samples these will be defined as:

- greater than ± 20 minutes for the 0-4 h timepoints
- greater than ± 30 minutes for the 4-8 h and 8-12 h timepoints
- greater than ± 1 h for the 12-24 h timepoint for Dose 1 and Dose 7

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 participants who have at least one quantifiable plasma concentration of ERT or ZID will be included in the PK Analysis Population. Drug concentrations in plasma (µg/mL) and urine (mg) will be summarized by Treatment Group and listed by participant:

- Participant level concentrations of ERT and ZID in plasma (total concentrations in Listing 10 and free concentrations in Listing 11) and in urine (Listing 20).

Participant level 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 concentrations will be presented in tables and figures by Treatment Group and nominal timepoint:

- The GM and coefficient of variation (CV%) of individual total and free concentrations in plasma will be presented tabularly by Treatment Group for ERT (Table 15 for Dose 1, Table 16 for Doses 2-6, and Table 17 for Dose 7) and ZID (Table 48 for Dose 1, Table 49 for Doses 2-6, and Table 50 for Dose 7).
- Individual concentrations in plasma and summary statistics will be presented tabularly for each Treatment Group for ERT (total concentrations beginning at Table 18 and continuing through Table 32 and free concentrations beginning at Table 33 and continuing through Table 47**)** and for ZID (total concentrations beginning at Table 51 and continuing through Table 65 and free concentrations beginning at Table 66 and continuing through Table 80).
- Individual total concentrations in plasma will be presented graphically for ERT at Dose 1 (Figure 3) and Dose 7 (Figure 4). Trough concentrations for Doses 2-8 (Figure 5) and concentrations 12h after dosing on Doses 1-7 (Figure 6) will also be presented. These figures will also be presented for total ZID concentrations in plasma (Figure 11 through Figure 14, respectively).
- Individual free concentrations in plasma will be presented graphically for ERT at Dose 1 (Figure 7) and Dose 7 (Figure 8). Trough concentrations for Doses 2-8 (Figure 9) and concentrations 12h after dosing on Days 1-7 (Figure 10) will also be presented. These figures will also be presented for free ZID concentrations in plasma (Figure 15 through Figure 18, respectively).
- Semi-log plots of individual total concentration-time profiles in plasma will be presented graphically for ERT at Dose 1 (Figure 19) and Dose 7 (Figure 20) and for ZID at Dose 1 (Figure 23) and Dose 7 (Figure 24).
- Semi-log plots of individual free concentration-time profiles in plasma will be presented graphically for ERT at Dose 1 (Figure 21) and Dose 7 (Figure 22) and for ZID at Dose 1 (Figure 25) and Dose 7 (Figure 26).
- Graphically, plots of mean concentration in plasma profiles will be presented with error bars representing ± 1 SD around each sample timepoint for total and free concentrations of both ERT (Figure 27 and Figure 28) and ZID (Figure 31 and Figure 32). Mean trough concentrations will be presented for Doses 1-7 for total and free ERT (Figure 29) and ZID (Figure 33). Mean concentrations in plasma 12h after dosing will be presented for total and free ERT (Figure 30) and ZID (Figure 34).
- Semi-log plots of mean concentration in plasma profiles will be presented with ± 1 SD around each sample timepoint for total and free concentrations of ERT (Figure 35 and Figure 36) and ZID (Figure 39 and Figure 40). Semi-log plots of mean trough concentrations will be presented for Doses 1-7 for total and free ERT (Figure 37) and ZID (Figure 41). Semi-log plots of mean concentrations in plasma 12h after dosing will be presented for total and free ERT (Figure 38) and ZID (Figure 42).

- Summary statistics for percent protein binding at each collection timepoint will be presented by Treatment Group in Table 129 through Table 133 for ERT and Table 134 through Table 138 for ZID. Percent binding will be calculated as $((C_{total}-C_{free})/C_{total}) \times 100\%$, where C_{total} is the total concentration of ERT/ZID in plasma and C_{free} is the free concentration of ERT/ZID in plasma. Percent protein binding will be presented graphically for ERT in Figure 43 for Dose 1 and Dose 7 and Figure 44 for Doses 1-7, and for ZID in Figure 45 for Dose 1 and Dose 7 and Figure 46 for Doses 1-7.
- The GM and CV% of urine concentrations are reported by Treatment Group for ERT (Table 139 for Dose 1 and Table 140 for Dose 7) and ZID (Table 141 for Dose 1 and Table 142 for Dose 7).
- Individual concentrations in urine and summary statistics will be presented tabularly for each Treatment Group for ERT (beginning at Table 143 and continuing through Table 152) and for ZID (beginning at Table 153 and continuing through Table 162).
- Individual cumulative amount of ERT excreted into urine will be presented graphically (Dose 1 in Figure 53 and Dose 7 in Figure 54). Individual cumulative amount of ZID excreted into urine will be presented in Figure 45 for Dose 1 and Figure 56 for Dose 7.
- Plots of mean cumulative amount excreted into urine will be presented by Treatment Group for ERT (Figure 57) and ZID (Figure 58).

10.1. Noncompartmental Analysis

PK parameters from plasma PK data will be estimated through NCA using version 8.3.4 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 Treatment Group will be presented in tables. Summary statistics will include the mean, SD, min, max, CV% and GM:

- Single-dose plasma PK parameters (defined in Section 10.1.1) will be summarized and presented tabularly for all Treatment Groups for total concentrations of ERT (Table 81) and ZID (Table 83) and for free concentrations of ERT (Table 82) and ZID (Table 84).
- Multiple-dose plasma PK parameters (defined in Section 10.1.2) will be summarized and presented tabularly for all Treatment Groups for total concentrations of ERT (Table 85) and ZID (Table 87) and for free concentrations of ERT (Table 86) and ZID (Table 88).
- Detailed summary statistics of each single-dose plasma PK parameter will be presented tabularly for each Treatment Group for concentrations of total ERT in plasma (beginning at Table 89 and continuing through Table 93) and concentrations of total ZID in plasma (beginning at Table 99 and continuing through Table 103). PK parameters will be presented for concentrations of free ERT in plasma (beginning at Table 94 and continuing through Table 98) and for concentrations of free ZID in plasma (beginning at Table 104 and continuing through Table 108).
- Detailed summary statistics of each multiple-dose plasma PK parameter will be presented tabularly for each Treatment Group for concentrations of total ERT in plasma (beginning at Table 109 and continuing through Table 113) and concentrations of total ZID in plasma (beginning at Table 119 and continuing through Table 123). PK parameters will be presented for concentrations of free ERT in

plasma (beginning at Table 114 and continuing through Table 118) and for concentrations of free ZID in plasma (beginning at Table 124 and continuing through Table 128).

- Urine PK parameters will be summarized and presented tabularly for all Treatment Groups for ERT (Table 163 for Dose 1 and Table 164 for Dose 7) and ZID (Table 165 for Dose 1 and Table 166 for Dose 7).
- Detailed summary statistics of each urine PK parameter will be presented tabularly for each Treatment Group for ERT (beginning at Table 167 and continuing through Table 175) and ZID (beginning at Table 176 and continuing through Table 185).
- Participant specific single-dose PK parameters for total and free concentrations of ERT in plasma (total concentrations in Listing 12 and free concentrations in Listing 13) and for total and free concentrations of ZID in plasma (total concentrations in Listing 14 and free concentrations in Listing 15).
- Participant specific multiple-dose PK parameters for total and free concentrations of ERT in plasma (total concentrations in Listing 16 and free concentrations in Listing 17) and for total and free concentrations of ZID in plasma (total concentrations in Listing 18 and free concentrations in Listing 19).
- Participant specific urine PK parameters for ERT (Listing 21 for Dose 1 and Listing 22 for Dose 7) and for ZID (Listing 23 for Dose 1 and Listing 24 for Dose 7).

The definition of CV% is described below:

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

$$CV\% = \sqrt{\exp(s^2) - 1} \times 100\%$$

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

- Linear Up Log Down calculation method
- Uniform weighting
- K_e Acceptance Criteria
  - Rsq_adjusted $\geq$ 0.90
  - Includes at least 3 timepoints after T_{max}

10.1.1. Single-Dose Plasma PK Parameters

These parameters will be computed (if estimable) from the plasma total and free concentration-time data over the 24-hour following Dose 1 for each study drug:

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 participant's PK profile, then C_{max} will be missing for that participant. C_{max} will be reported in units of µg/mL. The dose-normalized parameter C_{max}/Dose will also be reported from **Cmax_D** in WinNonlin.

C_{min}

C_{min} is defined as the observed minimum concentration at the end of the dosing interval. It will be obtained from the **Cmin** parameter calculated by WinNonlin.

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 participant's PK profile, then T_{max} will be missing for that participant. T_{max} will be reported in units of h.

K_e

The terminal phase elimination rate constant (K_e or 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). K_e will be computed as the slope of a terminal region consisting of ≥ 3 successive points in the plot of log-transformed concentration data versus time. K_e will be estimated using uniform weighting.

Timepoints used in the estimation of K_e 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 K_e 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 K_e 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 [$AUC_{0\text{-}inf}$], total clearance [CL], and apparent volume of distribution during terminal phase [V_d]) will be treated as missing.

This parameter will be obtained from the **Lambda_z** parameter calculated by WinNonlin. K_e 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 $\ln(2)/ K_e$. It will be obtained from the **HL_Lambda_z** parameter calculated by WinNonlin. Half-life will be reported in units of h.

AUC

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

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

$$AUC_{0\text{-}inf} = AUC_{0\text{-}last} + \frac{C_{last}}{Ke}$$

Where C_{last} is the last measured concentration $\geq$ 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.

$AUC_{0\text{-}24}$ will be calculated as the AUC extrapolated to 24 h after dosing. This will be obtained from the WinNonlin **AUC0_24** parameter.

$AUC_{0\text{-}tau}$ will be calculated as the AUC to the end of the dosing interval. The dose-normalized parameter $AUC_{0\text{-}tau}$/Dose will also be reported. These parameters will be obtained from the **AUC_tau** and **AUC_tau_D** parameters in WinNonlin, respectively.

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

CL_T

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

V_d

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

10.1.2. Multiple-Dose Plasma PK Parameters

These parameters will be computed (if estimable) from the drug total and free concentration-time data over the 24-hour dosing interval following Dose 7 for each study drug. Note that these parameter estimates assume that steady state has been achieved.

$C_{max,ss}$

$C_{max,ss}$ is the observed maximum concentration at steady state. This will be obtained from the **Cmax** parameter calculated by WinNonlin for Dose 7.

$C_{min,ss}$

$C_{min,ss}$ is the observed minimum concentration at the end of the dosing interval at steady state. This will be obtained from the **Cmin** parameter calculated by WinNonlin for Dose 7.

C_{avg}

C_{avg} is the calculated average concentration during the dosing interval. It is calculated as $AUC_{0\text{-}tau,ss}$/tau. This will be obtained from the **Cavg** parameter calculated by WinNonlin for Dose 7.

$T_{max,ss}$

$T_{max,ss}$ is the time of maximum concentration (C_{max}) at steady state. This will be obtained from the **Tmax** parameter calculated by WinNonlin for Dose 7.

T_{min}

T_{min} is the time to minimum concentration (C_{min}). This will be obtained from the **Tmin** parameter calculated by WinNonlin for Dose 7.

$AUC_{(0-24),ss}$

$AUC_{(0-24),ss}$ is calculated as the area under the plasma concentration - time curve extrapolated to 24 h after dosing (see Section 10.1.1 for additional details).

$AUC_{(0-tau),ss}$

$AUC_{(0-tau),ss}$ is calculated as the area under the plasma concentration - time curve to the end of the dosing interval at steady state.

$t_{1/2}$

$t_{1/2}$ will be obtained from the **HL_Lambda_z** parameter calculated by WinNonlin for Dose 7.

CL_{ss}

CL_{ss} will be obtained from the **CLss_F** parameter calculated by WinNonlin.

$V_{d,ss}$

$V_{d,ss}$ is the volume of distribution at steady state. It will be obtained from **Vz_obs** in WinNonlin.

Linearity Index

The Linearity Index is calculated as $AUC_{(0-tau),ss}$ (Dose 7) / $AUC_{(0-\infty)}$ (Dose 1).

RAUC

RAUC is the accumulation ratio for AUC, which is estimated as $AUC_{(0-tau),ss}$ (Dose 7) / $AUC_{(0-24)}$ (Dose 1) where $AUC_{(0-tau),ss}$ (Dose 7) and $AUC_{(0-24)}$ (Dose 1) are both taken from the 0-24h interval on their respective days.

RC_{max}

RC_{max} is the accumulation ratio for C_{max}, which is estimated as C_{max} (Dose 7) / C_{max} (Dose 1).

10.1.3. Urine PK Parameters

Ae,urine

Ae,urine is defined as the amount of unchanged drug excreted in urine during each collection interval following Dose 1 and Dose 7 (i.e., at 0-4, 4-8, 8-12, 12-24 h after initiation of infusion).

$Ae,urine_{(0-24)}$ is the cumulative amount of unchanged drug excreted in urine from zero (predose) to 24 h following Dose 1.

$Ae,urine_{(0-24),ss}$ is the cumulative amount of unchanged drug excreted in urine from zero (predose) to 24 h after Dose 7.

fe,urine

fe,urine is defined as the fraction (%) of dose excreted unchanged in urine during each collection interval following Dose 1 and Dose 7 (i.e., at 0-4, 4-8, 8-12, 12-24 h after initiation of infusion).

$fe,urine_{(0-24)}$ is the fraction (%) of dose excreted unchanged in urine from zero (predose) to 24 h after Dose 1.

$fe,urine_{(0\text{-}24),ss}$ is the fraction (%) of dose excreted unchanged in urine from zero (predose) to 24 h following Dose 7.

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.

$CL_{r(0\text{-}24)}$ will be calculated as the renal clearance until the last collected concentration for Dose 1 (24h) and $CL_{r,ss}$ will be calculated as the renal clearance until the last collected concentration for Dose 7.

$AUC_{0\text{-}t1}$ 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 ERT or ZID will be reported in units of mL/min.

10.1.4. Assessment of Dose Proportionality

The presence of dose proportionality in plasma in terms of exposure parameters (C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ for Dose 1 and $C_{max,ss}$, $AUC_{(0\text{-}24),ss}$, and $AUC_{(0\text{-}tau),ss}$ for Dose 7) over the range of studied doses will be assessed for ERT and ZID for the WCK 6777 cohorts using a power model approach with methods described by Smith et al. [10]. 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). Dose proportionality assessments will be presented graphically and tabularly for Dose 1 and Dose 7 exposure parameters of ERT and ZID using the WCK 6777 dose groups:

- Tabular results of statistics and parameters from the plasma dose proportionality power model will be presented for total and free plasma concentrations of both ERT and ZID in Table 186 and Table 187 for Dose 1 and for total and free plasma concentrations of ERT and ZID in Table 188 and Table 189 for Dose 7.
- Predicted values from a power model, including 90% pointwise prediction bands, will be overlaid on plots of the single-dose 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 dose level.

- Figures will be presented for all exposure parameters. For total and free ERT and ZID in plasma, C_{max} will be presented in Figure 59, $AUC_{0\text{-last}}$ in Figure 60, $AUC_{0\text{-inf}}$ in Figure 61, $C_{max,ss}$ in Figure 62, $AUC_{(0\text{-}24),ss}$ in Figure 63, and $AUC_{(0\text{-tau}),ss}$ in Figure 64.

10.1.5. Assessment of Drug-Drug Interactions

The presence of drug-drug interactions for ZID and ERT in the WCK 6777 cohorts will be assessed using an analysis of variance (ANOVA) approach for the log-transformed dose-normalized exposure parameters (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-tau}}$, $AUC_{0\text{-inf}}$, $C_{max,ss}$, and $AUC_{0\text{-tau},ss}$) and protein binding parameters (% Bound Day 1, % Bound Day 7, Amount Bound Day 1, and Amount Bound Day 7). For 2 g ERT and 2 g ZID dose groups, the exposure parameters will be compared to those for 4 g WCK 6777 (2 g ERT + 2 g ZID). For 3 g ERT and 3 g ZID dose groups, the exposure parameters will be compared to those for 6 g WCK 6777 (3 g ERT + 3 g ZID). The PK Analysis Subset will be used for this analysis.

ANOVA models will be fit for exposure parameters estimated for total ERT in plasma, free ERT in plasma, total ZID in plasma, and free ZID in plasma. Assuming kinetics are linear, the mixed effects model for the ANOVA analysis of $AUC_{0\text{-last}}$ for total ERT in plasma, for example, may be specified as

$$\log\left(\frac{AUC_{0-last}}{\rho_j}\right)_{ij} = \mu + a_{i(j)} + \gamma_j + \varepsilon_{ij},$$

where μ is the overall mean of the log-transformed dose-normalized $AUC_{0\text{-last}}$, $a_{i(j)}$ $(i = 1, \ldots, 5)$ is a random participant-specific intercept, γ_j $(j = 1,2,3,4)$ represents the fixed dose cohort effect, ρ_j is the jth dose / lowest dose studied in monotherapy (i.e., 2 g), and the errors ε_{ij} are assumed independent and identically distributed from the standard normal distribution.

The linearity of the kinetics assumption for the above models will be assessed via comparisons of the estimated GM of the dose-normalized PK exposure parameters for the comparison groupings listed above. If the linearity of kinetics assumption does not hold, dose-specific ANOVA models will be fit with only two fixed dose cohort effects, including ERT or ZID alone and ERT + ZID in combination at the specific dose (2 g or 3 g).

The GMs of dose-normalized exposure parameters and ratios of geometric least-squares means of exposure parameters after their transformation from the log-transformed analysis back to their original scale, as well as their corresponding 95% and 90% confidence intervals, respectively, will be presented in Table 190 for the PK Analysis Subset and Table 191 for the PK Analysis Subset Subgroup.

For the drug-drug interaction ANOVA analysis, the following pseudocode will be used to estimate the dose-normalized GMs of exposure parameters and ratios of the geometric least-squares means with their corresponding confidence intervals.

```
/* Get data only for specific drug (free or total) and PK parameter */
data drug_conc_param;
set dataset; where trt in ("drug 2 g", "drug 3 g", "WCK 6777 4 g", "WCK 6777 6 g");
if param="Parameter Name" and pkconc="Free/Total drug";
run;

/* Fit Mixed-Effects ANOVA model and estimate log-transformed PK parameter estimates and
ratios*/
proc mixed data=drug_conc_param; *Update to correct parameter, such as Cmax;
class subject trt;
model log_dose_norm_param = trt / ddfm=kr2;
random intercept / subject=subjid;
```

```
estimate '2 g standalone drug vs combination' trt 1 0 -1 0 / cl alpha=0.1; *log-
transformed GLSM ratios and 90% CIs;
estimate '3 g standalone drug vs combination' trt 0 1 0 -1 / cl alpha=0.1;
lsmeans trt / cl alpha=0.05; *log-transformed mean estimates of parameter and 95% CIs,
adjusting for all model parameters;
odds output estimates=estimate_param; *output log transformed GLCM ratios;
lsmeans lsm_param; *output estimates from lsmeans statement;

run;
```

10.1.6. Assessment of Saturation and Linearity of Protein Binding

Percent protein binding vs total concentration of ERT in plasma will be presented separately for both ERT/ZID monotherapy and WCK combination therapy cohorts. Linear regressions will be fit for each cohort for Dose 1 and Dose 7 and presented alongside R-squared values for ERT in Figure 47 and for ZID Figure 48. Percent protein binding vs log-transformed total concentration is presented for ERT in Figure 49 and for ZID in Figure 50. Protein binding saturation of ERT will be presented separately for both ERT and WCK cohorts in Figure 51 and for ZID Figure 52.

11. IMMUNOGENICITY

Not applicable.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001" The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as >99%. Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

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

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 8.3.4 or later.

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

If there are any changes to the planned analyses prior to final data lock and after finalization of the SAP, they may be added to the SAP as an addendum. The SAP will not be amended after final data lock.

16. REFERENCES

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17. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.1 Overall Study Design and Plan Description

Table 1: Study Design

Cohort No.	Study Drug-Dose	Infusion time - frequency	Participants
Cohort 1	WCK 6777 2 g (ERT 1 g + ZID 1 g) or placebo	30 (±5) minutes - once daily-for 7 days	8 (6 drug combination, 2 placebo)
Cohort 2	ERT 2 g or placebo	60 (±10) minutes - once daily-for 7 days	8 (6 drug, 2 placebo)
Cohort 3	ZID 2 g	60 (±10) minutes - once daily-for 7 days	6 (all drug)
Cohort 4	WCK 6777 4 g (ERT 2 g + ZID 2 g) or placebo	60 (±10) minutes - once daily-for 7 days	8 (6 drug combination, 2 placebo)
Cohort 5	ERT 3 g or placebo	120 (±10) minutes - once daily-for 7 days	8 (6 drug, 2 placebo)
Cohort 6	ZID 3 g	120 (±10) minutes - once daily-for 7 days	6 (all drug)
Cohort 7	WCK 6777 6 g (ERT 3 g + ZID 3 g) or placebo	120 (±10) minutes - once daily-for 7 days	8 (6 drug combination, 2 placebo)

Table 2: Schedule of Study Procedures

Evaluation (↓)	Screening [1]	Check-in/ Enrollment	In-patient Treatment								Out-patient follow-up	Unscheduled / Early Termination
Visit (V)	1	2									3	
Study Day (D)	-28 to -2	-1	1	2	3	4	5	6	7	8	11 (+3)	
Informed consent	X											
Confirmation of eligibility criteria	X	X [2]	X [2]									
Medical History	X											
Demographics	X											
Height, Weight and BMI [3]	X											
Weight		X [2]								X		
MH update		X [2]	X [2]									
Prior and Concomitant medications [4]	X	X	X [4]	X [4]	X [4]	X [4]	X [4]	X [4]	X [4]	X [4]	X [4]	X [4]
Physical examination (PE)	X	X								X	X	X
Symptom directed (focused) PE [5]			X	X	X	X	X	X	X			
Vital signs [6]	X	X	X	X	X	X	X	X	X	X	X	X
ECG [7]	X	X								X	X	X
Clinical Laboratory testing (HEM, CHEM, and COAG) [8]	X	X		X		X		X		X	X	X
Urinalysis [9]	X	X				X				X	X	X
Viral serology [10]	X											
Serum HCG pregnancy test (all females) and FSH (post-menopausal females only) [11]	X											
Urine pregnancy test (all females) [11]		X										
Urine drug screen [12]	X	X										
Urine alcohol test	X	X										
Urine cotinine test	X	X										

Table 2: Schedule of Study Procedures *(continued)*

Evaluation (↓)	Screening [1]	Check-in/ Enrollment	In-patient Treatment								Out-patient follow-up	Unscheduled / Early Termination
Admission of eligible participants /Assignment to treatment cohort / Randomization [13]		X										
Study drug administration [14]			X	X	X	X	X	X	X			
Assessment of adverse events [15]			X	X	X	X	X	X	X	X	X	X
Assessment of infusion and blood drawing sites [16]			X	X	X	X	X	X	X	X	X	X
Plasma PK [17]			X [17]	X [17]	X [17]	X [17]	X [17]	X [17]	X [17]	X [17]		X [18]
Urine PK [19]			X [19]						X [19]			
Discharge from in-patient site										X		
Final visit / Discharge from study											X	
Counseling	X	X	X	X	X	X	X	X	X	X	X	X

