CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 20-0012

Study Title:

A Phase I, Open-Label Study to Assess Lung Pharmacokinetics and Safety of a Single Dose of Apramycin Administered Intravenously in Healthy Adult Subjects

NCT05590728

Version 1.0

7 February 2023

RESTRICTED

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 20-0012**
Development Phase:	Phase 1
Products:	Apramycin
Form/Route:	Intravenous (IV) infusion
Indication Studied:	Multi-drug resistant bacterial infections
Sponsor:	Division of Microbiology and Infectious Diseases (DMID) National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH)
Clinical Trial Initiation Date:	TBD
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	7 February 2023
Version Number:	v1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AC	Alveolar Cell
AE	Adverse Event
ALT	Alanine Aminotransferase
AM	Alveolar Macrophage
AMR	Alliance for Multispecialty Research
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Concentration-Time Curve
$AUC_{(0\text{-}24)}$	Area Under the Concentration-Time Curve from Time of Dosing to 24 h
$AUC_{(0\text{-}last)}$	Area Under the Concentration-Time Curve from Time of Dosing to Time of Last Measurable Concentration
$AUC_{(0\text{-}t)}$	Area Under the Concentration-Time Curve from Time of Dosing to Time t
$AUC_{(0\text{-}\infty)}$	Area Under the Concentration-Time Curve Extrapolated to Infinity
β-HCG	Beta Human Chorionic Gonadotropin
BAL	Bronchoalveolar Lavage
BAL AC	Number of total alveolar cells per mL of BAL volume
BAL AM	Bronchoalveolar Lavage Alveolar Macrophage
BAL ELF	Bronchoalveolar Lavage Epithelial Lining Fluid
BAL SUP	Bronchoalveolar Lavage Supernatant
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per Minute
BQL	Below the Quantification Limit
BUN	Blood Urea Nitrogen
C	Celsius
CHEM	Chemistry
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology collaboration equation for estimating GFR

List of Abbreviations *(continued)*

CL_T	Total Clearance
C_{max}	Maximum Concentration
COAG	Coagulation
ConMed	Concomitant Medication
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CTU	Clinical Trial Unit
CV	Coefficient of Variation
ΔQTcF	Pre-dose, baseline difference in QTcF interval
ΔΔQTcF	Time-matched, baseline-adjusted difference in QTcF interval
dB	Decibel
DBP	Diastolic Blood Pressure
dL	Deciliter
DMID	Division of Microbiology and Infectious Diseases
DPOAE	Distortion Product Otoacoustic Emission
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ELF	Epithelial Lining Fluid
F	Fahrenheit
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in the first second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
g	Gram(s)
GM	Geometric Mean
h	Hour(s)
HBsAg	Hepatitis B-virus Surface Antigen
HCV	Hepatitis C-virus
HEENT	Head, Eyes, Ears, Nose, and Throat

List of Abbreviations *(continued)*

HEM	Hematology
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HPF	High-Powered Field
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medical Product
INR	International Normalized Ratio
IUD	Intrauterine Device
IV	Intravenous
K_e	Elimination Rate Constant
kg	Kilogram(s)
kHz	Kilohertz
KIM-1	Kidney Injury Molecule 1
L	Liter(s)
LC-MS/MS	Liquid Chromatography Tandem-Mass Spectrometry
LLOQ	Lower Limit of Quantification
Max	Maximum Value
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram(s)
mg	Milligram(s)
MH	Medical History
Min	Minimum Value
mL	Milliliter(s)
mmHg	Millimeters of Mercury
mmol	Millimole(s)
MOP	Manual or Procedures
msec	Millisecond(s)
N	Number (typically refers to participants)
NCA	Noncompartmental Analysis
NCS	Not Clinically Significant

List of Abbreviations *(continued)*

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
ONR	Outside Normal Range
OTC	Over the Counter
PE	Physical Examination
PI	Principal Investigator
PK	Pharmacokinetics
Protime	Prothrombin Time
PT	Preferred Term
QNS	Quantity Not Sufficient
QTcF	Corrected QT Interval of the ECG using Fridericia's Formula
RBC	Red Blood Cell
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SDTM	Study Data Tabulation Model
sec	Second(s)
SMC	Safety Monitoring Committee
SNR	Signal-to-Noise Ratio
SOC	System Organ Class
$t_{½}$	Terminal Elimination Half-Life
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time of Maximum Concentration
TSH	Thyroid Stimulating Hormone
UA	Urinalysis
V_d	Volume of Distribution
VS	Vital Signs

List of Abbreviations *(continued)*

WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase I, Open-Label Study to Assess Lung Pharmacokinetics and Safety of a Single Dose of Apramycin Administered Intravenously in Healthy Adult Subjects" (DMID Protocol 20-0012) describes and expands upon the statistical information presented in the protocol.

The document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation 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 of 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 the safety and pharmacokinetic (PK) outcomes, and (4) a list of proposed tables and figures. Within the table, figure, and listing mock-ups (Appendix 1, Appendix 2, and Appendix 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

Aminoglycosides are a class of antibiotics established with the introduction of streptomycin in the 1940s for the treatment of tuberculosis and have defended a strong clinical presence ever since and until today. Mainly due to the common recognition of the rapid bactericidal activity of aminoglycosides – also at very high bacterial burden – the drug class has established itself as an important therapeutic component in the treatment of serious hospital infections worldwide. Despite the introduction of several new chemical classes of antibacterial agents over the past few decades, aminoglycosides still remain an extremely important therapeutic option.

The therapeutic efficacy of standard-of-care aminoglycosides currently in clinical use is compromised by significant rates of antimicrobial resistance acquired by horizonal gene transfer. Infections with antibiotic-resistant bacteria caused an estimated 33,000 deaths in Europe in 2015 [6]. According to the CDC's *Antibiotic Resistance Threats in the United States, 2019*, more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result [7]. Bacterial pathogens highly resistant to various classes of antibiotics are estimated to account for a total of about 700,000 deaths annual worldwide. Without successful intervention, the burden of continued emergence and global spread of antimicrobial resistance is expected to multiply by the year 2050 [7,8]. New antibiotics are needed to adequately respond to the increasing prevalence of drug-resistant infections.

Apramycin is a mono-substituted 2-deoxystreptamine compound that is significantly different from the di-substituted 2-deoxystreptamines which include all the standard-of-care aminoglycoside antibiotics (gentamicin, amikacin, tobramycin, arbekacin, plazomicin and other) and, therefore, represents a subclass of aminoglycosides [9]. Apramycin is active against a wide variety of pathogen Gram-positive and Gram-negative bacteria including pathogens with resistance to gentamicin and all other clinical aminoglycosides of relevance.

This is a Phase 1, open-label study of a single dose of apramycin conducted at a single center. A total of 20 participants will be enrolled to one of 5 cohorts, each corresponding to a timepoint after initiation of infusion at which a single fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) is performed. There will be 4 participants per cohort.

2.1. Purpose of the Analyses

These analyses will assess the safety and plasma and intrapulmonary PK of a single dose of 30 mg/kg apramycin administered as an IV infusion over a period of 30 (± 5) minutes.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary:

- To assess plasma pharmacokinetic profile of apramycin and lung penetration of apramycin in epithelial lining fluid (ELF) and alveolar macrophages (AM) after single IV apramycin dose of 30 mg/kg in healthy participants.

Secondary:

- To assess the safety of single IV administration of 30 mg/kg apramycin in healthy participants.
- To assess changes in otoacoustic testing.

Exploratory:

- To assess changes in kidney function biomarkers.

3.2. Endpoints

Primary:

- Lung concentration and PK parameters of total apramycin:
  - ELF: Area under the concentration-time curve (AUC) from time of dosing to 24 h ($AUC_{(0-24)}$), AUC from time of dosing to time t ($AUC_{(0-t)}$), AUC extrapolated to infinity ($AUC_{(0-\infty)}$), maximum concentration (C_{max}), time to maximum concentration (T_{max}), terminal elimination half-life ($t_{½}$)
  - AM: $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, T_{max}, $t_{½}$
- Plasma concentration and PK parameters of total apramycin:
  - $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, T_{max}, $t_{½}$, total clearance (CL_T), volume of distribution (V_d) central
- Ratio of exposure parameters of Lung PK to Plasma PK:
  - ratio of C_{max} in ELF over C_{max} in plasma
  - ratio of C_{max} in AM over C_{max} in plasma
  - ratio of $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ in ELF over $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ in plasma
  - ratio of $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ in AM over $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ in plasma

Secondary:

- Type and incidence of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs) to Day 30 (± 4 days) after dosing.
- Frequency of clinically significant TEAEs in physical examination (PE) findings and of changes from baseline in vital signs and clinical laboratory parameters until Day 14 (± 3 days) after dosing.
- Frequency of changes in electrocardiogram (ECG) intervals (QTcF, PR, QRS, heart rate [HR]), and of morphological changes from baseline until 24 ± 1 h after dosing.

- Type and incidence of TEAEs related to auditory (cochlear) function tests (pure-tone audiometry and distortion product otoacoustic emissions [DPOAEs]) to Day 30 (± 4 days) after dosing.

Exploratory:

- Changes from baseline in urinary kidney injury molecule 1 (KIM-1) and serum cystatin C concentrations until Day 30 (± 4 days) after dosing.

3.3. Study Definitions and Derived Variables

3.3.1. Timepoints for Safety and PK Endpoints

Table 1 shows the analysis timepoints in the order that will appear in tables and figures along with the safety and PK endpoints measured at each timepoint for all participants. Endpoints analyzed by timepoint include chemistry clinical laboratory results (CHEM), hematology clinical laboratory results (HEM), coagulation clinical laboratory results (COAG), and urinalysis laboratory results (UA); urinary KIM-1 and serum cystatin C; vital signs (VS); ECG; ENT examination and otoacoustic (pure-tone audiometry and DPOAE) tests (listed in the table below as Audiology); and blood (plasma) PK and lung BAL PK results (see Section 3.3.2 for derivations of BAL PK parameters). Serology, toxicology, and pregnancy testing at Screening and/or Check-In will not be included in tables or figures but will be presented in listings.

Table 1: Analysis Timepoints for Safety and PK Endpoints

Analysis Timepoint	Abbreviated Label	Endpoints
Screening	N/A	CHEM, HEM, COAG, UA, VS, ECG, Audiology
Check-In	D-2	CHEM, HEM, COAG, UA, KIM-1, Cystatin C, VS, ECG, Audiology
Day -1	D-1	VS, ECG
Day 1, Pre-Dose	0 h	CHEM, HEM, COAG, UA, KIM-1, Cystatin C, VS, ECG, Plasma PK
Maximum Severity Post Baseline	N/A	CHEM, HEM, COAG, UA, VS, ECG, Audiology
Day 1, 0.5 h Post-Dose	0.5 h	VS, Plasma PK, BAL PK
Day 1, 1 h Post-Dose	1 h	VS, ECG, Plasma PK
Day 1, 2 h Post-Dose	2 h	Plasma PK, BAL PK
Day 1, 4 h Post-Dose	4 h	VS, ECG, Plasma PK, BAL PK
Day 1, 8 h Post-Dose	8 h	Plasma PK, BAL PK
Day 1, 16 h Post-Dose	16 h	VS, ECG, Plasma PK
Day 2, 24 h Post-Dose	24 h	CHEM, HEM, COAG, UA, VS, ECG, Plasma PK, BAL PK
Day 2, 36 h Post-Dose	36 h	VS, ECG, Plasma PK
Day 3, 48 h Post-Dose	48 h	CHEM, HEM, COAG, UA, KIM-1, Cystatin C, VS, ECG, Plasma PK
Day 3, 60 h Post-Dose	60 h	VS, ECG, Plasma PK
Day 3[a]	D3	Audiology
Day 14	D14	CHEM, HEM, COAG, UA, KIM-1, Cystatin C, VS, ECG, Audiology
Day 30	D30	KIM-1, Cystatin C, Audiology

[a] Day 3 refers to any time on Day 3.

3.3.2. BAL Pharmacokinetics Parameters

There are two BAL components collected in this study, ELF (Section 3.3.2.1) and AM (Section 3.3.2.2), and apramycin concentrations and PK parameters will be measured and estimated separately in each component.

3.3.2.1. Apramycin Concentrations in ELF

The estimated concentration of apramycin in the ELF component of the BAL supernatant (*Apramycin ELF*) will be calculated as follows using the urea method [10, 11, 12]:

- *Volume ELF = Volume BAL SUP x (Urea BAL SUP / Urea Plasma)* (equation 1)
- *Apramycin ELF = Apramycin BAL SUP x (Volume BAL SUP / Volume ELF)* (equation 2)
- *Apramycin ELF = Apramycin BAL SUP x (Urea Plasma / Urea BAL SUP)* (equation 3)

Where,

- *Volume ELF* is the estimated volume of ELF in the BAL supernatant (BAL SUP), which is calculated from the following parameters:
  - *Volume BAL SUP* is the measured total volume of BAL SUP after centrifugation of BAL#2 (combined volume of aspirated BAL in tubes 2, 3 and 4)[1]; and
  - *Urea Plasma* and *Urea BAL SUP* are the measured concentrations of urea in plasma and the BAL supernatant, respectively[2].
- *Apramycin BAL SUP* is the measured apramycin concentration in the BAL supernatant fluid[2].
- Note: Equation 3 is the result of merge of equations 1 and 2

3.3.2.2. Apramycin Concentrations in AM

The estimated concentration of apramycin in the AM component of the BAL cell pellet (*Apramycin AM*) will be calculated as follows:

- *Apramycin BAL AC = Concentration BAL AC x total volume of the BAL Pellet in suspension* (equation 4)
- *Volume AM = BAL AC x BAL Volume x % AM x 2.42 µL / 10^6* (equation 5)
- *Apramycin AM = Apramycin BAL AC / Volume AM* (equation 6)

Where,

- *Apramycin BAL AC* is the measured amount of apramycin in the total volume of alveolar cell (AC) suspension, which is calculated from the following parameters:
  - *Concentration BAL AC* is the apramycin concentration in BAL Pellet[2]; and
  - *Total volume of BAL Pellet in suspension* (the total volume in which the cell pellet is suspended in after centrifugation of BAL#2)[1].
- *Volume AM* is the total volume of alveolar macrophages in the BAL pellet, which is calculated from the following parameters:

[1] Reported by the study site (Alliance for Multispecialty Research [AMR])
[2] Reported by the bioanalytical laboratory (KCAS)

- *BAL AC* is the counted number of total alveolar cells per mL of BAL volume[3];
- *BAL volume* is the measured total volume of BAL#2 (combined volume of aspirated BAL in tubes 2, 3 and 4) before centrifugation[3];
- *% AM* is the percentage of alveolar macrophages in total alveolar cells (BAL cell pellet)[3]; and
- 2.42 µL is the mean cell volume of 10^6 AM cells[4].

3.3.3. Baseline

Baseline for clinical laboratory, VS, and audiology results will be defined as the last value recorded before administration of study drug.

For ECG measurements, pre-dose baseline is defined as the last value recorded before administration of study drug, and time-matched baseline is defined as the value recorded at the same timepoint on the day before administration of study drug (Day -1) as on Day 1. If triplicate ECG measurements were performed, the mean value of the ECG measurements will be used as the pre-dose and time-matched baseline values.

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

3.3.4. Study Day

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

[3] Reported by the study site (Alliance for Multispecialty Research [AMR])
[4] Reported in the literature [11,12]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 1, single center, open-label study to evaluate the plasma and lung PK, safety and tolerability of a single IV dose of apramycin in 20 healthy male and female participants 18 to 45 years of age (inclusive). Each participant will be enrolled into one of five cohorts (T1-T5) before dosing on Day 1. Four participants will be allocated to each cohort. Each cohort corresponds to a timepoint after dosing when a single bronchoscopy with BAL will be performed: 0.5 h (± 5 min) (Cohort T1), 2 h (± 5 min) (Cohort T2), 4 h (± 10 min) (Cohort T3), 8 h (± 15 min) (Cohort T4), and 24 (± 1 h) (Cohort T5). The timing of bronchoscopy and BAL in Cohort T5 is nominal. The final timepoint will be determined after analysis of apramycin concentrations in BAL in Cohorts T1-T4. If apramycin is detectable in BAL from Cohorts T1-T4, then T5 will be enrolled. If it is not detectable, then Cohort T5 will not be enrolled.

A diagram of the overall study design is shown in Figure 1. Participants will participate in the study for approximately 58 days, including a 28-day screening period, consisting of an out-patient period of 26 days (Day -28 to Day -3) with 1 to 2 site visits and 2 in-patient days; Day -2 and Day -1, to confirm eligibility for admission (Day -2) and eligibility for enrollment (Day -1), complete baseline assessments for ENT and otoacoustic tests (Day -2), and complete time-matched ECGs (Day -1); a 3-day in-patient treatment period, to confirm eligibility for dosing (Day 1), complete baseline VS, clinical labs, and exploratory labs before dosing (Day 1), administer treatment (Day 1), perform bronchoscopy with BAL within 24 hours after dosing (timepoints T1-T4 on Day 1 and T5 on Day 2), and complete in-patient follow up on Days 2 and 3; and a 27-day out-patient follow-up period to complete site visits on Day 14 (± 3 days) and Day 30 (± 4 days), the last follow-up visit. It is anticipated that the duration of the study will be about 6 months to enroll Cohort T1-T4 and 10 months to complete Cohort T5, if enrolled, following an interim data analysis to review lung PK data.

Enrollment will be rolling and will be coordinated with the bronchoscopy service. Tentative reservations will be made and confirmed once participant eligibility is determined. Enrollment and treatment of participants will be staggered and no more than two participants will be dosed on a single day not less than 2 hours apart. Additional participants may be admitted to the Clinical Trial Unit (CTU) before dosing and may serve as back-up study participants. A participant assigned to one of the T1 to T4 cohorts may be reassigned to another cohort depending on the availability of a bronchoscopy time slot (Section 4.4.3).

A schedule of all study events can be found in Table 2. Safety monitoring during the inpatient period will include: (a) Scheduled assessments per protocol: a PE, VS; 12-lead standard ECG (in triplicate at scheduled timepoints on Day-1 matching planned timepoints on Day 1); clinical safety laboratory tests (HEM, COAG, CHEM, including estimated Glomerular Filtration rate [eGFR], and UA); and audiology testing (middle ear examination and cochlear testing [hearing testing, consisting of pure-tone audiometry and DPOAEs). Exploratory plasma and urinary nephrotoxicity biomarkers (plasma cystatin C and urinary KIM-1) will also be measured. In addition, (b) Unscheduled assessments after bronchoscopy will be performed according to orders by the attending pulmonologist and as needed. Participants with on-going TEAEs will be followed until resolution or stability of the TEAE as assessed by the principal investigator (PI).

A Safety Monitoring Committee (SMC) will be appointed to oversee the safe conduct of the trial, review safety data and provide recommendations on safety monitoring in the current and future clinical trials with apramycin. A scheduled interim SMC meeting will be held after all participants in Cohorts T1-T4 complete all assessments. If the last cohort (T5) will be enrolled for dosing, a final SMC will be held to review cumulative data on all participants. If Cohort T5 is not dosed, the interim meeting will be considered final. If

criteria for halting the trial are met, enrollment and dosing of new participants will be suspended, and an *ad hoc* SMC meeting will be held to review all available safety data.

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

As the main focus of this protocol is to evaluate the PK, safety, and tolerability of a single dose of apramycin, and there is no control group, all participants will receive the same dose of apramycin with the same PK blood collection timepoints. Participants will be assigned to one of five BAL sampling timepoints with a total of 4 participants assigned to each BAL sampling time. The timing of bronchoscopy and BAL in Cohort T5 will be determined after analysis of apramycin concentrations in BAL in Cohorts T1-T4. If apramycin is detectable in BAL from Cohorts T1-T4, then T5 will be enrolled. If it is not detectable, then Cohort T5 will not be enrolled.

4.3. Selection of Study Population

The study population for this trial is 20 healthy male or female participants 18 to 45 years of age (inclusive) at the time of dosing. Only participants who consent to participate and meet all of the inclusion and none of the exclusion criteria will be eligible for enrollment into this study. No exemptions are granted on Inclusion/ Exclusion Criteria in DMID-sponsored studies.

Eligibility criteria from v3.0 of the protocol are listed below:

Inclusion Criteria:

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

1. Participant reads and signs the Informed Consent Form (ICF) and agree to have bronchoscopy with bronchoalveolar lavage under sedation or light anesthesia and comply with study procedures.
2. Healthy male or non-pregnant, non-lactating female participants 18 to 45 years of age (both inclusive) at the time of dosing.
    - **Note 1:** Determined by medical history (MH), medication use, physical examination (PE), and vital signs, clinical laboratory tests and 12-lead ECG within reference ranges at Screening and Day-2. (See protocol Sections 8.1 and 8.2, and Appendix B, Table 2, Table 3, and Table 4).

      Exceptions to blood pressure (BP), HR and laboratory test values being within normal ranges are:
        - Abnormal HR and BP on first measurement may be repeated twice more with the participant resting between measurements for at least 5 min according to protocol Section 8.1.6.
        - Participants with baseline HR ≥ 45 to 50 bpm may be accepted if otherwise healthy adults with known history of asymptomatic bradycardia.
        - Participants with baseline systolic BP up to 140 mmHg and diastolic BP up to 90 mmHg may be accepted if otherwise healthy.
        - A laboratory value that is Grade 1 will be allowed if not considered to be clinically significant by the investigator, with the exception of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), blood urea nitrogen (BUN), urine protein, serum creatinine or estimated glomerular filtration rate (eGFR) <70 mL/min /1.73 m^2 by the Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) equation.
3. Female participants of childbearing potential should use highly effective methods of contraception from the time of screening to 30 days after dosing.

- **Note 1:** A female is considered of childbearing potential unless post-menopausal (defined as history of ≥1 year of spontaneous amenorrhea and a follicle stimulating hormone [FSH] level >40 IU/L), or permanently surgically sterilized.
- **Note 2:** Highly effective contraceptive methods include: (a) surgical sterilization methods, such as tubal ligation, bilateral oophorectomy, salpingectomy, hysterectomy, or successful tubal obliteration (e.g., Essure®) with documented radiological confirmation test at least 90 days after the procedure, or (b) long-acting reversible contraception, such as progestin-releasing subdermal implants, copper intrauterine devices (IUDs), levonorgestrel-releasing IUDs.
- **Note 3:** A participant who is not sexually active and abstains from sexual intercourse can be enrolled and abstinence documented.

4. Males, including vasectomized men, having sexual intercourse with women of childbearing potential must agree to consistent use of condoms from investigational medical product (IMP) administration through at least 30 days after dosing, and must also agree to not donate sperm during this same time period.
   - **Note:** A participant who is not sexually active and abstains from sexual intercourse can be enrolled and abstinence documented.
5. BMI 18.0 to 32.0 kg/m^2 (inclusive) and body weight not less than 50 kg.
6. Participants with normal hearing, i.e., symmetric hearing with air conduction thresholds no worse than 20 dB hearing loss for the frequencies 0.5-1-2-4-6-8 kHz bilaterally.
7. Normal (reproducibility 70% or better) of distortion product otoacoustic emissions (DPOAEs).
8. Normal otoscopic findings in the ears, normal tympanic membrane mobility and stapedial reflex present.
9. From the signing of the informed consent until the last follow-up visit, participants must be willing to avoid exposure to loud music or noise.
   - **Note:** Noise avoidance to include continuous usage of earpieces at high volume, attending loud concerts or dance events, or using firearms or attending fireworks.
10. Normal lung function with Forced Expiratory Volume in the first second (FEV1) predicted ≥ 80% and FEV1/Forced Vital Capacity (FVC) > 70%.
11. Participants must be willing to avoid excessive physical exercise within 48 h prior to dosing until discharge from the CTU on Day 3, and 24 h before each follow-up visit (Day 14 ± 3 days and Day 30 ± 4 days).
12. No history of acute febrile or infectious illness for at least 7 days prior to the administration of the IMP.
13. No history of lower respiratory tract infection within 4 weeks prior to screening.
14. Have adequate venous access for infusion and blood draws.

Exclusion Criteria:

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

1. Lactating females.

Medical and surgical history:

2. Any history of hypersensitivity to aminoglycosides.
3. Any history of drug hypersensitivity, asthma, urticaria or other severe allergic diathesis.
4. Any history of seasonal allergies with ongoing symptoms for more than a week prior to dosing requiring glucocorticoids and/or frequent use of antihistamines for treatment.
5. Any history of a chronic condition that may increase risk to participant or interfere with endpoint assessment, or any unstable chronic disease.
    - **Note 1:** Unstable chronic disease is defined by need for frequent medical interventions that lead to a change in medications and/or required hospitalization, surgery or an invasive procedure or emergency department/urgent care visit.
    - **Note 2:** Any chronic disease, that has been diagnosed within 90 days of screening is excluded.
6. History of any psychiatric medical condition that has required hospitalization in the last 5 years or participant is considered psychologically unstable by the investigator.
7. History of acute or chronic problems with hearing and/or balance in the last 24 months.
    - **Note:** These include but not limited to use of hearing aid, head injury leading to otologic damage, tumor of the head or neck, autoimmune disease of the inner ear, tinnitus, vestibular disease, auditory neurinoma, endolymphatic hydrops and/or Meniere's disease, perilymphatic fistula, otitis media, labyrinthitis, sudden hearing loss, known retrocochlear hearing impairment, conductive hearing loss exceeding 10 dB at any frequency, ear canal and/or middle ear disease including inflammation or effusion, pathological tympanometry.
8. Past injury or surgery to the middle or inner ears.
    - **Note**: Myringotomy or tympanic tube insertion in childhood with complete healing and normal hearing test are excluded.
9. Family history of hearing loss before the age of 60.
10. Participants who have had previous intolerance or contraindications to medications applied for sedation or anesthesia during bronchoscopy.
    - **Note:** These include benzodiazepines or topical anesthetic agents (lidocaine or xylocaine) including reversal agents such as flumazenil.

Laboratory examinations:

11. Positive serum pregnancy test for women or urine pregnancy test at check-in.
12. Positive test for human immunodeficiency virus (HIV) antibodies, hepatitis B-virus surface antigen (HBsAg), or anti-hepatitis C-virus antibodies (anti-HCV).

Prior medication:

13. Use of any prescription or non-prescription medication prior to the dose of IMP as described in protocol Section 6.6.
    - **Note**: Exceptions are hormonal contraceptives, which are permitted throughout the study, and solitary doses of up to 1,000 mg paracetamol.

14. Use of any investigational drug product within 30 days or 5 half-lives (whichever is longer) before dosing.
15. Planned participation in a clinical research study that requires treatment with a study drug or blood draws or other invasive assessments during the study period (screening until final visit).