[1] Screening evaluations must be completed within 28 days prior to administration of study drug(s).
[2] Confirmation of eligibility for admission and enrollment and randomization on Day -1, and for dosing on Day 1 after completion of all baseline procedures before study intervention
Baselines are: Complete PE, weight, Clinical labs and ECG on Day-1; VS (within 30 min before dosing on Day 1), MH and Prior Medications updates, and Focused PE (as needed for new symptoms) predose on Day 1
[3] BMI ≥18-32 kg/m^2 and Weight ≥ 100 lbs (At Screening). Weight also measured on Day 8.
[4] Concomitant medications include any new medications taken only after initiation of first dose on Day 1.
[5] Symptoms directed (focused) PE for evaluation of new symptoms prior to dosing on Day 1, and for evaluation of TEAEs after dosing on Day 1 to the end of the study, or ET
[6] Vital Signs: collected after 5 minutes of resting in supine position and include SBP, DBP, HR and T (oral measurement). Recorded at Screening, Day -1, Days 1 to 7 (within 30 min prior to dosing, at the end of infusion (+10 min) and 1 hour (±5 min) after the end of infusion), Day 8, and Day 11 (+3), or ET.
[7] Participants must be lying supine or sitting for 10 minutes prior to ECG. ECG will be done in triplicate 2 minutes apart at Screening only. Single ECGs will be recorded on Days -1, 8, and 11 (+3).
[8] Clinical Laboratory testing for Hematology (HEM: Hemoglobin, hematocrit, RBC, WBC, WBC differential count, platelet count), Clinical Chemistry (CHEM: sodium, potassium, chloride, bicarbonate, BUN, creatinine, estimated CLCR (by the Cockcroft-Gault method), calcium, glucose, albumin, total protein, total bilirubin, direct bilirubin, ALT, AST, ALP and LDH) and Coagulation (COAG: PT and AP). – Lab values on Day -1 are considered baseline.
[9] Urinalysis: Dipstick urinalysis, including protein, glucose, ketones, bilirubin, occult blood, nitrate, leukocyte esterase, specific gravity, and pH. If dipstick UA is abnormal for blood, protein, glucose and leukocyte esterase, a microscopic UA will be done (for WBC, RBC, bacteria, and other cell counts), and results will supersede those of the dipstick UA. Lab values on Day -1 are considered baseline.
[10] Viral serology: HIV antibody, HBsAg, HCV antibody
[11] Serum pregnancy at Screening and Urine pregnancy test on Day-1 from all females; FSH at Screening only from post-menopausal females.
[12] Urine drug screen panel for: amphetamines, barbiturates, benzodiazepines, cocaine metabolites, cannabinoids (THC), opiates, phencyclidine, and tri-cyclic antidepressants – At Screening and Day -1
[13] Assignment to dosing cohort and randomization: Must occur after all inclusion and exclusion criteria have been confirmed on Day -1 and participant was admitted to the in-patient site.
[14] Study drug or placebo administered IV according to cohort and randomization assignment. Withhold solid food at least 4 h before starting the infusion and 1 h after completion of infusion. Oral liquids are allowed.
[15] Monitoring for treatment-emergent AEs and SAEs will begin upon initiation of the first dose of study product(s) and continue until the last visit, or ET.
[16] Assess and replace IV catheters no more frequently than every 72 to 96 h or as clinically indicated.
[17] Plasma PK collection times:
DAY 1 and DAY 7:
For the 30 min infusion (Cohort 1): Predose (within 30 min; t=0) and at 0.25 h (±5 min), 0.5 h (±5 min) (immediately at end of infusion), 1 h (±5 min), 2 h (±5 min), 3 (±10 min), 4 h (±10 min), 8 h (±15 min), 12 h (±15 min), 18 (±15 min) and 24 h (±30 min) after start of infusion
For the 60 min infusion (Cohorts 2, 3 and 4): Predose (within 30 min; t=0) and at 0.5 h (±5 min), 1 h (±5 min) (immediately at end of infusion), 2 h (±5 min), 3 h (±10 min), 4 h (±10 min), 8 h (±15 min), 12 h (±15 min), 18 h (±15 min) and 24 h (±30 min) after start of infusion

Table 2: Schedule of Study Procedures *(continued)*

Evaluation (↓)	Screening [1]	Check-in/ Enrollment	In-patient Treatment	Out-patient follow-up	Unscheduled / Early Termination
For the 120 min infusion (Cohorts 5, 6 and 7): Predose (within 30 min; t=0) and at 1 h (±5 min), 2 h (±5 min) (immediately end of infusion), 3 h (±10 min), 4 h (±10 min), 8 h (±15 min), 12 h (±15 min), 18 (±15 min) and 24 (±30 min) after start of infusion **DAY 2 to DAY 6:** Predose (within 30 min) and 12 (±5 min) h after start of infusion. [18] Unscheduled visit – plasma PK collection is optional [19] Urine PK collection times: **DAY 1 and DAY 7:** Before the start of infusion (within 60 min), and at the following intervals after the start of the infusion: 0 to 4 h (±10 min), 4 to 8 h (±15 min), 8 to 12 h (±15 min), and 12 to 24 h (±30 min).					

12.2.2 Displays of Adverse Events

Table 3: Clinical Vital Signs Adverse Event Toxicity Grading Scale

Clinical AEs	Reference range	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)
VITAL SIGNS [a]				
Fever -°C Fever -°F	36.1 - 37.2 [a] 97.0 - 99.0 [a]	37.3 - 38.4 99.1 - 101.1	38.5 - 38.9 101.2 - 102.0	>38.9 >102.0
Tachycardia - bpm	50 - 100 [b,c,d]	101 - 115	116 - 130	>130 or ventricular dysrhythmias
Bradycardia – bpm		45 - 49	40 - 44	<40
Hypertension (systolic) - mmHg	130/89 [b,c,d]	131 - 150	151 - 160	>160
Hypertension (diastolic) - mmHg		90 - 95	96 - 100	>100
Hypotension (systolic) - mmHg		85 - 88	80 - 84	<80
Tachypnea – breaths per min	10 - 20 [b,c,d]	21 - 25	26 - 30	>30

Notes: [a]No recent hot or cold beverages or smoking. A protocol should select either ^{0}C or ^{0}F for inclusion
[b]Assume awake and in supine position for 5 min at rest. Abnormal HR and BP on first measurement due to a technical (procedural) error may be repeated twice more with the participant resting between measurements for at least 5 min (See Protocol Section 8.1.6).
[c]Exceptions to screening BP and HR reference range are:
Participants with baseline HR ≥ 45 to 50 bpm may be accepted if otherwise healthy adults with known history of asymptomatic bradycardia
Participants with baseline SBP up to 140 mmHg and DBP up to 90 mmHg may be accepted if otherwise healthy.
[d]Isolated/individual abnormalities of VS would not be considered toward halting criteria. Abnormalities of VS will be described as "increased X" or "decreased X" (X = HR, BP, RR, temperature) if asymptomatic, transient and not associated with a systemic or organ-specific disorder and coded by MedDRA within the System Organ Class (SOC) "Investigations." These abnormalities will be graded per criteria in this table, but not considered in determining whether study stopping criteria have been met. On the other hand, abnormalities of VS that are either secondary to systemic or organ-specific clinical syndrome or primary disorders will be coded in the appropriate SOC (e.g., "cardiac disorders", "respiratory disorders", "immunological disorders", etc.). These abnormalities will be considered in determining whether stopping criteria have been met.

Table 4: Clinical Adverse Event Toxicity Grading Scale

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
CARDIOVASCULAR DISORDERS			
Arrhythmia (except Sinus tachycardia)		Asymptomatic or transient signs; no medical intervention required.	Recurrent and/or persistent signs; symptomatic medical intervention required.
Hemorrhage	Estimated blood loss ≤100 mL.	Estimated blood loss >100 mL; no transfusion required.	Blood transfusion required.
RESPIRATORY DISORDERS			
Cough	Transient cough; no treatment required.	Persistent cough; treatment required.	Interferes with daily activities.
Bronchospasm, Acute	Transient bronchospasm; no treatment required; FEV1 71-80% of predicted peak flow.	Requires treatment; normalizes with bronchodilator; FEV1 60-70% of predicted peak flow.	No normalization with bronchodilator; FEV1 <60% of predicted peak flow.
Dyspnea	Does not interfere with usual and social activities.	Interferes with usual and social activities; no treatment.	Prevents usual and social activities OR requires treatment.
EAR AND LABYRINTH DISORDERS			
Tinnitus	Mild symptoms: intervention not indicated.	Moderate symptoms; limiting instrumental ADL.	Severe symptoms; limiting self-care ADL.
Vertigo	Mild symptoms.	Moderate symptoms; limiting instrumental ADL.	Severe symptoms; limiting self-care ADL.
GASTROINTESTINAL DISORDERS			
Nausea	No interference with normal activity.	Some interference with normal activity.	Prevents daily activities.
Vomiting	No interference with activity OR 1-2 episodes in a 24-h period.	Some interference with activity OR >2 episodes in a 24-h period.	Prevents daily activity OR requires medical intervention.
Diarrhea	2-3 loose OR watery stools in a 24-h period.	4-5 loose OR watery stools in a 24-h period.	6 or more loose or watery stools in a 24-h period OR requires IV hydration OR requires medical intervention.
Oral Discomfort / Dysphagia	Mild discomfort; no difficulty swallowing.	Some limits on eating /drinking.	Eating/talking very limited; unable to swallow solid foods.
NEUROLOGICAL DISORDERS			
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental activities of daily life (ADL)	Severe unsteadiness or sensation of movement; limiting self-care ADL; medical intervention required
Headache	Mild pain; No interference with activity.	Moderate pain; repeated use of non-narcotic pain reliever for more than 24 h OR some interference with activity.	Significant pain; any use of narcotic pain reliever OR prevents daily activity OR requires triptans.

Table 4: Clinical Adverse Event Toxicity Grading Scale *(continued)*

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep including excessive daytime sleepiness
Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New onset seizures (partial or generalized); multiple seizures despite medical intervention
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor
Syncope	-	-	Fainting; orthostatic collapse
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care
Other	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care
PSYCHIATRIC DISORDERS			
Altered Mental Status: Includes agitation, confusion, disorientation, decreased mental acuity, changed mental status, somnolence, stupor			
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early; medical intervention required
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; limiting self-care; psychiatric intervention required
LOCAL IV CATHETER REACTION			
IV site reaction	Not applicable.	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis).	Ulceration or necrosis; severe tissue damage; operative intervention indicated.

Table 4: Clinical Adverse Event Toxicity Grading Scale *(continued)*

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
SYSTEMIC REACTIONS			
Anaphylaxis **	--	--	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema or angioedema; hypotension.
***Definition*: *A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness, and may lead to death.*			
Allergic Reaction	Pruritus without rash.	Localized urticaria OR requires oral therapy.	Generalized urticaria OR angioedema OR anaphylaxis OR requires epinephrine
Hypersensitivity (including drug fever)	Transient flushing or rash; temperature 38.0 – 38.4°C (100.4 – 101.1°F).	Rash; flushing; urticaria; dyspnea; temperature 38.5 – 38.9°C (101.2 – 102.0°F).	Symptomatic bronchospasm with or without urticaria; parenteral medication indicated; allergy-related edema or angioedema; hypotension; temperature >38.9°C (>102.0°F).
Fatigue	No interference with activity.	Some interference with activity.	Significant; prevents daily activity.
Myalgia	No interference with activity.	Some interference with activity.	Significant; prevents daily activity.
SKIN			
Mucocutaneous	Erythema, pruritus.	Diffuse, maculo-papular rash, dry desquamation.	Vesiculation OR moist desquamation OR ulceration.
Pruritus	No or minimal interference with usual social and functional activities.	Greater than minimal interference with usual social and functional activities.	Inability to perform usual social and functional daily activities.
ALL OTHER CONDITIONS			
Illness or clinical AE (as defined according to applicable regulations)	Require minimal or no treatment; does not interfere with the participant's daily activities.	Result in a low level of inconvenience or concern with therapeutic measures; may cause some interference with functioning.	Interrupt a participants's usual daily activity and may require systemic drug therapy or other treatment; are usually incapacitating.

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 5: Clinical Laboratory Reference Ranges and Toxicity Grading Scale

Laboratory AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Blood, serum, or plasma *			
HEMATOLOGY			
Hemoglobin decrease, Female, 18Y – g/dL	9.5 – 11.4	7.9 – 9.4	<7.9
Hemoglobin decrease, Female, >18Y – g/dL	9.7 – 11.6	8.1 – 9.6	<8.1
Hemoglobin decrease, Male, 18Y – g/dL	10.0 – 11.9	8.0 – 9.9	<8.0
Hemoglobin decrease, Male, >18Y – g/dL	11.2 – 13.1	9.2 – 11.1	<9.2
WBC increase 18Y – $x10^3$/ µL	13.1 – 15.0	15.1 – 20.0	>20.0
WBC increase >18Y – $x10^3$/ µL	10.9 – 15.0	15.1 – 20.0	>20.0
WBC decrease 18Y – $x10^3$/ µL	3.0 – 4.4	1.5 – 2.9	<1.5
WBC decrease >18Y – $x10^3$/ µL	2.3 – 3.7	1.1 – 2.2	<1.1
Neutrophils decrease 18Y – cells/ µL	1,200 – 1,799	750 – 1,199	<750
Neutrophils decrease >18Y – cells/ µL	1,000 – 1,499	750 – 999	<750
Lymphocytes decrease 18Y– cells/ µL	850 – 1,199	400 – 849	<400
Lymphocytes decrease >18Y – cells/ µL	500 - 849	300 - 499	<300
Monocytes increase – 18Y – cells/ µL	901 – 2,000	2,001 – 3,000	>3,000
Monocytes increase >18Y – cells/ µL	951 – 2,000	2,001 – 3,000	>3,000
Eosinophils increase >6Y– cells/ µL	501 – 750	751 – 1,000	>1,000
Basophils increase >6Y– cells/ µL	201 – 500	501 – 800	>800
Platelets decrease – $x10^3$/ µL	90 – <140	55 – <90	<55
COAGULATION			
PT INR	>1.1 – 1.8	>1.8 – 2.1	>2.1

Table 5: Clinical Laboratory Reference Ranges and Toxicity Grading Scale *(continued)*

Laboratory AEs	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Prothrombin Time - sec	>11.5 – 15.0	>15.0 – 18.6	>18.6
Activated Partial Thromboplastin Time (APTT) - sec	>32 – 54	>54 – 75	>75
CHEMISTRY			
Sodium decrease – mmol/L	130 - 134	124 –129	<124
Sodium increase – mmol/L	147 - 150	151 – 156	>156
Potassium increase, 19Y - mmol;/L	5.2 – 6.0	6.1 – 6.5	>6.5
Potassium increase, >19Y - mmol/L	5.4 – 6.0	6.1 – 6.5	>6.5
Potassium decrease, 19Y – mmol/L	3.2 – 3.7	2.6 – 3.1	<2.6
Potassium decrease, >19Y - mmol/L	3.0 – 3.4	2.5 – 2.9	<2.5
Carbon dioxide increase – mmol/L	33 – 36	37 – 40	>40
Carbon dioxide decrease – mmol/L	17 – 19	14 – 16	<14
Calcium increase, Male, 4 -19Y – mg/dL	10.5 – 11.2	11.3 – 12.3	>12.3
Calcium increase, Male, 20 - 49Y – mg/dL	10.4 – 11.4	11.5 – 12.5	>12.5
Calcium increase, Female, 4 -19Y – mg/dL	10.5 – 11.4	11.5 – 12.5	>12.5
Calcium increase, Female 20 - 49Y – mg/dL	10.3 – 11.4	11.5 – 12.5	>12.5
Calcium decrease, Male, 4 -19Y – mg/dL	8.1 – 8.8	7.3 – 8.0	<7.3
Calcium decrease, Male, 20 - 49Y – mg/dL	8.1 – 8.5	7.3 – 8.0	<7.3
Calcium decrease, Female, 4 -19Y – mg/dL	8.1 – 8.8	7.3 – 8.0	<7.3
Calcium decrease, Female, 20-49Y – mg/dL	8.1 – 8.5	7.3 – 8.0	<7.3
Blood urea nitrogen (BUN) increase, 19Y - mg/dL	21 – 58	59 – 120	>120
Blood urea nitrogen (BUN) increase, >19Y- mg/dL	26 – 58	59 – 120	>120
Glucose decrease, fasting – mg/dL	47 – 64	40 – 46	<40
Glucose increase, fasting – mg/dL	100 – 160	161 – 250	>250
Glucose increase, non-fasting – mg/dL	140 – 200	201 – 250	>250

Table 5: Clinical Laboratory Reference Ranges and Toxicity Grading Scale *(continued)*

Laboratory AEs	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Creatinine increase, Male, 18 - 29Y – mg/dL	1.25 – 1.62	1.63 – 2.24	>2.24
Creatinine increase, Male, 30 – 39 Y – mg/dL	1.27 – 1.64	1.65 – 2.27	>2.27
Creatinine increase, Male, 40 - 49Y – mg/dL	1.30 – 1.68	1.69 – 2.32	>2.32
Creatinine increase, Female, 18 - 29Y – mg/dL	0.97 – 1.25	1.26 – 1.73	>1.73
Creatinine increase, Female, 30 - 39Y – mg/dL	0.98 – 1.26	1.27 – 1.75	>1.75
Creatinine increase, Female, 40 - 49Y – mg/dL	1.00 – 1.29	1.30 – 1.78	>1.78
Direct bilirubin	0.3 – 0.6	0.7 – 1.2	>1.2
Total bilirubin (serum) increase (with other LFTs in the normal range), 19Y – mg/dL	1.2 – 1.7	1.8 – 2.5	>2.5
Total bilirubin (serum) increase (with other LFTs in the normal range), >19Y – mg/dL	1.3 – 1.8	1.9 – 2.6	>2.6
Total bilirubin (serum) increase (accompanied by a >3 x ULN increase in ALT or AST), 19Y – mg/dL	1.2 – 2.0	2.1 – 2.8	>2.8
Total bilirubin (serum) increase (accompanied by a >3 x ULN increase in ALT or AST), >19Y – mg/dL	1.3 – 2.1	2.2 – 3.0	>3.0
Total protein decrease, 19Y – g/dL	5.3 – 6.2	4.5 – 5.2	<4.5
Total protein decrease, >19Y – g/dL	5.1 – 6.0	4.3 – 5.0	<4.3
Albumin, decrease - g/dL	3.0 – 3.5	2.0– 2.9	<2.0
AST increase, 19Y – U/L	33 – 64	65 – 96	>96
AST increase, 20-49Y – U/L	41 – 80	81 – 120	>120
ALT increase, Male, 19Y – U/L	47 – 92	93 – 138	>138
ALT increase, Male, >19Y – U/L	47 – 92	93 – 138	>138
ALT increase, Female, 19Y – U/L	33 – 64	65 – 96	>96
ALT increase, Female, >19Y – U/L	30 – 58	59 – 87	>87

Table 5: Clinical Laboratory Reference Ranges and Toxicity Grading Scale *(continued)*

Laboratory AEs	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Alkaline phosphatase (AP) increase, Male, 19Y – U/L	170 – 338	339 – 507	>507
Alkaline phosphatase (AP) increase, Male, ≤49Y – U/L	131 – 260	261 – 345	>345
Alkaline phosphatase (AP) increase, Female, 19Y – U/L	129 – 256	257 – 384	>384
Alkaline phosphatase (AP) increase, Female, ≤49Y – U/L	126 – 250	251 – 375	>375
Urine			
URINALYSIS by Dipstick			
Protein	1+	2+	>2+
Blood (occult)	1+	2+	>2+
Glucose	1+	2+	>2+
Leukocyte esterase	1+	2+	>2+
URINE MICROSCOPY			
Red blood cells (RBC) per HPF	3 – 10	11 – 40	>40 and/or gross blood
WBC (microscopic) – WBC per HPF	6 – 10	11 – 40	>40 and/or symptomatic urogenital infection
Bacteria (microscopic)	few	moderate	Many

Note 1: With the exception of AST, ALT, AP, total and direct bilirubin, BUN, creatinine, CL_{CR} (by the Cockcroft-Gault method), and urine protein, which should be within reference range, lab values of other analytes in the grade 1 range are acceptable for enrollment if (a) they are not considered to be clinically significant by the investigator and (b) there is no cluster of abnormal labs that combined are suggestive of an underlying disorder.

Note 2: Other Exceptions to screening laboratory tests' normal reference ranges are:

a. Racially based low total WBC or neutrophil counts up to toxicity Grade 1 are allowed, but toxicity Grades 2 or 3 are exclusionary.

b. Labs performed as part of a panel but not listed above are to be recorded in the database. If abnormal, they are not exclusionary and are not to be graded per Toxicity table, however, the investigator would make a clinical decision about their clinical significance and, if clinically significant, they will be graded according to the criteria in Protocol Section 9.2.1. (Examples include mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), and nucleated red blood cell count (NRBC CT), which are included in a CBC with differential.)

Note 3: If a subject was accepted into the trial with a laboratory value of an analyte that overlaps with values used for grading Grade 1 laboratory abnormalities, a TEAE will be reported if the on-study value of the same analyte increases in severity to Grade 2 or higher compared to the baseline.

Note 4: If the dipstick UA is abnormal for blood, protein, glucose and leukocyte esterase, a microscopic UA will be performed, and the results will supersede the results of the dipstick UA.

Note 5: Menstruating females with a positive dipstick UA or microscopic UA may be retested following cessation of menses. Gross blood in urine that is confirmed due to menses is not a TEAE (but is for all other reasons.

Note 6: Isolated laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or due to collection or laboratory error may be repeated once.

Note 7: For the microscopic UA, Lab-reported ranges 3 -10 for RBC and 6-10 for WBC would be Grade 1; 10-20 and 20-40 for both RBC and WBC would be Grade 2; and > 40 for both RBC and WBC would be Grade 3.

Table 6: ECG Toxicity Grading Scale

ECG interval abnormality	Reference range	Grade 1	Grade 2	Grade 3
QTcF interval prolonged (msec): • Male • Female	 • ≤450 msec • ≤470 msec	Asymptomatic, QTcF • 451 - 479 msec • 471 - 479 msec	Asymptomatic, QTcF 480-500 msecOR increase in interval 30-59 msec above baseline	Asymptomatic, QTcF >500 msec OR increase in interval ≥60 msec above baseline
PR interval prolonged (msec)	≤ 210 msec	211-250 msec	>250 msec	Type II 2nd degree AVblock OR ventricular pause >3.0 sec

Note 1: Events will be coded as treatment-emergent SAEs if there are life-threatening associated symptoms or signs (arrhythmia, CHF, hypotension, syncope, TdP, etc.).
Note 2: If a male participant was accepted into the trial with a QTcF value that overlaps with values used for grading Grade 1 QTcF prolongation, a TEAE will be reported if the QTcF value is higher than the baseline value.

10.2 Protocol Deviations

Table 7: Distribution of Protocol Deviations by Category, Type, and Treatment Group

Category	Deviation Type	Number of Participants (Number of Deviations)								
		WCK 6777 2g (N=X)	ERT 2g (N=X)	ZID 2g (N=X)	WCK 6777 4g (N=X)	ERT 3g (N=X)	ZID 3g (N=X)	WCK 6777 6g (N=X)	Placebo (N=X)	All Participants (N=X)
Eligibility/enrollment	Any type	x (x)	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)	x (x)
	Met exclusion criterion	x (x)	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)	x (x)
	Other	x (x)	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)	x (x)
	Out of window visit	x (x)	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)	x (x)
	Missed treatment administration	x (x)	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)	x (x)
	Other	x (x)	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)	x (x)
	Out of window visit	x (x)	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)	x (x)
	Other	x (x)	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)	x (x
	Incorrect version of ICF signed	x (x)	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)	x (x)
	Urine not collected	x (x)	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)	x (x)

Table 7: Distribution of Protocol Deviations by Category, Type, and Treatment Group *(continued)*

Category	Deviation Type	Number of Participants (Number of Deviations)								
		WCK 6777 2g (N=X)	ERT 2g (N=X)	ZID 2g (N=X)	WCK 6777 4g (N=X)	ERT 3g (N=X)	ZID 3g (N=X)	WCK 6777 6g (N=X)	Placebo (N=X)	All Participants (N=X)
	Too few aliquots obtained	x (x)	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)	x (x)
	Required procedure not conducted	x (x)	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)	x (x)
	Study product temperature excursion	x (x)	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)	x (x)
	Other	x (x)	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)	x (x)
	Required procedure done incorrectly	x (x)	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)	x (x)
	Other	x (x)	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)	x (x)
	Treatment unblinded	x (x)	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)	x (x)

Note: N= Number of participants randomized.

14.1 Description of Study Participants

14.1.1 Disposition of Participants

Table 8: Participant Disposition by Treatment Group

Participant Disposition	WCK 6777 2g (N=X) n (%)	ERT 2g (N=X) n (%)	ZID 2g (N=X) n (%)	WCK 6777 4g (N=X) n (%)	ERT 3g (N=X) n (%)	ZID 3g (N=X) n (%)	WCK 6777 6g (N=X) n (%)	Placebo (N=X) n (%)	All Participants (N=X) n (%)
Screened	--	--	--	--	--	--	--	--	x
Enrolled/Randomized	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)	x (100)
Included in the Safety Population (Received at least One Dose of Study Product)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Received All Planned Doses of Study Product	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Included in the PK Analysis Population (Had at least One Quantifiable Post-Dosing Plasma Drug Concentration Measured)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Included in the PK Analysis Subset (Had at least one estimable PK parameter)	x (x)	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)	x (x)
Completed all PK Urine Samples	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Completed Final Study Visit	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Early Termination	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Note: N= Number of participants randomized.

Table 9: Analysis Population Exclusions by Treatment Group

Analysis Populations	Reason Participants Excluded	WCK 6777 2g (N=X) n (%)	ERT 2g (N=X) n (%)	ZID 2g (N=X) n (%)	WCK 6777 4g (N=X) n (%)	ERT 3g (N=X) n (%)	ZID 3g (N=X) n (%)	WCK 6777 6g (N=X) n (%)	Placebo (N=X) n (%)	All Participants (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)	x (x)
PK Analysis Population	Any Reason	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Participant received placebo	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Did not receive at least one dose of study drug	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Participant has no measurable concentration of drug in plasma at any timepoint	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
PK Analysis Subset	Any Reason	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Exclusion from PK Analysis Population	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	No estimable PK parameters	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
PK Analysis Subset Subgroup	Any Reason	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Excluded from PK Analysis Subset	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Missing at least one planned PK sample on both Day 1 and Day 7	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Note: N= Number of participants randomized.

Table 10: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Total number of screen failures		x	100
Eligible but not Enrolled	Any reason	x	xx
	[Reason 1]	x	xx
	[Reason 2]	x	xx
Inclusion and Exclusion	**Number of participants failing any eligibility criterion**	x	xx
Inclusion	Any inclusion criterion	x	xx
	Provide a signed and dated written informed consent and agrees to comply with the studyprocedures and length of confinement to the research site.	x	xx
	Be able to understand and willing to comply with study procedures, restrictions, andrequirements, as determined by the Site Principal Investigator (PI) or authorized clinician(s) (listed on FDA Form 1572).	x	xx
	Adults 18 to 45 years of age inclusive, including non-pregnant, non-lactating females.	x	xx
	Have suitable veins for cannulation or repeated venipuncture.	x	xx
	Be in good general health at the time of enrollment.	x	xx
	Sexually active females must be of non-childbearing potential or must use a highly effective method of birth control from screening to 30 days following the last dose ofstudy product.	x	xx
	Sexually active males must be vasectomized or agree to use barrier contraception and notdonate sperm from first dose of study product until 30 days following the last dose.	x	xx
	Participants must be willing to avoid excessive physical exercise within 48 h prior to dosinguntil discharge from the CTU on Day 8, and 24 h before the last visit (Day 11 +3 days).	x	xx
	No history of acute febrile or infectious illness for at least 7 days prior to theadministration of study drug(s).	x	xx
Exclusion	Any exclusion criterion	x	xx

Table 10: Ineligibility Summary of Screen Failures *(continued)*

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Total number of screen failures		x	100
	Known history of a clinically significant food or drug allergy/hypersensitivity includingknown allergy/hypersensitivity to ERT, any β-lactam drugs or other related drugs.	x	xx
	Current seasonal allergies with ongoing symptoms for more than a week prior to dosingrequiring glucocorticoids and/or frequent use of antihistamines for treatment.	x	xx
	Any history of a chronic condition including renal failure that may increase risk to participant or interfere with endpoint assessment, or any unstable chronic disease.	x	xx
	History of any psychiatric condition that has required hospitalization in the last 12 months or participant is considered psychologically unstable by the investigator.		
	History of any clinically significant (CS) disease or disorder, medical/surgical procedure,or trauma within 4 weeks prior to initiation of administration of study product(s).		
	History of *Clostridium difficile* induced diarrhea within 1 year before screening		
	Known history of past or current epilepsy or seizure disorders, excluding febrile seizuresof childhood.		
	Prior exposure to Zidebactam.		
	Use of any prohibited prescription or non-prescription medication within 14 days prior tothe first dose of study drug(s) as described in Protocol Section 6.6.		
	Use of any investigational drug product within 30 days or 5 half-lives (whichever is longer) before investigational product administration in this study.		
	Planned participation in a clinical research study that requires treatment with a study drug, blood draws or other invasive assessments during the study period (screening until final visit).		

Table 10: Ineligibility Summary of Screen Failures *(continued)*

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Total number of screen failures		x	100
	Blood or plasma donation of 500 mL within 3 months or more than 100 mL within 30 days before signing informed consent or planned donation prior to completion of this trial.		
	Positive serum pregnancy test for women at screening and urine pregnancy test at check-in.		
	Positive urine alcohol test or urine drug screen test at screening or check-in (Day -1).		
	Positive test for HIV antibodies, hepatitis B-virus surface antigen (HBsAg), oranti-hepatitis C-virus antibodies (anti-HCV) at screening.		
	History of ≥10 pack-years smoking in the 5-year period before screening, or positiveurine cotinine screen at check-in.		
	History of binge drinking or heavy drinking of alcohol at any time in the 6 months beforestudy product administration.		

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

14.1.2 Demographic Data by Study Group

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

Variable	Characteristic	WCK 6777 2g (N=X)		ERT 2g (N=X)		ZID 2g (N=X)		WCK 6777 4g (N=X)		ERT 3g (N=X)		ZID 3g (N=X)		WCK 6777 6g (N=X)		Placebo (N=X)		All Participants (N=X)	
		n	%	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	x	xx
	Female																		
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Hispanic or Latino																		
	Not Reported																		
	Unknowns																		
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Asian																		
	Native Hawaiian or Other Pacific Islander																		
	Black or African American																		
	White																		
	Multi-Racial																		
	Unknown																		

Note: N=Number of participants in the Safety Population

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

Variable	Statistic	WCK 6777 2g (N=X)	ERT 2g (N=X)	ZID 2g (N=X)	WCK 6777 4g (N=X)	ERT 3g (N=X)	ZID 3g (N=X)	WCK 6777 6g (N=X)	Placebo (N=X)	All Participants (N=X)
Age (years)	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Standard Deviation	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Maximum	xx	xx	xx	xx	xx	xx	xx	xx	xx
Height (cm)	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Weight (kg)	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
BMI (kg/m^2)	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Note: N=Number of participants in the Safety Population

14.1.3 Prior and Concurrent Medical Conditions

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

MedDRA System Organ Class	WCK 6777 2g (N=X)		ERT 2g (N=X)		ZID 2g (N=X)		WCK 6777 4g (N=X)		ERT 3g (N=X)		ZID 3g (N=X)		WCK 6777 6g (N=X)		Placebo (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]																		
[SOC 2]																		

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

14.2 Tolerability Data

Table 14: Tolerability by Treatment Group

	WCK 6777 2g (N=X)		ERT 2g (N=X)		ZID 2g (N=X)		WCK 6777 4g (N=X)		ERT 3g (N=X)		ZID 3g (N=X)		WCK 6777 6g (N=X)		Placebo (N=X)		All Participants (N=X)	
Participants who:	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Discontinued study drug due to an AE	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chose to withdraw from the study due to an AE	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Were withdrawn from the study by the investigator due to an AE	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: N=Number of participants in the Safety Population; n=number of participants meeting each tolerability category criteria.

14.3 Pharmacokinetic Data

Table 15: ERT Concentrations in Plasma by Treatment Group – Dose 1

	Nominal Time[a] (h)										
Treatment Group	**0**	**0.25**	**0.5**	**1**	**2**	**3**	**4**	**8**	**12**	**18**	**24**
Total ERT											
WCK 6777 2g	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
ERT 2g	x (x)	-	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
WCK 6777 4g	x (x)	-	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
ERT 3g	x (x)	-	-	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
WCK 6777 6g	x (x)	-	-	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Free ERT											
…											

Notes: Concentrations are reported in units of µg/mL. Timepoints where data was not collected are denoted by "-". Timepoints where data was not estimable are denoted by "NE".
Values of GM (CV %) are shown.
[a] Times are relative to time of dosing. Time 0 concentrations are drawn within 30 minutes prior to dosing.

Table 16: ERT Concentrations in Plasma by Treatment Group – Doses 2-6

	Nominal Time[a] (h)									
	Dose 2		Dose 3		Dose 4		Dose 5		Dose 6	
Treatment Group	0	12	0	12	0	12	0	12	0	12
Total ERT										
WCK 6777 2g	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
ERT 2g	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
WCK 6777 4g	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
ERT 3g	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
WCK 6777 6g	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Free ERT										
…										

Notes: Concentrations are reported in units of µg/mL. Timepoints where data was not estimable are denoted by "NE".
Values of GM (CV %) are shown.
[a] Times are relative to time of dosing. Time 0 concentrations are drawn within 30 minutes prior to dosing on the given day.

Tables with similar format:

Table 17: ERT Concentrations in Plasma by Treatment Group – Dose 7

[Repeat Table 15 for Dose 7]

Table 18: Summary Statistics for Total ERT Concentrations in Plasma – WCK 6777 2g, Dose 1

	Nominal Time[a] (h)										
Participant ID	**0**	**0.25**	**0.5**	**1**	**2**	**3**	**4**	**8**	**12**	**18**	**24**
99ZZZ001	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
99ZZZ002	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
99ZZZ003	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
…	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Statistics											
N[b]	x	x	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x	x	x
SD	x	x	x	x	x	x	x	x	x	x	x
CV%	x	x	x	x	x	x	x	x	x	x	x
GM	x	x	x	x	x	x	x	x	x	x	x
Median	x	x	x	x	x	x	x	x	x	x	x
(Min, Max)	x	x	x	x	x	x	x	x	x	x	x

Notes: Timepoints where data was not estimable are denoted by "NE".
[a] Times are relative to time of first dosing. Time 0 concentrations are drawn within 30 minutes prior to dosing.
[b] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 19: Summary Statistics for Total ERT Concentrations in Plasma – WCK 6777 2g, Doses 2-6

	Nominal Time[a] (h)									
	Dose 2		Dose 3		Dose 4		Dose 5		Dose 6	
Participant ID	**0**	**12**	**0**	**12**	**0**	**12**	**0**	**12**	**0**	**12**
99ZZZ001	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
99ZZZ002	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
99ZZZ003	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
…	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Statistics										
N[b]	x	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x	x
SD	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
Median	x	x	x	x	x	x	x	x	x	x
(Min, Max)	x	x	x	x	x	x	x	x	x	x

Notes: Concentrations are reported in units of µg/mL. Timepoints where data was not estimable are denoted by "NE".
[a] Times are relative to time of dosing. Time 0 concentrations are drawn within 30 minutes prior to dosing on the given day.
[b] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Tables with similar format:

Table 20: Summary Statistics for Total ERT Concentrations in Plasma – WCK 6777 2g, Dose 7

Table 21: Summary Statistics for Total ERT Concentrations in Plasma – ERT 2g, Dose 1

Table 22: Summary Statistics for Total ERT Concentrations in Plasma – ERT 2g, Doses 2-6

Table 23: Summary Statistics for Total ERT Concentrations in Plasma – ERT 2g, Dose 7

Table 24: Summary Statistics for Total ERT Concentrations in Plasma – WCK 6777 4g, Dose 1

Table 25: Summary Statistics for Total ERT Concentrations in Plasma – WCK 6777 4g, Doses 2-6

Table 26: Summary Statistics for Total ERT Concentrations in Plasma – WCK 6777 4g, Dose 7

Table 27: Summary Statistics for Total ERT Concentrations in Plasma – ERT 3g, Dose 1

Table 28: Summary Statistics for Total ERT Concentrations in Plasma – ERT 3g, Doses 2-6

Table 29: Summary Statistics for Total ERT Concentrations in Plasma – ERT 3g, Dose 7

Table 30: Summary Statistics for Total ERT Concentrations in Plasma – WCK 6777 6g, Dose 1

Table 31: Summary Statistics for Total ERT Concentrations in Plasma – WCK 6777 6g, Doses 2-6

Table 32: Summary Statistics for Total ERT Concentrations in Plasma – WCK 6777 6g, Dose 7

Table 48: ZID Concentrations in Plasma by Treatment Group – Dose 1

	Nominal Time[a] (h)										
Treatment Group	**0**	**0.25**	**0.5**	**1**	**2**	**3**	**4**	**8**	**12**	**18**	**24**
Total ZID											
WCK 6777 2g	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
ZID 2g	x (x)	-	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
WCK 6777 4g	x (x)	-	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
ZID 3g	x (x)	-	-	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
WCK 6777 6g	x (x)	-	-	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Free ZID											
…											

Notes: Concentrations are reported in units of µg/mL. Timepoints where data was not collected are denoted by "-". Timepoints where data was not estimable are denoted by "NE".
Values of GM (CV %) are shown.
[a] Times are relative to time of dosing. Time 0 concentrations are drawn within 30 minutes prior to dosing.

Tables with similar format:

Table 49: ZID Concentrations in Plasma by Treatment Group – Doses 2-6

[This Table will be similar to Table 16 for total ERT.]

Table 50: ZID Concentrations in Plasma by Treatment Group – Dose 7

[This Table will be similar to Table 17 for total ERT.]

Tables with similar format to Table 18/19:

Table 51: Summary Statistics for Total ZID Concentrations in Plasma – WCK 6777 2g, Dose 1

Table 52: Summary Statistics for Total ZID Concentrations in Plasma – WCK 6777 2g, Doses 2-6

Table 53: Summary Statistics for Total ZID Concentrations in Plasma – WCK 6777 2g, Dose 7

Table 54: Summary Statistics for Total ZID Concentrations in Plasma – ZID 2g, Dose 1

Table 55: Summary Statistics for Total ZID Concentrations in Plasma – ZID 2g, Doses 2-6

Table 56: Summary Statistics for Total ZID Concentrations in Plasma – ZID 2g, Dose 7

Table 57: Summary Statistics for Total ZID Concentrations in Plasma – WCK 6777 4g, Dose 1

Table 58: Summary Statistics for Total ZID Concentrations in Plasma – WCK 6777 4g, Doses 2-6

Table 59: Summary Statistics for Total ZID Concentrations in Plasma – WCK 6777 4g, Dose 7

Table 60: Summary Statistics for Total ZID Concentrations in Plasma – ZID 3g, Dose 1

Table 61: Summary Statistics for Total ZID Concentrations in Plasma – ZID 3g, Doses 2-6

Table 62: Summary Statistics for Total ZID Concentrations in Plasma – ZID 3g, Dose 7

Table 63: Summary Statistics for Total ZID Concentrations in Plasma – WCK 6777 6g, Dose 1

Table 64: Summary Statistics for Total ZID Concentrations in Plasma – WCK 6777 6g, Doses 2-6

Table 65: Summary Statistics for Total ZID Concentrations in Plasma – WCK 6777 6g, Dose 7

Table 81: Summary Statistics for Total ERT Single-Dose PK Parameters in Plasma by Treatment Group

PK Parameter (Units)	WCK 6777 2g	ERT 2g	WCK 6777 4g	ERT 3g	WCK 6777 6g
PK Analysis Subgroup					
C_{max}, (µg/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
C_{max}/Dose, ((µg/mL)/mg)	x (x)	x (x)	x (x)	x (x)	x (x)
C_{min}, (µg/mL)	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)
$AUC_{(0\text{-}t)}$, (µg*h/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0\text{-}inf)}$, (µg*h/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0\text{-}24)}$, (µg*h/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0\text{-}last)}$, (µg*h/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0\text{-}tau)}$, (µg*h/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0\text{-}tau)}$/Dose, ((µg*h/mL)/mg)	x (x)	x (x)	x (x)	x (x)	x (x)
$t_{1/2}$, (h)	x (x)	x (x)	x (x)	x (x)	x (x)
CL_T, (L/h)	x (x)	x (x)	x (x)	x (x)	x (x)
Ke, (1/h)	x (x)	x (x)	x (x)	x (x)	x (x)
V_d, (L)	x (x)	x (x)	x (x)	x (x)	x (x)
PK Analysis Subgroup Subset					
…					

Note: Single-dose parameters are calculated over the 24-hour period following Dose 1.
Values of GM (CV %) are shown, except for T_{max} for which values of median (min-max) are shown.

Tables with similar format:

Table 82: Summary Statistics for Free ERT Single-Dose PK Parameters in Plasma by Treatment Group

Table 83: Summary Statistics for Total ZID Single-Dose PK Parameters in Plasma by Treatment Group

Table 84: Summary Statistics for Free ZID Single-Dose PK Parameters in Plasma by Treatment Group

Table 85: Summary Statistics for Total ERT Multiple-Dose PK Parameters in Plasma by Treatment Group

PK Parameter (Units)	WCK 6777 2g	ERT 2g	WCK 6777 4g	ERT 3g	WCK 6777 6g
PK Analysis Subgroup					
$C_{max,ss}$, (µg/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
$C_{max,ss}$/Dose, ((µg/mL)/mg)	x (x)	x (x)	x (x)	x (x)	x (x)
$C_{min,ss}$, (µg/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
C_{avg}, (µg/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
$T_{max,ss}$, (h)	x (x - x)	x (x - x)	x (x - x)	x (x - x)	x (x - x)
T_{min}, (h)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0-24),ss}$, (µg*h/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0-tau),ss}$, (µg*h/mL)	x (x)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0-tau),ss}$/Dose, ((µg*h/mL)/mg)	x (x)	x (x)	x (x)	x (x)	x (x)
$t_{1/2}$, (h)	x (x)	x (x)	x (x)	x (x)	x (x)
CL_T, (L/h)	x (x)	x (x)	x (x)	x (x)	x (x)
$V_{d,ss}$, (L)	x (x)	x (x)	x (x)	x (x)	x (x)
Linearity Index[a]	x (x)	x (x)	x (x)	x (x)	x (x)
RAUC[b]	x (x)	x (x)	x (x)	x (x)	x (x)
RC_{max}[c]	x (x)	x (x)	x (x)	x (x)	x (x)
PK Analysis Subgroup Subset					
…					

Note: Multi-dose parameters are calculated over the 24-hour period following Dose 7. Values of GM (CV %) are shown, except for T_{max} for which values of median (min-max) are shown.
[a]Linearity Index is defined as $AUC_{(0-tau),ss}$ (Dose 7) / $AUC_{(0-\infty)}$ (Dose 1)
[b]RAUC is defined as $AUC_{(0-tau)}$ (Dose 7) / $AUC_{(0-24)}$ (Dose 1)
[c]RC_{maz} is defined as C_{max} (Dose 7) / C_{max} (Dose 1)

Tables with similar format:

Table 86: Summary Statistics for Free ERT Multiple-Dose PK Parameters in Plasma by Treatment Group

Table 87: Summary Statistics for Total ZID Multiple-Dose PK Parameters in Plasma by Treatment Group

Table 88: Summary Statistics for Free ZID Multiple-Dose PK Parameters in Plasma by Treatment Group

Table 89: Summary Statistics for Total ERT Single-Dose PK Parameters in Plasma – WCK 6777 2g

PK Parameter (Units)	N	Mean (SD)	Minimum, Maximum	Geometric Mean (CV%)
PK Analysis Subgroup				
C_{max}, (µg/mL)	x	x (x.x)	x, x	x (x.x)
C_{max}/Dose, ((µg/mL)/mg)	x	x (x.x)	x, x	x (x.x)
C_{min}, (µg/mL)	x	x (x.x)	x, x	x (x.x)
T_{max}, (h)	x	x (x.x)	x, x	x (x.x)
$AUC_{(0\text{-}t)}$, (µg*h/mL)	x	x (x.x)	x, x	x (x.x)
$AUC_{(0\text{-}inf)}$, (µg*h/mL)	x	x (x.x)	x, x	x (x.x)
$AUC_{(0\text{-}24)}$, (µg*h/mL)	x	x (x.x)	x, x	x (x.x)
$AUC_{(0\text{-}last)}$, (µg*h/mL)	x	x (x.x)	x, x	x (x.x)
$AUC_{(0\text{-}tau)}$, (µg*h/mL)	x	x (x.x)	x, x	x (x.x)
$AUC_{(0\text{-}tau)}$/Dose, ((µg*h/mL)/mg)	x	x (x.x)	x, x	x (x.x)
$t_{1/2}$, (h)	x	x (x.x)	x, x	x (x.x)
CL_T, (L/h)	x	x (x.x)	x, x	x (x.x)
Ke, (1/h)	x	x (x.x)	x, x	x (x.x)
V_d, (L)	x	x (x.x)	x, x	x (x.x)
PK Analysis Subgroup Subset				
…				

Tables with similar format:

Table 90: Summary Statistics for Total ERT Single-Dose PK Parameters in Plasma – ERT 2g

Table 91: Summary Statistics for Total ERT Single-Dose PK Parameters in Plasma – WCK 6777 4g

Table 92: Summary Statistics for Total ERT Single-Dose PK Parameters in Plasma – ERT 3g

Table 93: Summary Statistics for Total ERT Single-Dose PK Parameters in Plasma – WCK 6777 6g

Table 94: Summary Statistics for Free ERT Single-Dose PK Parameters in Plasma – WCK 6777 2g

Table 95: Summary Statistics for Free ERT Single-Dose PK Parameters in Plasma – ERT 2g

Table 96: Summary Statistics for Free ERT Single-Dose PK Parameters in Plasma – WCK 6777 4g

Table 97: Summary Statistics for Free ERT Single-Dose PK Parameters in Plasma – ERT 3g

Table 98: Summary Statistics for Free ERT Single-Dose PK Parameters in Plasma – WCK 6777 6g

Table 99: Summary Statistics for Total ZID Single-Dose PK Parameters in Plasma – WCK 6777 2g

Table 100: Summary Statistics for Total ZID Single-Dose PK Parameters in Plasma – ZID 2g

Table 101: Summary Statistics for Total ZID Single-Dose PK Parameters in Plasma – WCK 6777 4g

Table 102: Summary Statistics for Total ZID Single-Dose PK Parameters in Plasma – ZID 3g