Lifestyle restrictions:

16. More than low-risk alcohol consumption (men: ≥ 24 g of pure alcohol regularly per day; women: ≥12 g of pure alcohol regularly per day) for the previous 3 months.
17. Any history of alcohol or drug abuse or positive urine alcohol screening test.
18. Suspicion of illicit drug use / abuse or positive urine drug screen test (See protocol Section 6.7.4 and Section 8.2.4 for prohibited substances).
19. History of ≥10 pack-years smoking, or history of any nicotine use in the 6 months before check-in (Day -2) or positive urine cotinine screen at check-in.
    - **Note 1:** Nicotine products include cigarettes, e-cigarettes, pipe, cigar, chewing tobacco, nicotine patch.
    - **Note 2:** A positive urine cotinine at screening is allowed if negative at check-in (Day -2).
20. Caffeinated beverages/foods are prohibited within 48 hours before dosing to Day 3 of the trial. During the follow up period, consumption is restricted to not more than 3 cups or equivalent per day.
21. Judged by the investigator to have occupational noise exposure of high risk during the trial (e.g., construction site workers, military workers, etc.).
22. 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.

4.4. Treatments

4.4.1. Treatments Administered

Participants will receive a single 30 mg/kg dose of apramycin administered as an IV infusion of 30 mL in a forearm vein over 30 min (± 5 min) using a syringe or infusion pump.

4.4.2. Identity of Investigational Product(s)

Apramycin for infusion, the IMP, is formulated as 150 mg free base /mL in sterile aqueous solution, pH 5.5 to 6.0 adjusted with sulfuric acid. The study product is supplied in 20 mL glass vials. A volume of ≥18 mL can be withdrawn from each vial. To protect the solution from light, the vials are stored in folding boxes.

The clinical research site will provide the diluent, 0.9% sodium chloride injection, USP. The diluent will be commercial source, USP grade 0.9% Sodium Chloride Injection, or normal saline, a sterile, nonpyrogenic, clear in color isotonic solution; each mL contains sodium chloride 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied only in single-dose vials. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3, range 4.5 to 7.0). This product should be used to dilute apramycin to the desired concentration.

4.4.3. Method of Assigning Participants to Treatment Groups

Twenty healthy participants who consent to participate in the trial and meet the eligibility criteria will be enrolled following admittance to the CTU and confirmation of eligibility. Participants will be registered using Advantage eClinical®, developed and maintained by the Statistical and Data Coordinating Center (SDCC).

Since this is an open-label study of a single dose of IMP, participants will be enrolled on a rolling basis. Four participants will be assigned to each one of five cohorts, T1-T5, corresponding to a single Lung PK sampling timepoint (Section 4.1) with equal allocation (1:1:1:1:1). Each cohort corresponds to a single Lung PK sampling timepoint. It is planned to enroll participants into cohorts T1 to T4 according to availability of the bronchoscopy suite. However, on the day of bronchoscopy, a participant may be reassigned to another cohort than planned on the same day, depending on emergencies at the bronchoscopy suite at the time originally planned, or cancelled.

Appointments for the bronchoscopy suite will be made in advance and every effort will be made to admit, dose, and perform bronchoscopy with BAL according to the schedule. However, if a scheduled bronchoscopy cannot be performed according to schedule on a dosing day, the following steps may be taken according to the time of cancellation before or after dosing:

- *If the procedure is cancelled before administration of study drug*, an effort will be made to reschedule the procedure.
- *If the procedure is cancelled after administration of the study drug*, every effort will be made to reschedule the bronchoscopy to a later time (up to 8 hours after dosing) to accommodate an available Lung PK timepoint or the procedure will be cancelled.
    - If bronchoscopy is rescheduled, the registration in the Advantage eClinical® will be updated to indicate the cohort that the participant completed and a future participant would be assigned in the registry to complete the missing Lung PK timepoint.
    - If it is not feasible to reschedule bronchoscopy, the participant will be terminated from participation in the study and will be replaced. The participant will be asked to remain in the study to complete safety and otoacoustic testing until Final Visit (Day 30 ± 4 days). If the participant declines to remain in the study for safety assessments, appropriate early termination assessment will be completed prior to discharge from the CTU (see protocol v3.0 Section 5.3.3 and Section 7.7).

4.4.4. Selection of Doses in the Study

A single dose of 30 mg/kg had been selected for this study based on the favorable safety and tolerability profile observed in the first in human clinical trial in healthy participants [13]. In addition, based on the translational PK-PD modeling study to assess efficacy, 30 mg/kg of EBL-1003 (apramycin) is the anticipated therapeutic dose for future clinical investigations in patients [14].

4.4.5. Selection and Timing of Dose for Each Participant

This trial will evaluate the plasma and lung PK and safety of a single 30 mg/kg dose of apramycin administered as a 30-minute IV infusion on Day 1. A single bronchoscopy with BAL will be performed after initiation of dosing at one of the following timepoints in the respective cohorts: 30 min (± 5 min) (T1), 2 h (± 5 min) (T2), 4 h (± 10 min) (T3), 8 h (± 15 min) (T4), and 24 h (± 1 h) (T5). Refer to Figure 1 for additional details regarding the timing schedule for the BAL timepoints following dosing.

4.4.6. Blinding

This is an open-label, unblinded study. Blinding (masking) is not needed.

4.4.7. Prior and Concomitant Therapy

Medications include the following: prescription drugs, birth control hormonal preparations, non-prescription 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, and solitary doses of up to 1,000 mg acetaminophen (paracetamol).

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

- Use of any investigational drug product within 30 days or 5 half-lives (whichever is longer) before dosing or planned use during the study period (screening until Final Visit).
- Use of aminoglycosides within 3 months prior to dosing.
- Use of neuromuscular blocking agents within 1 week or 5 half-lives (whichever is longer) prior to dosing.
- Use of potentially nephrotoxic medication 2 weeks prior to dosing: Renin– angiotensin-aldosterone system inhibitors: angiotensin-converting enzyme-inhibitors, angiotensin II-receptor antagonists (enalapril, lisinopril, ramipril captopril, benazepril), spironolactone, eplerenone; non-steroidal anti-inflammatory drugs (aspirin, ibuprofen, naproxen, indomethacin, etc.) including cyclooxygenase 2 selective inhibitors (Bextra, Celebrex, Vioxx).
- Use of potentially ototoxic medication 3 months prior to dosing: vancomycin, loop diuretics (bumetanide, ethacrynic acid, furosemide), quinine and quinidine derivatives including mefloquine with the exception of occasional intake of quinine containing beverages.

Non-prescription medications, herbs, vitamins, and nutritional supplements will not be taken within 15 days before dosing and during the trial. ***Exceptions***: vitamins and over the counter (OTC) medications taken for < 48 h for the treatment of common symptoms (e.g., headache, indigestion, muscle pain) may be allowed if approved by the designated study clinician.

Blood/blood products (red blood cells [RBCs], white blood cells [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 sub-investigator.

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 study clinician (listed on FDA Form 1572) will note whether the use was medically indicated and immediately necessary. Any use of medications not authorized by the study PI or authorized clinician will be recorded as a deviation.

4.4.8. Treatment Compliance

Since each dose of apramycin 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 unable to receive the full volume of apramycin infusion will be withdrawn from data analysis and followed for safety as described in protocol v3.0 section 5.3.3.

Infusion interruptions, not exceeding 10 minutes in total, are permitted per protocol:

- For **non-drug safety related issues**, infusion interruption(s) causing a delay of 9 minutes or less is permitted.
    - The allowable window for the infusion will be increased to 30 minutes (-5/+10) to account for the interruption
        - Participant will remain in the PK analysis population.
- For **infusion interruption delays of 10 minutes or greater** in total, causing the participant not to receive the entire infusion volume:
    - The participant will be withdrawn from the bronchoscopy and pharmacokinetics procedures but encouraged to remain in the study to be followed for safety.
    - Participant removed from the PK analysis population.
    - All participants withdrawn due to infusion interruptions will be replaced.

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. Refer to Section 3 for a list of primary, secondary, and exploratory objectives and endpoints.

4.5.1. Safety Variables

Incidence, relatedness, and severity of TEAEs and SAEs will be recorded from the time of dosing through the Final Visit on Day 30 (± 4 days), or early termination. All AEs will be graded for severity and the relationship to the study product, as described in protocol v3.0 Section 9.2. Clinical AEs will be graded using the toxicity grading scales in Table 3.

Abnormal clinical laboratory, VS, and ECG results will be assessed using the toxicity grading scales in Table 4, Table 5, and Table 6, respectively. Audiology results will be graded according to the toxicity grading scales in Table 3.

In addition to AEs, the following safety endpoints will be assessed at baseline and each post-dose timepoint collected. For continuous parameters, change from baseline will also be summarized for all post-dose timepoints. For definitions of baseline for safety endpoints, refer to Section 3.3.3.

- Clinical safety laboratory evaluations (CHEM, HEM, COAG, UA)
    - Clinical laboratory tests will be performed at Screening, Check-In (Day -2), pre-dose on Day 1, Day 2 (24 h post-dose), Day 3 (48 h post-dose), and Day 14.
    - The following parameters will be measured:

- CHEM: sodium, potassium, glucose (fasting), BUN, creatinine, eGFR, calcium, chloride, magnesium, total carbon dioxide, albumin, total protein, AP, ALT, AST, total bilirubin, direct bilirubin, thyroid stimulating hormone (TSH), free thyroxine (T4), and free triiodothyronine (T3)
- HEM: hemoglobin, hematocrit, platelets, WBC count, and differential WBC count (neutrophils, lymphocytes, eosinophils, basophils, and monocytes)
- COAG: activated partial thromboplastin time (aPTT), prothrombin time (Protime), and international normalized ratio (INR)
- UA: urine dipstick, including protein, glucose, occult blood, and urine microscopy, including WBC count, RBC count, and bacteria, if urine dipstick is abnormal

  - Additionally, tests for exploratory biomarkers for renal injury, serum cystatin C, urinary KIM-1, and KIM-1 normalized per mg urinary creatinine, will be performed at Check-In (Day -2), pre-dose on Day 1, Day 3 (48 hours post-dose), Day 14, and Day 30.

- VS
  - VS will be measured at Screening, Check-In (Day -2), Day -1, Day 1 (pre-dose and 0.5 h, 1 h, 4 h, and 16 h post-dose), Day 2 (24 h and 36 h post-dose), Day 3 (48 h and 60 h post-dose), and Day 14.
  - The following parameters will be measured: systolic BP, diastolic BP, HR, respiratory rate, and oral temperature.
- 12-lead standard ECG
  - ECG will be performed in either triplicate or single at Screening, Check-In (Day -2), Day -1 (at timepoints matching those on Day 1), Day 1 (pre-dose and 1 h, 4 h, and 16 h post-dose), Day 2 (24 h and 36 h post-dose), Day 3 (48 h and 60 h post-dose), and Day 14.
    - For ECG measurements performed in triplicate, the mean of the replicates will be used for analysis, including analyses of change from baseline.
  - At each timepoint, the overall interpretation of the ECG will be reported as Normal; Abnormal, Not Clinically Significant (NCS); or Abnormal, Clinically Significant (CS). For post-dose timepoints, the change from baseline will be also reported as No change from baseline; NCS, change from baseline; or CS, change from baseline.
  - The following parameters will be measured: PR interval, QRS interval, QT interval, corrected QT interval using Fridericia's Formula (QTcF correction), RR internal, and ventricular rate.
    - For replicate ECGs recorded on Day -1 and Day 1, the mean time-matched change-from-baseline QTcF values (ΔΔQTcF) will be evaluated to quantify the QTcF prolongation. For single ECG recoded after dosing, the mean pre-dose change-from-baseline (ΔQTcF) will also be analyzed.
- Audiology
  - The following audiology tests will be conducted:
    - Valsalva test, Tympanometry and Stapedial Reflexes at Screening only.
    - Ear otoscopy at Screening, Check-In (Day -2), Day 3, Day 14, and Day 30.

  - Pure tone audiometry at standard frequencies (0.5 to 8.0 kHz) at Screening and at both standard and higher frequencies (9.0 to 20.0 kHz) at Check-In (Day -2), Day 3, Day 14, and Day 30.
  - DPOAEs (1.5 to 6.0 kHz) at Screening, Check-In (Day -2), Day 3, Day 14, and Day 30.
- Physical Examination
  - A complete PE to assess general appearance; head, eyes, ears, nose, and throat (HEENT); heart, lungs, abdomen, skin, musculoskeletal system, and lymph nodes; and a neurological exam will be performed at Screening, Check-In (Day -2), Day 3 (60 h post-dose), and Day 14.
  - An abbreviated PE will be performed at Day -1. An abbreviated PE differs from a complete PE in that the abdomen and neurological system are not evaluated.
  - A symptom-directed (focused) PE may be performed on Day 1 and at any time after dosing for evaluation of TEAEs.
  - Height and weight will be measured, and BMI calculated, at Screening only. Weight only will be measured on Day -2 and Day 14.

4.5.2. Pharmacokinetic Variables

A valid liquid chromatography tandem-mass spectrometry (LC-MS/MS) method will be used to determine concentrations of apramycin in plasma and BAL samples as well as urea in plasma and BAL (ELF).

- Blood (Plasma) for apramycin concentrations
  - Blood (plasma) samples for assay of apramycin PK will be collected at the following study days and timepoints: On Day 1 within 30 min before dosing, and 0.5 h (±5 min, immediately at end of infusion), 1 h (±5 min), 2 h (±5 min), 4 h (±10 min), 8 h (±15 min), and 16 h (±15 min) after dosing; on Day 2 at 24 h (± 1 h) and 36 h (± 1 h) after dosing; and on Day 3 at 48 h (± 1 h) and 60 h (± 1 h) after dosing, or ET if occurs within 24 h of dosing.
  - If BAL is delayed, blood (plasma) for apramycin will be collected within the prespecified window of the nominal timepoint and a second sample will be collected within 5 min of the last BAL sample.
- Bronchoscopy with BAL
  - During bronchoscopy with BAL, samples will be obtained at the following timepoints during the study: 0.5 h ± 5 min, 2 h ± 5 min, 4 h ± 10 min, 8 h ±15 min and 24 h ± 1 h after the start of the infusion. Each participant will have a bronchoscopy with BAL at one timepoint only, for a total of 4 samples at each timepoint.
- Urea
  - Urea will be assayed in plasma samples collected at baseline (as part of the total apramycin plasma PK) and at 0.5 h (± 5 min) 2 h (± 5 min), 4 h (± 10 min), 8 h (± 15 min) and 24 h (± 1 h) after the start of the infusion), and in BAL SUP samples corresponding to plasma PK timepoints. If BAL is delayed and a second plasma sample is collected within 5 min of the last BAL sample, plasma urea will be measured only in the second sample.

5. SAMPLE SIZE CONSIDERATIONS

This is Phase 1 study to assess the safety and PK of apramycin. Since the study is primarily aimed at safety and PK, no formal power calculations based on testing a statistical hypothesis were constructed. Enrollment of 20 participants assigned into 5 cohorts, T1-T5, with 4 participants per cohort is based on clinical experience and judgment and should provide adequate clinical information to meet the objectives of the study.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Summary statistics for continuous data will include the number of participants included in the analysis (N), mean, standard deviation (SD), median, minimum (min), and maximum (max). Summary statistics for categorical 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 safety and PK analyses will be performed for all participants combined across cohorts, within the respective analysis populations. No analyses will be performed by cohort. The Safety Population and Safety Subset Population will both be used for summaries of safety endpoints, and the PK Analysis Subset Population will be used for summaries of PK endpoints. For the safety endpoints, the population used will be noted in the table, figure, or listing title.

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

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

6.2. Timing of Analyses

The final analysis will be performed after database lock.

One interim PK review is planned following Cohort T4 to analyze the plasma and BAL (ELF and AM) apramycin concentrations and PK data from cohorts T1 to T4.

The SMC will review safety data at the following times:

- Following Cohort T4 to review cumulative, interim safety data of all participants in cohorts T1 to T4
- After completion of dosing and final visit for all participants, including Cohort T5
- *Ah hoc* meeting(s): as required in response to halting criteria (see Protocol v3.0 Section 9.5) or at the request of DMID to review a potential safety concern identified by either the Site PI or DMID medical monitor

6.3. Analysis Populations

All analysis populations to be used in the final analysis are described in this section. A tabular listing of all enrolled participants excluded from an analysis population (a Safety Population or a PK Analysis Population) will be included in the CSR (Listing 4). Although there may be multiple reasons for exclusion from an analysis population, only one reason will be counted when summarizing reasons for exclusion from analysis populations in Table 11. The order that reasons will be considered is the same as the order shown in Table 11.

6.3.1. Safety Population

The Safety Population will include all participants that received any amount of study product (apramycin).

6.3.1.1. Safety Subset Population

The per protocol Safety Subset Population will be based on the Safety Population and will include all participants who received a complete dose of apramycin. Participants who had an infusion interruption lasting 10 minutes or longer will be withdrawn and excluded from the Safety Subset Population if they did not receive the full dose of apramycin.

6.3.2. PK Populations

6.3.2.1. Lung PK Population

The Lung PK Analysis Population will consist of all participants who received a complete dose of apramycin, underwent BAL at the assigned sampling timepoint with BAL return volume adequate for analysis, and have a quantifiable post-dose drug concentration separately for BAL SUP (for calculation of ELF) and BAL AC (for calculation of AM).

6.3.2.2. Plasma PK Population

The Plasma PK Analysis Population will consist of all participants who received a complete dose of apramycin and have at least one quantifiable post-dose plasma drug concentration measured.

6.3.2.3. PK Subset Population

The PK Analysis Subset Population will be based on the Lung PK and Plasma PK analysis populations, which include all participants who completed the lung PK and plasma PK parts of the trial without any protocol deviations that would likely affect the PK results and who have evaluable plasma PK and BAL PK concentration data for apramycin from which at least a subset of the designated PK parameters can be determined. Potential protocol deviations include infusion interruptions or samples collected out of window. Participants who had an infusion interruption lasting 10 minutes or longer will be withdrawn and excluded from the PK Analysis Subset Population. If any participants are found to be noncompliant with respect to dosing or have incomplete data, a decision to include them in the analysis will be made on a case-by-case basis.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses.

6.5. Missing Data

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

6.6. Interim Analyses and Data Monitoring

An interim analysis of PK data is planned to follow the completion of Cohort T4 (see Section 6.2). Concentration-time data will be presented tabularly and graphically for participants in the PK Analysis Population for both plasma and BAL (ELF and AM) apramycin concentrations. Non-compartmental analysis (NCA) PK parameters will be summarized for the plasma and BAL PK data. Tables and figures for analyses described in Section 10 will be used for the interim analysis.

An SMC meeting to review cumulative safety data is planned after Cohort T4. Safety data, including TEAEs, SAEs, clinical laboratory results (CHEM, HEM, COAG, and UA), VS, ECGs, and audiology testing results will be presented. The SMC may also review safety data during an *ad hoc* meeting if a halting rule (see Protocol v3.0 Section 9.5) is met.

6.7. Multicenter Studies

This is a single-site study.

6.8. Multiple Comparisons/Multiplicity

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

7. STUDY 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 and reason not enrolled (Table 10). Enrolled participants who were ineligible for inclusion in analysis populations will be summarized by reason for exclusion and Cohort (Table 11). Individual reasons for participants who were excluded from a Safety or a PK Analysis Population will be listed (Listing 4).

Participant disposition will be summarized (Table 8), showing the number of participants who were screened, enrolled, started infusion, completed infusion, completed bronchoscopy with BAL, completed all PK blood draws, completed all plasma urea blood draws, completed follow-up on Day 14, and completed the final study visit on Day 30. Enrolled participant who discontinued treatment or terminated early will be summarized by reason and Cohort in Table 9.

Participants who discontinued treatment or terminated early from the study will be listed (Listing 1).

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 Cohort.

7.2. Protocol Deviations

A summary of participant-specific protocol deviations will be presented by deviation category, deviation type, and Cohort (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 2 and Listing 3, 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 Safety Subset Population.

Any medical condition that is present at the time the participant is screened will be considered baseline and not reported as an AE, unless it worsens in severity or increases in frequency during the study. The denominators for proportion values will be indicated within the table or table header. AEs will be summarized for the number of participants who experienced an AE and the number of events by Medical Dictionary for Regulatory Activities (MedDRA®) category. Toxicity grading scales for clinical adverse events are provided in Table 3. All AEs reported will be included in the summaries and analyses.

9.1. Demographic and Other Baseline Characteristics

Sex, ethnicity, and race will be summarized by Cohort (Table 12). Ethnicity is categorized by "Hispanic or Latino", "Not Hispanic or Latino", "Not Reported", or "Unknown". In accordance with NIH reporting policy, 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 BMI at Screening will be summarized by Cohort (Table 13). Individual participant listings will be presented for all demographic and baseline characteristics (Listing 5).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA coded using MedDRA dictionary version 23.1 or higher. Summaries of participants' pre-existing medical conditions by MedDRA system organ class (SOC) and Cohort will be presented in Table 14. Individual participant listings will be presented for all medical conditions (Listing 6).

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 81 for prior medications and Table 82 for ConMeds). Individual participant listings will be presented for all prior and concomitant medications (separately in Listing 27 for prior medications and Listing 28 for ConMeds).

9.2. Measurements of Treatment Compliance

Infusion start and end dates and times, including the amount of study product received and infusion interruptions, will be listed (Listing 7).

9.3. Adverse Events

Refer to Section of 9.2 of the protocol for definitions of TEAEs, severity, and relatedness. When calculating the proportions of participants with AEs within a given MedDRA category, each participant will be counted once and any repetitions of AEs within a participant will be ignored, and the event will be reported according to the highest severity recorded (separately for related and unrelated AEs, when both severity and relatedness are tabulated). The denominators for percent values will be indicated within the table or table header.

9.3.1. Treatment Emergent Adverse Events

An overall summary of TEAEs will be presented in Table 15 for the Safety Population and Table 16 for the Safety Subset Population, including the number of participants with at least one TEAE, the number of participants with at least one related TEAE, and the number of participants with at least one SAE.

All AEs will be presented in Listing 8. A listing of non-serious TEAEs of moderate or greater severity will also be reported (Table 22).

The following summaries for TEAEs will be presented by SOC, high level group term (HLGT), and preferred term (PT):

- The total number of TEAEs and the number and proportion of participants reporting at least one TEAE, regardless of severity or relationship to study product. Ninety-five percent (95%) CIs will be presented for proportions (Table 17 for the Safety Population and Table 18 for the Safety Subset Population).
- The number and proportion of participants reporting at least one TEAE by maximum severity and relationship to study product (Table 19 for the Safety Population and Table 20 for the Safety Subset Population).
- Bar chart displaying the proportion of participants with related serious or non-serious TEAEs by maximum severity and SOC (Figure 3 for the Safety Population and Figure 4 for the Safety Subset Population). This figure describes the number of participants with an event (each participant is counted once per SOC).
- Bar chart displaying the number of related serious and non-serious TEAEs by severity and SOC (Figure 5 for the Safety Population and Figure 6 for the Safety Subset Population). This figure described the total number of occurrences of each event, including multiple occurrences per participant.

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

Individual data listings of deaths and other SAEs will be provided (Table 21). The listing will include participant ID, Cohort, AE Number, 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

An individual data listings of pregnancy reports will be presented if any pregnancies occur (Listing 29, Listing 30, Listing 31, Listing 32, and Listing 33).

Birth control method(s) will be listed for each participant with start and end dates (Listing 34).

9.6. Clinical Laboratory Evaluations

Toxicity grading criteria for clinical laboratory results can be found in Table 4. Unscheduled clinical laboratory evaluations will be included in listings but excluded from tabular and graphical summaries, except when calculating the maximum severity post-baseline. Any pre-existing abnormal lab results at Screening and Baseline will be graded and presented in listings but will not be reported as an AE unless it is treatment-emergent (i.e., severity worsens [increases to Grade 2 or higher] after dosing).

The following parameters will be presented (in order):

- CHEM: sodium, potassium, glucose (fasting), BUN, creatinine, eGFR, calcium, chloride, magnesium, total carbon dioxide, albumin, total protein, AP, ALT, AST, total bilirubin, direct bilirubin, TSH, free T4, and free T3
- HEM: hemoglobin, hematocrit, platelets, WBC count, neutrophils, lymphocytes, eosinophils, basophils, and monocytes
- COAG: aPTT, Protime, and INR
- UA: protein by dipstick, glucose by dipstick, occult blood by dipstick, WBC by microscopy, RBC by microscopy, and bacteria by microscopy (microscopy only completed if urine dipstick is abnormal)

All safety laboratory results (CHEM, HEM, COAG, and UA) will be listed in Listing 9, Listing 10, Listing 11, and Listing 12, respectively. Abnormal laboratory results, including results outside of the normal range (ONR), will be listed in Table 23, Table 24, Table 25, and Table 26 for chemistry, hematology, coagulation, and urinalysis, respectively. Abnormal laboratory results that do not have toxicity grading ranges defined in the protocol may not be reported as AEs by the site and will not have severity indicated in tables and listings of abnormal laboratory results, except as ONR.

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

Laboratory results will be summarized in tables and figures:

- The proportion of participants with abnormal laboratory results by parameter and timepoint will be summarized for CHEM (Table 27 for the Safety Population and Table 28 for the Safety Subset Population), HEM (Table 33 for the Safety Population and Table 34 for the Safety Subset Population), COAG (Table 39 for the Safety Population and Table 40 for the Safety Subset Population), and UA (Table 45 for the Safety Population and Table 46 for the Safety Subset Population).
- The proportion of participants with mild, moderate, or severe laboratory results by parameter and timepoint will be summarized for CHEM (Table 29 for the Safety Population and Table 30 for the Safety Subset Population), HEM (Table 35 for the Safety Population and Table 36 for the Safety Subset Population), COAG (Table 41 for the Safety Population and Table 42 for the Safety Subset Population), and UA (Table 47 for the Safety Population and Table 48 for the Safety Subset Population).
- Summary statistics of measurements and change from baseline by parameter and timepoint for CHEM (Table 31 for the Safety Subset Population and Table 32 for the Safety Population), HEM (Table 37 for the Safety Population and Table 38 for the Safety Subset Population), and COAG (Table 43 for the Safety Population and Table 44 for the Safety Subset Population). UA character results will be excluded from change from baseline summaries.
- Change from baseline at each scheduled timepoint will be visualized using box plots for each parameter. The safety population used for each figure will be noted in the title. UA character results will be excluded from graphical summaries.
    - CHEM: Beginning at Figure 7 and continuing through Figure 46
    - HEM: Beginning at Figure 47 and continuing through Figure 64

- COAG: Figure 65, Figure 66, Figure 67, Figure 68, Figure 69, and Figure 70

Screening laboratory results will be listed. Serology result will be shown in Listing 14. Urine drug and cotinine and alcohol breathalyzer test results will be shown in Listing 15. Pregnancy testing and FSH test results will be shown in Listing 16.

9.6.1. Exploratory Biomarkers for Renal Injury

Kidney function biomarkers, serum cystatin C, urinary KIM-1, and KIM-1 normalized per mg urinary creatinine, will be summarized for measurements and change from baseline by parameter and timepoint in Table 49 for the Safety Population and in Table 50 for the Safety Subset Population. Additionally, results will be visualized using box plots showing the change from baseline at each scheduled timepoint for serum cystatin C in Figure 71 and Figure 72, KIM-1 in Figure 73 and Figure 74, and KIM-1 normalized per mg urinary creatinine in Figure 75 and Figure 76 for the Safety Population and Safety Subset Population, respectively.

Results for all kidney function biomarker tests will be listed (Listing 13).