Table 103: Summary Statistics for Total ZID Single-Dose PK Parameters in Plasma – WCK 6777 6g

Table 104: Summary Statistics for Free ZID Single-Dose PK Parameters in Plasma – WCK 6777 2g

Table 105: Summary Statistics for Free ZID Single-Dose PK Parameters in Plasma – ZID 2g

Table 106: Summary Statistics for Free ZID Single-Dose PK Parameters in Plasma – WCK 6777 4g

Table 107: Summary Statistics for Free ZID Single-Dose PK Parameters in Plasma – ZID 3g

Table 108: Summary Statistics for Free ZID Single-Dose PK Parameters in Plasma – WCK 6777 6g

Table 109: Summary Statistics for Total ERT Multiple-Dose PK Parameters in Plasma – WCK 6777 2g

PK Parameter (Units)	N	Mean (SD)	Minimum, Maximum	Geometric Mean (CV%)
PK Analysis Subgroup				
$C_{max,ss}$, (µg/mL)	x (x)	x (x)	x (x)	x (x)
$C_{max,ss}$/Dose, ((µg/mL)/mg)	x (x)	x (x)	x (x)	x (x)
$C_{min,ss}$, (µg/mL)	x (x)	x (x)	x (x)	x (x)
C_{avg}, (µg/mL)	x (x)	x (x)	x (x)	x (x)
$T_{max,ss}$, (h)	x (x - x)	x (x - x)	x (x - x)	x (x - x)
T_{min}, (h)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0-24),ss}$, (µg*h/mL)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0-tau),ss}$, (µg*h/mL)	x (x)	x (x)	x (x)	x (x)
$AUC_{(0-tau),ss}$/Dose, ((µg*h/mL)/mg)	x (x)	x (x)	x (x)	x (x)
$t_{1/2}$, (h)	x (x)	x (x)	x (x)	x (x)
CL_T, (L/h)	x (x)	x (x)	x (x)	x (x)
$V_{d,ss}$, (L)	x (x)	x (x)	x (x)	x (x)
Linearity Index[a]	x (x)	x (x)	x (x)	x (x)
RAUC[b]	x (x)	x (x)	x (x)	x (x)
RC_{max}[c]	x (x)	x (x)	x (x)	x (x)
PK Analysis Subgroup Subset				
…				

Note: Values of GM (CV %) are shown, except for T_{max} for which values of median (min-max) are shown.
[a]Linearity Index is defined as $AUC_{(0-tau),ss}$ (Dose 7) / $AUC_{(0-\infty)}$ (Dose 1)
[b]RAUC is defined as $AUC_{(0-tau)}$ (Dose 7) / $AUC_{(0-24)}$ (Dose 1)
[c]RC_{maz} is defined as C_{max} (Dose 7) / C_{max} (Dose 1)

Tables with similar format:

Table 110: Summary Statistics for Total ERT Multiple-Dose PK Parameters in Plasma – ERT 2g

Table 111: Summary Statistics for Total ERT Multiple-Dose PK Parameters in Plasma – WCK 6777 4g

Table 112: Summary Statistics for Total ERT Multiple-Dose PK Parameters in Plasma – ERT 3g

Table 113: Summary Statistics for Total ERT Multiple-Dose PK Parameters in Plasma – WCK 6777 6g

Table 114: Summary Statistics for Free ERT Multiple-Dose PK Parameters in Plasma – WCK 6777 2g

Table 115: Summary Statistics for Free ERT Multiple-Dose PK Parameters in Plasma – ERT 2g

Table 116: Summary Statistics for Free ERT Multiple-Dose PK Parameters in Plasma – WCK 6777 4g

Table 117: Summary Statistics for Free ERT Multiple-Dose PK Parameters in Plasma – ERT 3g

Table 118: Summary Statistics for Free ERT Multiple-Dose PK Parameters in Plasma – WCK 6777 6g

Table 119: Summary Statistics for Total ZID Multiple-Dose PK Parameters in Plasma – WCK 6777 2g

Table 120: Summary Statistics for Total ZID Multiple-Dose PK Parameters in Plasma – ZID 2g

Table 121: Summary Statistics for Total ZID Multiple-Dose PK Parameters in Plasma – WCK 6777 4g

Table 122: Summary Statistics for Total ZID Multiple-Dose PK Parameters in Plasma – ZID 3g

Table 123: Summary Statistics for Total ZID Multiple-Dose PK Parameters in Plasma – WCK 6777 6g

Table 124: Summary Statistics for Free ZID Multiple-Dose PK Parameters in Plasma – WCK 6777 2g

Table 125: Summary Statistics for Free ZID Multiple-Dose PK Parameters in Plasma – ZID 2g

Table 126: Summary Statistics for Free ZID Multiple-Dose PK Parameters in Plasma – WCK 6777 4g

Table 127: Summary Statistics for Free ZID Multiple-Dose PK Parameters in Plasma – ZID 3g

Table 128: Summary Statistics for Free ZID Multiple-Dose PK Parameters in Plasma – WCK 6777 6g

Table 129: Amount and Percent ERT Protein Binding – WCK 6777 2g

		Amount Bound		Percent Bound	
Nominal Time[a] (h)	n	Mean (SD)	Min, Max	Mean (SD)	Min, Max
Dose 1					
0	x	x	x.x	x.x	x.x
0.25	x	x	-	-	-
0.5	x	x	x.x	x.x	-
1	x	x	x.x	x.x	x.x
2	x	x	x.x	x.x	x.x
3	x	x	x.x	x.x	x.x
4	x	x	x.x	x.x	x.x
8	x	x	x.x	x.x	x.x
12	x	x	x.x	x.x	x.x
18	x	x	x.x	x.x	x.x
24	x	x	x.x	x.x	x.x
Dose 2					
0	x	x	x.x	x.x	x.x
12	x	x	x.x	x.x	x.x
Dose 3					
…					
Dose 4					
…					
Dose 5					
…					
Dose 6					
…					
Dose 7					
…					

Notes: Timepoints where data was not collected are denoted by "-". Timepoints where data was not estimable are denoted by "NE".
n= Number of participants with estimable amount/percent binding at the given timepoint.
Values of GM (CV %) are shown.
Amount bound will be calculated as Ctotal-Cfree. Percent bound will be calculated as ((Ctotal-Cfree)/Ctotal) x 100%.
[a] Times are relative to time of dosing.

Tables with similar format:

Table 130: Amount and Percent ERT Protein Binding – ERT 2g

Table 131: Amount and Percent ERT Protein Binding – WCK 6777 4g

Table 132: Amount and Percent ERT Protein Binding – ERT 3g

Table 133: Amount and Percent ERT Protein Binding – WCK 6777 6g

Table 134: Amount and Percent ZID Protein Binding – WCK 6777 2g

Table 135: Amount and Percent ZID Protein Binding – WCK ZID 2g

Table 136: Amount and Percent ZID Protein Binding – WCK 6777 4g

Table 137: Amount and Percent ZID Protein Binding – WCK ZID 3g

Table 138: Amount and Percent ZID Protein Binding – WCK 6777 6g

Table 139: ERT Concentrations in Urine by Treatment Group – Dose 1

	Nominal Time[a] (h)				
Treatment Group	**-1 - 0**	**0 - 4**	**4 - 8**	**8 - 12**	**12 - 24**
WCK 6777 2g	x (x)	x (x)	x (x)	x (x)	x (x)
ERT 2g	x (x)	x (x)	x (x)	x (x)	x (x)
WCK 6777 4g	x (x)	x (x)	x (x)	x (x)	x (x)
ERT 3g	x (x)	x (x)	x (x)	x (x)	x (x)
WCK 6777 6g	x (x)	x (x)	x (x)	x (x)	x (x)

Notes: Concentrations are reported in units of µg/mL. Timepoints where data was not collected are denoted by "-". Timepoints where data was not estimable are denoted by "NE".
Values of GM (CV %) are shown.
[a] Times are relative to time of dosing.

Tables with similar format:

Table 140: ERT Concentrations in Urine by Treatment Group – Dose 7

Table 141: ZID Concentrations in Urine by Treatment Group – Dose 1

Table 142: ZID Concentrations in Urine by Treatment Group – Dose 7

Table 143: ERT Summary Statistics for Concentrations in Urine – WCK 6777 2g, Dose 1

	Nominal Time[a] (h)				
Participant ID	**-1 - 0**	**0 - 4**	**4 - 8**	**8 - 12**	**12 - 24**
99ZZZ001	x (x)	x (x)	x (x)	x (x)	x (x)
99ZZZ002	x (x)	x (x)	x (x)	x (x)	x (x)
99ZZZ003	x (x)	x (x)	x (x)	x (x)	x (x)
…	x (x)	x (x)	x (x)	x (x)	x (x)
Statistics					
N[b]	x	x	x	x	x
Mean	x	x	x	x	x
SD	x	x	x	x	x
CV%	x	x	x	x	x
GM	x	x	x	x	x
Median	x	x	x	x	x
Min, Max	x, x	x, x	x, x	x, x	x, x

Notes: Timepoints where data was not estimable are denoted by "NE".
[a] Times are relative to time of first dosing.
[b] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Tables with similar format:

Table 144: ERT Summary Statistics for Concentrations in Urine – WCK 6777 2g, Dose 7

Table 145: ERT Summary Statistics for Concentrations in Urine – ERT 2g, Dose 1

Table 146: ERT Summary Statistics for Concentrations in Urine – ERT 2g, Dose 7

Table 147: ERT Summary Statistics for Concentrations in Urine – WCK 6777 4g, Dose 1

Table 148: ERT Summary Statistics for Concentrations in Urine – WCK 6777 4g, Dose 7

Table 149: ERT Summary Statistics for Concentrations in Urine – ERT 3g, Dose 1

Table 150: ERT Summary Statistics for Concentrations in Urine – ERT 3g, Dose 7

Table 151: ERT Summary Statistics for Concentrations in Urine – WCK 6777 6g, Dose 1

Table 152: ERT Summary Statistics for Concentrations in Urine – WCK 6777 6g, Dose 7

Table 153: ZID Summary Statistics for Concentrations in Urine – WCK 6777 2g, Dose 1

Table 154: ZID Summary Statistics for Concentrations in Urine – WCK 6777 2g, Dose 7

Table 155: ZID Summary Statistics for Concentrations in Urine – ZID 2g, Dose 1

Table 156: ZID Summary Statistics for Concentrations in Urine – ZID 2g, Dose 7

Table 157: ZID Summary Statistics for Concentrations in Urine – WCK 6777 4g, Dose 1

Table 158: ZID Summary Statistics for Concentrations in Urine – WCK 6777 4g, Dose 7

Table 159: ZID Summary Statistics for Concentrations in Urine – ZID 3g, Dose 1

Table 160: ZID Summary Statistics for Concentrations in Urine – ZID 3g, Dose 7

Table 161: ZID Summary Statistics for Concentrations in Urine – WCK 6777 6g, Dose 1

Table 162: ZID Summary Statistics for Concentrations in Urine – WCK 6777 6g, Dose 7

Table 163: Summary Statistics for ERT PK Parameters in Urine by Treatment Group, Dose 1

	WCK 6777 2g	ERT 2g	WCK 6777 4g	ERT 3g	WCK 6777 6g
PK Analysis Subgroup					
Ae,urine (mg) 0-4 h	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae,urine (mg) 4-8 h	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae,urine (mg) 8-12 h	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
Ae,urine (mg) 12-24 h	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
$Ae,urine_{(0-24)}$ (mg)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
fe,urine 0-4 h	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
fe,urine 4-8 h	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
fe,urine 8-12 h	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
fe,urine 12-24 h	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
$fe,urine_{(0-24)}$	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
$CL_{R(0-24)}$	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)	x (xx, xx)
PK Analysis Subgroup Subset					
…					

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.

Tables with similar format:

Table 164: Summary Statistics for ERT PK Parameters in Urine by Treatment Group, Dose 7

[Implementation Note: Repeat Table 163 for Dose 7 with rows for $AE,urine_{(0\text{-}24),ss}$ (mg), $fe,urine_{(0\text{-}24),ss}$, and $CL_{R,ss}$ instead of $AE,urine_{(0\text{-}24)}$ (mg), $fe,urine_{(0\text{-}24)}$, and $CL_{R(0\text{-}24)}$.]

Table 165: Summary Statistics for ZID PK Parameters in Urine by Treatment Group, Dose 1

Table 166: Summary Statistics for ZID PK Parameters in Urine by Treatment Group, Dose 7

[Implementation Note: Repeat Table 165 for Dose 7 with rows for $AE,urine_{(0\text{-}24),ss}$ (mg), $fe,urine_{(0\text{-}24),ss}$, and $CL_{R,ss}$ instead of $AE,urine_{(0\text{-}24)}$ (mg), $fe,urine_{(0\text{-}24)}$, and $CL_{R(0\text{-}24)}$.]

Table 167: Summary Statistics for ERT PK Parameters in Urine – WCK 6777 2g, Dose 1

Statistics	Ae,urine 0-4 h (mg)	Ae,urine 4-8 h (mg)	Ae,urine 8-12 h (mg)	Ae,urine 12-24 h (mg)	$Ae,urine_{(0-24)}$ (mg)	fe,urine 0-4 h (%)	fe,urine 4-8 h (%)	fe,urine 8-12 h (%)	fe,urine12-24 h (%)	$fe,urine_{(0-24)}$ (%)	$CL_{R(0-24)}$
PK Analysis Subgroup											
N	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
Median	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
GM	x	x	x	x	x	x	x	x	x	x	x
CV %	x	x	x	x	x	x	x	x	x	x	x
PK Analysis Subgroup Subset											
…											

Tables with similar format:

Table 168: Summary Statistics for ERT PK Parameters in Urine – ERT 2g, Dose 1

Table 169: Summary Statistics for ERT PK Parameters in Urine – WCK 6777 4g, Dose 1

Table 170: Summary Statistics for ERT PK Parameters in Urine – ERT 3g, Dose 1

Table 171: Summary Statistics for ERT PK Parameters in Urine – WCK 6777 6g, Dose 1

Table 172: Summary Statistics for ERT PK Parameters in Urine – ERT 2g, Dose 7

Statistics	Ae,urine 0-4 h (mg)	Ae,urine 4-8 h (mg)	Ae,urine 8-12 h (mg)	Ae,urine 12-24 h (mg)	$Ae,urine_{(0-24),ss}$ (mg)	fe,urine 0-4 h (%)	fe,urine 4-8 h (%)	fe,urine 8-12 h (%)	fe,urine12-24 h (%)	$fe,urine_{(0-24),ss}$ (%)	$CL_{R,ss}$
PK Analysis Subgroup											
N	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
Median	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
GM	x	x	x	x	x	x	x	x	x	x	x
CV %	x	x	x	x	x	x	x	x	x	x	x
PK Analysis Subgroup Subset											
…											

Tables with similar format:

Table 173: Summary Statistics for ERT PK Parameters in Urine – WCK 6777 4g, Dose 7

Table 174: Summary Statistics for ERT PK Parameters in Urine – ERT 3g, Dose 7

Table 175: Summary Statistics for ERT PK Parameters in Urine – WCK 6777 6g, Dose 7

Tables with similar format to Table 173/178:

Table 176: Summary Statistics for ZID PK Parameters in Urine – WCK 6777 2g, Dose 1

Table 177: Summary Statistics for ZID PK Parameters in Urine – ZID 2g, Dose 1

Table 178: Summary Statistics for ZID PK Parameters in Urine – WCK 6777 4g, Dose 1

Table 179: Summary Statistics for ZID PK Parameters in Urine – ZID 3g, Dose 1

Table 180: Summary Statistics for ZID PK Parameters in Urine – WCK 6777 6g, Dose 1

Table 181: Summary Statistics for ZID PK Parameters in Urine – WCK 6777 2g, Dose 7

Table 182: Summary Statistics for ZID PK Parameters in Urine – ZID 2g, Dose 7

Table 183: Summary Statistics for ZID PK Parameters in Urine – WCK 6777 4g, Dose 7

Table 184: Summary Statistics for ZID PK Parameters in Urine – ZID 3g, Dose 7

Table 185: Summary Statistics for ZID PK Parameters in Urine – WCK 6777 6g, Dose 7

Table 186: Assessment of Dose Proportionality of WCK 6777 in Plasma – Dose 1, PK Analysis Subset

Statistic	ERT			ZID		
	C_{max}	$AUC_{0\text{-}last}$	$AUC_{0\text{-}inf}$	C_{max}	$AUC_{0\text{-}last}$	$AUC_{0\text{-}inf}$
	(µg/mL)	(µg*h/mL)	(µg*h/mL)	(µg/mL)	(µg*h/mL)	(µg*h/mL)
Total						
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
Free						
…						

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).

Tables with similar format:

Table 187: Assessment of Dose Proportionality of WCK 6777 in Plasma – Dose 1, PK Analysis Subset Subgroup

Table 188: Assessment of Dose Proportionality of WCK 6777 in Plasma – Dose 7, PK Analysis Subset

[Implementation note: this table will contain $C_{max,ss}$ $AUC_{(0\text{-}24),ss}$ and $AUC_{(0\text{-}tau),ss}$ instead of the above parameters]

Table 189: Assessment of Dose Proportionality of WCK 6777 in Plasma – Dose 7, PK Analysis Subset Subgroup

[Implementation note: this table will contain $C_{max,ss}$ $AUC_{(0\text{-}24),ss}$ and $AUC_{(0\text{-}tau),ss}$ instead of the above parameters]

Table 190: Assessment of Drug-Drug Interactions of ERT and ZID for Concentrations of WCK 6777 in Plasma – PK Analysis Subset

Treatment Group	C_{max}/Dose (µg/mL)		AUC_{0-last}/Dose (µg/mL)		AUC_{0-tau}/Dose (µg/mL)		AUC_{0-inf}/Dose (µg/mL)		$C_{max,ss}$/Dose (µg/mL)		$AUC_{0-tau,ss}$/Dose (µg/mL)		% Bound Day 1		% Bound Day 7		Amount Bound Day 1		Amount Bound Day 7	
	GM (95% CI)	GLS MR (90% CI)	GM (95% CI)	GLS MR (90% CI)	GM (95% CI)	GLS MR (90% CI)	GM (95% CI)	GLS MR (90% CI)	GM (95% CI)	GLS MR (90% CI)	GM (95% CI)	GLS MR (90% CI)	GM (95% CI)	GLS MR (90% CI)	GM (95% CI)	GLS MR (90% CI)	GM (95% CI)	GLS MR (90% CI)	GM (95% CI)	GLS MR (90% CI)
Total ERT																				
2 g ERT	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)	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)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
4 g WCK 6777	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)	-	x.xx (x.xx, x.xx)	-	x.xx (x.xx, x.xx)	-
3 g ERT	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)	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)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
6 g WCK 6777	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)	-	x.xx (x.xx, x.xx)	-	x.xx (x.xx, x.xx)	-
Total ZID																				
2 g ZID	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)	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)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
4 g WCK 6777	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)	-	x.xx (x.xx, x.xx)	-	x.xx (x.xx, x.xx)	-

Table 190: Assessment of Drug-Drug Interactions of ERT and ZID for Concentrations of WCK 6777 in Plasma – PK Analysis Subset
(continued)

3 g ZID	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)	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)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
6 g WCK 6777	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)	-	x.xx (x.xx, x.xx)	-	x.xx (x.xx, x.xx)	-
Free ERT																				
2 g ERT	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)	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)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
4 g WCK 6777	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)	-	x.xx (x.xx, x.xx)	-	x.xx (x.xx, x.xx)	-
3 g ERT	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)	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)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
6 g WCK 6777	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)	-	x.xx (x.xx, x.xx)	-	x.xx (x.xx, x.xx)	-
Free ZID																				
2 g ZID	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)	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)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
4 g WCK 6777	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)	-	x.xx (x.xx, x.xx)	-	x.xx (x.xx, x.xx)	-

Table 190: Assessment of Drug-Drug Interactions of ERT and ZID for Concentrations of WCK 6777 in Plasma – PK Analysis Subset
(continued)

3 g ZID	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)	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)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
6 g WCK 6777	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)	-	x.xx (x.xx, x.xx)	-	x.xx (x.xx, x.xx)	-

Notes: DN = Dose-Normalized. CI = Confidence Interval. GM = Geometric Mean. GLSMR = Geometric Least-Squares Mean Ratio.
Estimates and CIs are obtained using an ANOVA model for the log-transformed dose-normalized exposure parameter with the lowest dose studied in standalone, 2 g, as the reference dose. Dose-normalized GLSMRs are calculated using the relevant WCK 6777 dose group as the denominator.

Tables with similar format:

Table 191: Assessment of Drug-Drug Interactions of ERT and ZID for Concentrations of WCK 6777 in Plasma – PK Analysis Subset Subgroup

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 192: Overall Summary of Adverse Events

	WCK 6777 2g (N=X)		ERT 2g (N=X)		ZID 2g (N=X)		WCK 6777 4g (N=X)		ERT 3g (N=X)		ZID 3g (N=X)		WCK 6777 6g (N=X)		Placebo (N=X)		All Participants (N=X)	
Participants[a] with	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
At least one adverse event	x	x	x	x													x	x
At least one related adverse event	x	x	x	x													x	x
Mild (Grade 1)	x	x	x	x													x	x
Moderate (Grade 2)	x	x	x	x													x	x
Severe (Grade 3)	x	x	x	x													x	x
At least one severe (Grade 3) unsolicited adverse event	x	x	x	x													x	x
Related	x	x	x	x													x	x
Unrelated	x	x	x	x													x	x
At least one serious adverse event	x	x	x	x													x	x
At least one related, serious adverse event	x	x	x	x													x	x
At least one adverse event leading to early termination[b]	x	x	x	x													x	x

N = Number of participants in the Safety Population
[a] Participants are counted once for each category regardless of the number of events.
[b] As reported on the Adverse Event eCRF.

Table 193: Adverse Events Occurring in 5% of Participants in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - Safety Population

MedDRA System Organ Class	MedDRA Preferred Term	WCK 6777 2g (N=X)			ERT 2g (N=X)			ZID 2g (N=X)			WCK 6777 4g (N=X)			ERT 3g (N=X)			ZID 3g (N=X)			WCK 6777 6g (N=X)			Placebo (N=X)			All Participants (N=X)		
		n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events																												
All	All	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
PT1	SOC1	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
Etc.	Etc.																											
Other (Non-serious) Adverse Events																												
All	All	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
PT1	SOC1	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
Etc	Etc																											

N = number of participants in the Safety Population (number of participants at risk).
n = number of participants reporting event.
Events = total frequency of events reported.

14.3.1.1 Adverse Events

Table 194: Summary of Adverse Events by MedDRA System Organ Class, High Level Group Term, Preferred Term, and Treatment Group

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

Repeat for the following treatment groups: WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo]

Treatment Group	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	n (%)	95% CI[a]	Number of Events
All Participants (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
WCK 6777 2g (N=X)	…		…	x (x)	xx, xx	x
…	…		…	x (x)	xx, xx	x
Placebo (N=X)	…		…	x (x)	xx, xx	x

Notes: N=Number of participants in the Safety Population in the specified treatment group.
n=number of participants reporting adverse events within each SOC/HLGT/PT.
A participant is only counted once per PT per treatment group.
[a] Exact Clopper-Pearson Confidence Interval.

Table 195: Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group

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

Repeat for the following treatment groups: WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo]

Treatment Group	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Severity	Related n (%)	Not Related n (%)	Total n (%)
All Participants (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 (%)
WCK 6777 2g (N=X)	Any SOC		Any PT	Any Severity	x (%)	x (%)	x (%)
…	…		…	…	x (%)	x (%)	x (%)
Placebo (N=X)	…		…	…	x (%)	x (%)	x (%)

Notes: N=Number of participants in the Safety Population in each treatment group.
Participants are only counted once per PT and treatment group, in the highest reported severity.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 196: Listing of Non-Serious 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 Treatment Group, Participant ID, and AE Number.

Treatment Group order: WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term
Participant ID: , Treatment Group: , AE Number:											
Comments:											
Participant ID: , Treatment Group: , AE Number:											
Comments:											

Table 197: 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 Treatment Group, Participant ID, and AE Number.

Treatment Group order: WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term
Participant ID: , Treatment Group: , AE Number:													
Comments:													
Participant ID: , Treatment Group: , 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 Participant)

Table 198: 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: Treatment Group, Participant ID, Timepoint, and Parameter.

Treatment Group order: WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo]

Participant ID	Treatment Group	Sex	Age (years)	Planned Timepoint	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?

Table 199: 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: Treatment Group, Participant ID, Timepoint, and Parameter

Treatment Group order: WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo]

Participant ID	Treatment Group	Sex	Age (years)	Planned Timepoint	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?

Table 200: 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: Treatment Group, Participant ID, Timepoint, and Parameter.

Treatment Group order: WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo]

Participant ID	Treatment Group	Sex	Age (years)	Planned Timepoint	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?

Table 201: 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 by Microscopy (/HPF). The test type used to obtain the results will also be indicated in the Laboratory Parameter column (e.g., Bilirubin by Dipstick, Red Blood Cells by Microscopy, etc.). 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: Treatment Group, Participant ID, Timepoint, and Parameter.

Treatment Group order: WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo]

Participant ID	Treatment Group	Sex	Age (years)	Planned Timepoint	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 202: Chemistry Laboratory Toxicity Grade by Parameter, Treatment Group, Timepoint, and Severity

[Implementation Note: If there is not at least one Mild, Moderate, or Severe event for a Treatment 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".]

Treatment Group	Timepoint	N	Mild	Moderate	Severe
			n (%)	n (%)	n (%)
Chemistry - Any Parameter					
All Participants	Baseline	x	x (x)	x (x)	x (x)
	Maximum Severity Post Baseline	x	x (x)	x (x)	x (x)
	Day 2	x	x (x)	x (x)	x (x)
	Day 4	x	x (x)	x (x)	x (x)
	Day 6	x	x (x)	x (x)	x (x)
	Day 8	x	x (x)	x (x)	x (x)
	Day 11	x	x (x)	x (x)	x (x)
WCK 6777 2g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ERT 2g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ZID 2g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
WCK 6777 4g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ERT 3g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ZID 3g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
WCK 6777 6g	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 participant at any timepoint post baseline, including unscheduled assessments.
N=Number of participants in the Safety Population with the laboratory result assessed at the respective timepoint.

Table 203: Chemistry Summary Statistics Measurement and Change from Baseline by Parameter, Treatment Group, and Timepoint

Treatment Group	Timepoint	N	Measurement				Change from Baseline			
			Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Sodium (mmol/L)										
All Participants	Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Day 2	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 6	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 8	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 11	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
WCK 6777 2g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ERT 2g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ZID 2g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
WCK 6777 4g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ERT 3g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ZID 3g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
WCK 6777 6g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Placebo		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
[Repeat for all parameters]										

Note: N=Number of participants in the Safety Population with the laboratory result assessed at the respective timepoint.

14.3.5.2 Hematology Results

Table 204: Hematology Laboratory Toxicity Grade by Parameter, Treatment Group, Timepoint, and Severity

[This table will repeat Table 199 for Hematology Parameters]

Table 205: Hematology Summary Statistics Measurement and Change from Baseline by Parameter, Treatment Group, and Timepoint

[This table will repeat Table 200 for Hematology Parameters]

14.3.5.3 Coagulation Results

Table 206: Coagulation Laboratory Toxicity Grade by Parameter, Treatment Group, Timepoint, and Severity

[This table will repeat Table 199 for Coagulation Parameters]

Table 207: Coagulation Summary Statistics Measurement and Change from Baseline by Parameter, Treatment Group, and Timepoint

[This table will repeat Table 200 for Coagulation Parameters]

14.3.5.4 Urinalysis Results

Table 208: Urinalysis Laboratory Toxicity Grade by Parameter, Treatment Group, Timepoint, and Severity

[This table will repeat Table 199 for Urinalysis Parameters with timepoints baseline, day 4, day 8, day 11]

Table 209: Urinalysis Summary Statistics Measurement and Change from Baseline by Parameter, Treatment Group, and Timepoint

[This table will repeat Table 200 for Urinalysis Parameters with timepoints baseline, day 4, day 8, day 11]

14.3.5 Displays of Vital Signs

Table 210: Vital Sign Toxicity Grade by Parameter, Treatment Group, Timepoint, and Severity

[Implementation Note: If there is not at least one Mild, Moderate, or Severe event for a Treatment 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".]

Treatment Group	Timepoint	N	Mild	Moderate	Severe
			n (%)	n (%)	n (%)
Any Parameter					
All Participants	Baseline	x	x (x)	x (x)	x (x)
	Maximum Severity Post Baseline	x	x (x)	x (x)	x (x)
	Day 1	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 5	x	x (x)	x (x)	x (x)
	Day 6	x	x (x)	x (x)	x (x)
	Day 7	x	x (x)	x (x)	x (x)
	Day 8	x	x (x)	x (x)	x (x)
	Day 11	x	x (x)	x (x)	x (x)
WCK 6777 2g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ERT 2g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ZID 2g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
WCK 6777 4g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ERT 3g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ZID 3g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
WCK 6777 6g	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)					
All Participants	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 participant at any timepoint post baseline, including unscheduled assessments.
N=Number of participants in the Safety Population with the vital sign assessed at the respective timepoint.

Table 211: Vital Sign Summary Statistics Measurement and Change from Baseline by Parameter, Treatment Group, and Timepoint

Treatment Group	Timepoint	N	Measurement				Change from Baseline			
			Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Systolic Blood Pressure										
All Participants	Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Day 1	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 2	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 3	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 5	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 6	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 7	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 8	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 11	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
WCK 6777 2g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ERT 2g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ZID 2g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
WCK 6777 4g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ERT 3g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ZID 3g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
WCK 6777 6g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x

Table 211: Vital Sign Summary Statistics Measurement and Change from Baseline by Parameter, Treatment Group, and Timepoint
(Continued)

Treatment Group	Timepoint	N	Measurement				Change from Baseline			
			Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Systolic Blood Pressure										
Placebo		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
[Repeat for all parameters]										
Note: N=Number of participants in the Safety Population with the vital sign assessed at the respective timepoint.										

Table 212: Summary of Post Dose ECG Change in Overall Interpretations from Baseline by Treatment Group and Timepoint

Change from Baseline in ECG Interpretation	WCK 6777 2g n (%)	ERT 2g n (%)	ZID 2g n (%)	WCK 6777 4g n (%)	ERT 3g n (%)	ZID 3g n (%)	WCK 6777 6g n (%)	Placebo n (%)	All Participants n (%)
Day 8									
N	x	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)	x (x)
Normal to Abnormal, NCS	x (x)	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)	x (x)
Day 11									
N	x	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)	x (x)
Normal to Abnormal, NCS	x (x)	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)	x (x)

Notes: N=Number of participants in the Safety Population with ECG measurements at the timepoints indicated.
NCS = Not clinically significant, CS = Clinically significant.

Table 213: ECG Toxicity Grade by Parameter, Severity, Treatment Group, and Timepoint

[Implementation Note: If there is not at least one Mild, Moderate, or Severe event for a Treatment Group within a parameter, then only the Maximum Severity Post Baseline row will be shown for that parameter.]

Treatment Group	Timepoint	N	Mild	Moderate	Severe
			n (%)	n (%)	n (%)
QTcF Interval (msec)					
All Participants	Baseline	x	x (x)	x (x)	x (x)
	Maximum Severity Post Baseline	x	x (x)	x (x)	x (x)
	Day 8	x	x (x)	x (x)	x (x)
	Day 11	x	x (x)	x (x)	x (x)
WCK 6777 2g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ERT 2g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ZID 2g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
WCK 6777 4g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ERT 3g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
ZID 3g	Baseline	x	x (x)	x (x)	x (x)
	…	x	x (x)	x (x)	x (x)
WCK 6777 6g	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 participants at any timepoint post baseline, including unscheduled assessments.
N=Number of participants in the Safety Population with ECG results assessed at the respective timepoint.

Table 214: ECG Summary Statistics Measurement and Change from Baseline by Parameter, Severity, Treatment Group, and Timepoint

Treatment Group	Timepoint	N	Measurement				Change from Baseline			
			Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
PR Interval (msec)										
All Participants	Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Day 8	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 11	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
WCK 6777 2g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ERT 2g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ZID 2g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
WCK 6777 4g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ERT 3g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
ZID 3g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
WCK 6777 6g		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Placebo		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
…		x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
[Repeat for all parameters]										
Note: N=Number of participants in the Safety Population with ECG measurements at the respective timepoint.										

14.4 Summary of Prior and Concomitant Medications

Table 215: Number and Percentage of Participants with Prior Medications by WHO Drug Classification and Treatment Group

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	WCK 6777 2g (N=X)		ERT 2g (N=X)		ZID 2g (N=X)		WCK 6777 4g (N=X)		ERT 3g (N=X)		ZID 3g (N=X)		WCK 6777 6g (N=X)		Placebo (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]																		
	[ATC 2 - 1]																		
	[ATC 2 - 2]																		
	[ATC 2 - 3]																		
[ATC Level 1 – 2]	[ATC 2 - 1]																		
	[ATC 2 - 2]																		
	[ATC 2 - 3]																		

N = Number of participants in the Safety Population. n=Number of participants reporting taking at least one medication in the specific WHO Drug Class.

Table 216: Number and Percentage of Participants with Concomitant Medications by WHO Drug Classification and Treatment Group

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	WCK 6777 2g (N=X)		ERT 2g (N=X)		ZID 2g (N=X)		WCK 6777 4g (N=X)		ERT 3g (N=X)		ZID 3g (N=X)		WCK 6777 6g (N=X)		Placebo (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]																		
	[ATC 2 - 1]																		
	[ATC 2 - 2]																		
	[ATC 2 - 3]																		
[ATC Level 1 – 2]	[ATC 2 - 1]																		
	[ATC 2 - 2]																		
	[ATC 2 - 3]																		

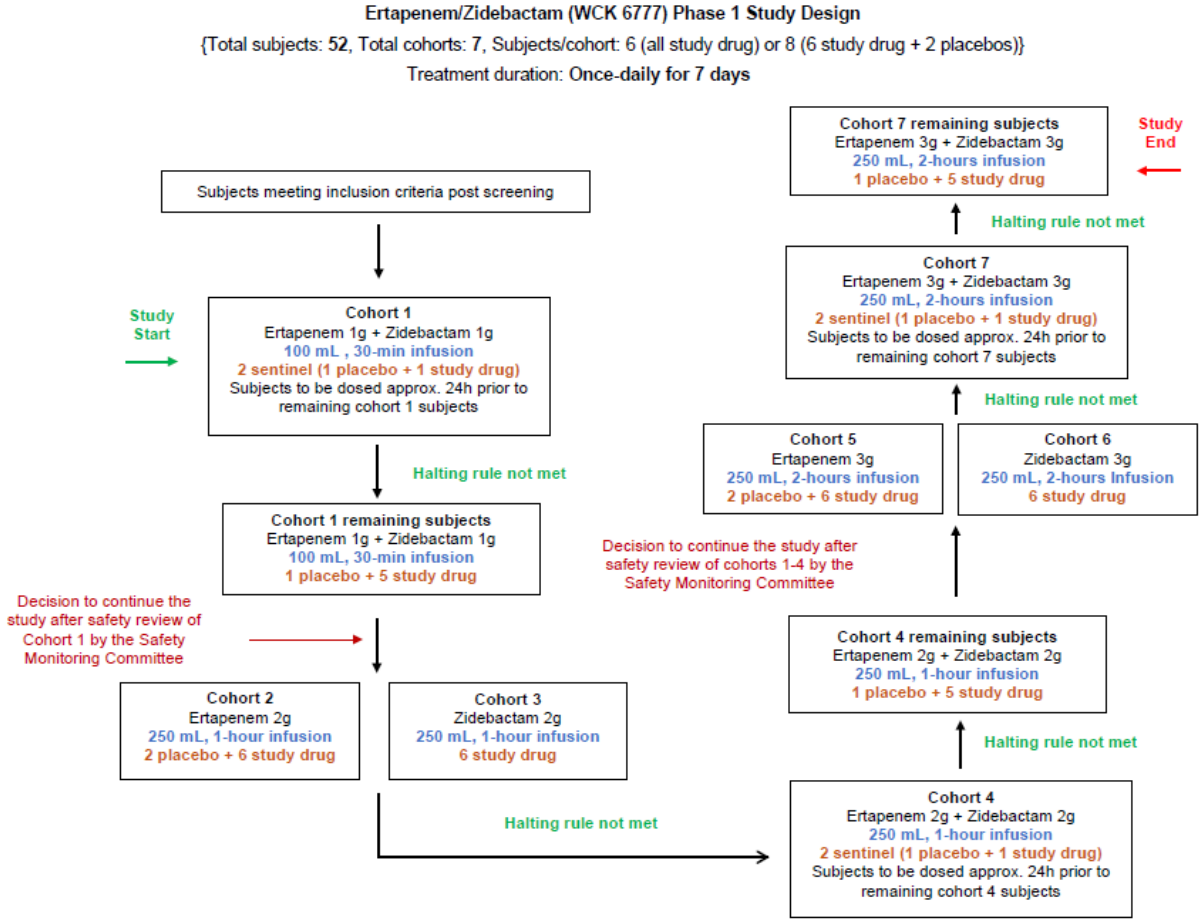
N = Number of participants in the Safety Population. n=Number of participants reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

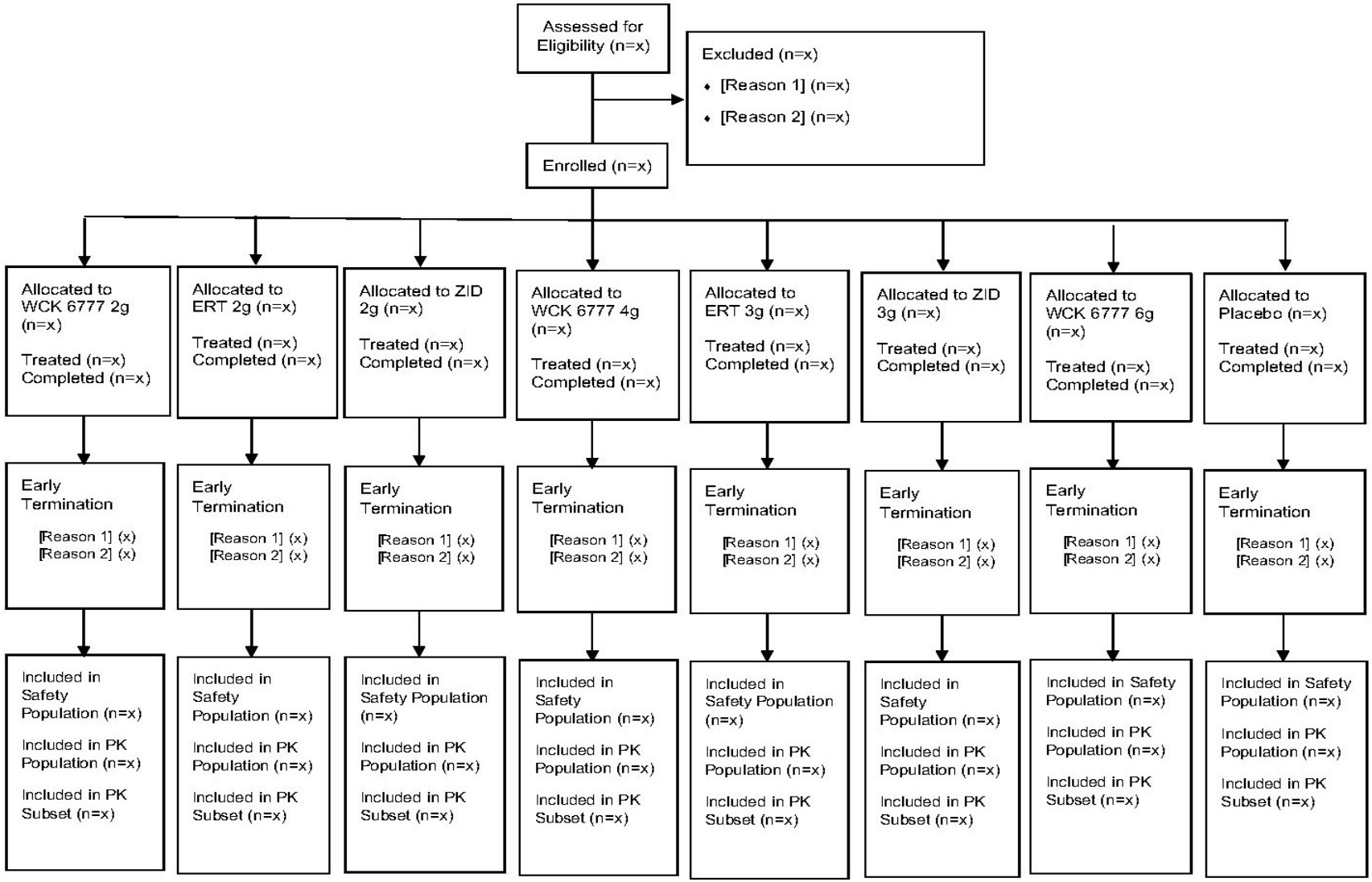
9.5.1 Safety Measurements Assessed and Flow Chart

Figure 1: Schematic of Study Design



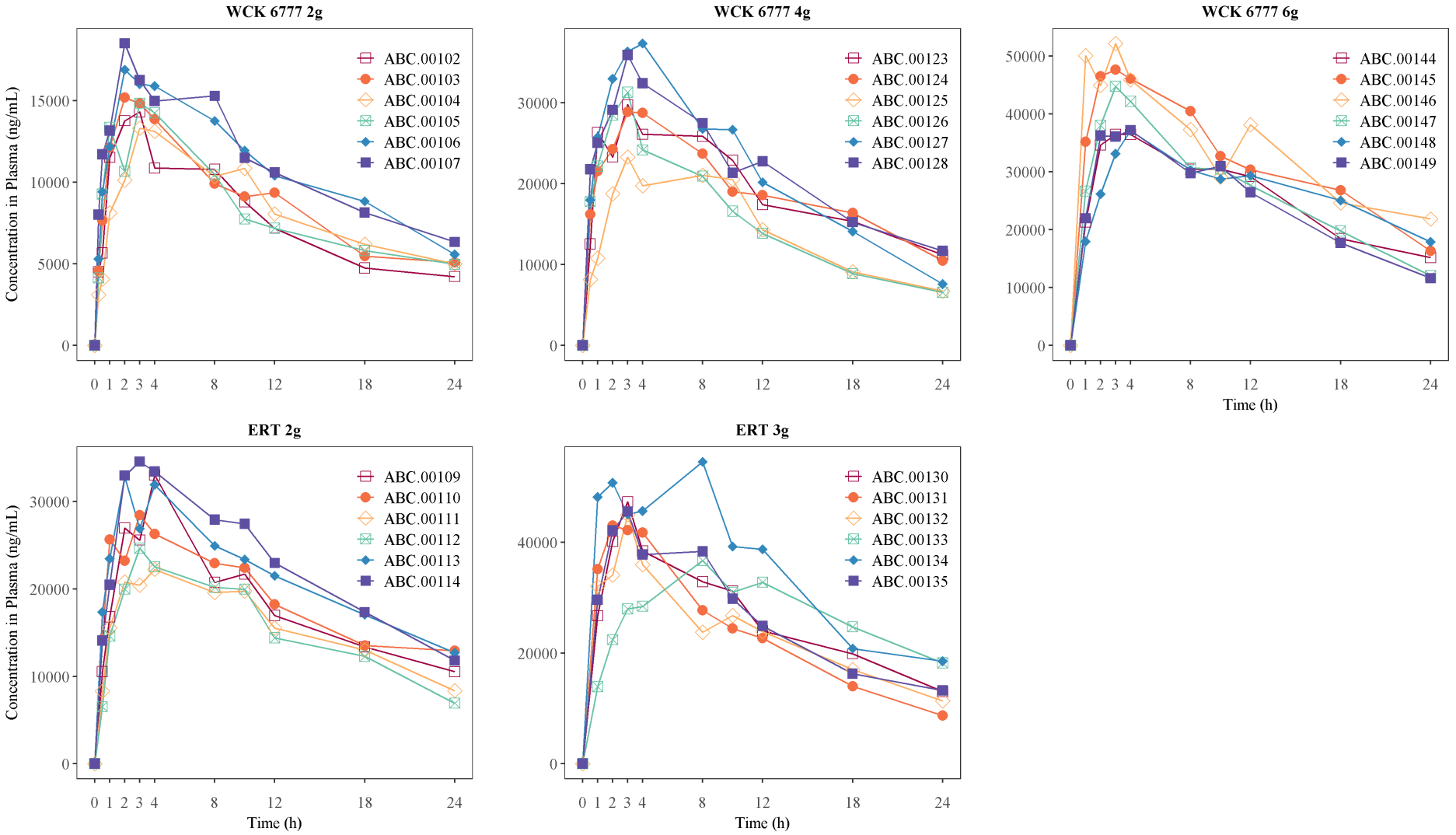
10.1 Disposition of Participants

Figure 2: CONSORT Flow Diagram



14.2.2 Displays of PK Results

Figure 3: Individual Total ERT Concentration in Plasma Profiles, Dose 1



Similar figures:

Figure 4: Individual Total ERT Concentration in Plasma Profiles, Dose 7

[Repeat above figure for Dose 7]

Figure 5: Individual Total Trough ERT Concentration in Plasma Profiles, Doses 1 - 7

[This will repeat the above figure for the t=0 pre-dose time point for Doses 1-7 and the 24 h post-dose time point for Dose 7. (The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 6: Individual Total ERT Concentration in Plasma Profiles 12h After Dosing, Doses 1-7

[This will repeat the above figure for time=12h for Doses 1-7. The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 7: Individual Free ERT Concentration in Plasma Profiles, Dose 1

[This will repeat the above figure for Dose 1 free concentrations]

Figure 8: Individual Free ERT Concentration in Plasma Profiles, Dose 7

[Repeat above figure for Dose 7 free concentrations]

Figure 9: Individual Free ERT Trough Concentration in Plasma Profiles, Doses 1-7

[This will repeat the above figure for the t=0 pre-dose time point for Doses 1-7 and the 24 h post-dose time point for Dose 7. (The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 10: Individual Free ERT Concentration in Plasma Profiles 12h After Dosing, Doses 1-7

[This will repeat the above figure for time=12h for Doses 1-7. The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 11: Individual Total ZID Concentration in Plasma Profiles, Dose 1

[Repeat ERT figure for ZID]

Figure 12: Individual Total ZID Concentration in Plasma Profiles, Dose 7

[Repeat ERT figure for ZID]

Figure 13: Individual Total Trough ZID Concentration in Plasma Profiles, Doses 1-7

[Repeat ERT figure for ZID]

Figure 14: Individual Total ZID Concentration in Plasma Profiles 12h After Dosing, Doses 1-7

[Repeat ERT figure for ZID]