9.7. Vital Signs and Physical Evaluations

Toxicity grading criteria for VS results can be found in Table 5. Unscheduled VS measurements will be listed but excluded from tabular and graphical summaries by timepoint, except when calculating the maximum severity post-baseline. VS parameters that have grading criteria for both decreases (results lower than normal range) and increases (result higher than normal range) will be summarized separately by direction of change.

The following VS parameters will be summarized (in order): systolic BP, diastolic BP, HR, respiratory rate, and oral temperature.

VS parameters will be summarized in tables and figures:

- The proportion of participants with mild, moderate, or severe VS results by parameter and timepoint will be summarized (Table 51 for the Safety Population and Table 52 for the Safety Subset Population).
- Summary statistics of measurements and change from baseline by parameter and timepoint will be summarized (Table 53 for the Safety Population and Table 54 for the Safety Subset Population).
- Change from baseline at each scheduled timepoint will be visualized using box plots for each parameter (Beginning at Figure 77 and continuing through Figure 86).

All VS measurements, including height, weight, and BMI, will be presented in Listing 17.

In the case of an abnormal VS measurement, measurements may be repeated up to 2 more times, for a maximum of 3 measurements including the initial measurement at each timepoint. The following rules will be used to decide which measurement to include in the analysis if more than one replicate was entered into the clinical database. VS replicates not used in the analysis will still be included in listings.

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 first replicate will be used if it has a severity greater or equal to the second replicate, or the second replicate will be used if the second replicate has a higher severity than the first replicate.
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 first replicate will be used if it has a severity greater or equal to the third replicate, or the third replicate will be used if the third replicate has a higher severity than the first replicate.

Abnormal PE findings will be presented in Listing 18.

9.8. 12-Lead Standard Electrocardiogram

Toxicity grading criteria for 12-lead standard ECG parameters (QTcF and PR Intervals) can be found in Table 6. Unscheduled 12-lead ECG measurements will be listed but excluded from tabular and graphical summaries, except when calculating the maximum severity post-baseline. When ECG measurements are conducted in triplicate, the mean of the triplicate values will be used for analysis.

The following ECG parameters will be presented (in order): PR interval, QRS duration, QT interval, QTcF correction (refer to protocol Section 11.4.6.1 for formula), RR interval, and ventricular rate.

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

- Summary of 12-lead ECG categorical change in overall interpretation from baseline will be presented by timepoint (Table 55 for the Safety Population and Table 56 for the Safety Subset Population).
- Summary of 12-lead ECG categorical change from pre-dose baseline will be presented by timepoint (Table 57 for the Safety Population and Table 58 for the Safety Subset Population).
- The proportion of participants with mild, moderate, or severe 12-lead ECG results will be presented for QTcF Interval and PR Interval by parameter and timepoint (Table 59 for the Safety Population and Table 60 for the Safety Subset Population).
- Summary statistics of measurements and change from pre-dose baseline, including the 90% CI (see equation below), by parameter and timepoint will be summarized (Table 61 for the Safety Population and Table 62 for the Safety Subset Population).
- For ECGs collected on Day 1, summary statistics of change from time-matched baseline, including the 90% CI (see equation below), by parameter and timepoint will be summarized (Table 63 for the Safety Population and Table 64 for the Safety Subset Population).
- A categorical summary of QTcF Interval (Table 65 for the Safety Population and Table 66 for the Safety Subset Population) and PR interval, QRS duration, and RR interval (Table 67 for the Safety Population and Table 68 for the Safety Subset Population) will be presented by timepoint.
- Change from pre-dose baseline at each scheduled timepoint will be visualized using box plots for each parameter (Beginning at Figure 87 and continuing through Figure 98).

Due to the small sample size (N < 30) and unknown population variance, the 90% CI for the change from baseline will be calculated as follows:

$$\left(\bar{x} - t_{n-1,1-\alpha/2} \times \sqrt{\frac{\sigma^2}{n}},\quad \bar{x} + t_{n-1,1-\alpha/2} \times \sqrt{\frac{\sigma^2}{n}}\right)$$

Where,

$\bar{x}$ is the mean change from baseline

$t_{n-1,1-\alpha/2}$ is the t-value with n-1 degrees of freedom at a confidence level of α (for 90% CI, α = 0.1)

σ is the standard deviation

n is the number of observations

All individual ECG measurements will be presented in Listing 19. Overall interpretations and changes from baseline will be presented in Listing 20.

9.9. Otoacoustic Testing

Toxicity grading criteria for pure-tone audiometry testing can be found in Table 3. Unscheduled otoacoustic testing will be listed but excluded from tabular and graphical summaries, except when calculating the maximum severity post-baseline.

Otoacoustic test results, including ear otoscopy, pure-tone audiometry, and DPOAEs, will be summarized in tables and figures:

- For ear otoscopy, summary of change in results from baseline will be presented by ear and timepoint (Table 69 for the Safety Population and Table 70 for the Safety Subset Population).
- For pure-tone audiometry:
  - The proportion of participants with mild, moderate, or severe pure-tone audiology test results will be presented by timepoint (Table 71 for the Safety Population and Table 72 for the Safety Subset Population).
  - Summary statistics of measurements and change from baseline by timepoint, frequency, and ear will be summarized (Table 73 for the Safety Population and Table 74 for the Safety Subset Population).
  - Change from baseline at each timepoint and ear will be visualized using line plots with standard error bars for each frequency (Figure 99 and Figure 100 for frequencies 0.5, 1.0, 2.0, 4.0, 6.0 and 8.0 kHz; Figure 101 and Figure 102 for frequencies 9.0, 10.0, 11.0, 12.5, 14.5, 16.0,18.0, and 20.0 kHz for the Safety Population and Safety Subset Population, respectively).
- For DPOAEs, including DPOAE, signal-to-noise ratio (SNR), and overall result:
  - Summary statistics of change from baseline by timepoint, frequency, and ear will be summarized (Table 75 and Table 76 for DPOAEs and Table 79 and Table 80 for SNR for the Safety Population and Safety Subset Population, respectively).
  - Summary of categorical DPAOE test results (present/absent) by timepoint, frequency, and ear will be presented (Table 77 for the Safety Population and Table 78 for the Safety Subset Population).
  - Change from baseline at each frequency and ear will be visualized using line plots with standard error bars for each scheduled timepoint and result (Figure 103 and Figure 104 for DPOAE results and Figure 105 and Figure 106 for SNR results for the Safety Population and Safety Subset Population, Respectively).

All otoacoustic testing results will be listed: ear otoscopy test results will be presented in Listing 21; pure-tone audiometry test results will be presented in Listing 22; and DPOAE test results will be presented in

Listing 23. Additionally, screening Valsalva, tympanometry, and stapedial reflex test results will be presented in Listing 24, Listing 25, and Listing 26, respectively.

10. PHARMACOKINETICS

10.1. Graphical and Tabular Summaries of Pharmacokinetic Profiles

The PK Subset Population will be used when summarizing plasma and lung PK concentrations. Participants enrolled who did not complete dosing will not be included in the PK analysis, but the participant will have concentrations and PK parameters included in listings.

For plasma concentrations, results below the limit of quantification (BQL) collected before the first measurable plasma concentration above the lower limit of quantification (LLOQ) will be treated as zero (0) for plotting, all calculations (including noncompartmental analysis [NCA]) and summary statistics. All other plasma BQL values observed after the first measurable concentration will be treated as missing. Similarly, all BQL lung PK concentrations 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 lung samples outside of the protocol defined time window for the timepoint will not result in exclusion of the sample results from NCA. Plasma or lung samples collected out of window will be evaluated on a case-by-case basis. Results from PK 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 samples that were collected outside twice the size of the protocol required windows and are as follows: ±10 min of the nominal timepoint for the 0.5 h, 1, h, and 2 h post-dose samples; ±20 min for the 4 h post-dose sample; ±30 min for the 8 h and 16 h post-dose samples; and ±2 h for the 24 h and 36 post-dose samples on Day 2 and 48 h and 60 h post-dose samples on Day 3.

If the exact time of 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 exact collection time is not known, 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.

In the case the bronchoscopy with BAL procedure is delayed, an additional plasma PK sample will be collected within 5 minutes of the last BAL sample. These samples will only be included in the lung PK analysis when calculating the lung PK/plasma PK concentration ratios and PK parameters, and not included in the NCA.

The bioanalytical lab will report concentrations of total and free apramycin in plasma, total apramycin in BAL SUP and BAL AC, and concentrations of urea in plasma in units of µg/mL. All concentrations will be reported in the same units in the CSR. Apramycin concentrations in BAL ELF and BAL AM will be calculated as described in Section 3.3.2. The ratio of free plasma concentration in apramycin to total plasma concentration in apramycin will be calculated to determine the free portion (fu, % unbound) of plasma apramycin. Drug concentrations will be summarized and listed by participant:

- Participant level concentrations of total apramycin and free apramycin in plasma (Listing 35 and Listing 36, respectively).
- Participant level free portion (fu, % unbound) of plasma apramycin (Listing 37).
- Participant level parameters used to derive apramycin concentrations in ELF (see Section 3.3.2.1) and calculated apramycin concentrations in ELF (Listing 39).

- Participant level parameters used to derive apramycin concentrations in AM (see Section 3.3.2.2) and calculated apramycin concentrations in AM (Listing 40).
- Participant level ELF and AM to total apramycin in plasma concentration ratios (Listing 41).
- Participant level BAL cell counts (Listing 42).

Participant level PK parameter concentration listings will include separate columns for concentrations reported by the lab and concentrations used for analysis. The lab reported concentrations may also include codes such as "BQL" and "QNS" (Quantity Not Sufficient), while the analysis concentrations will contain numeric data only, including imputed values, such as 0 for BQL samples collected prior to the first quantifiable sample. Listings will also indicate the nominal time (i.e., the planned sampling timepoint) and the actual post-dose collection time in hours and will note which samples were collected out of window, substantially out of window, or imputed.

PK plasma concentrations of apramycin will be presented in tables and figures by nominal timepoint:

- Individual concentrations in plasma and summary statistics will be presented tabularly for total apramycin in plasma (Table 83) and free apramycin in plasma (Table 84).
- Summary statistics for the free portion of plasma apramycin (fu, % unbound), calculated as the ratio of free to total apramycin concentrations in plasma (Table 85).
- Linear plots of individual participant concentration-time profiles for total apramycin in plasma (Figure 107).
- Semi-log plots of individual participant concentration-time profiles for total apramycin in plasma (Figure 108).
- Linear plots of mean concentration-time profiles for total apramycin in plasma, with error bars representing ± 1 SD (Figure 109).
- Semi-log plots of mean concentration-time profiles for total apramycin in plasma (Figure 110).

Additionally, lung PK (ELF and AM) apramycin concentrations in plasma will be presented in tables and figures by nominal timepoint. ELF and AM concentrations will be calculated as described in Section 3.3.2. For tables and figures of lung PK concentrations that include plasma concentrations, only the plasma samples collected at the same time as the BAL procedure will be used.

- Summary statistics by BAL sampling timepoint for apramycin in ELF concentrations, total apramycin in plasma concentrations, and the concentration ratio of ELF to plasma concentrations will be presented (Table 87).
- Summary statistics by BAL sampling timepoint for apramycin in AM concentrations, total apramycin in plasma concentrations, and the concentration ratio of AM to plasma concentration will be presented (Table 88).
- Plot of individual total apramycin in plasma, ELF, and AM concentrations at each BAL sampling timepoint (Figure 111).
- Linear plots of GM apramycin concentrations by compartment (total apramycin in plasma, apramycin in ELF, and apramycin in AM) at each BAL sampling timepoint (Figure 112).
- Semi-log plots of GM apramycin concentrations by compartment (total apramycin in plasma, apramycin in ELF, and apramycin in AM) at each BAL sampling timepoint (Figure 113).

- Plot of individual ELF and AM to total apramycin in plasma concentration ratios at each BAL sampling timepoint (Figure 114).
- Plot of GM ELF and AM to total apramycin in plasma concentration ratios at each BAL sampling timepoint (Figure 115).

10.2. Noncompartmental Analysis

PK parameters for plasma and lung PK data will be estimated through NCA using version 8.2 or higher of Phoenix WinNonlin®. Actual post-dose times will be used for the estimation of plasma PK parameters, and nominal time will be used for the estimation lung (ELF and AM) PK parameters. In the case of unknown sample collection times, the imputed time will be included in NCA. Any outliers identified in the PK analysis will be discussed in the analysis report. Outliers will not be excluded from the PK analysis.

Individual plasma PK parameter estimates for total apramycin will be listed (Listing 38). Plasma PK parameters will be summarized in Table 86 for total apramycin. Summary statistics will include mean, SD, min, max, GM, and coefficient of variation as a percent (CV%).

The CV% will be calculated using the method for log-normally distributed data:

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

Where s^2 is the variance of the natural log-transformed data.

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

- Linear Up Log Down calculation method
- Uniform weighting
- IV infusion
- Lambda Z Acceptance Criteria
  - Rsq _adjusted ≥ 0.90
  - Span ≥ 3 half-lives
  - Includes at least 3 timepoint after T_{max}

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

C_{max}

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

T_{max}

Time of maximum concentration (T_{max}) is defined as the time at which the C_{max} occurs. It will be obtained from the **Tmax** parameter calculated by WinNonlin. If there is no measurable C_{max} in the 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) 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 $\geq$ 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 satisfy the Lambda Z Acceptance Criteria described above. Otherwise, the elimination rate constant and all derived parameters (apparent terminal elimination half-life [$t_{½}$], AUC Extrapolated to Infinity [$AUC_{(0-\infty)}$], clearance [CL], and volume of distribution [V_d]) will be treated as missing.

Drug concentration used to calculate K_e will be indicated in Listing 35. This parameter will be obtained from the **Lambda_z** parameter calculated by WinNonlin. K_e will be reported in units of 1/h.

$t_{½}$

The $t_{½}$ 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 $t_{½}$ 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. If the Lambda Z Acceptance Criteria is not met, $t_{½}$ will be treated as missing.

AUC

$AUC_{(0-8)}$ and $AUC_{(0-24)}$ are defined as the areas under the concentration-time curve from dosing (time 0) to 8 h and 24 h post infusion start, respectively. $AUC_{(0-last)}$ is defined as the area under the concentration-time curve from dosing (time 0) to the time of the last measured concentration. $AUC_{(0-8)}$, $AUC_{(0-24)}$, and $AUC_{(0-last)}$ will be estimated using the Linear Up Log Down calculation method and obtained from the **AUClast** parameter calculated by WinNonlin (for $AUC_{(0-8)}$ and $AUC_{(0-24)}$, data will be subset to only include results collected up to and including the 8 h and 24 h post-dose timepoint, respectively, and a separate NCA will be run).

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

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

Where C_{last} is the last measured concentration $\geq$ LLOQ. $AUC_{(0-\infty)}$ will be obtained from the **AUCINF_obs** parameter calculated by WinNonlin®. If the Lambda Z Acceptance Criteria are not met, $AUC_{(0-\infty)}$ will be treated as missing.

$\%AUC_{ex}$ is defined as percentage of $AUC_{(0-\infty)}$ 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 $AUC_{(0-\infty)}$:

$$\%AUC_{ex} = \frac{AUC_{(0-\infty)} - AUC_{(0-last)}}{AUC_{(0-\infty)}},$$

If $\%AUC_{ex}$ is >20% or the Lambda Z Acceptance Criteria is not met, the estimated $AUC_{(0-\infty)}$ will be excluded from statistical summaries of PK parameter estimates and downstream calculations. $\%AUC_{ex}$ will be obtained from the **AUC_%Extrap_obs** parameter calculated by WinNonlin.

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

CL

Clearance (CL) is defined as the volume of plasma completely cleared of drug per unit time and is estimated in trials of an IV-administered drug as the dose divided by the $AUC_{(0-\infty)}$. It will be obtained from the **CL_obs** parameter calculated by WinNonlin. If $\%AUC_{ex}$ is >20% or the Lambda Z Acceptance Criteria are not met, the estimated CL value will be flagged when listed in the report and will be excluded from statistical summaries of parameter estimates and downstream calculations. CL will be reported in units of L/h.

V_d

Volume of distribution (V_d) central is estimated in trials of an IV-administered drug of CL divided by K_e. It will be obtained from the **Vz_obs** parameter calculated in WinNonlin. If $\%AUC_{ex}$ is >20% or the Lambda Z Acceptance Criteria is not met, the estimated V_d value will be flagged when listed in the report and will be excluded from statistical summaries of parameter estimates and downstream calculations. V_d will be reported in units of L/h.

10.2.1. Ratio of Lung PK to Plasma PK

Only plasma samples collected at the same time as the BAL procedure will be used in the calculations of the Lung PK to Plasma PK ratios. The GM concentrations of apramycin in ELF, AM, and plasma from the BAL sampling timepoints will be used to estimate the population average C_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-24)}$, and $AUC_{(0-last)}$. $AUC_{(0-\infty)}$, $AUC_{(0-24)}$, and $AUC_{(0-last)}$ will be estimated using the Linear Up Log Down calculation method. Since the calculated concentrations used at each timepoint will be based on measurements from multiple participants, nominal timepoints will be used when estimating these parameters.

The population estimates of $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, T_{max}, and $t_{½}$ for apramycin in ELF and AM will be presented in Table 89. The population estimates of C_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-24)}$, and $AUC_{(0-last)}$ in plasma, ELF, and AM, as well as the ratios of ELF-to-plasma and AM-to-plasma exposure parameters will be presented in Table 90 for total apramycin.

11. IMMUNOGENICITY

There are no immunogenicity endpoints in this trial.

12. OTHER ANALYSES

No applicable.

13. REPORTING CONVENTIONS

The mean, median, SD, and other statistics will be reported to 1 decimal place greater than the original data. The min and max will use the same number of decimal places as the original data. Proportions will be presented to 2 decimal places; values greater than zero but < 0.01 will be presented as "<1". Percentages will be reported to the nearest whole number; values greater than zero by < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as ">99%".

For PK parameters, AUCs will be reported using 3 significant digits. t½, T_{max}, CL, 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.

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

14. TECHNICAL DETAILS

SAS version 9.4 or above or R version 4.1 or above will be used to generate all tables, figures, and listings. PK parameters will be estimated through NCA using Phoenix® WinNonlin version 8.2 or later.

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

If there are any changes to the planned analysis 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 Appendix 1, Appendix 2 and Appendix 3.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.5.1 Pharmacokinetic and Safety Measurements Assessed and Flow Chart

Table 2: Schedule of Study Procedures

Procedures and Evaluations	Out-patient	In-patient	In-patient	Treatment Period (In-patient)												Follow-up (out-patient)		Early Termination	Unscheduled
	Day -28 to -3	Day -2	Day -1	Day 1								Day 2		Day 3		Day 14 (± 3 days)	Day 30 (±4 days)		
	Screening [1]	Check-in	Baseline	Pre-dose	0 h (dose)	0.5 h (±5 min)	1 h (±5 min)	2 h (±5 min)	4 h (±10 min)	8 h (±15 min)	16 h (±15 min)	24 h (±1 h)	36 h (±1 h)	48 h (±1 h)	60 h (±1 h)				
Informed consent	X																		
Demographics	X																		
Inclusion and exclusion criteria	X [2]																		
Review of Inclusion and exclusion criteria [3]		X [3]	X [3]	X [3]															
Medical history (including family history of auditory loss, renal disorders and sudden death)	X																		
Medical History update [4]		X [4]	X [4]	X [4]															
Prior medication	X	X	X	X															
Concomitant medication					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical examination (PE)	X	X													X	X		X	
Abbreviated PE			X																
Symptom-directed (Focused) PE				X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Vital signs (BP, HR, RR, T) [5]	X	X	X	X		X	X		X		X	X	X	X	X	X		X	X
Height, Weight, BMI calculation	X																		
Weight		X														X		X	
Spirometry (FEV1 and FEV1/FVC)	X																		
12-lead ECG (single recording) [6]	X	X										X	X	X	X	X		X	X
12-lead ECG (triplicate recording)[7]			X [7]	X [7]			X [7]		X [7]		X [7]								
Viral Serology [8]	X																		
Alcohol breathalyzer test	X	X																	
Urine drug toxicity and cotinine	X	X																	
Clinical laboratory tests [9]	X	X		X								X		X		X		X	X
Calculation of glomerular filtration rate (CKD-EPI) [10]	X	X		X								X		X		X		X	
Urinalysis [11]	X	X		X								X		X		X		X	X
Serum β-HCG pregnancy test (females only)	X																		
Serum FSH (post-menopausal females only)	X																		

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

Procedures and Evaluations	Out-patient	In-patient	In-patient	Treatment Period (In-patient)												Follow-up (out-patient)		Early Termination	Unscheduled
	Day -28 to -3	Day -2	Day -1	Day 1								Day 2		Day 3		Day 14 (± 3 days)	Day 30 (±4 days)		
	Screening [1]	Check-in	Baseline	Pre-dose	0 h (dose)	0.5 h (±5 min)	1 h (±5 min)	2 h (±5 min)	4 h (±10 min)	8 h (±15 min)	16 h (±15 min)	24 h (±1 h)	36 h (±1 h)	48 h (±1 h)	60 h (±1 h)				
Urine pregnancy test (females only)		X																	
Blood sample for exploratory biomarkers [12]		X		X										X		X	X	X	
Urine sample for exploratory biomarkers [13]		X		X										X		X	X	X	
Ear otoscopy, Valsalva test, tympanometry, stapedial reflexes	X																		
Ear otoscopy		X												X		X	X	X	
Ear audiometry and otoacoustic tests [14]	X	X												X		X	X	X	
Admission [15]		X																	
Enrollment and Assignment to T cohorts [16]			X																
Discharge [17]															X				
IV administration of apramycin [18]					X-------[21]														
Check of infusion site					X	X	X				X	X	X	X	X	X		X	
Treatment- emergent adverse events (TEAE) and serious AEs (SAEs) [19]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood (plasma) sampling for apramycin PK [20]				X		X	X	X	X	X	X	X	X	X	X			X	
Protein Binding Test [21]						X							X						
Administration of sedative or anesthetic medication [22]						X		X	X	X		X							
Bronchoscopy /BAL for ELF and AM PK) [23]						X		X	X	X		X							
Oxygenation support (TBC)					X	X	X	X	X	X	X	X							
Drinking schedule [24]					X	X	X	X	X	X	X	X	X	X				X	
Counseling [25]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	

[1]. Screening including Ear -Nose-Throat (ENT)/Audiology assessments are planned to be completed in a single Screening Visit. If schedule cannot be accommodated, ENT/Audiology assessments will be completed on a second visit within the screening period.
[2]. Inclusion and exclusion criteria regarding ENT/Audiology assessments to be reviewed by audiologist.
[3]. Review of inclusion and exclusion criteria on Day -2 to determine eligibility for admission; on Day -1, before 12-lead ECG, to determine eligibility for enrollment; and on Day 1 pre-dose to confirm the participant remains eligible for dosing.
[4] Medical history update to include pre-dose events.
[5]. Vital signs include systolic and diastolic BP, heart rate, respiratory rate and oral temperature.
[6]. 12-lead ECG single recording with 10 sec rhythm strip.

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

Procedures and Evaluations	Out-patient	In-patient	In-patient	Treatment Period (In-patient)												Follow-up (out-patient)		Early Termination	Unscheduled
	Day -28 to -3	Day -2	Day -1	Day 1								Day 2		Day 3		Day 14 (± 3 days)	Day 30 (±4 days)		
	Screening [1]	Check-in	Baseline	Pre-dose	0 h (dose)	0.5 h (±5 min)	1 h (±5 min)	2 h (±5 min)	4 h (±10 min)	8 h (±15 min)	16 h (±15 min)	24 h (±1 h)	36 h (±1 h)	48 h (±1 h)	60 h (±1 h)				

[7]. 12-lead ECG: triplicate safety ECGs with 10 sec rhythm strips on Day -1 at the same timepoints as the projected timepoints for ECGs to be recorded on Day 1 within 30 min of dosing, and at 1h (± 5 min), 4h (± 10 min) and 16 h (± 15 min) after starting the apramycin dose). Record ECG before VS and PK draws and, at 4 h post-dosing, before administration of sedation or anesthetic for BAL in cohort T3.
[8]. Hepatitis B surface antigen (HBsAg), hepatitis virus C antibody (HCV) and human immunodeficiency virus (HIV) antibody.

[9]. Clinical laboratory tests under fasting conditions: hematology, coagulation, and clinical chemistry panels and thyroid stimulating hormone (TSH) & free T3/free T4.
[10].The CKD-EPI equation, expressed as a single equation, is GFR = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] _ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κor 1, and max indicates the maximum of Scr/κ or 1 [Levey 2009].(Formula will be used and result will be included in the lab report)
[11]. Urinalysis (UA) by dipstick. If abnormal for blood, protein and glucose, perform microscopic UA. The results of microscopic UA supersede those of UA by dipstick. UA may be postponed in a menstruating female. Abnormal UA in a menstruating female is not graded as a TEAE; the UA should be completed after the end of menstruation.
[12]. Cystatin C in serum.
[13] Kidney-injury molecule 1 (KIM-1) in urine.
[14] Pure-tone audiometry with standard frequencies and distortion product otoacoustic emissions (DPOAEs) AE assessments at screening. Pure-tone audiometry including high frequencies and DPOAEs at check-in (Day -2) and at Days 3, 14 (± 3 days), and 30 (± 4 days), or ET.
[15] Participants will be admitted to the ward on Day -2 after confirmation of eligibility.
[16] Assignment to Lung PK timepoint cohorts (T1 – T5) and Enrollment to be performed before 12-lead ECG on Day -1 - Participants with ECGs on Day-1 and pre-dose on Day 1 with clinically significant abnormalities according to the PI should not be eligible for receiving study drug and should be withdrawn and replaced.
[17] Participant may be discharged from the CTU after Day 3 collection of the 60-h plasma PK sample.
[18].Duration of apramycin infusion is 30 ± 5 min.
[19]. Adverse events from the start of dosing to the end of the trial are considered treatment-emergent adverse events (TEAE) or serious AEs (SAE).
[20]. Blood samples for plasma PK are taken pre-dose, and at 30 (± 5) minutes (end of infusion) and 1 h (±5 min), 2 h (±5 min), 4 h (±10 min), 8 h (±15 min), 16 h (±15 min), 24 h (±1 h), 36 h (±1 h), 48 h (±1 h) and 60 h (±1 h) after start of the infusion - Blood samples for plasma PK are taken at the nominal timepoints. If collection of BAL is delayed, plasma PK will be collected at the nominal timepoint and again 5 min after collection of the last BAL sample. In that case, total apramycin concentration will be measured in both samples, but only the drug concentration in the delayed plasma PK sample will be used to calculate the Lung PK/Plasma PK ratio.
[21]. A protein binding test for the measurement of free apramycin will be performed using aliquots of plasma PK samples collected at 0.5 h (± 5 min) and 36 h (± 1 h) after start of infusion.
[22]. Type of sedation or light anesthesia medication for bronchoscopy/BAL procedure and local anesthetic TBD by the anesthesia and bronchoscopy protocols.
[23]. Each participant is assigned to a single bronchoscopy/BAL procedure. Lung PK samples (for measurement of total apramycin concentration) after initiation of infusion and corresponding cohorts (T) are: (Cohort T1), 30 min (±5 min); (Cohort T2), 2 h (±5 min); (Cohort T3), 4 h (±10 min); (Cohort T4), 8h (± 15 min); and (Cohort T5), 24 h (± 1 h). Lung PK timepoints are aligned with plasma PK samples for measurement of total and free apramycin concentration at 30 min (±5 min), 2 h (±5 min), 4 h (±10 min), 8 h (±15 min) and 24 h (±1 h) after start of apramycin infusion. If BAL is delayed, plasma sample will be collected at the nominal timepoint and again within 5 minutes after the last BAL sample collection. Urea will be measured at the same timepoints in plasma and BAL (ELF) samples.
[24] Participants to be kept hydrated water starting 30 min before until 24 h after start of infusion (document time and volume of water intake).
[25]. Provide counseling at the end of each encounter with the participant. Counsel on use of contraception (males and females), avoidance of pregnancy (women of childbearing potential), avoidance of sperm donation, and avoidance of prohibited medications, illicit drugs, alcohol, nicotine products, vigorous exercise, and exposure to loud noises.

12.2.2 Displays of Adverse Events

Table 3: Clinical Adverse Event Toxicity Grading Scales

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
CARDIOVASCULAR			
Arrhythmia		Asymptomatic or transient signs; no medical intervention required.	Recurrent and/or persistent signs; symptomatic medical intervention required.
Hemorrhage	Estimated blood loss ≤100 mL.	Estimated blood loss >100 mL; no transfusion required.	Blood transfusion required.
RESPIRATORY			
Cough	Transient cough; no treatment required.	Persistent cough; treatment required.	Interferes with daily activities.
Bronchospasm, Acute	Transient bronchospasm; no treatment required; 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			
Hearing Impairment (Adult enrolled on a Monitoring Program (on a 1, 2, 4, 3, 6, and 8 kHz audiogram)	Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear.	Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear.	Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated.
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			
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.

12.2.2 Displays of Adverse Events

Table 3: Clinical Adverse Event Toxicity Grading Scales (*Continued*)

Clinical AEs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
LOCAL IV CATHETER REACTION			
IV site reaction	Not applicable.	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis).	Ulceration or necrosis; severe tissue damage; operative intervention indicated.
SYSTEMIC REACTIONS			
Anaphylaxis **	--	--	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema or angioedema; hypotension.
***Definition*: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness, and may lead to death.*			
Allergic Reaction	Pruritus without rash.	Localized urticaria OR requires oral therapy.	Generalized urticaria OR angioedema OR anaphylaxis OR requires epinephrine
Hypersensitivity (including drug fever)	Transient flushing or rash; temperature 38.0-38.4°C (100.4-101.1°F).	Rash; flushing; urticaria; dyspnea; temperature 38.5 - 38.9°C (101.2 – 102.0°F).	Symptomatic bronchospasm with or without urticaria; parenteral medication indicated; allergy-related edema or angioedema; hypotension; temperature >38.9°C (>102.0°F).
Headache	No interference with activity.	Repeated use of non-narcotic pain reliever for more than 24 h OR some interference with activity.	Significant; any use of narcotic pain reliever OR prevents daily activity OR requires triptans.
Fatigue	No interference with activity.	Some interference with activity.	Significant; prevents daily activity.
Myalgia	No interference with activity.	Some interference with activity.	Significant; prevents daily activity.
SKIN			
Mucocutaneous	Erythema, pruritus.	Diffuse, maculo-papular rash, dry desquamation.	Vesiculation OR moist desquamation OR ulceration.
Pruritus	No or minimal interference with usual social and functional activities.	Greater than minimal interference with usual social and functional activities.	Inability to perform usual social and functional daily activities.

12.2.2 Displays of Adverse Events

Table 3: Clinical Adverse Event Toxicity Grading Scales (*Continued*)

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

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 4: Clinical Laboratory Reference Ranges and Toxicity Grading Scales

Laboratory AEs	Reference Ranges	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Blood, serum, or plasma				
HEMATOLOGY				
Hemoglobin decrease, female – g/dL	11.1 – 15.9	9.6 – 11.0	8.0 – 9.5	<8.0
Hemoglobin decrease, male – g/dL	13.0 – 17.7	11.0 – 12.9	8.5 – 10.9	<8.5
WBC increase – $x10^3$/ µL	3.4 – 10.8	>10.8 – 15.0	>15.0 – 20.0	>20.0
WBC decrease – $x10^3$/ µL	3.4 – 10.8	2.4 – <3.4	1.4 – <2.4	<1.4
Neutrophils decrease – $x10^3$/ µL	1.4 – 7.0	1.0 – <1.4	0.75 – <1.0	<0.75
Lymphocytes decrease – $x10^3$/ µL	0.7 – 3.1	<0.7 –0.4	<0.4 – 0.3	<0.30
Monocytes increase – $x10^3$/ µL	0.1 - 0.9	>0.9 – 2.0	>2.0 – 3.0	>3.0
Eosinophils increase – $x10^3$/ µL	0.0 – 0.4	>0.4 – 0.75	>0.75 – 1.0	>1.0
Basophils increase – $x10^3$/ µL	0.0 – 0.2	>0.2 – 0.5	>0.5 – 0.8	>0.8
Platelets decrease – $x10^3$/ µL	150 - 450	90 – <150	55 – <90	<55
COAGULATION				
PT INR	0.9 – 1.2	>1.2 – 1.8	>1.8 – 2.1	>2.1
Prothrombin Time	9.1 – 12.0	>12.0 – 15.0	>15.0 – 18.6	>18.6
Activated Partial Thromboplastin Time (APTT)	24 - 33	>33.0 – 54.0	>54.0 – 75.0	>75.0
CHEMISTRY				
Sodium decrease – mmol/L	134 – 144	130 - 133	124 –129	<124
Sodium increase – mmol/L	134 – 144	145 - 150	151 – 156	>156
Potassium increase – mmol/L	3.5 – 5.2	5.3 – 6.0	6.1 – 6.5	>6.5
Potassium decrease – mmol/L	3.5 – 5.2	3.4– 3.2	2.5 – 2.9	<2.5
Total Carbon Dioxide (CO_2) increase – mmol/L	20 – 29	30 - 35	36 - 37	>37
Total Carbon Dioxide (CO_2) decrease – mmol/L	20 – 29	17 - 19	14 - 16	<14
Calcium decrease – mg/dL	8.7 – 10.2	7.8 – 8.6	7.0 – 7.7	<7.0
Calcium increase – mg/dL	8.7 – 10.2	10.3 – 11.4	11.5 – 12.5	>12.5
Magnesium decrease – mg/dL	1.6 – 2.3	1.2 – 1.5	1.1 – 0.9	<0.9
Blood urea nitrogen (BUN) increase, 18-39Y - mg/dL	6 – 20	21 - 58	59 – 120	>120
Blood urea nitrogen (BUN) increase, 40-59Y – mg/dL	6 – 24	25 - 58	59 – 120	>120
Glucose decrease, fasting – mg/dL	65 – 99	47 - 64	42 –46	<42
Glucose increase, fasting – mg/dL	65 – 99	100 – 160	161 – 250	>250
Creatinine increase, male – mg/dL	0.76 – 1.27	1.28 – 1.90	1.91 – 3.80	>3.80
Creatinine increase, female – mg/dL	0.57 – 1.00	0.58 – 1.50	1.51 – 3.00	>3.00
Direct bilirubin	0.0 – 0.40	0.41 – 0.70	0.71 – 1.20	>1.20
Total bilirubin (serum) increase – mg/dL (with other LFTs in the normal range)	0.0 – 1.2	1.3 – 2.0	2.1 – 2.5	>2.5
Total bilirubin (serum) increase – mg/dL (accompanied by a >3 x ULN increase in ALT or AST)	0.0 – 1.2	1.3 – 1.7	1.8 – 2.4	>2.4
Total protein decrease – g/dL	6.0 – 8.5	5.1 – 5.9	4.6 – 5.0	<4.6
Albumin, decrease, Male, 18-30Y - g/dL	4.1 – 5.2	4.0 – 3.5	2.0– 2.9	<2.0

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 4: Clinical Laboratory Reference Ranges and Toxicity Grading Scales (*Continued)*

Laboratory AEs	Reference Ranges	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Albumin decrease, Female, 18-30Y - g/dL	3.9 – 5.0	3.8 – 3.5	2.0– 2.9	<2.0
Albumin decrease, Male, 31-50Y – g/dL	4.0 – 5.0	3.9 – 3.5	2.0– 2.9	<2.0
Albumin decrease, Female, 31-50Y – g/dL	3.8 – 4.8	3.7 – 3.5	2.0– 2.9	<2.0
AST increase – U/L	0 – 40	41 – 80	81 – 120	>120
ALT increase, male – U/L	0 – 44	45– 88	89 - 132	>132
ALT increase, female – U/L	0 – 32	33 – 64	65 – 96	>96
Alkaline phosphatase (AP) increase, males 18-20Y – U/L	51 – 125	126 – 250	251 – 375	>375
Alkaline phosphatase (AP) increase, females, 18-20Y – U/L	42 – 106	107 – 250	251 – 375	>375
Alkaline phosphatase (AP) increase, 21-150Y – U/L	44 – 121	122 – 250	251 – 375	>375
Urine				
URINALYSIS by Dipstick				
Protein	negative / trace	1+	2+	>2+
Blood (occult)	negative	1+	2+	>2+
Glucose	negative	1+	2+	>2+
URINE MICROSCOPY				
Red blood cells (RBC) per HPF	0 - 2	6-10	11-50	>50 and/or gross blood
WBC (microscopic) – WBC per HPF	0 - 5	6-10	11-50	>50
Bacteria (microscopic)	none / few	few	moderate	many

Note 1: With the exception of AST, ALT, AP, bilirubin, electrolytes, urine protein, BUN and creatinine, 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 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 increases to Grade 2 or higher.
Note 4: If the dipstick UA is abnormal, a microscopic UA will be performed, and the results will supersede the results of the dipstick UA.
Note 5: If the laboratory reports RBC/HPF as a range and not absolute values, then the range 3-10 will be graded as Grade 1.
Note 6: Menstruating females with a positive dipstick UA or microscopic UA may be retested following cessation of menses.
Note 7: 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.

Table 5: Vital Signs Toxicity Grading Scales

Vital Sign AEs	Reference Ranges	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever - °C Fever - °F	36.1 - 37.2 [1] 97.0 - 99.0 [1]	37.3 - 38.4 99.1 - 101.1	38.5 - 38.9 101.2 - 102.0	>38.9 >102.0
Tachycardia - bpm	50 - 100 [2,3,4,5]	101 - 115	116 - 130	>130 or ventricular dysrhythmias
Bradycardia – bpm		45 - 49	40 - 44	<40
Hypertension (systolic) - mmHg	130/89 [2,3,4,5]	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 [2,3,4,5]	21 - 25	26 - 30	>30

Note 1: No recent hot or cold beverages or smoking. A protocol should select either ^{0}C or ^{0}F for inclusion

Note 2: Assume awake and in supine position for 5 min at rest. For TEAE, measurements at least 3 times with 2 concordant results (See Protocol Section 8.1.6)

Note 3: Abnormal HR and BP on first measurement may be repeated twice more with the participant resting between measurements for at least 5 min (See Protocol Section 8.1.6).

Note 4: Exceptions to screening BP and HR reference range are:

(a) Participants with baseline HR ≥ 45 to 50 bpm may be accepted if they do not have symptomatic bradycardia, including syncope, heart disease, ECG abnormalities, or history of syncope or use of medication

(b) Participants with baseline SBP up to 140 mmHg and DBP up to 90 mmHg may be accepted if they do not have MH of symptomatic hypertension, including paroxysmal hypertension, heart disease, renal disease, CNS disease, visual abnormalities or evidence of peripheral vascular disease, ECG abnormalities, use of medication, use of illicit drugs or FH of hypertension

Note 5: 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.

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 4: Clinical Laboratory Reference Ranges and Toxicity Grading Scales (*Continued)*

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 msec **OR** increase in interval 30-59 msec above baseline	Asymptomatic, QTcF >500 msec **OR** increase in interval ≥60 msec above baseline
PR interval prolonged (msec)	≤210 msec	211-250 msec	>250 msec	Type II 2nd degree AV block **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 Cohort – All Enrolled Participants

[Implementation Note: Only deviations reported during the course of the study will be included.]

Category	Deviation Type	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		All Participants (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Did not meet inclusion criterion												
	Met exclusion criterion												
	ICF not signed prior to study procedures												
	Other												
Treatment administration schedule	Any type												
	Out of window visit												
	Missed visit/visit not conducted												
	Incomplete treatment administration												
	Delayed treatment administration												
	Other												
Follow-up visit schedule	Any type												
	Out of window visit												
	Missed visit/visit not conducted												
	Other												
Protocol procedure/assessment	Any type												
	Incorrect version of ICF signed												
	Blood not collected												

10.2 Protocol Deviations

Table 7: Distribution of Protocol Deviations by Category, Type, and Cohort – All Enrolled Participants (*Continued*)

Category	Deviation Type	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		All Participants (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
	Urine not collected												
	Other specimen not collected												
	Too few aliquots obtained												
	Specimen result not obtained												
	Required procedure not conducted												
	Required procedure done incorrectly												
	Study product temperature excursion												
	Specimen temperature excursion												
	Other												
Treatment administration	Any type												
	Required procedure done incorrectly												
	Study product temperature excursion												
	Other												

Note: N = Number of participants enrolled.

14.1 Description of Study Participants

14.1.1 Disposition of Participants

Table 8: Participant Disposition by Cohort – All Enrolled Participants

Participant Disposition	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%
Screened	--	--	--	--	--	--	--	--	--	--	x	--
Enrolled	x	100	x	100	x	100	x	100	x	100	x	100
Started Infusion	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Infusion[a]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Bronchoscopy with BAL	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed All PK Blood Draws	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed All Plasma Urea Blood Draws	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 14) [a]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Final Study Visit (Study Day 30)[a]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Early Termination[a]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Note: N = Number of participants enrolled.
[a] Refer to Listing 16.2.1 for reasons participants discontinued or terminated early.

Table 9: Treatment Discontinuations or Early Terminations by Reason and Cohort – All Enrolled Participants

[Implementation Note: Only reasons for treatment discontinuation or early termination reported during the study will be included.]

Reason for Treatment Discontinuation or Early Termination	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%
Treatment Discontinuation												
Serious Adverse Event (other than death)	x	100	x	100	x	100	x	100	x	100	x	100
Adverse Event, Other than Serious Adverse Event	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Protocol Deviation	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Withdrawal by Participant	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Withdrawal by Investigator	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
COVID-19 Pandemic	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Termination of Site by Sponsor	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Termination of Study by Sponsor	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Death	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Technical Problems	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Not Eligible at Enrollment	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Became Ineligible After Enrollment	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Failure to Receive the Entire Volume of Study Drug Infusion	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Other	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Early Termination												
Serious Adverse Event (other than death)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Adverse Event, Other than Serious Adverse Event	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Protocol Deviation	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Note: N = Number of participants enrolled.												

Table 10: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Participants Excluded	
		n[a]	%[b]
Inclusion and Exclusion	Number of participants failing any eligibility criterion or eligible but not enrolled	x	100
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Eligible but Not Enrolled	Any reason eligible but not enrolled	x	xx
	[reason 1]	x	xx
	[reason 2]	x	xx
	[reason 3]	x	xx

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

Table 11: Analysis Population Exclusions by Cohort – All Enrolled Participants

Analysis Populations	Reason Participants Excluded	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Safety Population	Did not receive any amount of study product	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Safety Subset Population	Did not receive full amount of study product												
Lung PK Analysis Population	Any Reason												
	Did not receive full amount of study product												
	Did not undergo BAL at assigned sampling timepoint												
	BAL return volume not adequate for analysis												
	Has no measurable drug concentration for ELF or AM												
Plasma PK Analysis Population	Any Reason												
	Did not receive full amount of study product												
	Has no measurable drug concentration in plasma												
PK Analysis Subset Population	Any Reason												
	Excluded from Lung PK Analysis Population												
	Excluded from Plasma PK Analysis Population												
	Has protocol deviations that potentially impact PK												
	Plasma PK and BAL PK data insufficient to estimate any PK parameters												

Note: N = Number of participants enrolled.

14.1.2 Demographic Data by Study Group

Table 12: Summary of Categorical Demographic and Baseline Characteristics by Cohort – All Enrolled Participants

Variable	Characteristic	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Female	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Hispanic or Latino	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Unknown	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Asian	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Native Hawaiian or Other Pacific Islander	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Black or African American	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	White	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Multi-Racial	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Unknown	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Note: N = Number of participants enrolled.

Table 13: Summary of Continuous Demographic and Baseline Characteristics by Cohort – All Enrolled Participants

Variable	Statistic	Cohort 1 (N=X)	Cohort 2 (N=X)	Cohort 3 (N=X)	Cohort 4 (N=X)	Cohort 5 (N=X)	All Participants (N=X)
Age (years)	Mean	x.x	x.x	x.x	x.x	x.x	x.x
	SD	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x
	Min	x	x	x	x	x	x
	Max	x	x	x	x	x	x
Height (cm)	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Min	x.x	x.x	x.x	x.x	x.x	x.x
	Max	x.x	x.x	x.x	x.x	x.x	x.x
Weight (kg)	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Min	x.x	x.x	x.x	x.x	x.x	x.x
	Max	x.x	x.x	x.x	x.x	x.x	x.x
BMI (kg/m^2)	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Min	x.x	x.x	x.x	x.x	x.x	x.x
	Max	x.x	x.x	x.x	x.x	x.x	x.x

Note: N = Number of participants enrolled.

14.1.3 Prior and Concurrent Medical Conditions

Table 14: Summary of Participants with Pre-Existing Medical Conditions by MedDRA System Organ Class and Cohort – All Enrolled Participants

MedDRA System Organ Class	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]												
[SOC 2]												

Notes: N = Number of participants enrolled. n = Number of participants reporting medical history within the specified SOC. A participant is only counted once per SOC.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 15: Overall Summary of Adverse Events – Safety Population

Participants[a] with	All Participants (N=X)	
	n	%
At least one TEAE	x	xx
At least one related TEAE	x	xx
At least one Mild (Grade 1) related TEAE	x	xx
At least one Moderate (Grade 2) related TEAE	x	xx
At least one Severe (Grade 3) related TEAE	x	xx
At least one SAE[b]	x	xx
At least one related, SAE	x	xx
At least one TEAE leading to early termination[c]	x	xx

Note: N = Number of participants in the Safety Population.
[a] Participants are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Section 14.3.2.
[c] As reported on the Adverse Event eCRF.

Table with similar format:

Table 16: Overall Summary of Adverse Events – Safety Subset Population

14.3.1.2 Unsolicited Adverse Events

Table 17: Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class, High Level Group Term, and Preferred Term – Safety Population

[Implementation Note: If there is only 1 PT for an SOC, HLGT, there will be no "Any PT" row. Data will be presented in Alphabetical order by SOC, HLGT, and PT.]

MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	All Participants (N=X)			
			n	%	95% CI[a]	Number of Events
Any SOC	Any HLGT	Any PT	x	xx	xx, xx	x
[SOC 1]	Any HLGT	Any PT				
	[HLGT 1]	Any PT				
		[PT 1]				
		[PT 2]				
[SOC 2]	Any HLGT	Any PT				
	[HLGT 1]	Any PT				
		[PT 1]				
		[PT 2]				

Notes: N = Number of participants in the Safety Population. This table presents number and percentage of participants and the number of events. For the number of participants (n) and corresponding percent (%), a participant is only counted once per Preferred Term.
[a] Exact (Clopper-Pearson) confidence interval was used.

Table with similar format:

Table 18: Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class, High Level Group Term, and Preferred Term – Safety Subset Population

Table 19: Treatment Emergent Adverse Events by MedDRA System Organ Class, High Level Group Term, and Preferred Term, Maximum Severity and Relationship – Safety Population

[Implementation Note: If there is only 1 HLGT for a SOC, there will be no "Any HLGT" row. Similarly, if there is only 1 PT for an HLGT, there will be no "Any PT" row. Data will be presented in alphabetical order by SOC, HLGT, and PT.]

MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Severity	All Participants (N = X)					
				Related		Not Related		Total	
				n	%	n	%	n	%
Any SOC	Any HLGT	Any PT	Any Severity	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx
SOC 1	Any HLGT	Any PT	Any Severity	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx
	[HLGT 1]	Any PT	Any Severity	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx
		[PT 1]	Any Severity	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx

Note: N = Number of participants in the Safety Population. This table presents number and percentage of participants by relationship. For the number of participants (n) and corresponding percent (%), a participant is only counted once per relatedness and Preferred Term.

Table with similar format:

Table 20: Treatment Emergent Adverse Events by MedDRA System Organ Class, High Level Group Term, and Preferred Term, Maximum Severity and Relationship – Safety Subset Population

14.3.2 Listing of Deaths, Other Serious Adverse Events

Table 21: Listing of Serious Adverse Events

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. If the event is ongoing (no stop date), indicate "Ongoing" for the "Duration (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, separated by a colon. Listing should be sorted by Cohort, Participant ID, and AE Number.]

Adverse Event	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Study Day of AE Onset	No. of Days Post Dose the Event Became Serious	Duration (Days)	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
Cohort: , Participant ID: , AE Number:													
Comments:													
Cohort: , Participant ID: , AE Number:													
Comments:													

Table 22: Listing of Non-Serious, Moderate or Severe Treatment Emergent 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 (Days)". In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separated by a colon. Listing should be sorted by Cohort, Participant ID, and AE Number.]

Adverse Event	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Study Day of AE Onset	Duration (Days)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome
Cohort: , Participant ID: , AE Number:											
Comments:											
Cohort: , Participant ID: , AE Number:											
Comments:											

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

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

14.3.4 Abnormal Laboratory Value Listings (by Participant)

Table 23: Listing of Abnormal Laboratory Results – Chemistry

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing includes all abnormal Chemistry results (laboratory results outside of the normal range defined in the protocol). Normal chemistry results for other parameters that occurred on the same visit as the abnormal result will not be listed. Results that are outside the normal range but not mild, moderate, or severe will have "(ONR)" included after the result. Similarly, results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline) will be shown as ONR. Listing should be sorted by Cohort, Participant ID, Timepoint, and Parameter.]

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

Table 24: Listing of Abnormal Laboratory Results – Hematology

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing includes all abnormal Hematology results (laboratory results outside of the normal range defined in the protocol). Normal hematology results for other parameters that occurred on the same visit as the abnormal result will not be listed. Results that are outside the normal range but not mild, moderate, or severe will have "(ONR)" included after the result. Similarly, results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline) will be shown as ONR. Listing should be sorted by Cohort, Participant ID, Timepoint, and Parameter.]

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

Table 25: Listing of Abnormal Laboratory Results – Coagulation

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing includes all abnormal Coagulation results (laboratory results outside of the normal range defined in the protocol). Normal coagulation results for other parameters that occurred on the same visit as the abnormal result will not be listed. Results that are outside the normal range but not mild, moderate, or severe will have "(ONR)" included after the result. Similarly, results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline) will be shown as ONR. Listing should be sorted by Cohort, Participant ID, Timepoint, and Parameter.]

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

Table 26: Listing of Abnormal Laboratory Results - Urinalysis

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing includes all abnormal Urinalysis results (laboratory results outside of the normal range defined in the protocol). Normal urinalysis results for other parameters that occurred on the same visit as the abnormal result will not be listed. Results that are outside the normal range but not mild, moderate, or severe will have "(ONR)" included after the result. Similarly, results that meet grading criteria of mild, moderate, or severe but which are not treatment emergent (not worse than baseline) will be shown as ONR. Listing should be sorted by Cohort, Participant ID, Timepoint, and Parameter.]

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

14.3.5 Displays of Clinical Laboratory Results

14.3.5.1 Chemistry Results

Table 27: Chemistry Abnormal Results by Parameter and Timepoint – Safety Population

Parameter	Timepoint	N	Abnormal, Low		Abnormal, High	
			n	%	n	%
Chemistry – Any Parameter	Baseline	x	x	xx	x	xx
	Day 2, 24 h Post-Dose	x	x	xx	x	xx
	Day 3, 48 h Post-Dose	x	x	xx	x	xx
	Day 14	x	x	xx	x	xx
Sodium	Baseline	x	x	xx	x	xx
	Day 2, 24 h Post-Dose	x	x	xx	x	xx
	Day 3, 48 h Post-Dose	x	x	xx	x	xx
	Day 14	x	x	xx	x	xx
		x	x	xx	x	xx

Notes: N = Number of participants in the Safety Population with the laboratory result assessed at the respective timepoint. Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 28: Chemistry Abnormal Results by Parameter and Timepoint – Safety Subset Population

Table 29: Chemistry Laboratory Toxicity Grade by Parameter, Timepoint, and Severity – Safety Population

[Implementation Note: If there is not at least one mild, moderate, or severe event, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter. Chemistry parameters without grading criteria are not included in this table. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

Parameter	Time Point	N	Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%
Any Chemistry Parameter	Baseline	x	x	xx	x	xx	x	xx
	Maximum Severity Post Baseline	x	x	xx	x	xx	x	xx
	Day 2, 24 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 3, 48 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 14	x	x	xx	x	xx	x	xx
Sodium, Decrease	Baseline	x	x	xx	x	xx	x	xx
	Maximum Severity Post Baseline	x	x	xx	x	xx	x	xx
		x	x	xx	x	xx	x	xx
		x	x	xx	x	xx	x	xx

Notes: N = Number of participants in the Safety Population with the laboratory result assessed at the respective timepoint. Baseline = The most recent measurement prior to start of infusion. The "Maximum Severity Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments.

Table with similar format:

Table 30: Chemistry Laboratory Toxicity Grade by Parameter, Timepoint, and Severity – Safety Subset Population

Table 31: Chemistry Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Population

[Implementation Note: BUN should by summarized overall and separately by age (where specified in the toxicity table, for example, "BUN (mg/dL), Overall"; "BUN (mg/dL), 18-39 years"; "BUN (mg/dL), 40-59 years"). Creatinine and ALT should be summarized overall and separately by sex (for example, "Creatinine (mg/dL), Overall"; "Creatinine (mg/dL), Male"; "Creatinine (mg/dL), Female"). Albumin and AP should be summarized overall and separately by age and sex. Other parameters are not age or sex dependent and will be summarized overall.]

Parameter	Timepoint	N	Measurement				Change from Baseline			
			Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Sodium (mmol/L)	Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Day 2, 24 h Post-Dose	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 3, 48 h Post-Dose	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 14	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Potassium (mmol/L)	Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Day 2, 24 h Post-Dose	x	xx.xx	xx.xx	xx.xx	xx.x, xx.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

Notes: N = Number of participants in the Safety Population with the laboratory result assessed at the respective timepoint. Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 32: Chemistry Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Subset Population

14.3.5.2 Hematology Results

Table 33: Hematology Abnormal Results by Parameter and Timepoint – Safety Population

This table will repeat Table 27 for Hematology Parameters.