Figure 15: Individual Free ZID Concentration in Plasma Profiles, Dose 1

[Repeat ERT figure for ZID]

Figure 16: Individual Free ZID Concentration in Plasma Profiles, Dose 7

[Repeat ERT figure for ZID]

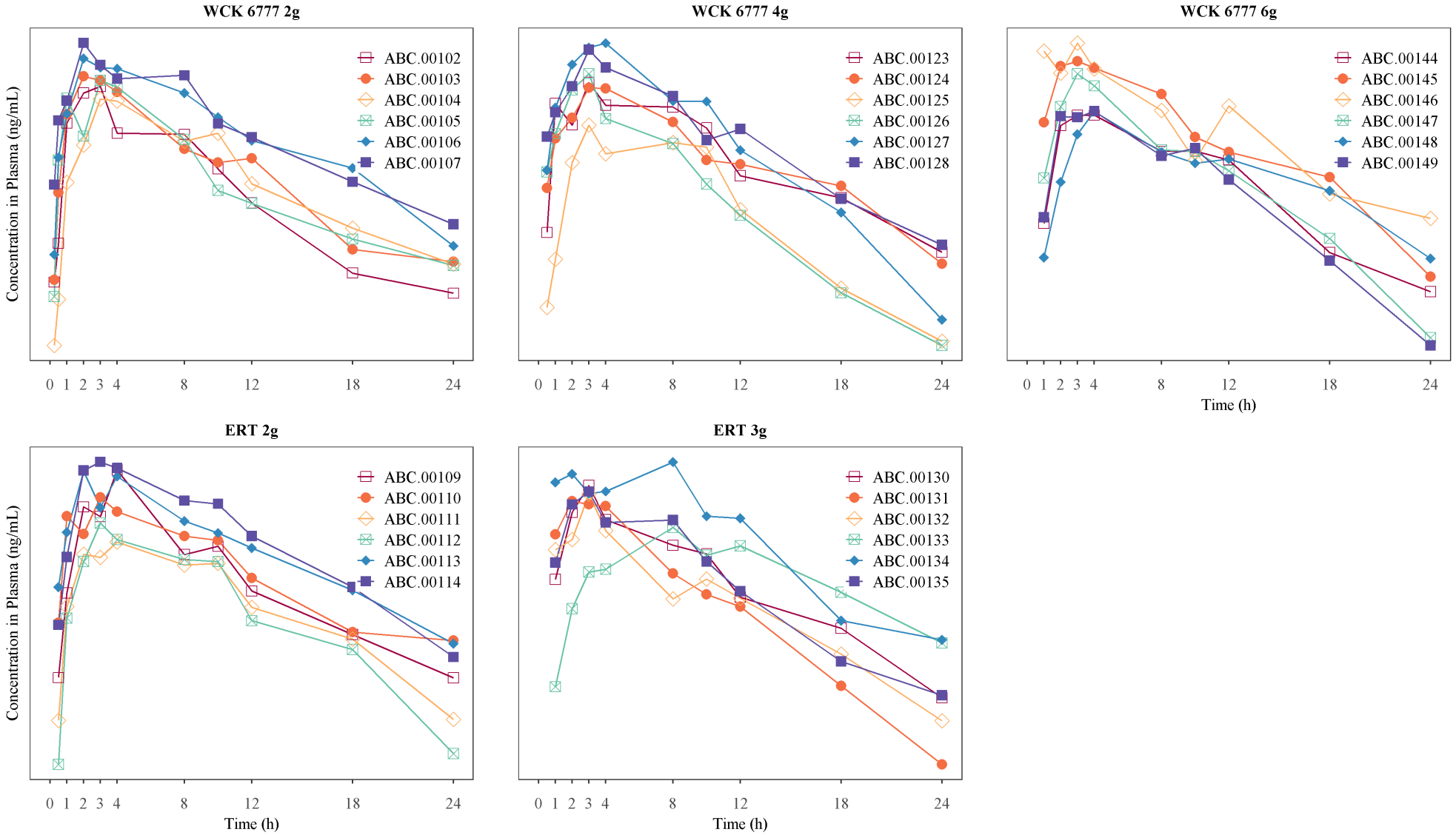
Figure 17: Individual Free ZID Trough Concentration in Plasma Profiles, Doses 1-7

[Repeat ERT figure for ZID]

Figure 18: Individual Free ZID Concentration in Plasma Profiles 12h After Dosing, Doses 1-7

[Repeat ERT figure for ZID]

Figure 19: Semi-Log Individual Total ERT Concentration in Plasma Profiles, Dose 1



Similar figures:

Figure 20: Semi-Log Individual Total ERT Concentration in Plasma Profiles, Dose 7

[Repeat above figure for Dose 7]

Figure 21: Semi-Log Individual Free ERT Concentration in Plasma Profiles, Dose 1

[Repeat above figure for free concentrations]

Figure 22: Semi-Log Individual Free ERT Concentration in Plasma Profiles, Dose 7

[Repeat above figure for Dose 7]

Figure 23: Semi-Log Individual Total ZID Concentration in Plasma Profiles, Dose 1

[Repeat figure above for ZID]

Figure 24: Semi-Log Individual Total ZID Concentration in Plasma Profiles, Dose 7

[Repeat figure above for ZID]

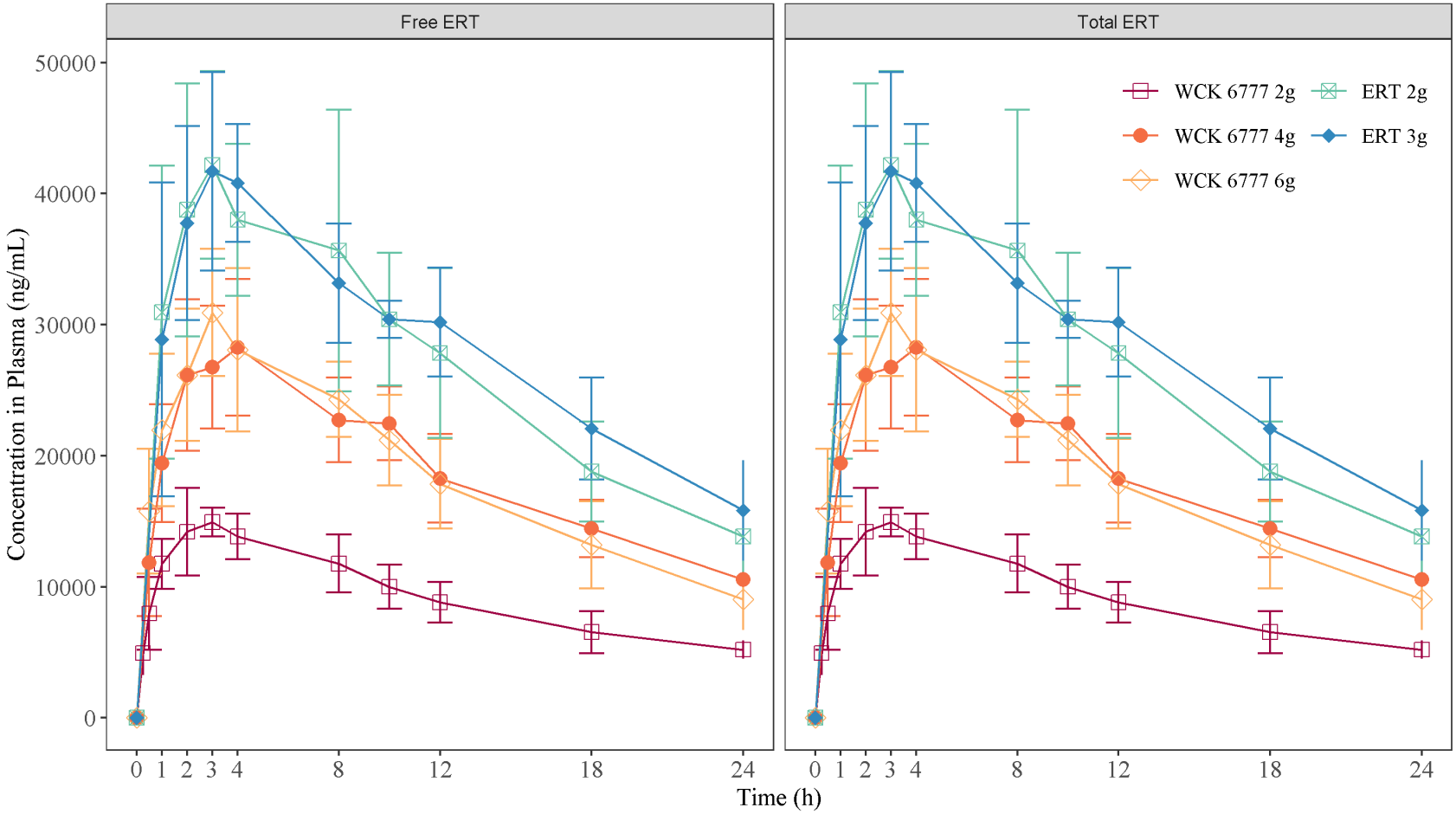
Figure 25: Semi-Log Individual Free ZID Concentration in Plasma Profiles, Dose 1

[Repeat figure above for ZID]

Figure 26: Semi-Log Individual Free ZID Concentration in Plasma Profiles, Dose 7

[Repeat figure above for ZID]

Figure 27: Mean ERT Concentration in Plasma Profiles by Treatment Group, Dose 1



Similar figures:

Figure 28: Mean ERT Concentration in Plasma Profiles by Treatment Group, Dose 7

[Repeat above figure for Dose 7]

Figure 29: Mean Trough ERT Concentration in Plasma Profiles by Treatment Group, Doses 1-7

[This will repeat the above figure for the t=0 pre-dose time point for Doses 1-7 and the 24 h post-dose time point for Dose 7. (The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 30: Mean ERT Concentration in Plasma Profiles by Treatment Group 12h After Dosing, Doses 1-7

[This will repeat the above figure for time=12h for Doses 1-7. The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 31: Mean ZID Concentration in Plasma Profiles by Treatment Group, Dose 1

[Repeat Figure 27 for ZID]

Figure 32: Mean ZID Concentration in Plasma Profiles by Treatment Group, Dose 7

[Repeat above figure for Dose 7]

Figure 33: Mean Trough ZID Concentration in Plasma Profiles by Treatment Group, Doses 1-7

[This will repeat the above figure for the t=0 pre-dose time point for Doses 1-7 and the 24 h post-dose time point for Dose 7. (The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 34: Mean ZID Concentration in Plasma Profiles by Treatment Group 12h After Dosing, Doses 1-7

[This will repeat the above figure for time=12h for Doses 1-7. The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 35: Semi-Log Mean ERT Concentration in Plasma Profiles by Treatment Group, Dose 1

Figure 36: Semi-Log Mean ERT Concentration in Plasma Profiles by Treatment Group, Dose 7

[Repeat above figure for Dose 7]

Figure 37: Semi-Log Mean Trough ERT Concentration in Plasma Profiles by Treatment Group, Doses 2-8

[This will repeat the above figure for the t=0 pre-dose time point for Doses 1-7 and the 24 h post-dose time point for Dose 7. (The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 38: Semi-Log Mean ERT Concentration in Plasma Profiles by Treatment Group 12h After Dosing, Doses 1-7

[This will repeat the above figure for time=12h for Doses 1-7. The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 39: Semi-Log Mean ZID Concentration in Plasma Profiles by Treatment Group, Dose 1

[Repeat Figure 27 for ZID]

Figure 40: Semi-Log Mean ZID Concentration in Plasma Profiles by Treatment Group, Dose 7

[Repeat above figure for Dose 7]

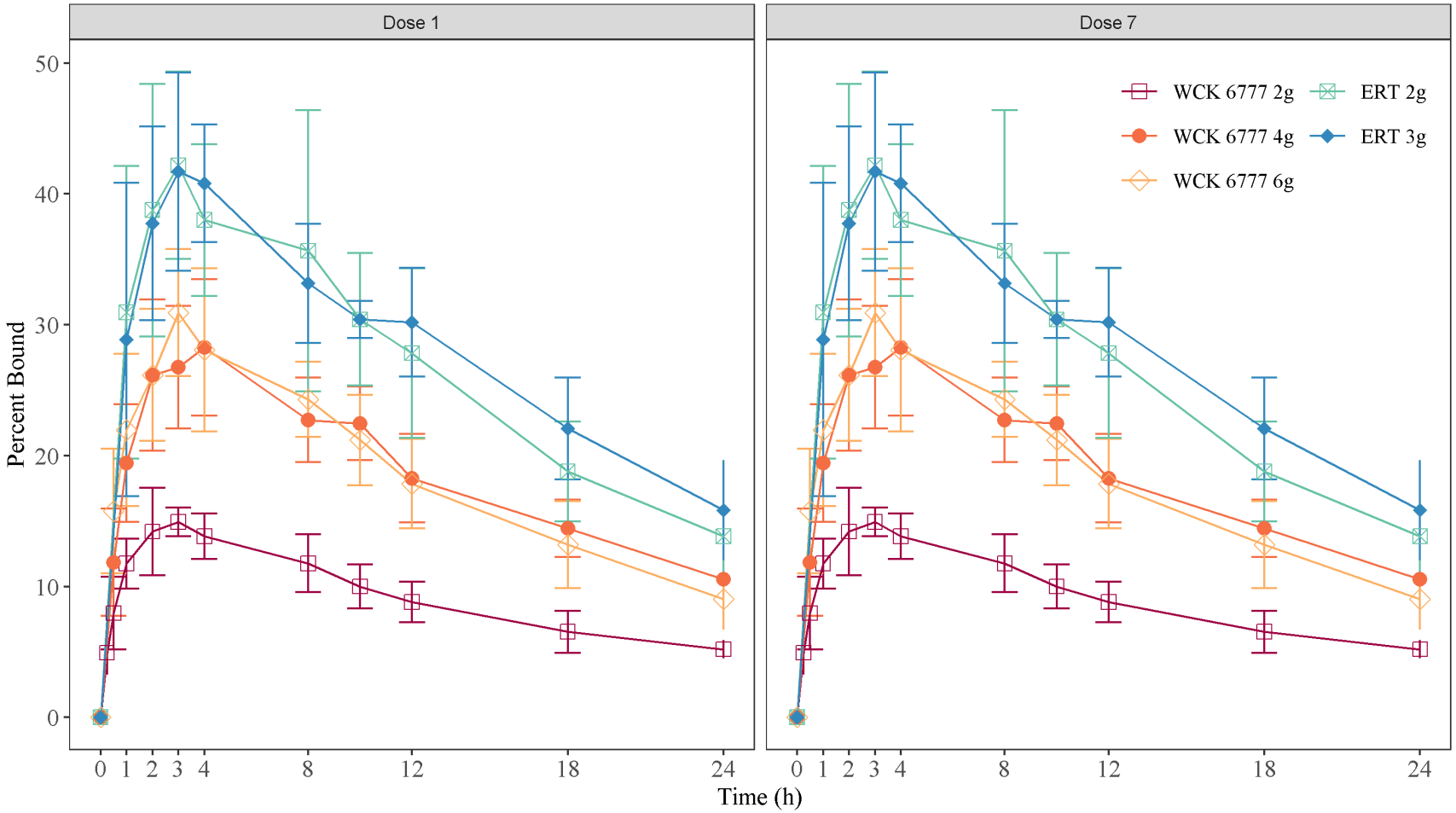
Figure 41: Semi-Log Mean Trough ZID Concentration in Plasma Profiles by Treatment Group, Doses 2-8

[This will repeat the above figure for the t=0 pre-dose time point for Doses 1-7 and the 24 h post-dose time point for Dose 7. (The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 42: Semi-Log Mean ZID Concentration in Plasma Profiles by Treatment Group 12h After Dosing, Doses 1-7

[This will repeat the above figure for time=12h for Doses 1-7. The x-axis label will be replaced with 'Doses' and tick marks will be (1,2,3,4,5,6,7)]

Figure 43: Mean Percent ERT Protein Binding, Dose 1 and Dose 7



Similar figures:

Figure 44: Mean Percent ERT Protein Binding, Doses 1-7

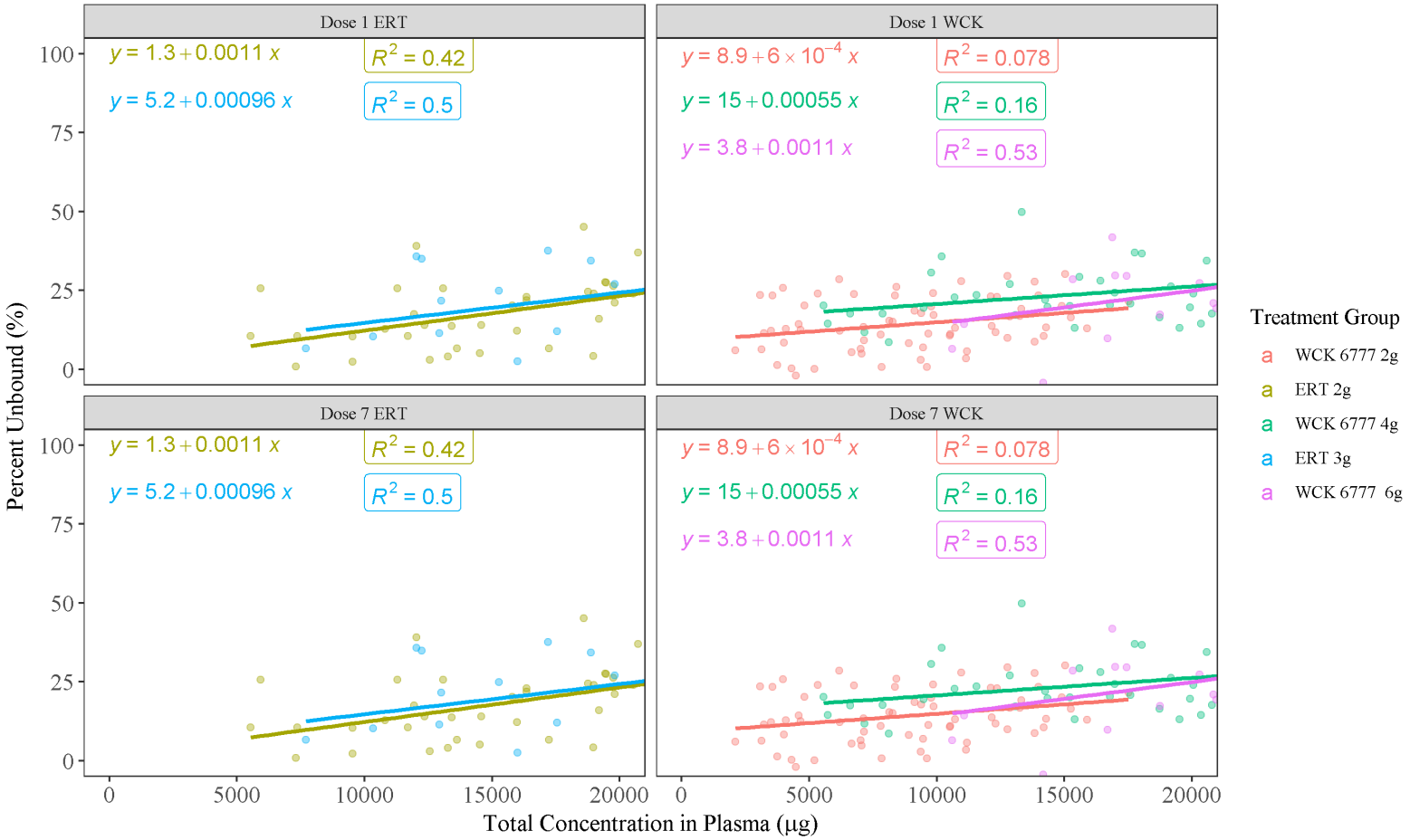
[Implementation note: replace 'Time (h)' with 'Doses' and tick marks with 1:7. Times 0 h and 12 h will be shown for each dose. Only one panel will be shown.]

Figure 45: Mean Percent ZID Protein Binding, Dose 1 and Dose 7

Figure 46: Mean Percent ZID Protein Binding, Doses 1-7

[Implementation note: replace 'Time (h)' with 'Doses' and tick marks with 1:7. Times 0 h and 12 h will be shown for each dose. Only one panel will be shown.]