Table 34: Hematology Abnormal Results by Parameter and Timepoint – Safety Subset Population

This table will repeat Table 28 for Hematology Parameters.

Table 35: Hematology Laboratory Toxicity Grade by Parameter, Timepoint, and Severity – Safety Population

[Implementation Note: If there is not at least one mild, moderate, or severe event, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

This table will repeat Table 29 for Hematology Parameters.

Table 36: Hematology Laboratory Toxicity Grade by Parameter, Timepoint, and Severity – Safety Subset Population

[Implementation Note: If there is not at least one mild, moderate, or severe event, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

This table will repeat Table 30 for Hematology Parameters.

Table 37: Hematology Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Population

[Implementation Note: Hemoglobin should be summarized overall and separately by sex (where specified in the toxicity table, for example, "Hemoglobin (g/dL), Overall"; "Hemoglobin (g/dL), Male"; "Hemoglobin (g/dL), Female"). Other parameters are not sex dependent and will be summarized overall.]

This table will repeat Table 31 for Hematology Parameters.

Table 38: Hematology Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Subset Population

[Implementation Note: Hemoglobin should be summarized overall and separately by sex (where specified in the toxicity table, for example, "Hemoglobin (g/dL), Overall"; "Hemoglobin (g/dL), Male"; "Hemoglobin (g/dL), Female"). Other parameters are not sex dependent and will be summarized overall.]

This table will repeat Table 32 for Hematology Parameters.

14.3.5.3 Coagulation Results

Table 39: Coagulation Abnormal Results by Parameter and Timepoint – Safety Population

This table will repeat Table 27 for Coagulation Parameters.

Table 40: Coagulation Abnormal Results by Parameter and Timepoint – Safety Subset Population

This table will repeat Table 28 for Coagulation Parameters.

Table 41: Coagulation Laboratory Toxicity Grade by Parameter, Timepoint, and Severity – Safety Population

[Implementation Note: If there is not at least one mild, moderate, or severe event, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

This table will repeat Table 29 for Coagulation Parameters.

Table 42: Coagulation Laboratory Toxicity Grade by Parameter, Timepoint, and Severity – Safety Subset Population

[Implementation Note: If there is not at least one mild, moderate, or severe event, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

This table will repeat Table 30 for Coagulation Parameters.

Table 43: Coagulation Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Population

This table will repeat Table 31 for Coagulation Parameters.

Table 44: Coagulation Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Subset Population

This table will repeat Table 32 for Coagulation Parameters.

14.3.5.4 Urinalysis Results

Table 45: Urinalysis Abnormal Results by Parameter and Timepoint – Safety Population

This table will repeat Table 27 for Urinalysis Parameters.

Table 46: Urinalysis Abnormal Results by Parameter and Timepoint – Safety Subset Population

This table will repeat Table 28 for Urinalysis Parameters.

Table 47: Urinalysis Laboratory Toxicity Grade by Parameter, Timepoint, and Severity – Safety Population

[Implementation Note: If there is not at least one mild, moderate, or severe event, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter. Urinalysis parameters without grading criteria are not included in this table. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

This table will repeat Table 29 for Urinalysis Parameters.

Table 48: Urinalysis Laboratory Toxicity Grade by Parameter, Timepoint, and Severity – Safety Subset Population

[Implementation Note: If there is not at least one mild, moderate, or severe event, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter. Urinalysis parameters without grading criteria are not included in this table. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

This table will repeat Table 30 for Urinalysis Parameters.

14.3.5.5 Kidney Function Biomarker Results

Table 49: Kidney Function Biomarker Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Population

Parameter	Timepoint	N	Measurement				Change from Baseline			
			Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Serum Cystatin C (mg/L)	Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Day 3, 48 h Post-Dose	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 14	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 30	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Urinary KIM-1 (ng/mL)	Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Day 3, 48 h Post-Dose	x	xx.xx	xx.xx	xx.xx	xx.x, xx.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
Urinary KIM-1 Normalized (ng/mg creatinine)	Baseline	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

Notes: N = Number of participants in the Safety Population with the laboratory result assessed at the respective timepoint. Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 50: Kidney Function Biomarker Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Subset Population

14.3.6 Displays of Vital Signs

Table 51: Vital Sign Toxicity Grade by Parameter, Timepoint, and Severity – Safety Population

[Implementation Note: If there is not at least one mild, moderate, or severe result with a parameter, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter. Toxicities representing an increase in the laboratory result will be summarized separately from decreases.]

Parameter	Time Point	N	Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%
Any Parameter	Baseline	x	x	xx	x	xx	x	xx
	Maximum Severity Post Baseline	x	x	xx	x	xx	x	xx
	Day 1, 0.5 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 1, 1 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 1, 4 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 1, 16 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 2, 24 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 2, 36 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 3, 48 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 3, 60 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 14	x	x	xx	x	xx	x	xx
Systolic Blood Pressure, Decrease	Baseline	x	x	xx	x	xx	x	xx
	Maximum Severity Post Baseline	x	x	xx	x	xx	x	xx
		x	x	xx	x	xx	x	xx
		x	x	xx	x	xx	x	xx

Notes: N = Number of participants in the Safety Population with the vital sign assessed at the respective timepoint. Baseline = The most recent measurement prior to start of infusion. The "Maximum Severity Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments.

Table with similar format:

Table 52: Vital Sign Toxicity Grade by Parameter, Timepoint, and Severity – Safety Subset Population

Table 53: Vital Sign Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Population

Parameter	Timepoint	N	Measurement				Change from Baseline			
			Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Systolic Blood Pressure (mmHg)	Baseline	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Day 1, 0.5 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 1, 1 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 1, 4 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 1, 16 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 2, 24 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 2, 36 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 3, 48 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 3, 60 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 14	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
Diastolic Blood Pressure (mmHg)	Baseline	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Day 1, 0.5 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
		x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
		x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx

Notes: N = Number of participants in the Safety Population with the vital sign assessed at the respective timepoint. Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 54: Vital Sign Summary Statistics Measurement and Change from Baseline by Parameter and Timepoint – Safety Subset Population

14.3.7 Displays of ECG Measurements

Table 55: ECG Overall Interpretations, Post-Dose Compared to Pre-Dose Baseline by Timepoint – Safety Population

Timepoint	N	Change from Pre-Dose Baseline in ECG Interpretation					
		Normal at Both Times n (%)	Normal to Abnormal, NCS n (%)	Normal to Abnormal, CS n (%)	Abnormal, NCS at Both Times n (%)	Abnormal, NCS to Abnormal, CS n (%)	Abnormal, NCS to Normal n (%)
Day 1, 1 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 1, 16 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 2, 24 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 2, 36 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 3, 48 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 3, 60 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 14	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)

Notes: N = Number of participants in the Safety Population with the ECG measurement assessed at the respective timepoint. Pre-Dose Baseline = The most recent measurement prior to start of infusion. CS = Clinically Significant. NCS = Not Clinically Significant.

Table with similar format:

Table 56: ECG Overall Interpretations, Post-Dose Compared to Pre-Dose Baseline by Timepoint – Safety Subset Population

Table 57: ECG Summary in Change from Pre-Dose Baseline by Timepoint – Safety Population

Timepoint	N	Change from Pre-Dose Baseline		
		No Change from Baseline n (%)	NCS, Change from Baseline n (%)	CS, Change from Baseline n (%)
Day 1, 1 h Post-Dose	x	x (xx)	x (xx)	x (xx)
Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)
Day 1, 16 h Post-Dose	x	x (xx)	x (xx)	x (xx)
Day 2, 24 h Post-Dose	x	x (xx)	x (xx)	x (xx)
Day 2, 36 h Post-Dose	x	x (xx)	x (xx)	x (xx)
Day 3, 48 h Post-Dose	x	x (xx)	x (xx)	x (xx)
Day 3, 60 h Post-Dose	x	x (xx)	x (xx)	x (xx)
Day 14	x	x (xx)	x (xx)	x (xx)

Notes: N = Number of participants in the Safety Population with the ECG measurement assessed at the respective timepoint. Pre-Dose Baseline = The most recent measurement prior to start of infusion. CS = Clinically Significant. NCS = Not Clinically Significant.

Table with similar format:

Table 58: ECG Summary in Change from Pre-Dose Baseline by Timepoint – Safety Subset Population

Table 59: ECG Toxicity Grade by Parameter, Timepoint, and Severity – Safety Population

[Implementation Note: If there is not at least one mild, moderate, or severe result with a parameter, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter. ECG parameters without grading criteria are not included in this table.]

Parameter	Time Point	N	Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%
Any Parameter	Baseline	x	x	xx	x	xx	x	xx
	Maximum Severity Post Baseline	x	x	xx	x	xx	x	xx
	Day 1, 1 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 1, 4 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 1, 16 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 2, 24 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 2, 36 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 3, 48 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 3, 60 h Post-Dose	x	x	xx	x	xx	x	xx
	Day 14	x	x	xx	x	xx	x	xx
QTcF Interval	Baseline	x	x	xx	x	xx	x	xx
	Maximum Severity Post Baseline	x	x	xx	x	xx	x	xx
		x	x	xx	x	xx	x	xx
		x	x	xx	x	xx	x	xx

Notes: N = Number of participants in the Safety Population with the ECG measurement assessed at the respective timepoint. Pre-Dose Baseline = The most recent measurement prior to start of infusion. The "Maximum Severity Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments.

Table with similar format:

Table 60: ECG Toxicity Grade by Parameter, Timepoint, and Severity – Safety Subset Population

Table 61: ECG Measurement and Change from Pre-Dose Baseline by Parameter and Timepoint – Safety Population

Parameter	Timepoint	N	Measurement				Change from Pre-Dose Baseline				
			Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max	90% CI
PR Interval (msec)	Baseline	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-	-
	Day 1, 1 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
	Day 1, 4 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
	Day 1, 16 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
	Day 2, 24 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
	Day 2, 36 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
	Day 3, 48 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
	Day 3, 60 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
	Day 14	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
QRS Duration (msec)	Baseline	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-	-
	Day 1, 1 h Post-Dose	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
		x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
		x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)

Notes: N = Number of participants in the Safety Population with the ECG measurement assessed at the respective timepoint. Pre-Dose Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 62: ECG Measurement and Change from Pre-Dose Baseline by Parameter and Timepoint – Safety Subset Population

Table 63: ECG Change from Time-Matched Baseline by Parameter and Timepoint – Safety Population

Parameter	Timepoint	Study Day	N	Measurement				Change from Time-Matched Baseline				
				Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max	90% CI
PR Interval (msec)	1 h Post-Dose	Baseline	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-	-
		Day 1	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
	4 h Post-Dose	Baseline	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-	-
		Day 1	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
	16 h Post-Dose	Baseline	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-	-
		Day 1	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
QRS Duration (msec)	1 h Post-Dose	Baseline	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-	-
		Day 1	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)
			x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx	(xx.x, xx.x)

Notes: N = Number of participants in the Safety Population with the ECG measurement assessed at the respective timepoint. Time-Matched Baseline = The measurements recorded on Day -1.

Table with similar format:

Table 64: ECG Change from Time-Matched Baseline by Parameter and Timepoint – Safety Subset Population

Table 65: Categorical Summary of QTcF Interval by Timepoint – Safety Population

Timepoint	N	QTcF Category				
		QTcF >450 - 480 msec n (%)	QTcF >480 - 500 msec n (%)	QTcF >500 msec n (%)	QTcF increase ≥30 – 59 msec from baseline n (%)	QTcF increase ≥60 msec from baseline n (%)
Day 1, 1 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 1, 16 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 2, 24 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 2, 36 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 3, 48 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 3, 60 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Day 14	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)

Notes: N = Number of participants in the Safety Population with the ECG measurement assessed at the respective timepoint. n = Number of participants who experienced the event. A participant may be counted in more than one category. Pre-Dose Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 66: Categorical Summary of QTcF Interval by Timepoint – Safety Subset Population

Table 67: Categorical Summary of PR Interval, QRS Duration, and RR Interval by Timepoint – Safety Population

Timepoint	N	PR Interval, QRS Duration, and RR Interval Category			
		PR change from baseline >25% increase resulting in PR >200 msec n (%)	QRS change from baseline >25% increase resulting in QRS >120 msec n (%)	HR change from baseline >25% decrease resulting in HR <50 bpm n (%)	HR change from baseline >25% increase resulting in HR >100 bpm n (%)
Day 1, 1 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)
Day 1, 4 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)
Day 1, 16 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)
Day 2, 24 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)
Day 2, 36 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)
Day 3, 48 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)
Day 3, 60 h Post-Dose	x	x (xx)	x (xx)	x (xx)	x (xx)
Day 14	x	x (xx)	x (xx)	x (xx)	x (xx)

Notes: N = Number of participants in the Safety Population with ECG measurements assessed at the respective timepoint. n = Number of participants who experienced the event. Participants may be counted in more than one category. Pre-Dose Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 68: Categorical Summary of PR Interval, QRS Duration, and RR Interval by Timepoint – Safety Subset Population

14.3.8 Displays of Audiology Results

Table 69: Ear Otoscopy Result, Post-Dose Compared to Baseline by Timepoint and Ear – Safety Population

[Implementation Note: If there are no problems at baseline (blockage of wax or foreign body or any problem other than wax or foreign body), only keep the "No Apparent Problem" rows.]

Ear	Time Point	Baseline Result	N	Post-Baseline Result					
				No Apparent Problem		Blockage of Wax or Foreign Body		Any Problem Other than Wax or Foreign Body	
				n	%	n	%	n	%
Right	Day 3	No Apparent Problem	x	x	xx	x	xx	x	xx
		Blockage of Wax or Foreign Body	x	x	xx	x	xx	x	xx
		Any Problem Other than Wax or Foreign Body	x	x	xx	x	xx	x	xx
	Day 14	No Apparent Problem	x	x	xx	x	xx	x	xx
		Blockage of Wax or Foreign Body	x	x	xx	x	xx	x	xx
		Any Problem Other than Wax or Foreign Body	x	x	xx	x	xx	x	xx
	Day 30	No Apparent Problem	x	x	xx	x	xx	x	xx
			x	x	xx	x	xx	x	xx
Left	Day 3	No Apparent Problem	x	x	xx	x	xx	x	xx
			x	x	xx	x	xx	x	xx
	Day 14	No Apparent Problem	x	x	xx	x	xx	x	xx
			x	x	xx	x	xx	x	xx
	Day 30	No Apparent Problem	x	x	xx	x	xx	x	xx
			x	x	xx	x	xx	x	xx

Notes: N = Number of participants in the Safety Population with ear otoscopy results at the respective timepoint. Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 70: Ear Otoscopy Result, Post-Dose Compared to Baseline by Timepoint and Ear – Safety Subset Population

Table 71: Pure-Tone Audiometry Toxicity Grade by Timepoint and Severity – Safety Population

[Implementation Note: If there is not at least one mild, moderate, or severe result, then only the "Baseline" and "Maximum Severity Post Baseline" rows will be shown for that parameter.]

Time Point	N	Any Graded Event		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
		n	%	n	%	n	%	n	%
Baseline	x	x	xx	x	xx	x	xx	x	xx
Maximum Severity Post Baseline	x	x	xx	x	xx	x	xx	x	xx
Day 3	x	x	xx	x	xx	x	xx	x	xx
Day 14	x	x	xx	x	xx	x	xx	x	xx
Day 30	x	x	xx	x	xx	x	xx	x	xx

Notes: N = Number of participants in the Safety Population with pure-tone audiometry assessed at the respective timepoint. Baseline = The most recent measurement prior to start of infusion. The "Maximum Severity Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments.

Table with similar format:

Table 72: Pure-Tone Audiometry Toxicity Grade by Timepoint and Severity – Safety Subset Population

Table 73: Pure-Tone Audiometry Threshold Measurement and Change from Baseline by Timepoint, Frequency, and Ear – Safety Population

Ear	Timepoint	Frequency (kHz)	N	Measurement (dB)				Change from Baseline (dB)			
				Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Right	Baseline	0.5	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		1.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		2.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		4.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		6.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		8.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		9.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		10.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		11.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		12.5	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		14.5	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		16.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		18.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		20.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Day 3	0.5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
		1.0	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 14	0.5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
			x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 30	0.5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
			x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
Left	Baseline	0.5	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
			x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-

Notes: N = Number of participants in the Safety Population with the pure-tone audiometry assessed at the respective timepoint and frequency. Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 74: Pure-Tone Audiometry Threshold Measurement and Change from Baseline by Timepoint, Frequency, and Ear – Safety Subset Population

Table 75: DPOAE Measurement and Change from Baseline by Timepoint, Frequency, and Ear – Safety Population

Ear	Timepoint	Frequency (kHz)	N	Measurement (dB)				Change from Baseline (dB)			
				Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Right	Baseline	1.5	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		2.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		3.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		4.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		6.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Day 3	1.5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
			x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 14	1.5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
			x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 30	1.5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
			x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
Left	Baseline	1.5	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
			x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-

Notes: N = Number of participants in the Safety Population with the DPAOEs assessed at the respective timepoint and frequency. Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 76: DPOAE Measurement and Change from Baseline by Timepoint, Frequency, and Ear – Safety Subset Population

Table 77: Summary of DPOAE Results by Timepoint, Frequency, and Ear – Safety Population

Ear	Timepoint	Frequency (kHz)	N	DPOAE Result			
				Present		Absent	
				n	%	n	%
Right	Baseline	1.5	x	x	xx	x	xx
		2.0	x	x	xx	x	xx
		3.0	x	x	xx	x	xx
		4.0	x	x	xx	x	xx
		6.0	x	x	xx	x	xx
	Day 3	1.5	x	x	xx	x	xx
			x	x	xx	x	xx
	Day 14	1.5	x	x	xx	x	xx
			x	x	xx	x	xx
	Day 30	1.5	x	x	xx	x	xx
			x	x	xx	x	xx
Left	Baseline	1,5	x	x	xx	x	xx
			x	x	xx	x	xx

Notes: N = Number of participants in the Safety Subset Population with the DPAOEs assessed at the respective timepoint and frequency.
Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 78: Summary of DPOAE Results by Timepoint, Frequency, and Ear – Safety Subset Population

Table 79: SNR Change from Baseline by Timepoint, Frequency, and Ear – Safety Population

Ear	Timepoint	Frequency (kHz)	N	Measurement				Change from Baseline (dB)			
				Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Right	Baseline	1.5	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		2.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		3.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		4.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		6.0	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Day 3	1.5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
			x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 14	1.5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
			x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Day 30	1.5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
			x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
Left	Baseline	1.5	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
			x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-

Notes: N = Number of participants in the Safety Population with the DPAOEs assessed at the respective timepoint and frequency. Baseline = The most recent measurement prior to start of infusion.

Table with similar format:

Table 80: SNR Change from Baseline by Timepoint, Frequency, and Ear – Safety Subset Population

14.4 Summary of Concomitant Medications

Table 81: Number and Percentage of Participants with Prior Medications by WHO Drug Classification and Cohort – Safety Population

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

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		All Participants (N=X)	
		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
[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]												

Notes: 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 82: Number and Percentage of Participants with Concomitant Medications by WHO Drug Classification and Cohort – Safety Population

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

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		All Participants (N=X)	
		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
[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]												

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

14.2 Pharmacokinetics Data

Table 83: Total Apramycin Concentrations in Plasma

[Implementation Note: Mark concentrations collected out of window with an asterisk (*) next to the concentration and include a footnote: "Samples collected out of window are noted by an asterisk (*)". Mark concentrations collected substantially out of window with two asterisks (**) next to the concentration and include a footnote: "Samples collected substantially out of window are noted by two asterisks (**)". Mark imputed concentration times with three asterisks (***) next to the concentration and include a footnote: "Samples with imputed collection times are noted by three asterisks (***)".]

	Nominal Time[a] (h)										
Participant ID	**0**	**0.5**	**1**	**2**	**4**	**8**	**16**	**24**	**36**	**48**	**60**
PH2.00123	x	x	x	x	x	x	x	x	x	x	x
PH2.00124	x	x	x	x	x	x	x	x	x	x	x
PH2.00125	x	x	x	x	x	x	x	x	x	x	x
Statistics	x	x	x	x	x	x	x	x	x	x	x
N[b]	x	x	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x	x	x
SD	x	x	x	x	x	x	x	x	x	x	x
GM	x	x	x	x	x	x	x	x	x	x	x
CV%	x	x	x	x	x	x	x	x	x	x	x
Min	x	x	x	x	x	x	x	x	x	x	x
Max	x	x	x	x	x	x	x	x	x	x	x

Notes: Concentrations are reported in units of µg/ml.
[Out of window footnotes here, if applicable]
[a] Times are relative to time of dosing.
[b] Number of data points used to compute the summary statistics. For calculation of summary statistics, BQL values were imputed as 0 if the sample was taken before the first measurable PK sample with a concentration above the LLOQ. BQL values were treated as missing otherwise.

Table with Similar Format:

Table 84: Free Apramycin Concentrations in Plasma

Table 85: Summary Statistics for the Free Portion of Plasma Apramycin

Nominal Time[a] (h)	N	Summary Statistics			
		Mean	SD	Median	Min, Max
0.5	x	xx.x	xx.x	xx.x	xx, xx
36	x	xx.x	xx.x	xx.x	xx, xx

Note: N = Number of data points used to calculate the summary statistics. Concentrations are reported in units of µg/mL.
[a] Times are relative to time of dosing.

Table 86: Summary Statistics for Total Apramycin in Plasma PK Parameters

Statistics	C_{max} (µg/mL)	T_{max} (h)	$AUC_{(0-24)}$ (µg *h/mL)	$AUC_{(0-last)}$ (µg*h/mL)	$AUC_{(0-\infty)}$ (µg*h/mL)	K_e (1/h)	$t_{1/2}$ (h)	CL (L/h)	V_d (L)
N	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x
SD	x	x	x	x	x	x	x	x	x
Min	x	x	x	x	x	x	x	x	x
Max	x	x	x	x	x	x	x	x	x
CV%	x	x	x	x	x	x	x	x	x
GM	x	x	x	x	x	x	x	x	X

Note: N = Number of data points used to compute the summary statistics.

Table 87: Summary Statistics for Apramycin in ELF Concentrations and Apramycin in ELF to Total Apramycin in Plasma Concentration Ratios

Statistics	Total Apramycin in Plasma Concentration (µg/mL)					Apramycin in ELF Concentration (µg/mL)					Concentration Ratio Apramycin in ELF to Total Apramycin in Plasma				
	0.5 h	2 h	4 h	8 h	24 h	0.5 h	2 h	4 h	8 h	24 h	0.5 h	2 h	4 h	8 h	24 h
N	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mean	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SD	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Min	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Max	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CV%	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
GM	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: N = Number of data points used to compute the summary statistics.

Tables with Similar Format:

Table 88: Summary Statistics for Apramycin in AM Concentrations and Apramycin in AM to Total Apramycin in Plasma Concentration Ratios

Table 89: Apramycin in ELF and Apramycin in AM Population PK Parameter Estimates

PK Parameter	Assay	N	Population Estimate
C_{max} (µg/mL)	ELF	x	x
	AM	x	x
$AUC_{(0-24)}$ (µg*h/mL)	ELF	x	x
	AM	x	x
$AUC_{(0-last)}$ (µg*h/mL)	ELF	x	x
	AM	x	x
$AUC_{(0-\infty)}$ (µg*h/mL)	ELF	x	x
	AM	x	x
T_{max} (h)	ELF	x	x
	AM	x	x
$t_{1/2}$ (1/h)	ELF	x	x
	AM	x	x
Note: N = Number of participants used to compute the PK parameter.			

Table 90: Apramycin in ELF to Total Apramycin in Plasma and Apramycin in AM to Total Apramycin in Plasma PK Parameter Ratios by PK Parameter

PK Parameter	Assay	N	Population Estimate	Lung PK to Plasma PK Ratio
C_{max} (µg/mL)	Total Plasma	x	x	NA
	ELF	x	x	x
	AM	x	x	x
$AUC_{(0-24)}$ (µg*h/mL)	Total Plasma	x	x	NA
	ELF	x	x	x
	AM	x	x	x
$AUC_{(0-last)}$ (µg*h/mL)	Total Plasma	x	x	NA
	ELF	x	x	x
	AM	x	x	x
$AUC_{(0-\infty)}$ (µg*h/mL)	Total Plasma	x	x	NA
	ELF	x	x	x
	AM	x	x	x

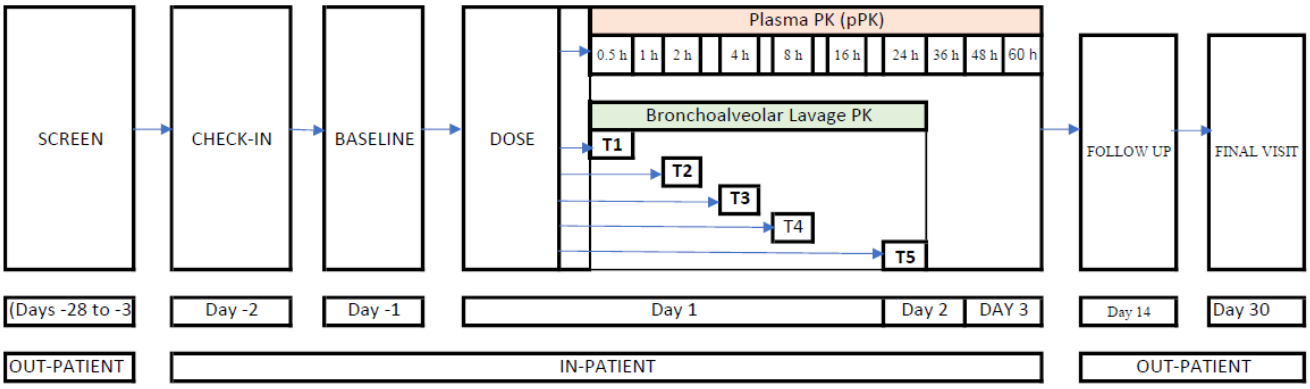
Note: N = Number of participants used to compute the PK parameter.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

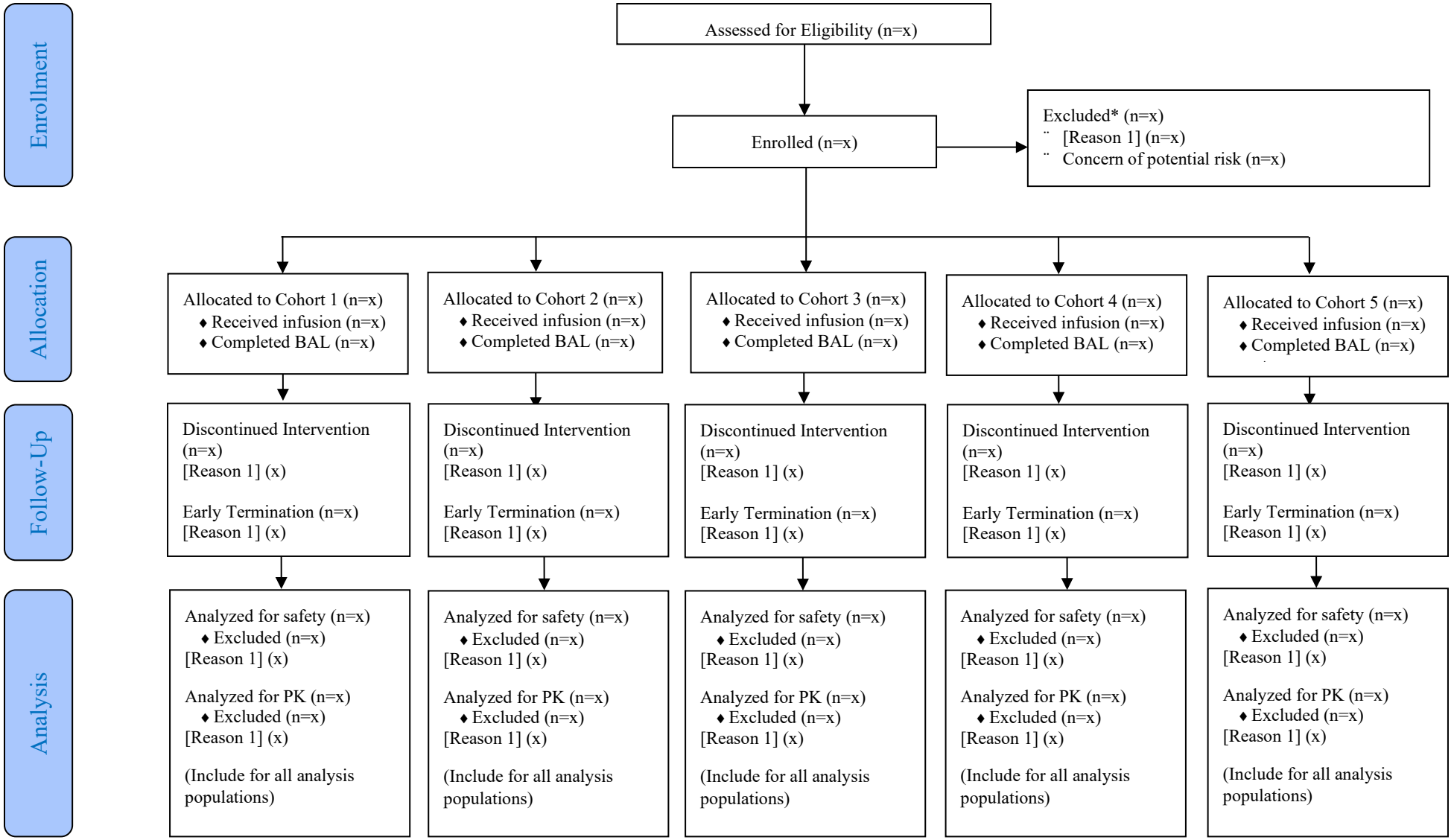
9.1 Overall Study Design and Plan Description

Figure 1: Schematic of Study Design



10.1 Disposition of Participants

Figure 2: CONSORT Flow Diagram



14.3.1.2 Unsolicited Adverse Events

Figure 3: Incidence of Related Adverse Events by MedDRA System Organ Class and Maximum Severity – Safety Population

[Implementation Note: Replace "Group A" with "All Participants (N=X)", where X is the number of participants in the Safety Population. The font and size of text in the figure should be the same as in the report.]

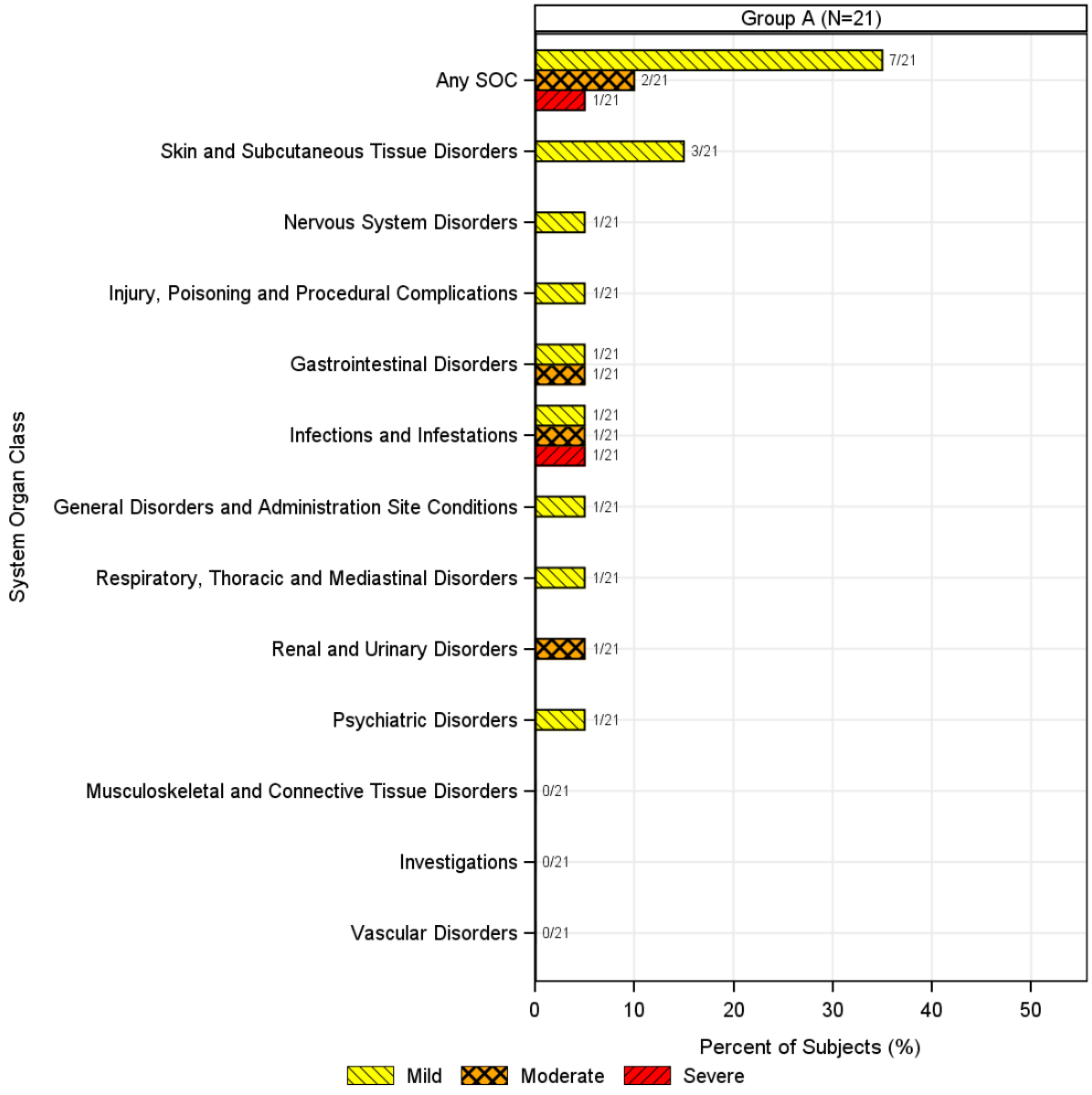


Figure with similar format:

Figure 4: Incidence of Related Adverse Events by MedDRA System Organ Class and Maximum Severity – Safety Subset Population

Figure 5: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity – Safety Population

[Implementation Note: Replace "Group A" with "All Participants (N=X)", where X is the number of participants in the Safety Subset Population. The font and size of text in the figure should be the same as in the report.]

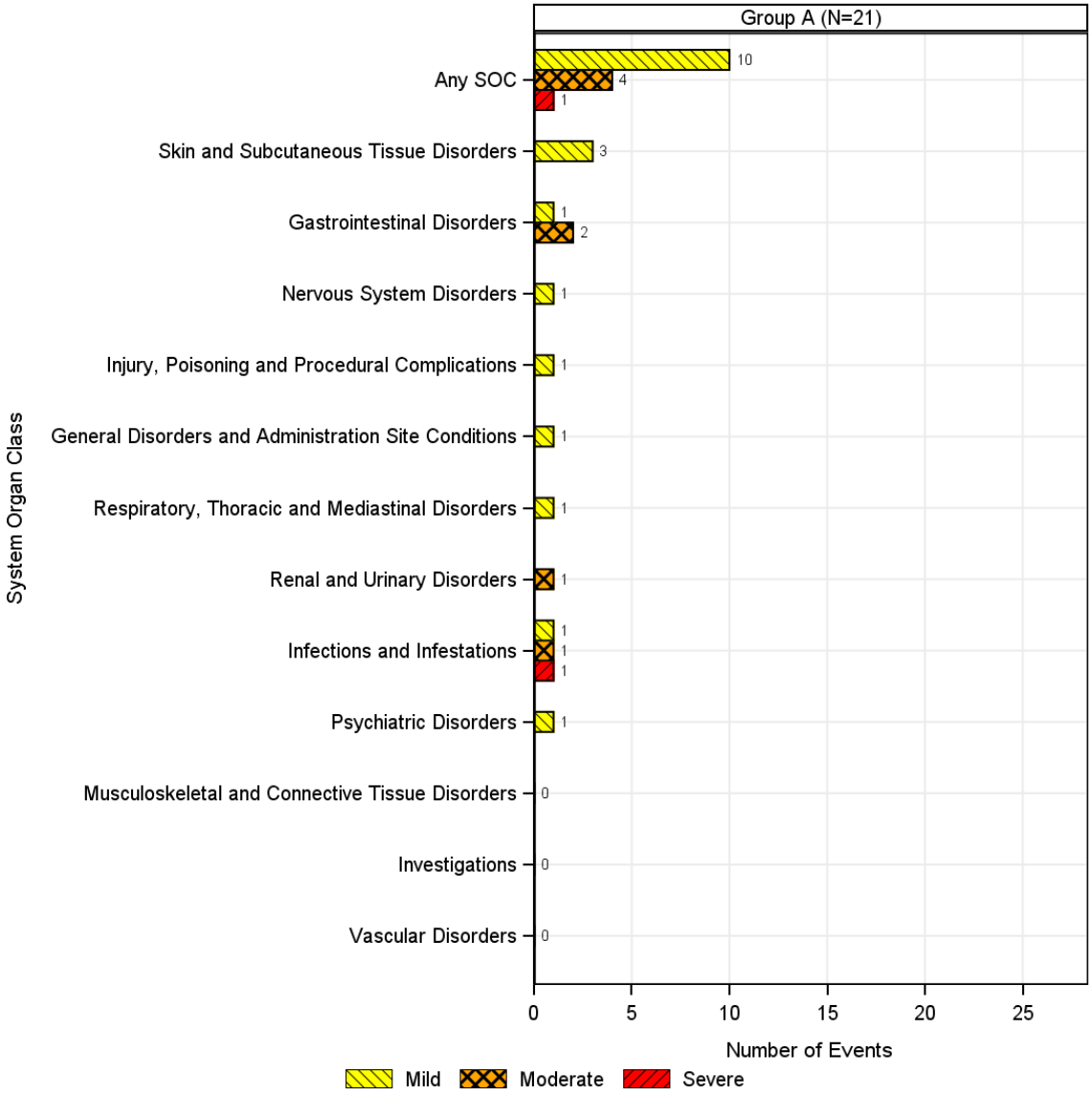


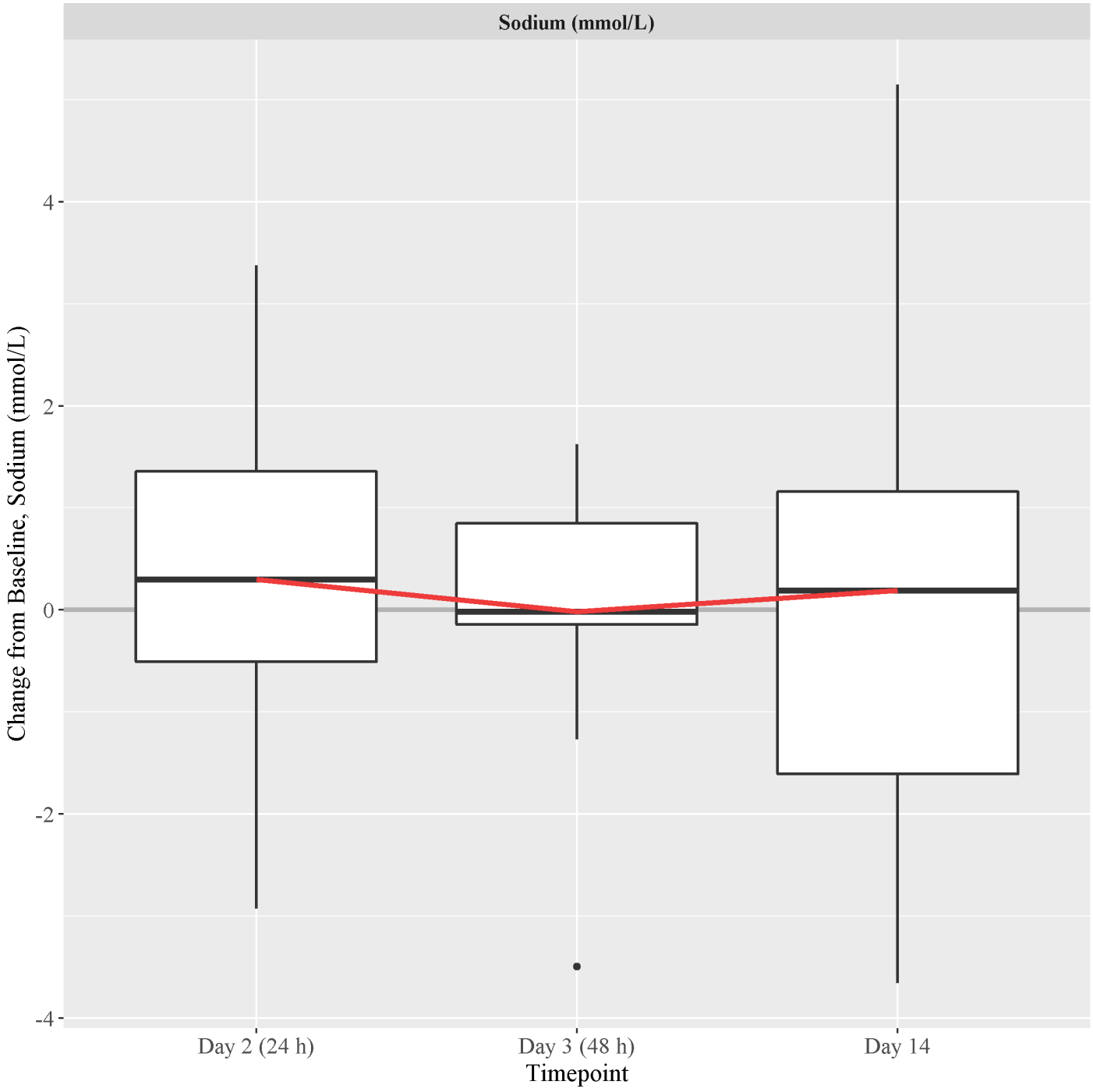
Figure with similar format:

Figure 6: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity – Safety Subset Population

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Figure 7: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Sodium - Safety Population



Figures with Similar Format:

Figure 8: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Sodium – Safety Subset Population

Figure 9: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Potassium – Safety Population

Figure 10: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Potassium – Safety Subset Population

Figure 11: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Glucose – Safety Population

Figure 12: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Glucose – Safety Subset Population

Figure 13: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Blood Urea Nitrogen – Safety Population

Figure 14: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Blood Urea Nitrogen – Safety Subset Population

Figure 15: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Creatinine – Safety Population

Figure 16: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Creatinine – Safety Subset Population

Figure 17: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – eGFR – Safety Population

Figure 18: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – eGFR – Safety Subset Population

Figure 19: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Calcium – Safety Population

Figure 20: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Calcium – Safety Subset Population

Figure 21: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Chloride – Safety Population

Figure 22: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Chloride – Safety Subset Population

Figure 23: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Magnesium – Safety Population

Figure 24: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Magnesium – Safety Subset Population

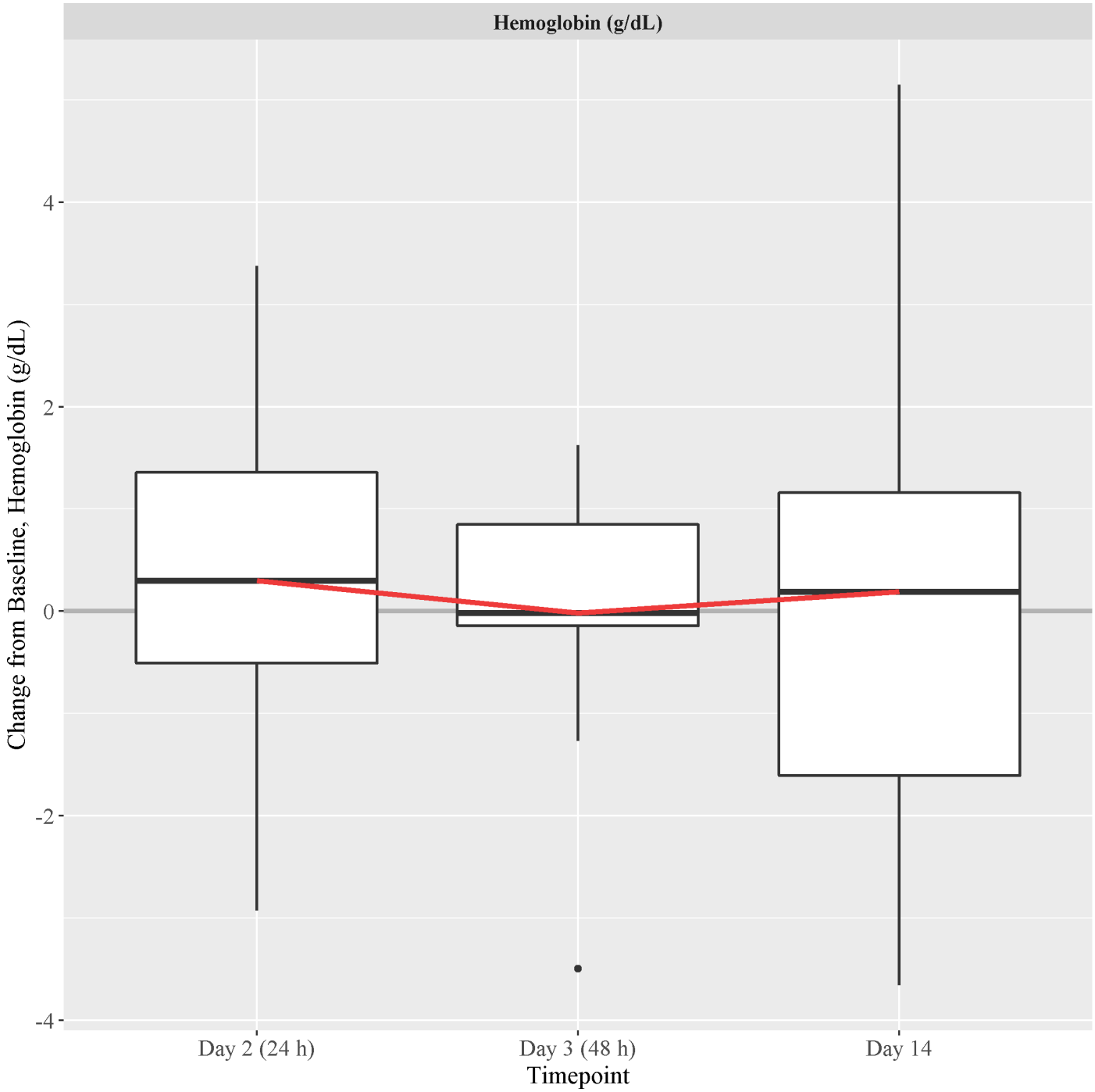
Figure 25: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint –Total Carbon Dioxide – Safety Population

Figure 26: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint –Total Carbon Dioxide – Safety Subset Population

Figure 46: Chemistry Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Free T3 – Safety Subset Population

14.3.5.2 Hematology Results

Figure 47: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Hemoglobin – Safety Population



Figures with Similar Format:

Figure 48: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Hemoglobin – Safety Subset Population

Figure 49: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Hematocrit – Safety Population

Figure 50: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Hematocrit – Safety Subset Population

Figure 51: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Platelets – Safety Population

Figure 52: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Platelets – Safety Subset Population

Figure 53: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – White Blood Cell Count – Safety Population

Figure 54: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – White Blood Cell Count – Safety Subset Population

Figure 55: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Neutrophils – Safety Population

Figure 56: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Neutrophils – Safety Subset Population

Figure 57: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Lymphocytes – Safety Population

Figure 58: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Lymphocytes – Safety Subset Population

Figure 59: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Eosinophils – Safety Population

Figure 60: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Eosinophils – Safety Subset Population

Figure 61: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Basophils – Safety Population

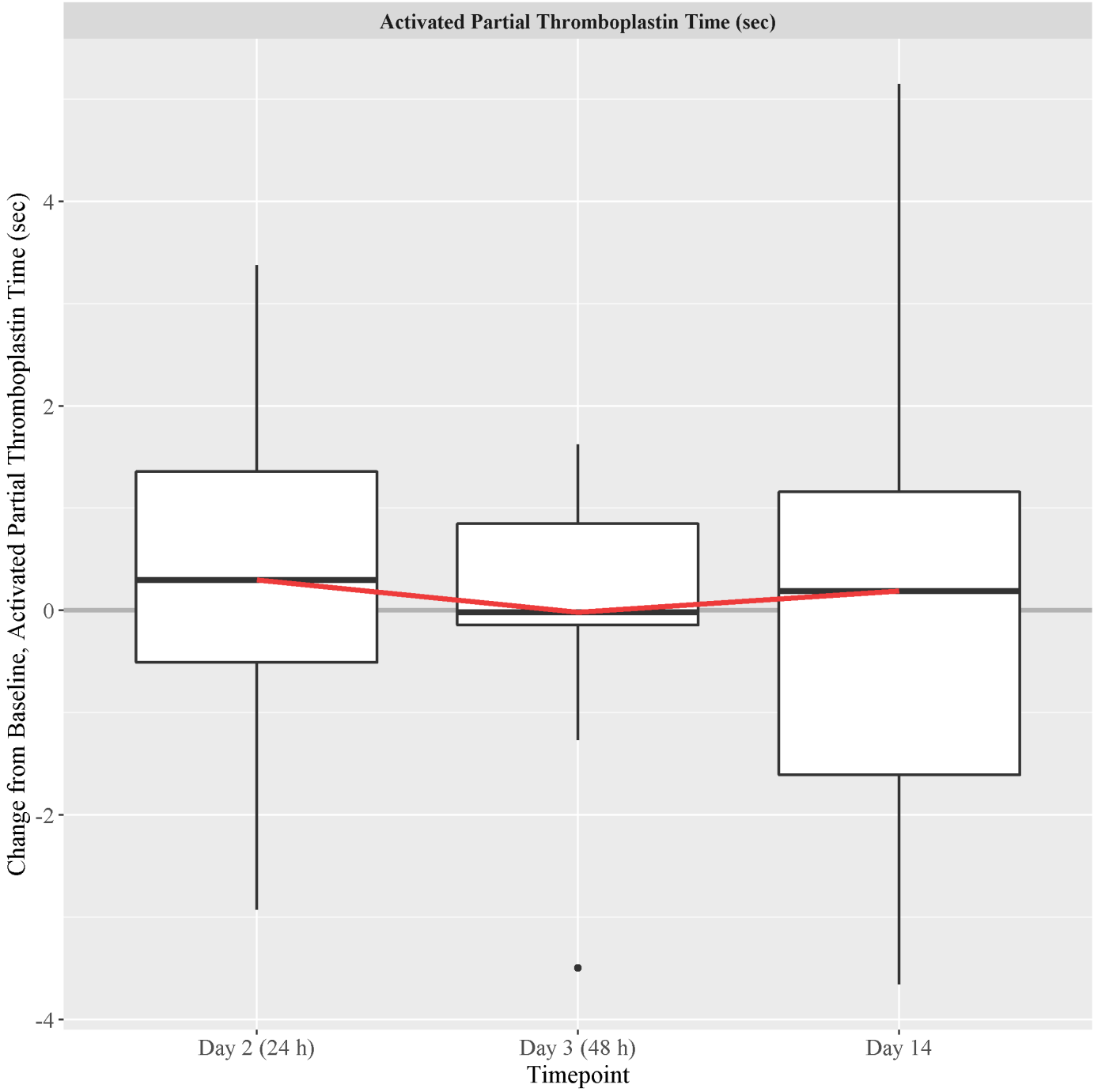
Figure 62: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Basophils – Safety Subset Population

Figure 63: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Monocytes – Safety Population

Figure 64: Hematology Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Monocytes – Safety Subset Population

14.3.5.3 Coagulation Results

Figure 65: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Activated Partial Thromboplastin Time – Safety Population



Figures with Similar Format:

Figure 66: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Activated Partial Thromboplastin Time – Safety Subset Population

Figure 67: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Prothrombin Time – Safety Population

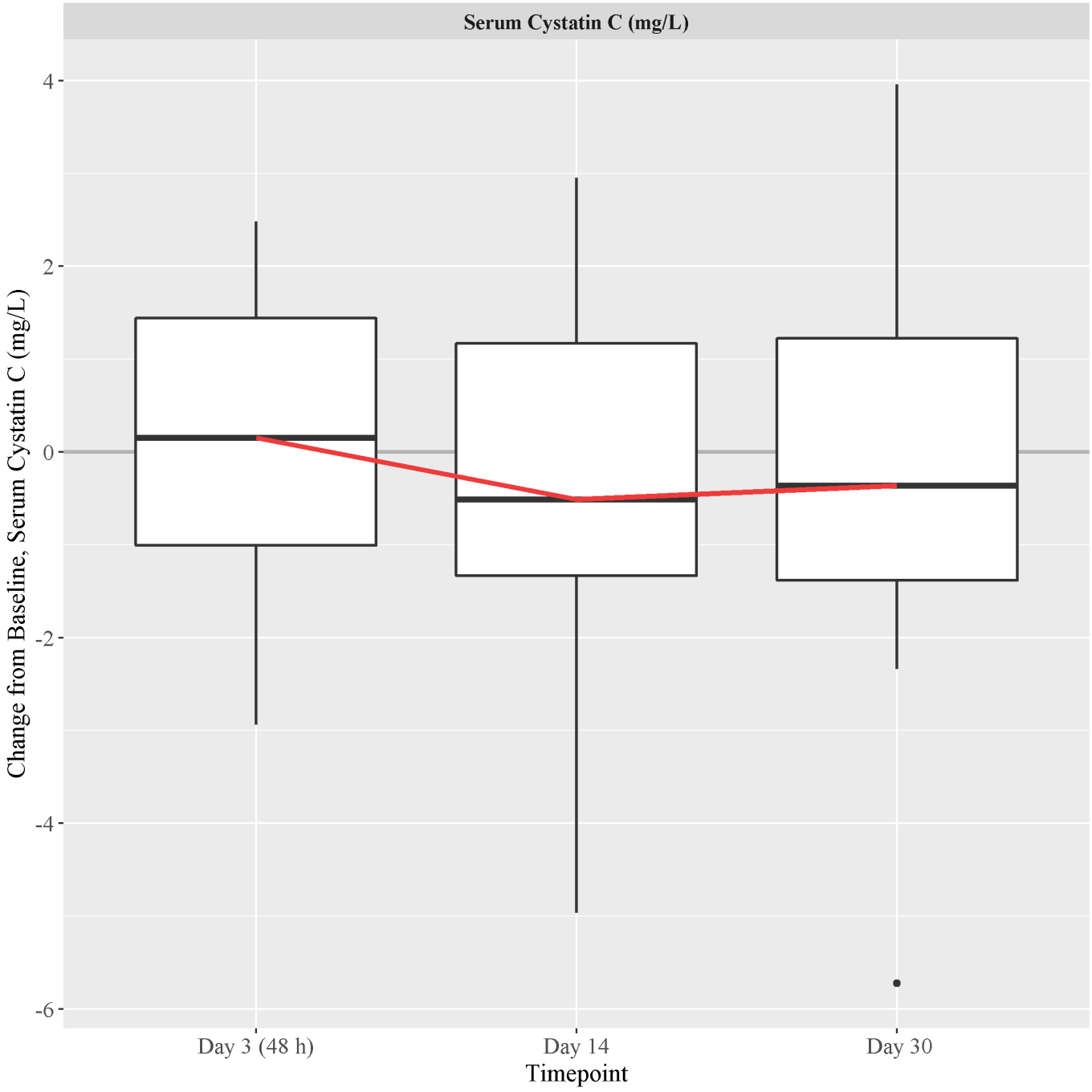
Figure 68: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Prothrombin Time – Safety Subset Population