Figure 47: Percent ERT Protein Binding vs Total Concentration, Dose 1 and Dose 7



Similar figures:

Figure 48: Percent ZID Protein Binding vs Total Concentration, Dose 1 and Dose 7

Figure 49: Percent ERT Protein Binding vs log10 Total Concentration, Dose 1 and Dose 7

[Implementation note: x-axis label will be updated to 'log10 Total Concentration in Plasma (µg)']

Figure 50: Percent ZID Protein Binding vs log10 Total Concentration, Dose 1 and Dose 7

[Implementation note: x-axis label will be updated to 'log10 Total Concentration in Plasma (µg)']

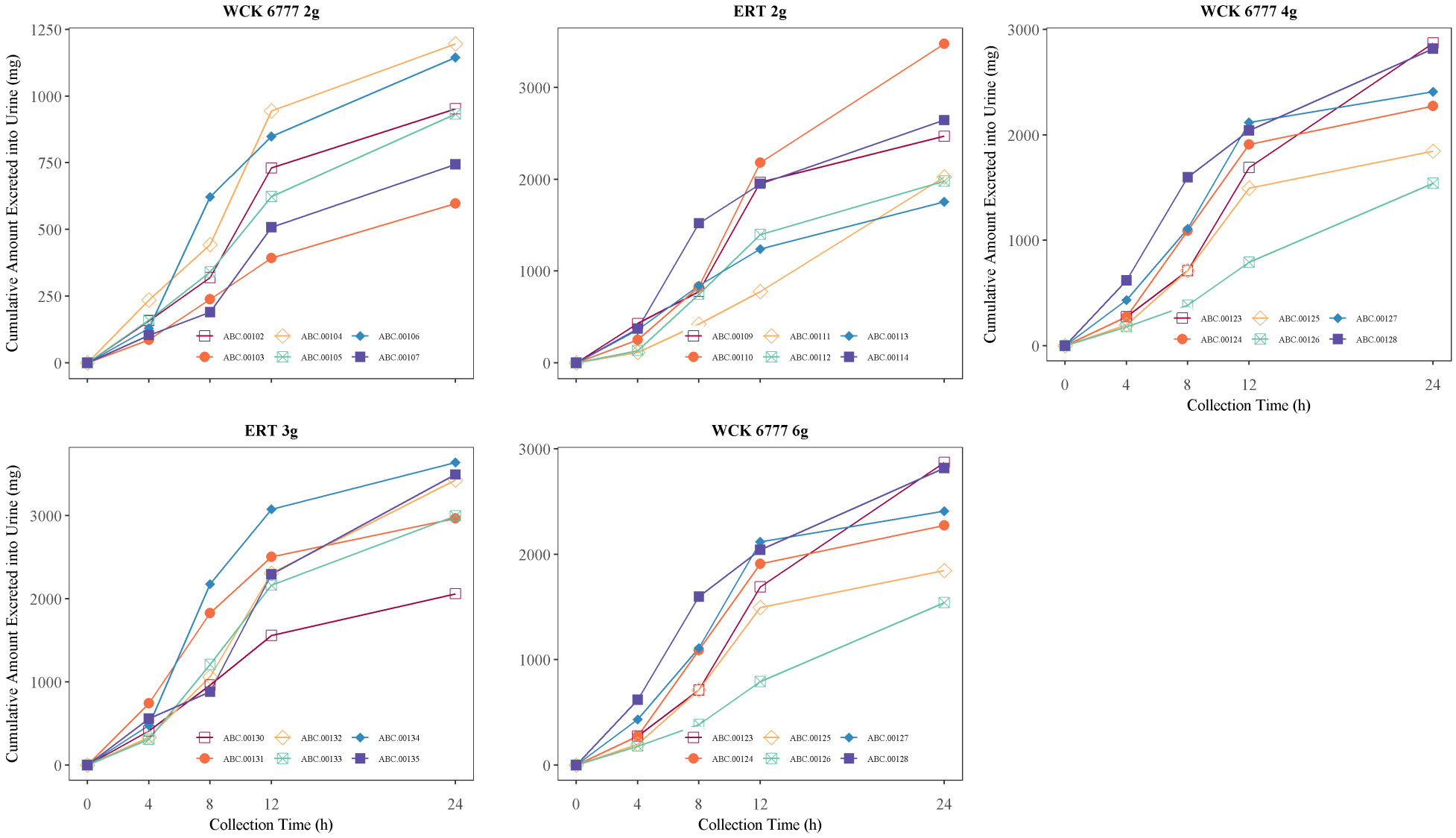
Figure 51: Amount ERT Bound vs Total Concentration, Dose 1 and Dose 7

[Implementation note: The y-axis will be replaced with 'Amount Bound (µg)']

Figure 52: Amount ZID Bound vs Total Concentration, Dose 1 and Dose 7

[Implementation note: The y-axis will be replaced with 'Amount Bound (µg)']

Figure 53: Individual Cumulative Amount of ERT Excreted into Urine, Dose 1



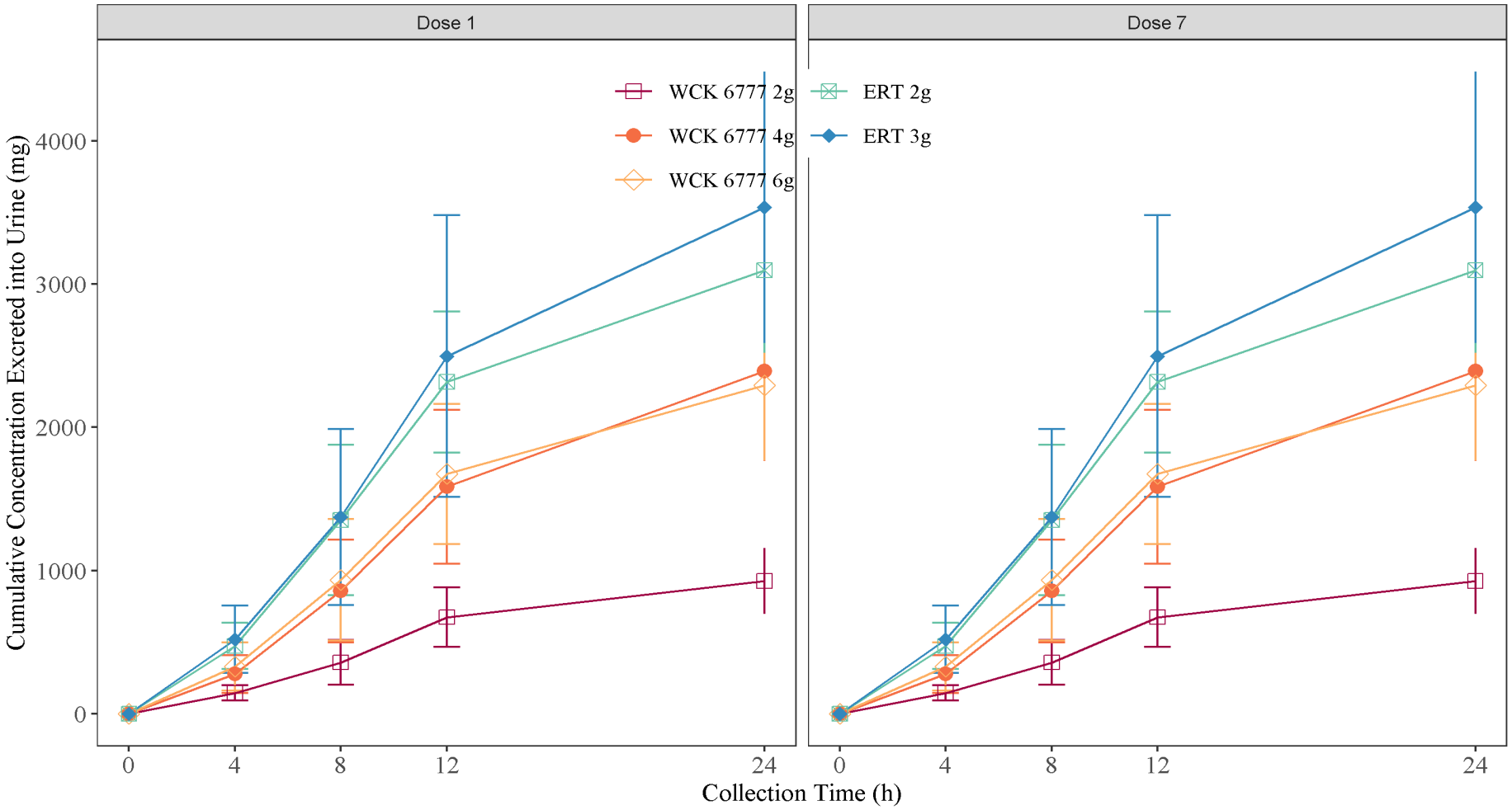
Similar figures:

Figure 54: Individual Cumulative Amount of ERT Excreted into Urine, Dose 7

Figure 55: Individual Cumulative Amount of ZID Excreted into Urine, Dose 1

Figure 56: Individual Cumulative Amount of ZID Excreted into Urine, Dose 7

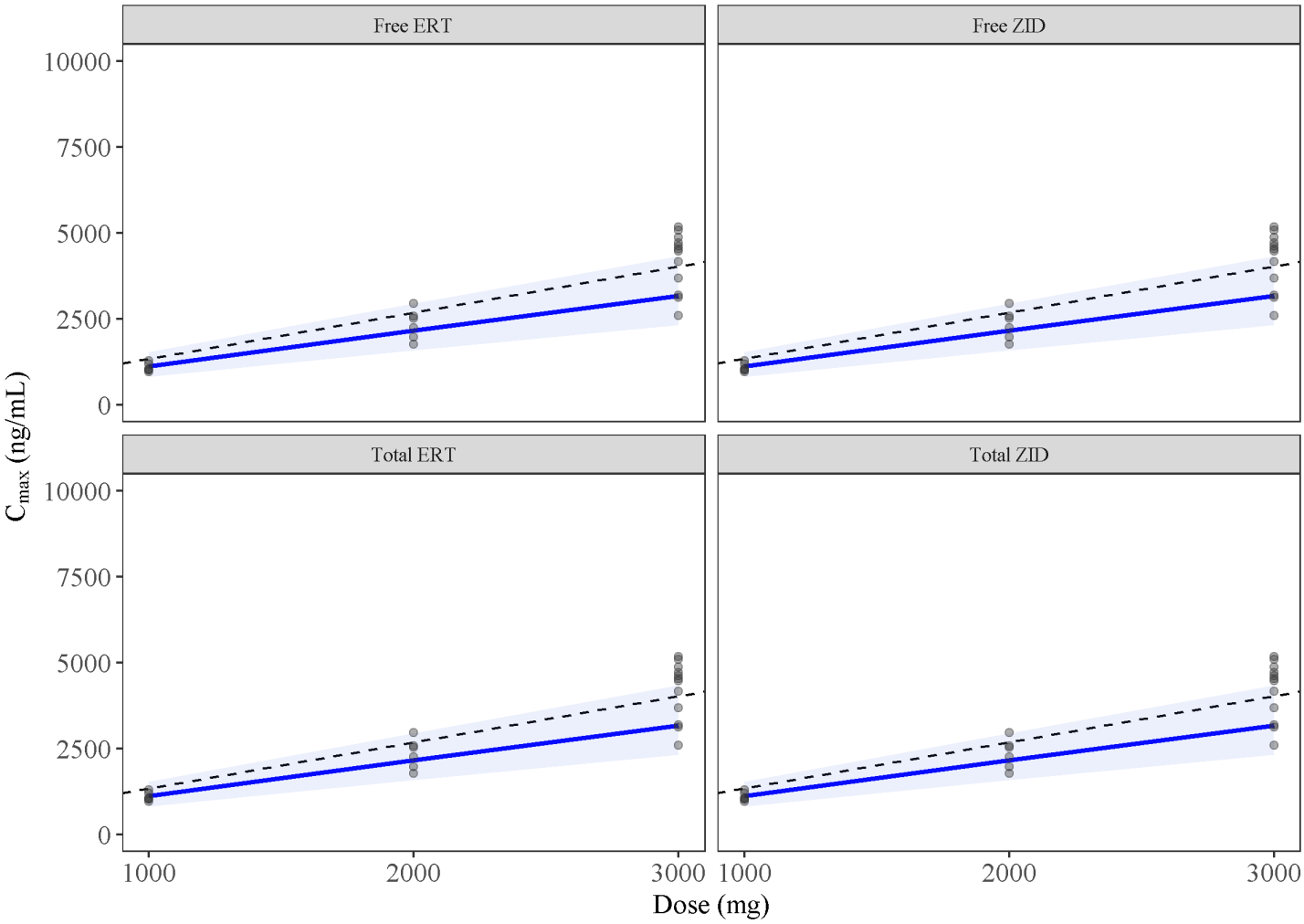
Figure 57: Mean Cumulative Amount of ERT Excreted into Urine by Treatment Group



Similar figure:

Figure 58: Mean Cumulative Amount of ZID Excreted into Urine by Treatment Group

Figure 59: Dose Proportionality, ERT and ZID Concentrations in Plasma - C_{max}



Notes: Blue line and shaded region represent predicted power model with 90% prediction bands.
Dotted line represents dose proportionality. Points represent each subject's exposure parameter for the given dose.

Similar figures:

Figure 60: Dose Proportionality, ERT and ZID Concentrations in Plasma – $AUC_{0\text{-last}}$

Figure 61: Dose Proportionality, ERT and ZID Concentrations in Plasma – $AUC_{0\text{-inf}}$

Figure 62: Dose Proportionality, ERT and ZID Concentrations in Plasma - $C_{max,ss}$

Figure 63: Dose Proportionality, ERT and ZID Concentrations in Plasma – $AUC_{(0\text{-}24),ss}$

Figure 64: Dose Proportionality, ERT and ZID Concentrations in Plasma – $AUC_{(0\text{-tau}),ss}$

14.3.1.2 Adverse Events

Figure 65: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity

[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 participants with each type of SOC. A participant will only be counted once for the same SOC for the maximum severity reported.

There will be one panel for each of the following groups:

All Participants, WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo

Order SOCs alphabetically.]

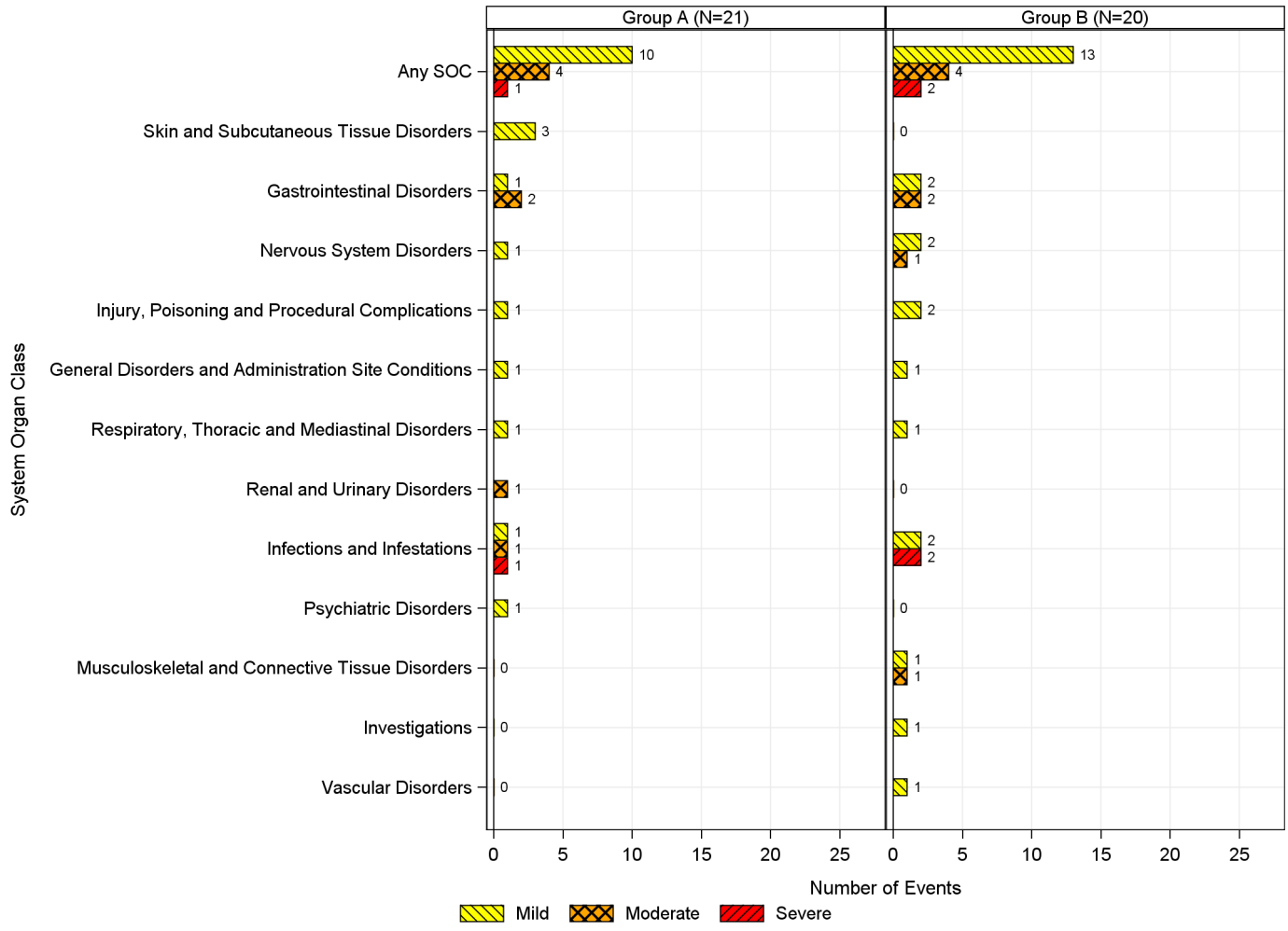


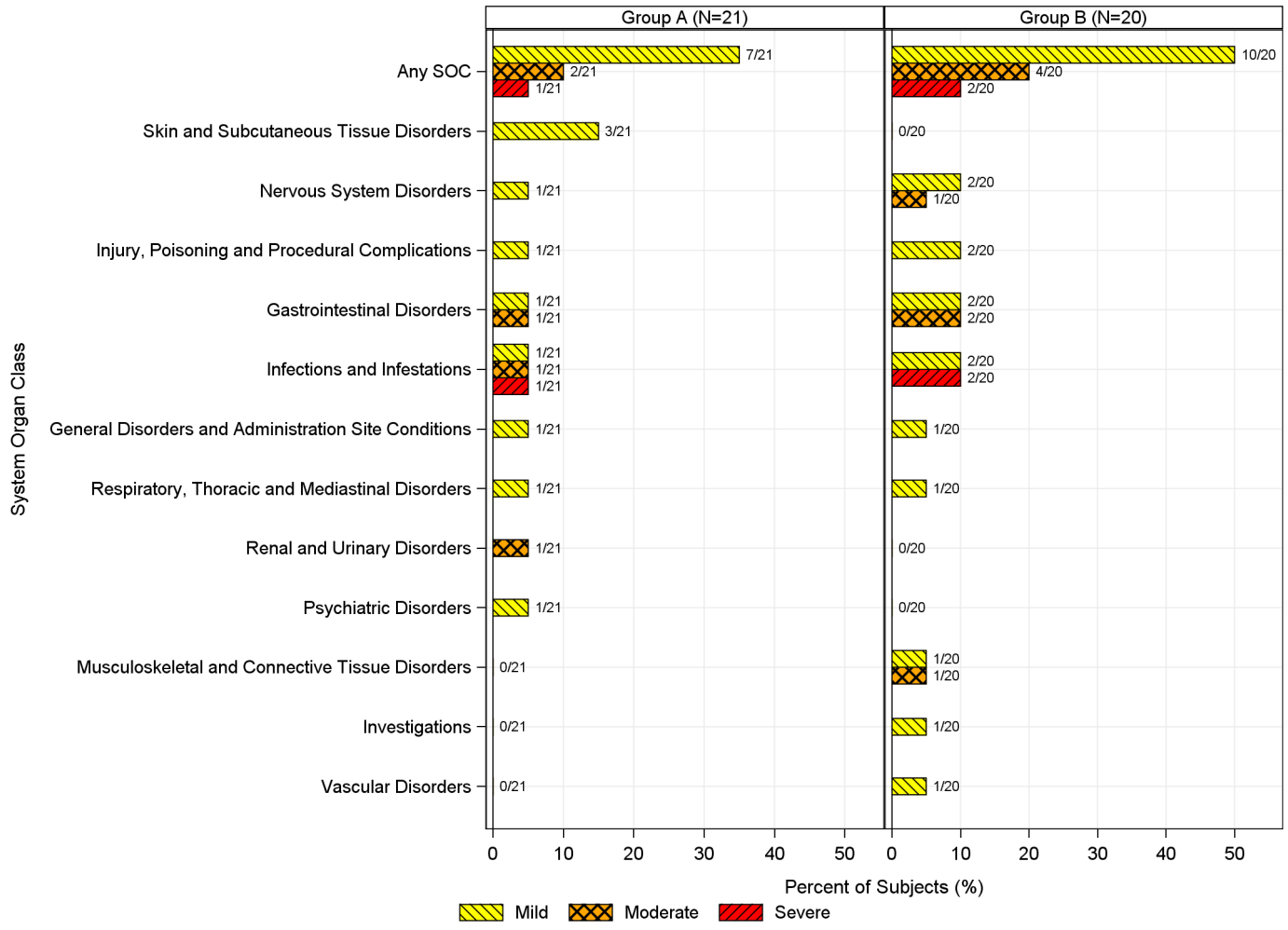
Figure 66: Incidence of Related Adverse Events by MedDRA System Organ Class and Maximum Severity

[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 participants with each type of SOC. A participant will only be counted once for the same SOC for the maximum severity reported.

There will be one panel for each of the following groups:

All Participants, WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g, Placebo

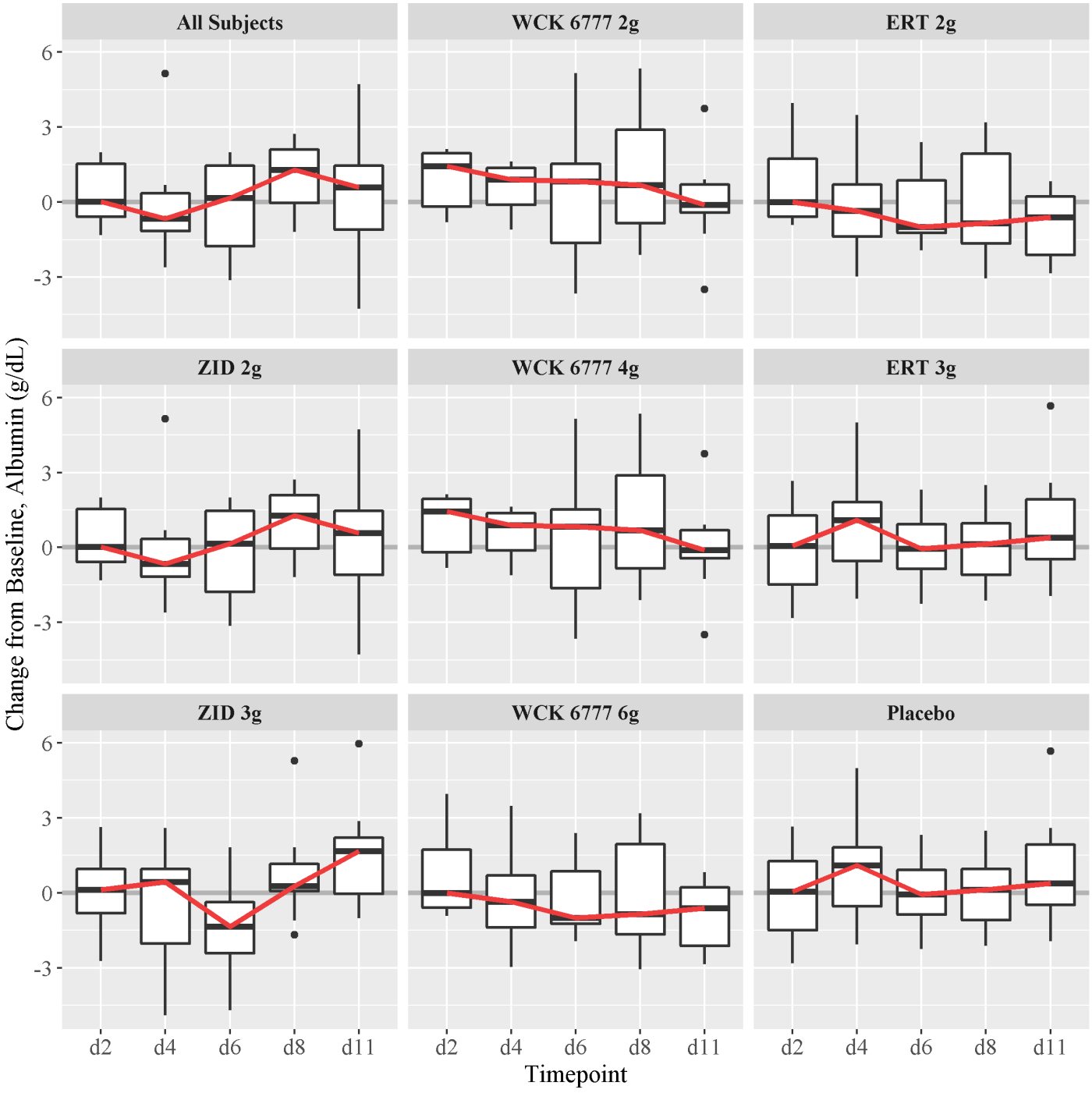
Order SOCs alphabetically.]