Figure 69: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – International Normalized Ratio – Safety Population

Figure 70: Coagulation Laboratory Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – International Normalized Ratio – Safety Subset Population

14.3.5.5 Kidney Function Biomarker Results

Figure 71: Kidney Function Biomarker Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Serum Cystatin C – Safety Population



Figures with Similar Format:

Figure 72: Kidney Function Biomarker Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Serum Cystatin C – Safety Subset Population

Figure 73: Kidney Function Biomarker Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Urinary KIM-1 – Safety Population

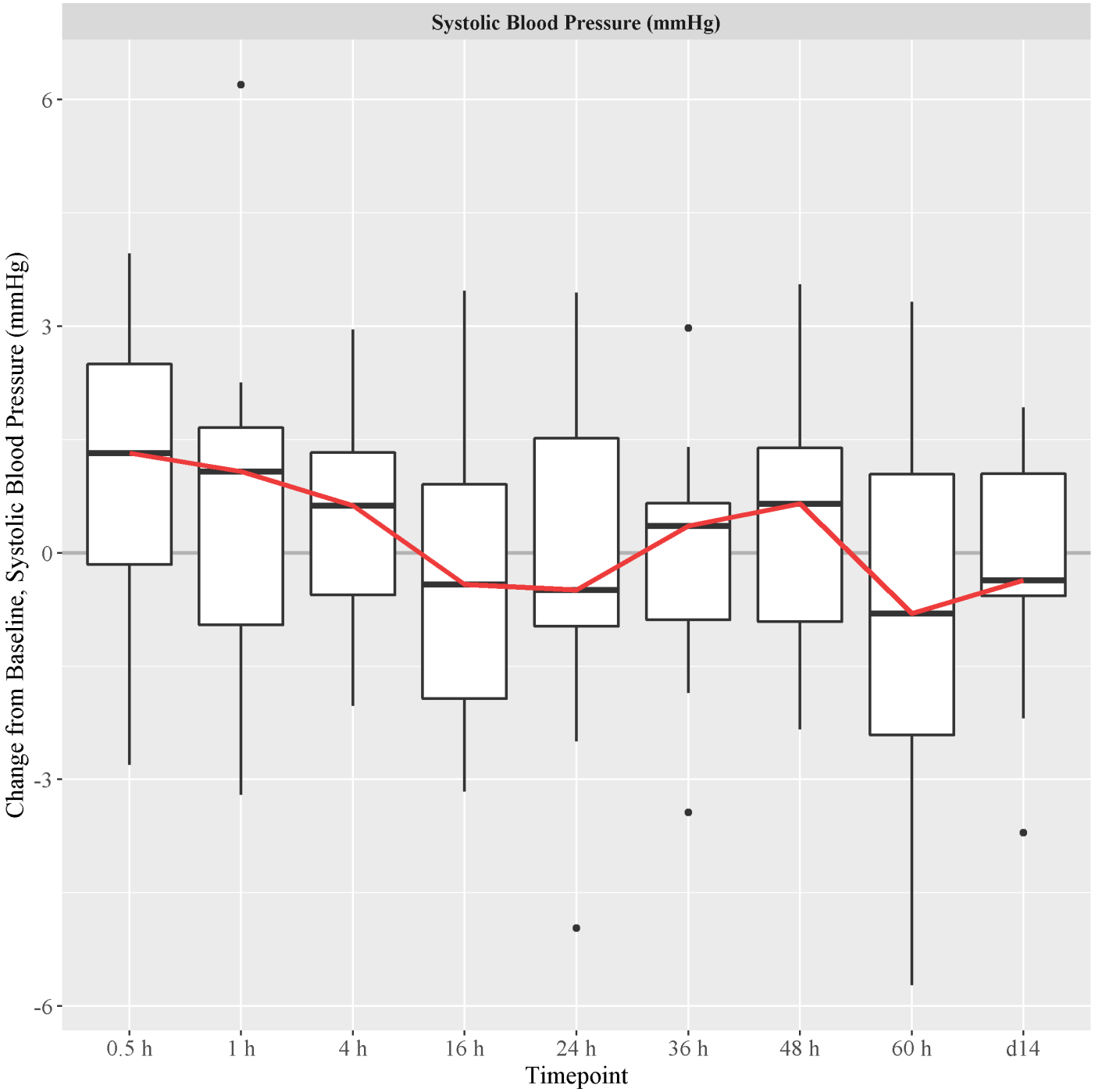
Figure 74: Kidney Function Biomarker Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Urinary KIM-1 – Safety Subset Population

Figure 75: Kidney Function Biomarker Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Urinary KIM-1 Normalized – Safety Population

Figure 76: Kidney Function Biomarker Results by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Urinary KIM-1 Normalized – Safety Subset Population

14.3.6 Displays of Vital Signs

Figure 77: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Systolic Blood Pressure – Safety Population



Figures with Similar Format:

Figure 78: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Systolic Blood Pressure – Safety Subset Population

Figure 79: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Diastolic Blood Pressure – Safety Population

Figure 80: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Diastolic Blood Pressure – Safety Subset Population

Figure 81: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Heart Rate – Safety Population

Figure 82: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Heart Rate – Safety Subset Population

Figure 83: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Respiratory Rate – Safety Population

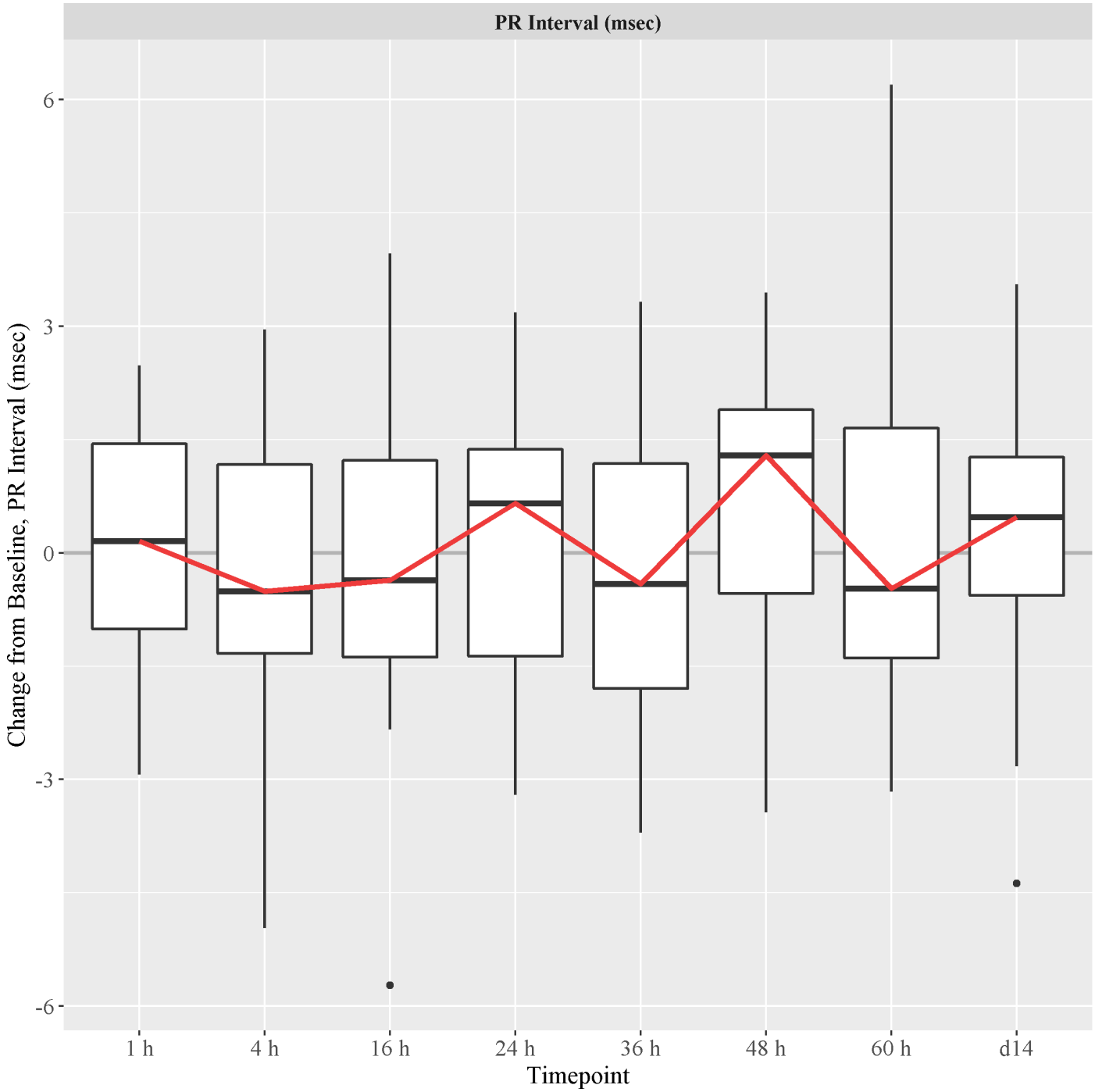
Figure 84: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Respiratory Rate – Safety Subset Population

Figure 85: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Temperature – Safety Population

Figure 86: Vital Signs by Scheduled Visits: Change from Baseline by Parameter and Timepoint – Temperature – Safety Subset Population

14.3.7 Displays of ECG Measurements

Figure 87: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – PR Interval – Safety Population



Figures with Similar Format:

Figure 88: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – PR Interval – Safety Subset Population

Figure 89: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – QRS Interval – Safety Population

Figure 90: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – QRS Interval – Safety Subset Population

Figure 91: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – QT Interval – Safety Population

Figure 92: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – QT Interval – Safety Subset Population

Figure 93: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – QTcF Interval – Safety Population

Figure 94: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – QTcF Interval – Safety Subset Population

Figure 95: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – RR Interval – Safety Population

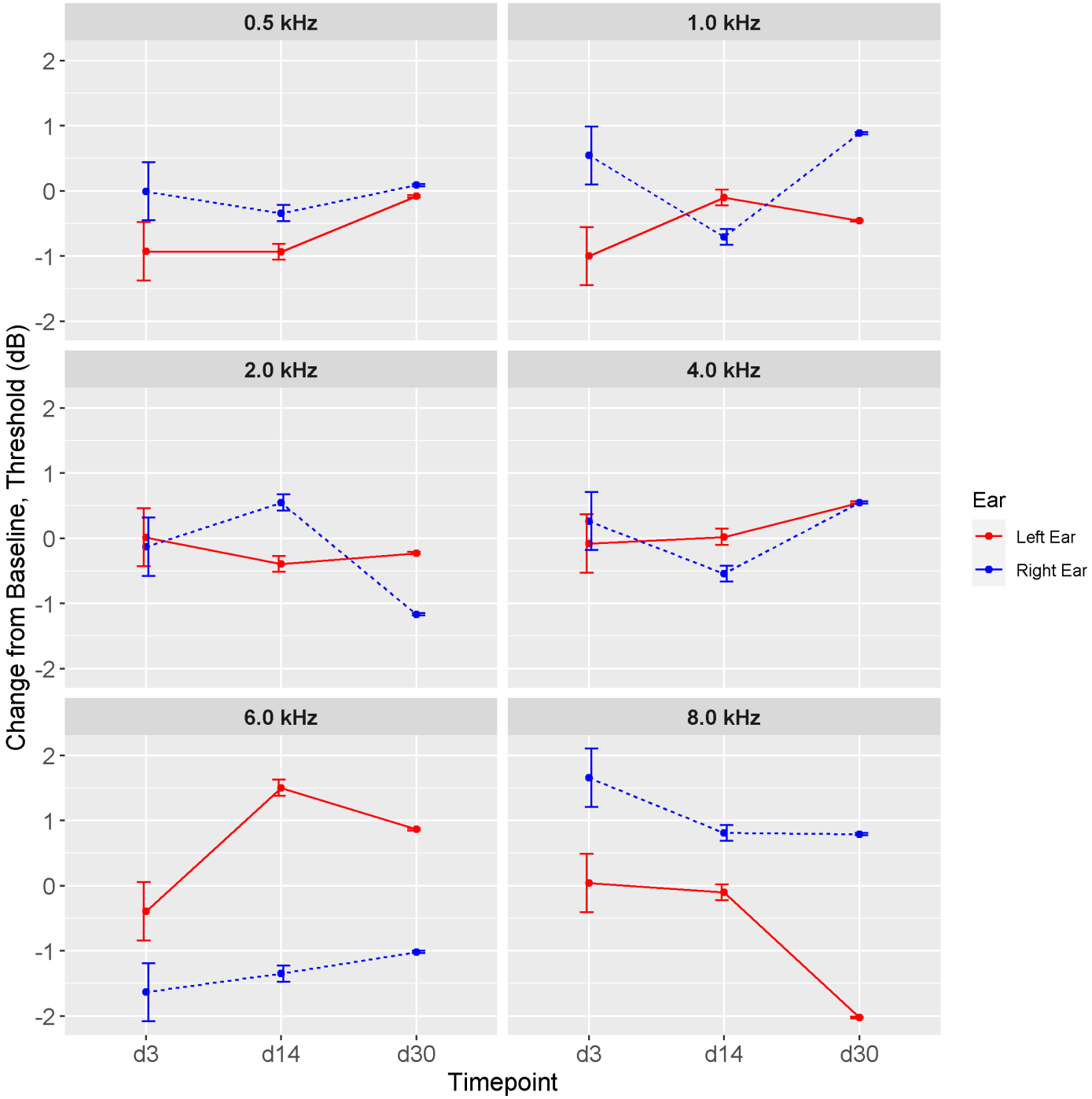
Figure 96: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – RR Interval – Safety Subset Population

Figure 97: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – Ventricular Rate – Safety Population

Figure 98: ECG by Scheduled Visits: Change from Pre-Dose Baseline by Parameter and Timepoint – Ventricular Rate – Safety Subset Population

14.3.8 Displays of Audiology Results

Figure 99: Audiology by Scheduled Visits: Change from Baseline by Timepoint, Frequency, and Ear – 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 kHz – Pure-Tone Audiometry – Safety Population



Figures with Similar Format:

Figure 100: Audiology by Scheduled Visits: Change from Baseline by Timepoint, Frequency, and Ear – 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 kHz – Pure-Tone Audiometry – Safety Subset Population

Figure 101: Audiology by Scheduled Visits: Change from Baseline by Timepoint, Frequency, and Ear – 9.0, 10.0, 11.0, 12.5, 14.5, 16.0, 18.0 and 20 kHz – Pure-Tone Audiometry – Safety Population

Figure 102: Audiology by Scheduled Visits: Change from Baseline by Timepoint, Frequency, and Ear – 9.0 10.0, 11.0, 12.5, 14.5, 16.0, 18.0 and 20 kHz – Pure-Tone Audiometry – Safety Subset Population

Figure 103: Audiology by Scheduled Visits: Change from Baseline by Timepoint, Frequency, and Ear – DPOAE – Safety Population

Figure 104: Audiology by Scheduled Visits: Change from Baseline by Timepoint, Frequency, and Ear – DPOAE – Safety Subset Population

Figure 105: Audiology by Scheduled Visits: Change from Baseline by Timepoint, Frequency, and Ear – SNR – Safety Population

Figure 106: Audiology by Scheduled Visits: Change from Baseline by Timepoint, Frequency, and Ear – SNR – Safety Subset Population

14.3.8 Displays for Pharmacokinetics Data

Figure 107: Individual Total Apramycin Concentration-Time Profiles in Plasma

[Implementation Note: Different lines (types and colors) will be used for each cohort.]

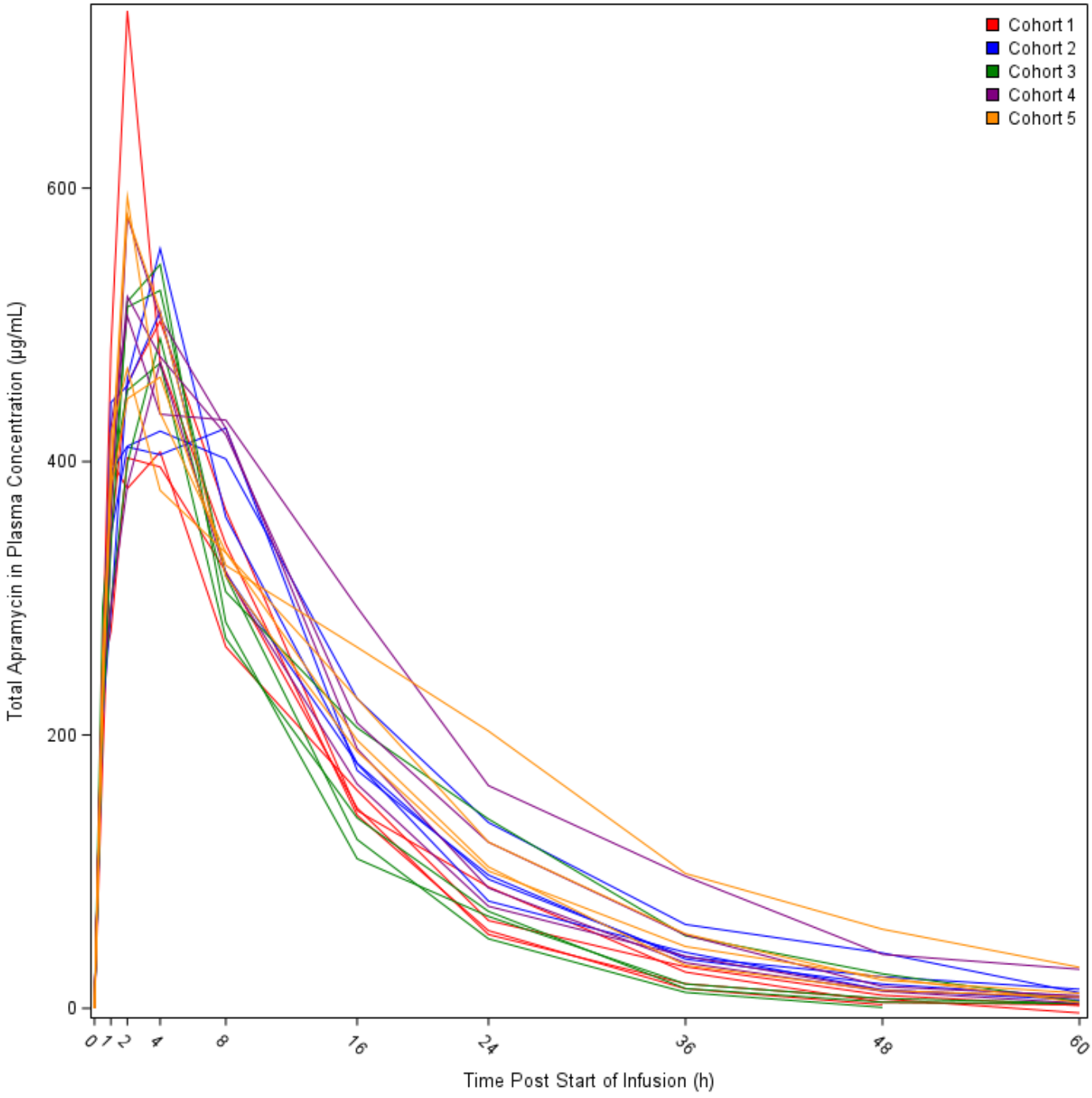


Figure 108: Semi-Log Individual Total Apramycin Concentration-Time Profiles in Plasma

[Implementation Note: Different line types and colors will be used for each cohort.]

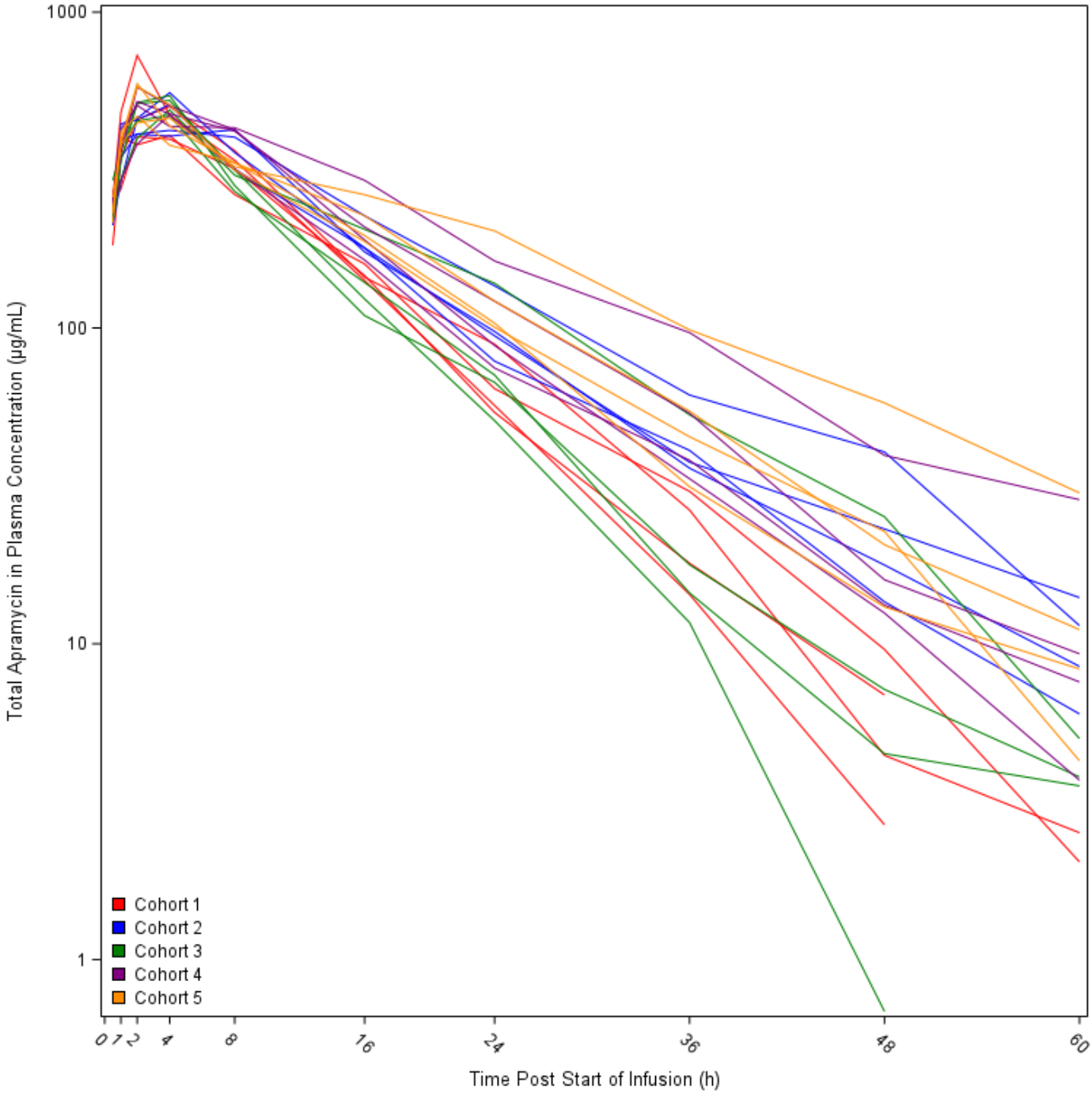


Figure 109: Mean Total Apramycin Concentration-Time Profiles in Plasma

[Implementation Note: Different symbols and line types will be used for each cohort. Error bars represent ± 1 SD.]

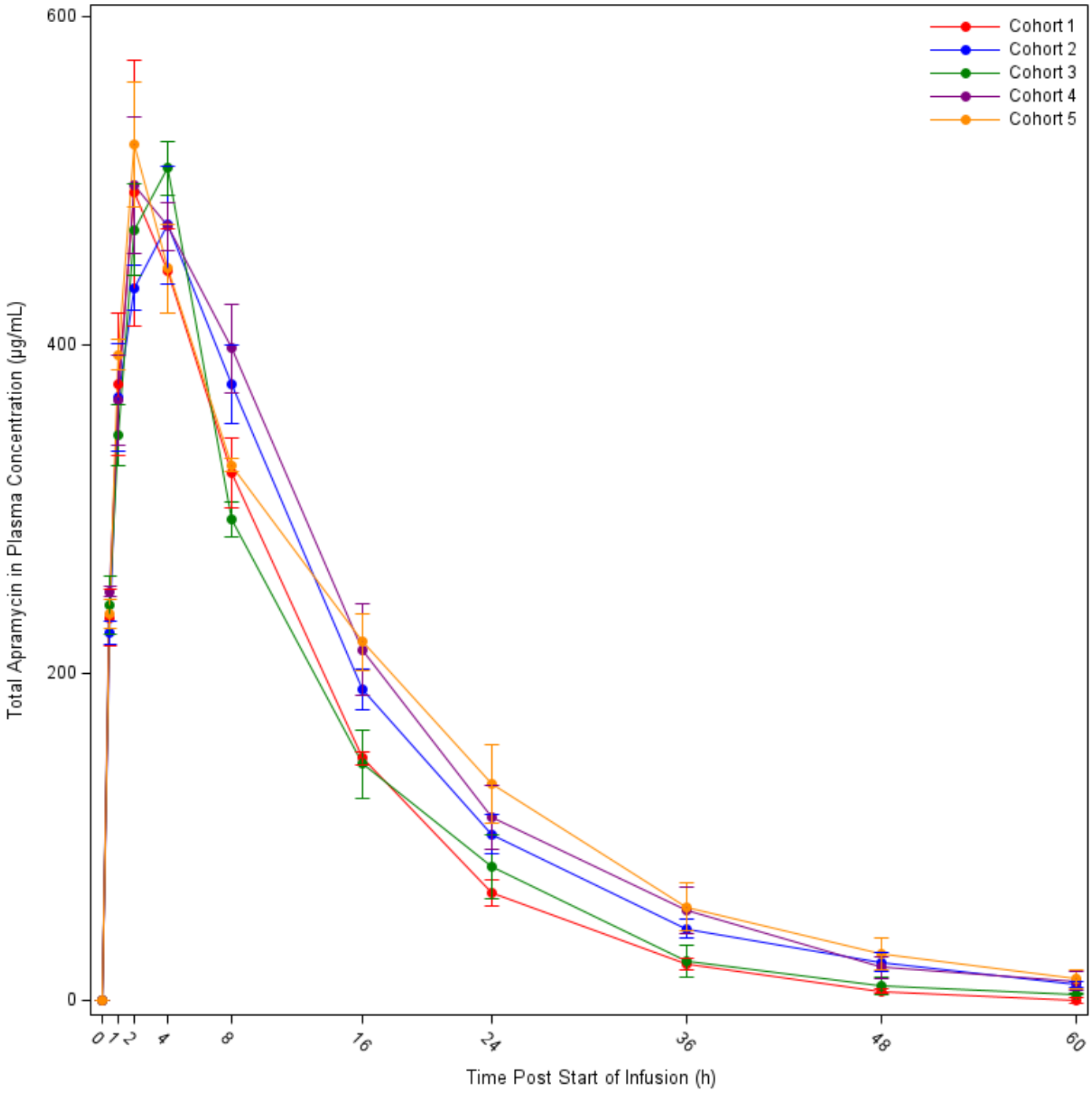


Figure 110: Mean Semi-Log Total Apramycin Concentration-Time Profiles in Plasma

[Implementation Note: Different symbols and line types will be used for each cohort.]