14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Figure 67: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Albumin



Similar Figures:

Figure 68: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Sodium

[Repeat Figure 61 for Sodium]

Figure 69: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Potassium

[Repeat Figure 61 for Potassium]

Figure 70: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Calcium

[Repeat Figure 61 for Calcium]

Figure 71: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Chloride

[Repeat Figure 61 for Chloride]

Figure 72: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Total Carbon Dioxide

[Repeat Figure 61 for CO2]

Figure 73: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Creatinine

[Repeat Figure 61 for Creatinine]

Figure 74: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Blood Urea Nitrogen

[Repeat Figure 61 for BUN]

Figure 75: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Glucose

[Repeat Figure 61 for Glucose]

Figure 76: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Total Bilirubin

[Repeat Figure 61 for Total Bilirubin]

Figure 77: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Direct Bilirubin

[Repeat Figure 61 for Direct Bilirubin]

Figure 78: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Alanine Aminotransferase

[Repeat Figure 61 for ALT]

Figure 79: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Aspartate Aminotransferase

[Repeat Figure 61 for AST]

Figure 80: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Alkaline Phosphatase

[Repeat Figure 61 for AP]

Figure 81: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Lactic Dehydrogenase

[Repeat Figure 61 for LDH]

Figure 82: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Total Protein

[Repeat Figure 61 for Total Protein]

14.3.5.2 Hematology Results

Figure 83: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Hemoglobin

[Repeat Figure 61 for Hgb]

Figure 84: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Hematocrit

[Repeat Figure 61 for Hct]

Figure 85: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – RBC

[Repeat Figure 61 for RBC]

Figure 86: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Platelet Count

[Repeat Figure 61 for Platelet Count]

Figure 87: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – WBC Count

[Repeat Figure 61 for WBC Count]

Figure 88: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Neutrophils

[Repeat Figure 61 for Neutrophils]

Figure 89: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Lymphocytes

[Repeat Figure 61 for Lymphocytes]

Figure 90: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Eosinophils

[Repeat Figure 61 for Eosinophils]

Figure 91: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Basophils

[Repeat Figure 61 for Basophils]

Figure 92: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Monocytes

[Repeat Figure 61 for Monocytes]

14.3.5.3 Coagulation Results

Figure 93: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – INR

[Repeat Figure 61 for INR]

Figure 94: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Prothrombin Time

[Repeat Figure 61 for PT]

Figure 95: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Activated Partial Thromboplastin Time

[Repeat Figure 61 for APTT]

14.3.5.4 Urinalysis Results

Figure 96: Urinalysis Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – Specific Gravity

[Repeat Figure 61 for Specific Gravity with timepoints d4, d8, d11]

Figure 97: Urinalysis Laboratory Results by Scheduled Visits: Change from Baseline by Parameter, Treatment Group, and Timepoint – pH

[Repeat Figure 61 for pH with timepoints d4, d8, d11]

14.3.5.5 Displays of Vital Signs

Figure 98: Vital Signs by Scheduled Visits: Change from Baseline by Parameter, Timepoint, and Treatment Group – Systolic Blood Pressure

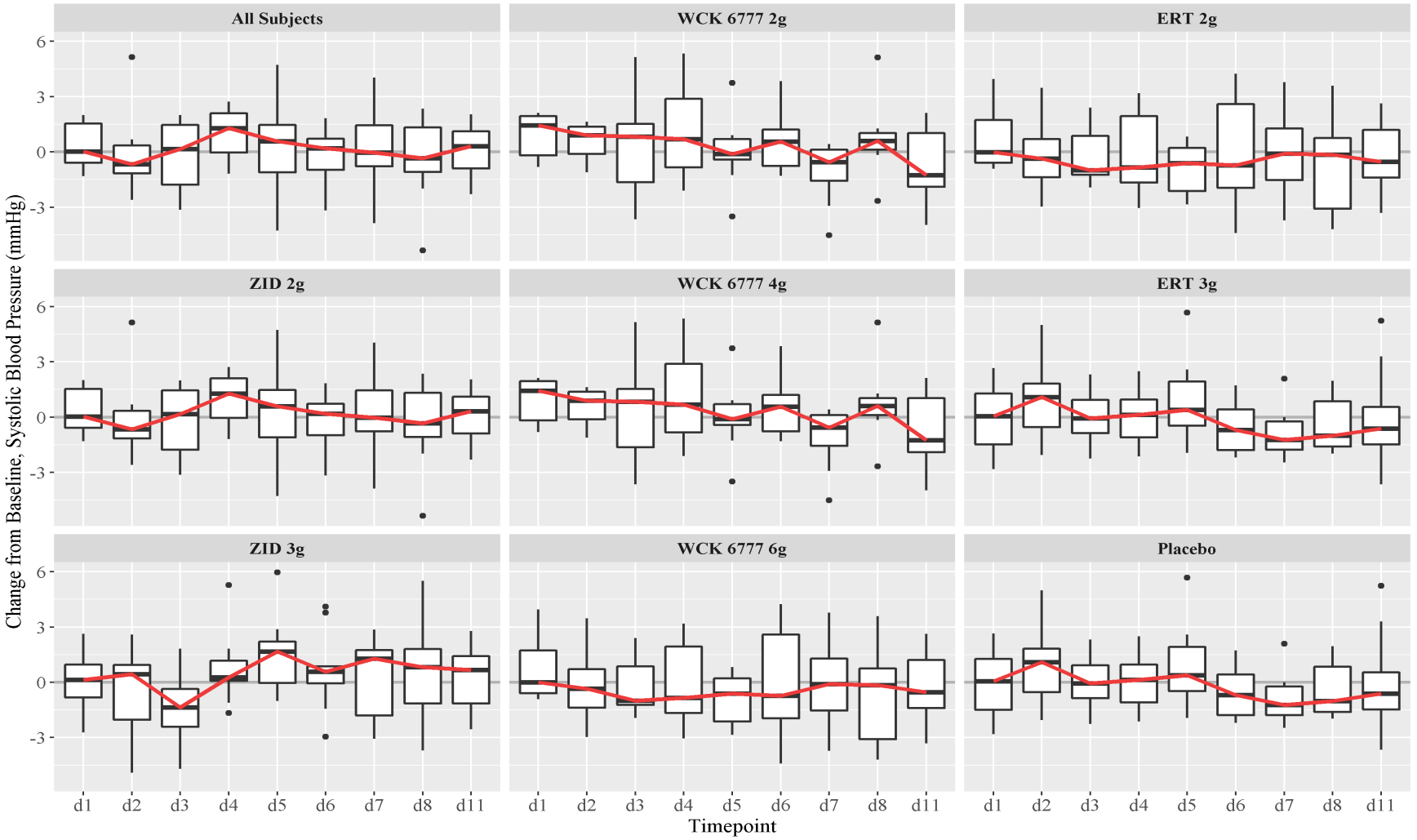


Figure 99: Vital Signs by Scheduled Visits: Change from Baseline by Parameter, Timepoint, and Treatment Group – Diastolic Blood Pressure

[Repeat Figure 91 for DBP]

Figure 100: Vital Signs by Scheduled Visits: Change from Baseline by Parameter, Timepoint, and Treatment Group – Heart Rate

[Repeat Figure 91 for Heart rate]

Figure 101: Vital Signs by Scheduled Visits: Change from Baseline by Parameter, Timepoint, and Treatment Group – Oral Temperature

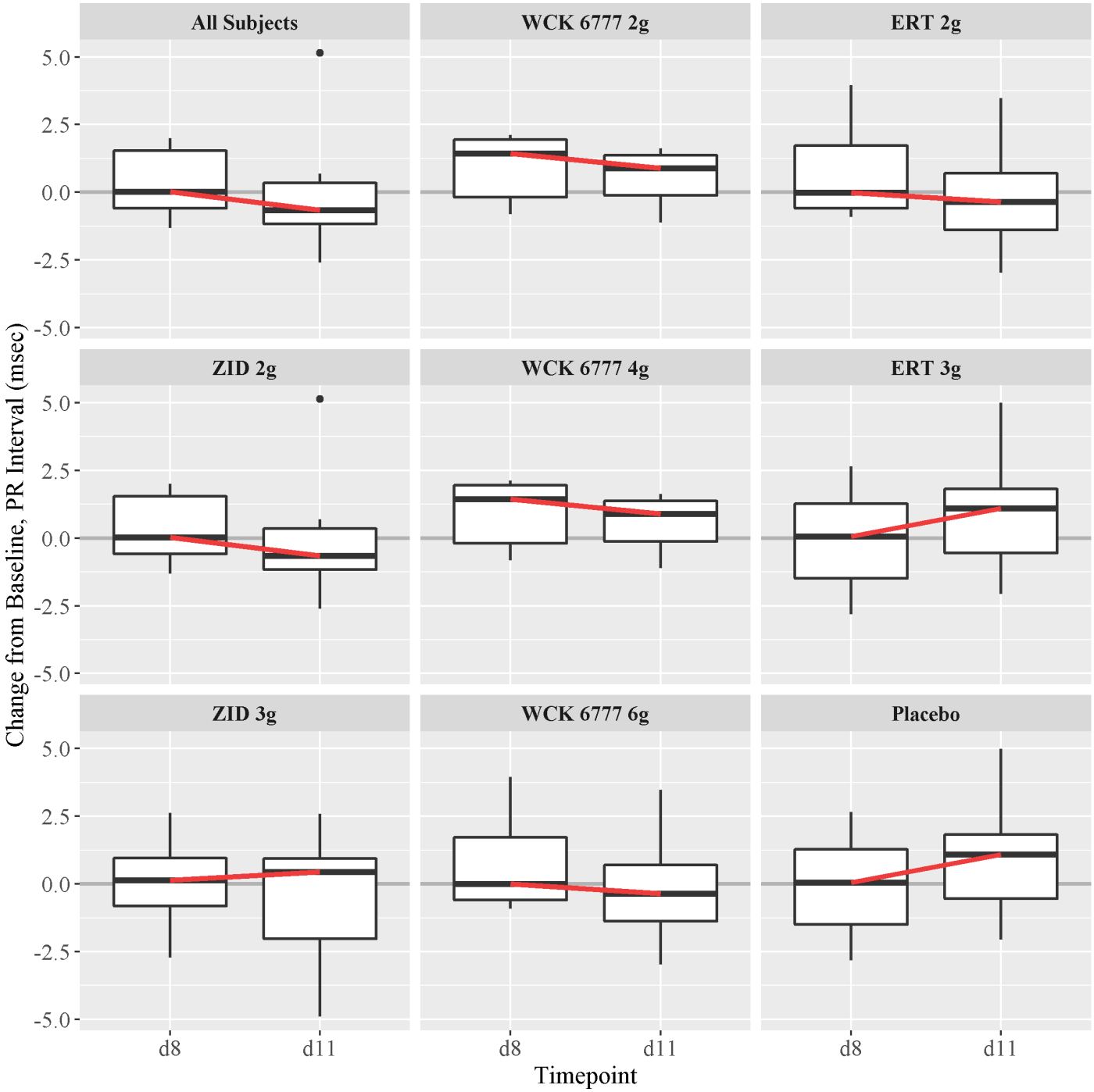
[Repeat Figure 91 for Temperature]

Figure 102: Vital Signs by Scheduled Visits: Change from Baseline by Parameter, Timepoint, and Treatment Group – Respiratory Rate

[Repeat Figure 91 for Respiratory rate]

14.3.5.7 Displays of ECG Measurements

Figure 103: ECG by Scheduled Visits: Change from Baseline by Parameter and Treatment Group – PR Interval



Similar figures:

Figure 104: ECG by Scheduled Visits: Change from Baseline by Parameter and Treatment Group – QRS Interval

Figure 105: ECG by Scheduled Visits: Change from Baseline by Parameter and Treatment Group – QT Interval

Figure 106: ECG by Scheduled Visits: Change from Baseline by Parameter and Treatment Group – QTcF Interval

Figure 107: ECG by Scheduled Visits: Change from Baseline by Parameter and Treatment Group – RR Interval

Figure 108: ECG by Scheduled Visits: Change from Baseline by Parameter and Treatment Group – Mean Ventricular Heart Rate

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

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

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

16.2 Database Listings by Participant

16.2.1 Discontinued Participants

Listing 2: 16.2.1: Early Terminations or Discontinued Participants

[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: Treatment Group, Participant ID, Category (in the case that a participant both terminates early and discontinues treatment).]

Treatment Group	Participant ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Participant-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: Participant refusal." If deviation resulted in AE or participant 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: Treatment Group, Participant ID, DV Number.]

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

Listing 4: 16.2.2.2: Non-Participant-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: Participant refusal."

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

Sort order: Start Date, Deviation.]

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

16.2.3 Participants Excluded from the Safety and/or PK Analysis

Listing 5: 16.2.3: Participants Excluded from Analysis Populations

[Implementation Note: This data in this listing should be congruent with the "Analysis Populations by Treatment Group" table. If a participant was not excluded from any analysis population, the participant will not appear in the listing. If the participant 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 Participant Excluded Specification".

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

Treatment Group	Participant ID	Analyses in which Participant is Included	Analyses from which Participant is Excluded	Results Available?	Reason Participant Excluded
		[e.g., Safety, PK Analysis, PK Analysis Subset]	[e.g., Safety, PK Analysis, PK Analysis Subset]		
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 participant is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)."

Sort order: Treatment Group, Participant ID.]

Treatment Group	Participant ID	Sex	Age at Enrollment (years)	Ethnicity	Race

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, Participant ID should be USUBJID (not PATID) for purposes of de-identification.

Sort order: Treatment Group, Participant ID, MH Number.]

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

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

Listing 8: 16.2.5: Compliance Data

[Implementation Note: For planned doses that did not occur, the date and time columns for those doses will be "not dosed."

Sort Order: Treatment Group, Participant ID]

Treatment Group	Participant ID	Dose Number	Planned Volume Administered?	Dose Date	Infusion Start Time	Infusion End Time
WCK 6777 2g	PHU.0123	x	Yes/No	ddMMMyyyy	hh:mm	hh:mm
…						

Listing 9: 16.2.5: Infusion Interruptions

[Implementation Note: If multiple interruptions occur, they will be listed sequentially by 'Interruption Number'.
Sort Order: Treatment Group, Participant ID, Dose Number]

Treatment Group	Participant ID	Dose Number	Interruption Number	Reason Infusion Interrupted	If Safety Related, Volume Received Prior to Interruption	Action Taken	Infusion Restarted?	Duration of Interruption	Comments

16.2.6 Participant Level PK Concentrations

Listing 10: Participant Level Total ERT and ZID 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: Treatment Group, Participant ID, Analyte (ERT then ZID, if both are available), Study Day, and Actual Time.]

Treatment Group	Participant ID	Analyte	Study Day	Nominal Time[a]	Actual Time[a]	Laboratory Reported Concentrations (µg/mL)	Analysis Concentrations (µg/mL)
WCK 6777 2g	PHU.00123	ERT	Day 1	0 h	0 h	0	0
WCK 6777 2g	PHU.00123	ZID	Day 1	0 h	0 h	0	0

Similar listing:

Listing 11: Participant Level Free ERT and ZID Concentrations – Plasma

Listing 12: Participant Specific Single-Dose ERT Plasma PK Parameters - Total

[Implementation Note: Sort order: Treatment Group, Participant ID.]

Treatment Group	Participant ID	Study Day	C_{max} (µg/mL)	C_{max}/Dose ((µg/mL)/mg)	C_{min} (µg/mL)	T_{max} (h)	T_{min} (h)	AUC_{0-t} (µg*h/mL)	AUC_{0-inf} (µg*h/mL)	AUC_{0-24} (µg*h/mL)	AUC_{0-last} (µg*h/mL)	AUC_{0-tau} (µg*h/mL)	AUC_{0-tau}/Dose ((µg*h/mL)/mg)	$t_{1/2}$ (h)	CL_T (L/h)	K_e (1/h)	V_d (L)

Similar listings:

Listing 13: Participant Specific Single-Dose ERT Plasma PK Parameters - Free

Listing 14: Participant Specific Single-Dose ZID Plasma PK Parameters – Total

Listing 15: Participant Specific Single-Dose ZID Plasma PK Parameters - Free

Listing 16: Participant Specific Multiple-Dose ERT Plasma PK Parameters - Total

[Implementation Note: Sort order: Treatment Group, Participant ID.]

Treatment Group	Participant ID	$C_{max,ss}$ (µg/mL)	$C_{max,ss}$/Dose ((µg/mL)/mg)	$C_{min,ss}$ (µg/mL)	C_{avg} (µg/mL)	$T_{max,ss}$ (h)	T_{min} (h)	$AUC_{0-24,ss}$ (µg*h/mL)	$AUC_{0-tau,ss}$ (µg*h/mL)	$AUC_{0-tau,ss}$/Dose ((µg*h/mL)/mg)	$t_{1/2}$ (h)	CL_{ss} (L/h)	$V_{d,ss}$ (L)	Linearity Index	RAUC	RC_{max}

Similar listings:

Listing 17: Participant Specific Multiple-Dose ERT Plasma PK Parameters - Free

Listing 18: Participant Specific Multiple-Dose ZID Plasma PK Parameters – Total

Listing 19: Participant Specific Multiple-Dose ZID Plasma PK Parameters - Free

Listing 20: Participant Level Total ERT and ZID Concentrations in 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: Treatment Group, Analyte (ERT then ZID, if both are available), Participant ID, Study Day, and Actual Time.]

Treatment Group	Analyte	Participant ID	Study Day	Nominal Collection Interval[a]	Actual Collection Interval[a]	Laboratory Reported Concentration (ng/mL)	Urine Volume (mL)	Analysis Concentrations (ng/mL)
WCK 6777 2g	ERT	PHU.00123	Day 1	0-6 h	0-6 h	0	100	0
WCK 6777 2g	ZID	PHU.00123	Day 1	0-6 h	0-6 h	0	100	0

[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 21: Participant Specific ERT Urine PK Parameters, Dose 1

[Sort Order: Treatment Group (WCK 6777 2g, ERT 2g, ZID 2g, WCK 6777 4g, ERT 3g, ZID 3g, WCK 6777 6g), Participant ID.]

Treatment Group	Participant ID	$Ae_{,urine}$ 0-4 h (mg)	$Ae_{,urine}$ 4-8 h (mg)	$Ae_{,urine}$ 8-12 h (mg)	$Ae_{,urine}$ 12-24 h (mg)	$Ae_{,urine(0-24)}$ (mg)	$Ae_{,urine(0-24),ss}$ (mg)	$fe_{,urine}$ 0-4 h (mg)	$fe_{,urine}$ 4-8 h (mg)	$fe_{,urine}$ 8-12 h (mg)	$fe_{,urine}$ 12-24 h (mg)	$fe_{,urine(0-24)}$ (mg)	$fe_{,urine(0-24),ss}$ (mg)	$CL_{R(0-24)}$	$CL_{R,ss}$
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	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

Similar listings:

Listing 22: Participant Specific ERT Urine PK Parameters, Dose 7

Listing 23: Participant Specific ZID Urine PK Parameters, Dose 1

Listing 24: Participant Specific ZID Urine PK Parameters, Dose 7

16.2.7 Adverse Events

Listing 25: 16.2.7.3: 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: Treatment Group, Participant ID, AE Number.]

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

16.2.8 Individual Laboratory Measurements

Listing 26: 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, Treatment Group, Participant ID, and Timepoint.]

Treatment Group	Participant ID	Sex	Age (years)	Actual Study Day	Planned Timepoint	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High	Change from Baseline

Listing 27: 16.2.8.2: Clinical Laboratory Results – Hematology

Treatment Group	Participant ID	Sex	Age (years)	Actual Study Day	Planned Timepoint	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High	Change from Baseline

Listing 28: 16.2.8.3: Clinical Laboratory Results – Coagulation

Treatment Group	Participant ID	Sex	Age (years)	Actual Study Day	Planned Timepoint	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High	Change from Baseline

Listing 29: 16.2.8.4: Clinical Laboratory Results – Urinalysis

[Implementation Note: The test type used to obtain the results will be indicated in the Laboratory Parameter column (e.g., Bilirubin by Dipstick, Red Blood Cells by Microscopy, etc.).]

Treatment Group	Participant ID	Sex	Age (years)	Actual Study Day	Planned Timepoint	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High	Change from Baseline

16.2.9 Individual Screening Measurements

Listing 30: 16.2.9.1: Screening Laboratory Results – Serology

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

Treatment Group	Participant ID	Visit	HIV Antibodies	HCV Antibodies	HBsAg
ERT 2g	PHU.00123	Screening	Negative	Negative	Negative
ERT 2g	PHU.00123	Unscheduled (Day 4)	Negative	Negative	Negative

Listing 31: 16.2.9.1: Screening Laboratory Results – hCG and Serum 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. Type of hCG test will be given in parentheses after the hCG result, e.g..., Negative (serum) or Negative (urine). If obtained, FSH testing results will be shown in this listing.]

Sort order: Treatment Group, Participant ID, Visit (visit order: Screening, Admission, Unscheduled).]

Treatment Group	Participant ID	Visit	HCG Result	FSH Test Result
ERT 2g	PHU.00123	Screening	Negative (serum)	ND
ERT 2g	PHU.00123	Baseline	Negative (urine)	ND

Note: ND=Test not performed

Listing 32: 16.2.9.1: Screening Laboratory Results – Urine Toxicology

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

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

Treatment Group	Participant ID	Visit	Amphetamines	Cocaine	Barbiturates	Benzodiazepines	Opiates	Cannabinoids	TCAs	Phencyclidine	Alcohol	Cotinine
ERT 2g	PHU.00123	Screening	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
ERT 2g	PHU.00123	Admission	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative

16.2.9 Vital Signs and Physical Exam Findings

Listing 33: 16.2.9.2: 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: Treatment Group, Participant ID, Parameter (order: Height, Weight, BMI, Systolic Blood Pressure, Diastolic Blood Pressure, Pulse, Respiratory Rate, Temperature), Timepoint, Date of Assessment, Time of Assessment.]

Treatment Group	Participant ID	Actual Study Day	Planned Timepoint	Date of Assessment	Time of Assessment	Result (Severity)	Change from Baseline
				ddMMMyyyy	hh:mm		

Listing 34: 16.2.9.3: Physical Exam Findings

[Implementation Note: This listing includes all physical exam findings, scheduled and unscheduled. If a participant 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: Treatment Group, Participant ID, Date of Assessment, Timepoint, Time of Assessment, Body System, and Finding.]

Treatment Group	Participant ID	Actual Study Day	Planned Timepoint	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.9 Individual ECG Results

Listing 35: 16.2.9.4: 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: Treatment Group, Participant ID, Parameter, Date of Assessment, Time of Assessment.]

Treatment Group	Participant ID	Sex	Parameter	Timepoint	Assessment Date	Assessment Time	Result (Severity)	Change from Baseline	Replicate Number
WCK 6777 2g	PHU.00123	Male	PR Interval	Baseline	ddMMMyyy	hh:mm	210	-	1
WCK 6777 2g	PHU.00123	Male	PR Interval	Day 4	ddMMMyyy	hh:mm	250 (Mild)	40	1

Listing 36: 16.2.9.4: Listing of ECG Overall Interpretation and Comments

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

Sort order: Treatment Group, Participant ID, Date of Assessment, Time of Assessment.]

Treatment Group	Participant ID	Sex	Timepoint	Assessment Date	Interpretation	Change from Baseline	Morphological Abnormalities Present?	Long QT?	Comments
WCK 6777 2g	PHU.00123	Male	Baseline	ddMMMyyy	Normal NCS	-	N	N	Sinus Bradycardia
WCK 6777 2g	PHU.00123	Male	Day 4	ddMMMyyy	Abnormal NCS	NCB	Y	N	Sinus Bradycardia
Notes: NCB= No change from baseline. NSB= Not clinically significant, change from baseline. CSB= Clinically significant change from baseline.									

16.2.10 Prior and Concomitant Medications

Listing 37: 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 or end date is more than 30 days before enrollment, then categorize Medication Start/End Day as follows:

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

Sort order: Treatment Group, Participant ID, and CM Number].

Treatment Group	Participant 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)
WCK 6777 2g	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 38: 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).

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, Participant ID should be USUBJID (not PATID) for purposes of de-identification.

Sort order: Treatment Group, Participant ID, and CM Number.]

Treatment Group	Participant ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)

16.2.11 Pregnancy Reports

Listing 39: 16.2.11.1: Pregnancy Reports – Maternal Information

[Implementation Note: Only include the "Pregnancy Number" column if a participant 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, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, Pregnancy Number.]

Treatment Group	Participant 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 40: 16.2.11.2: Pregnancy Reports – Gravida and Para

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

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

Listing 41: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

Participant 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 42: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

Participant 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 43: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Participant 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