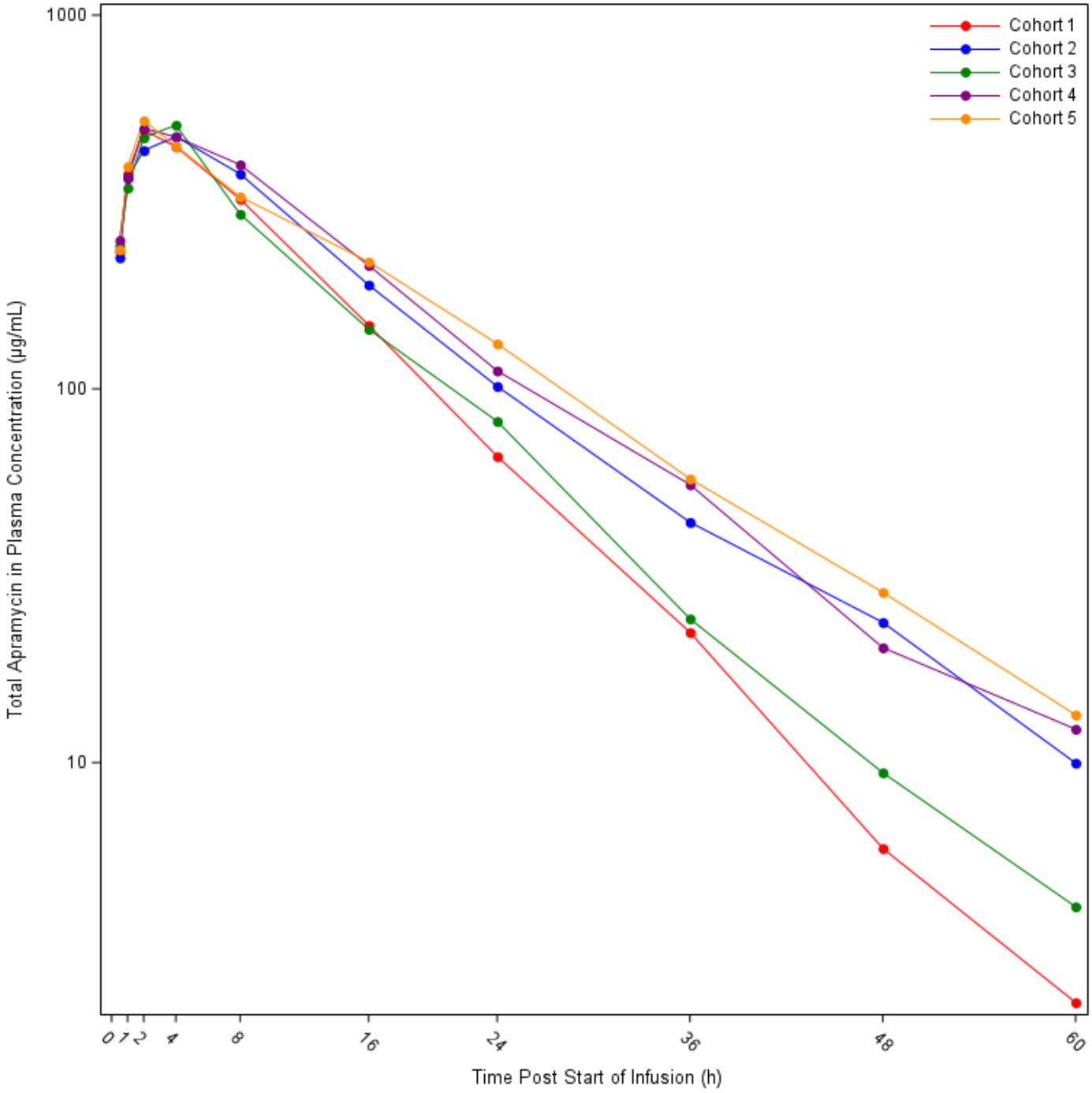


Figure 111: Total Apramycin Concentration in Plasma, ELF, and AM

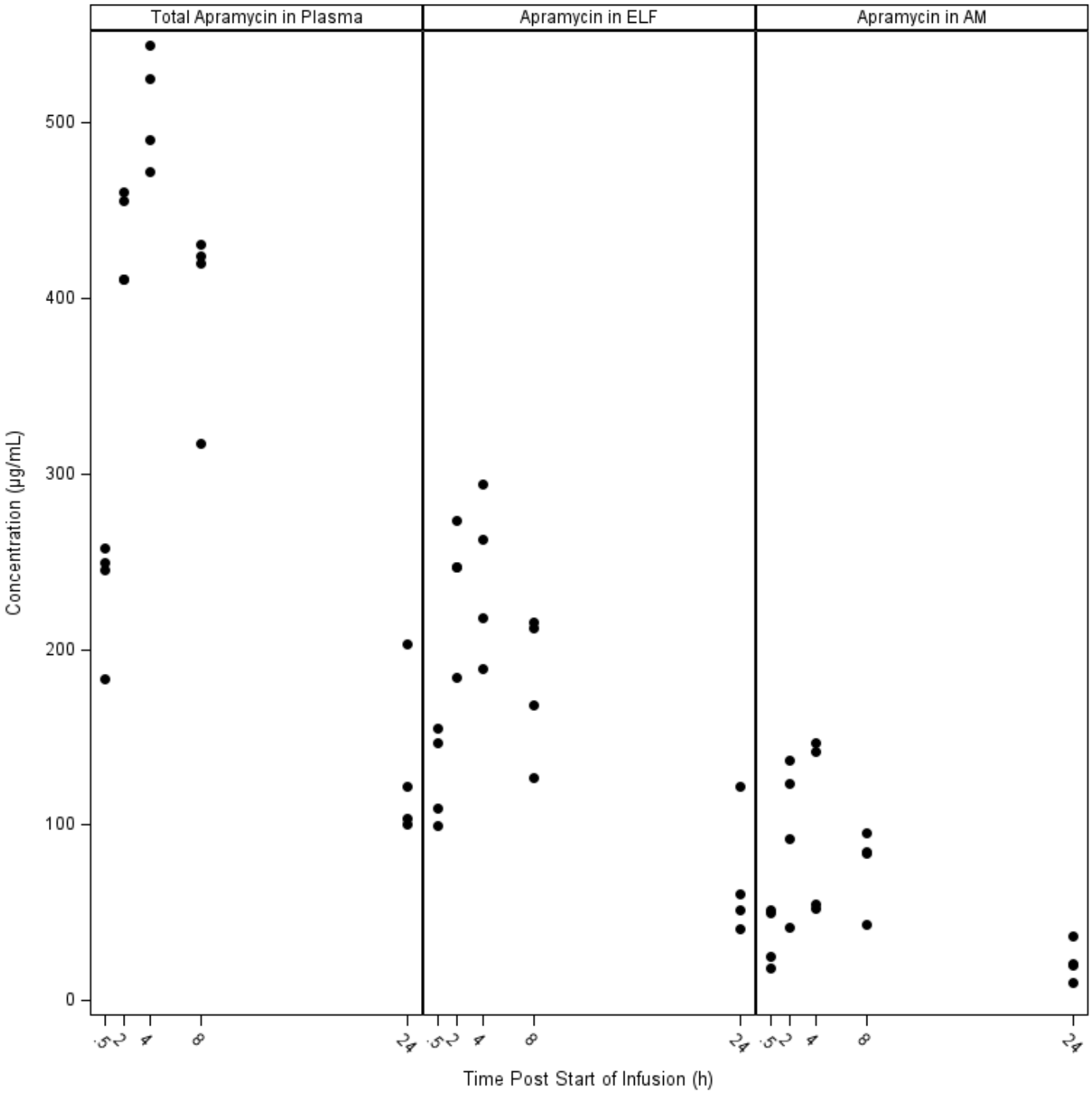


Figure 112: Population Geometric Mean Total Apramycin Concentrations in Plasma, ELF, and AM

[Implementation Note: Different symbols and line types will be used for each parameter.]

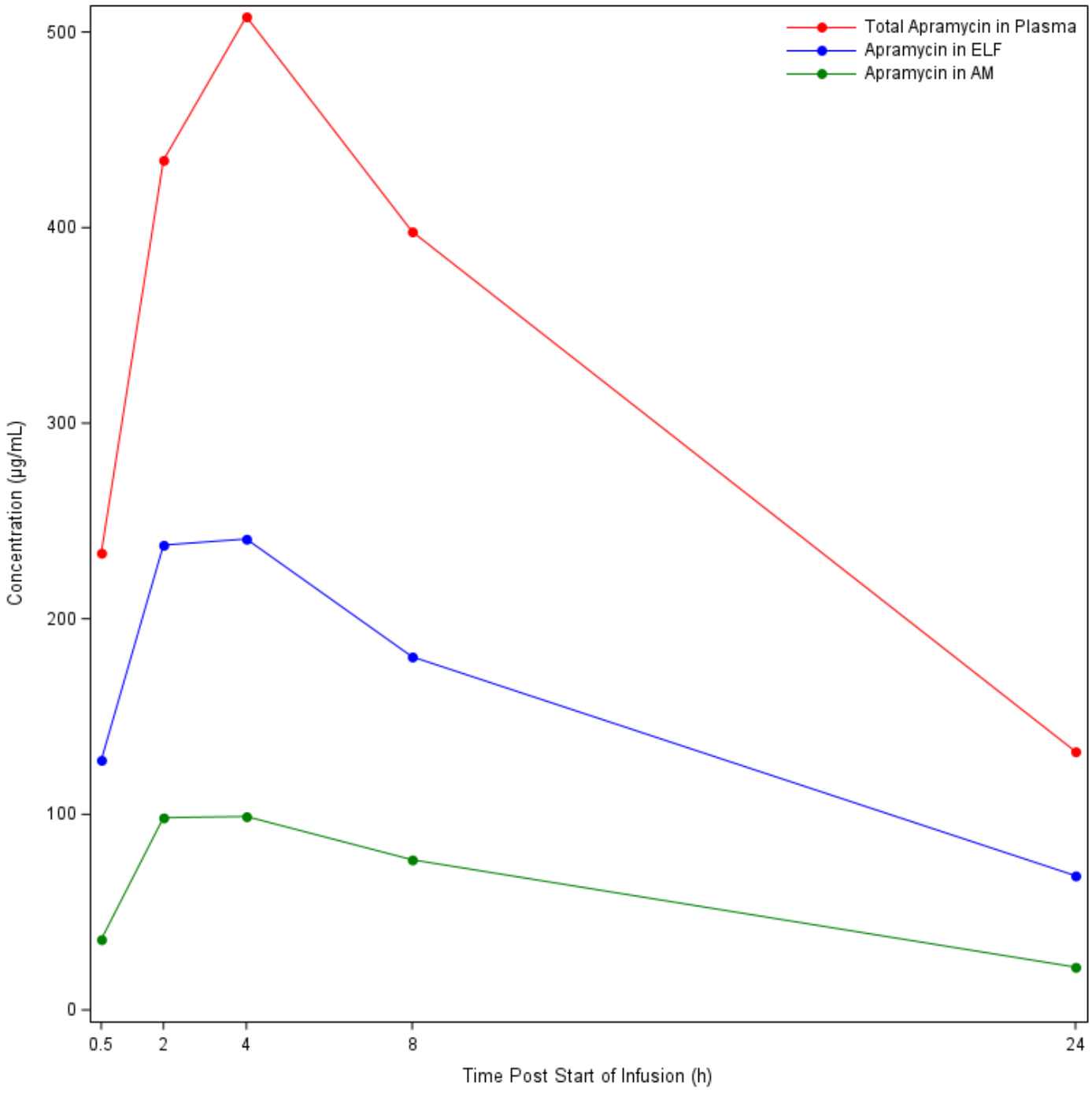


Figure 113: Population Semi-Log Geometric Mean Total Apramycin Concentrations in Plasma, ELF, and AM

[Implementation Note: Different symbols and line types will be used for each parameter.]

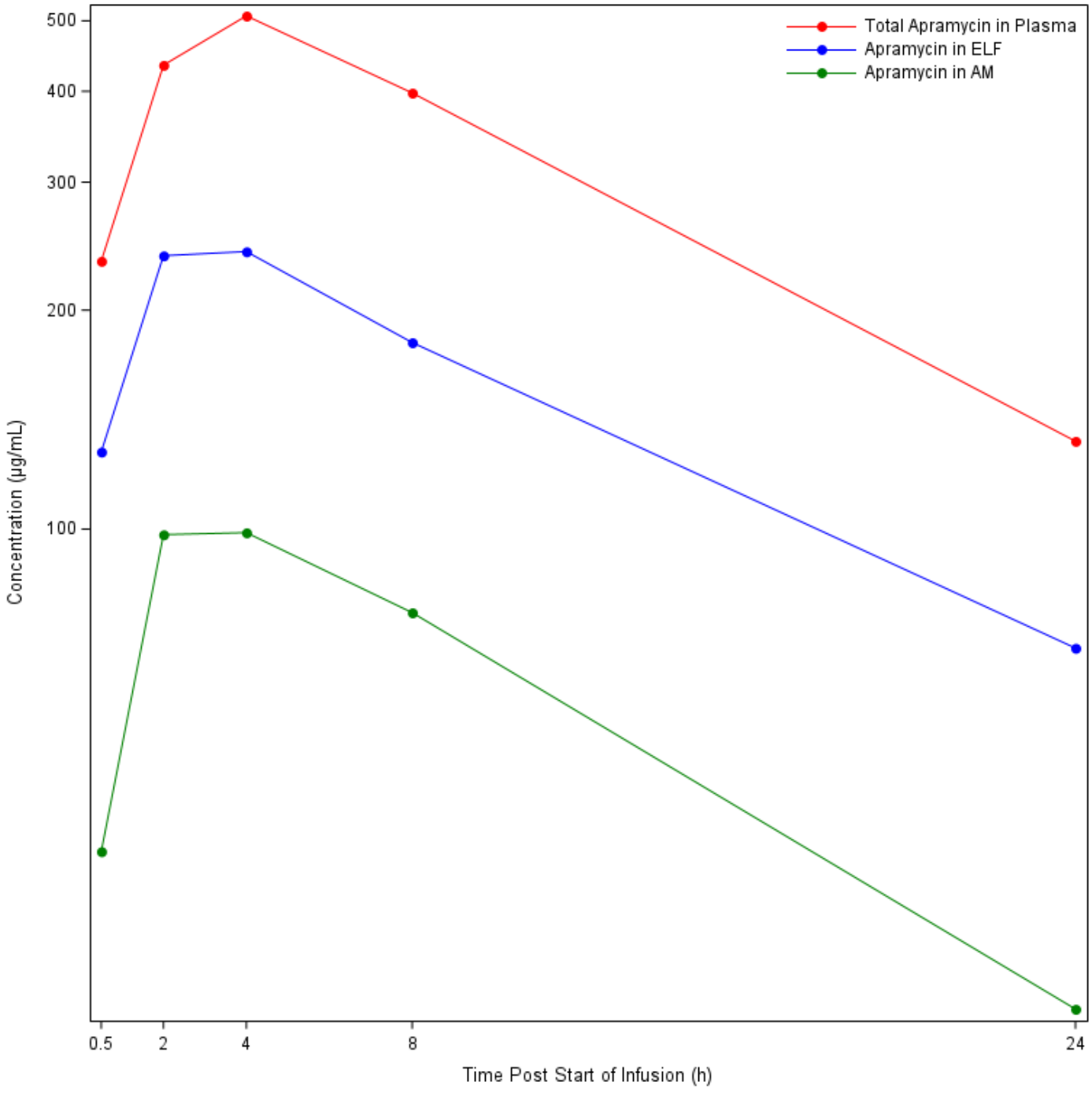


Figure 114: Individual Apramycin in ELF to Total Apramycin in Plasma and Apramycin in AM to Total Apramycin in Plasma Concentration Ratios

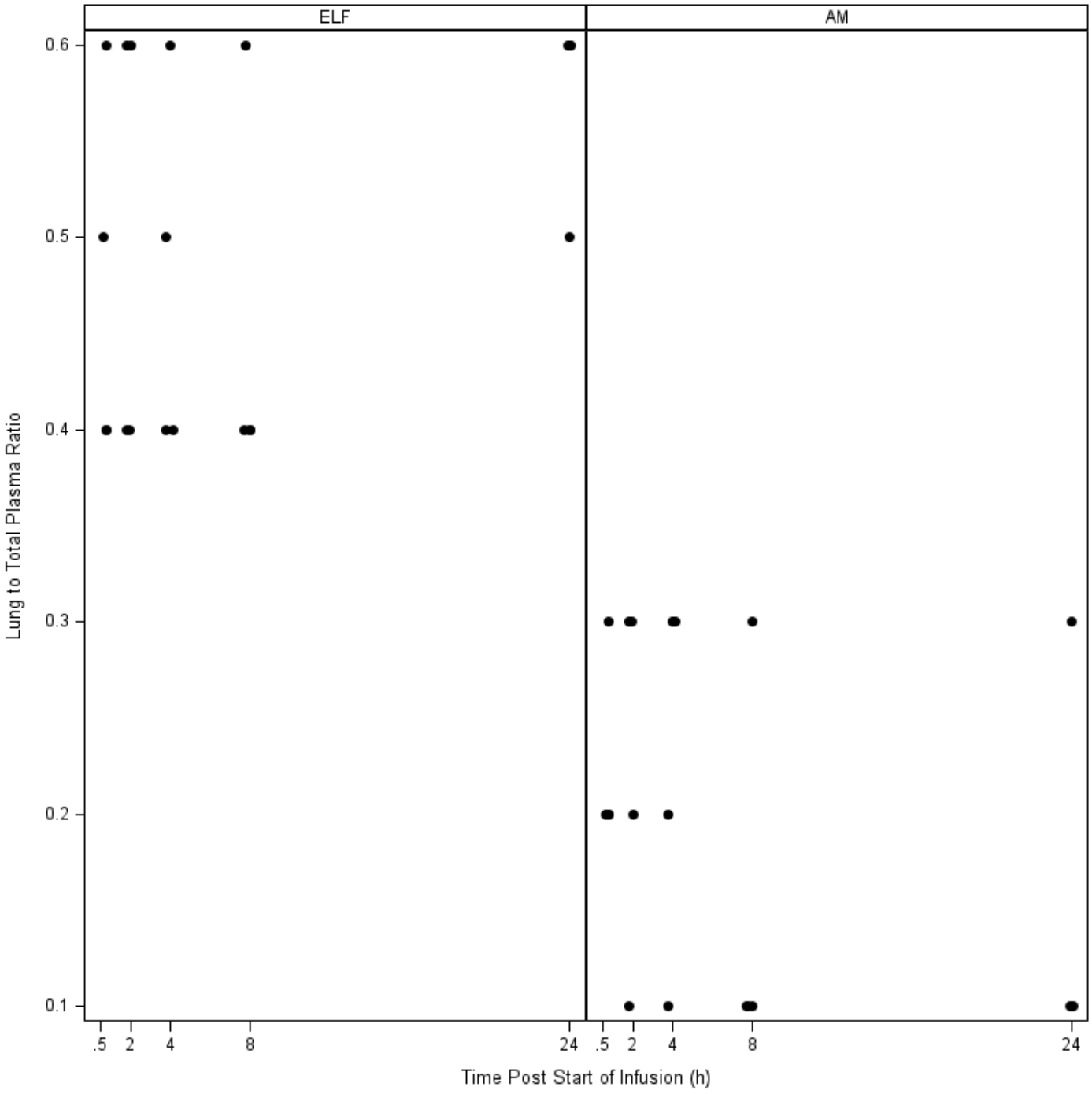
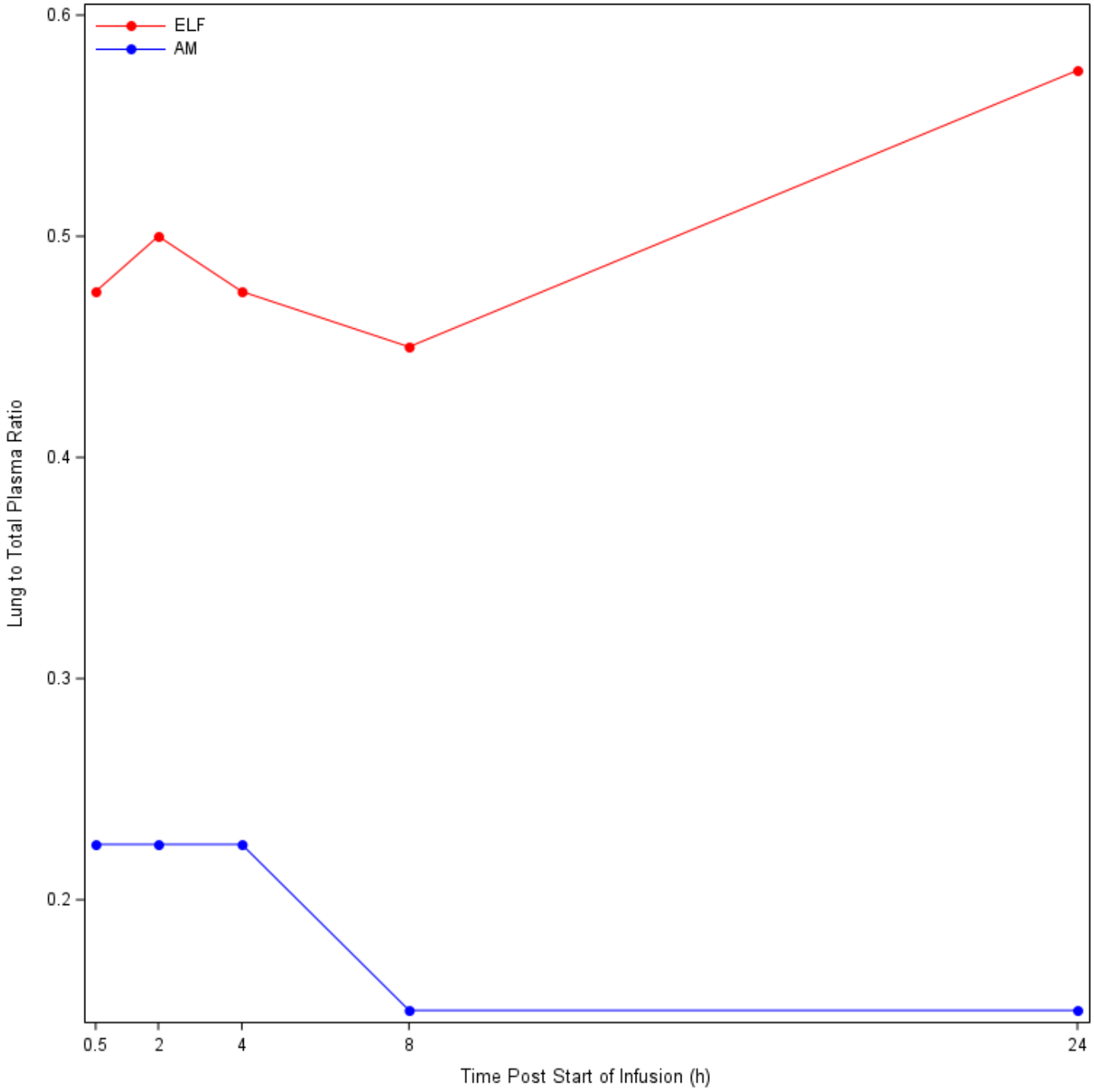


Figure 115: Geometric Mean Apramycin in ELF to Total Apramycin in Plasma and Apramycin in AM to Total Apramycin in Plasma Concentration Ratios

[Implementation Note: Different symbols and line types will be used for each parameter.]



APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

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 1: Early Terminations or Discontinued Participants

[Implementation Note: Category will be either "Early Termination" or "Treatment Discontinuation." In the "Reason" column, concatenate any "specify" fields, including AE number and DV number. Sort order: Cohort, Participant ID, Category (in the case a participant both terminates early and discontinues treatment).]

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

16.2.2 Protocol Deviations

Listing 2: 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, separated by a colon, e.g., "Other: Participant refusal." Sort order: Cohort, Participant ID, DV Number.]

Cohort	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 3: Non-Participant-Specific Protocol Deviations

[Implementation Note: In the "Deviation" column, concatenate any and all "specify" fields (including visit number, etc.). If the "Reason for Deviation" is "Other," concatenate "specify" field, separated by a colon, e.g., "Other: Participant refusal." In "Comments" column, replace any occurrences of PATID with USUBJID. Sort order: Start Date, Deviation.]

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

16.2.3 Participants Excluded from the Efficacy Analysis

Listing 4: Participants Excluded from Analysis Populations

[Implementation Note: The data in this listing should be congruent with the "Analysis Population by Cohort" table. If a participant was not excluded from any analysis population, the participant will not appear in the listing. If the participant is excluded from multiple analysis population, 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: Cohort, Participant ID, Analysis from which participant is excluded (order: Safety, Safety Subset, Lung PK, Plasma PK, PK Analysis Subset).]

Cohort	Participant ID	Analyses in which Participant is Excluded	Results Available?	Reason Participant Excluded	Reason Participant Excluded Specification
Cohort 1	PH2.00001	PK Analysis Subset	Yes	Has protocol deviations that potentially impact PK	Participant consumed food 1 hour prior to dosing.
Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.					

16.2.4 Demographic Data

Listing 5: Demographic Data

[Implementation Note: If a participant is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)." Sort order: Cohort, Participant ID.]

Cohort	Participant ID	Sex	Age at Enrollment (years)	Ethnicity	Race

Listing 6: Pre-Existing and Concurrent Medical Conditions

[Implementation Note: "Condition Start Day" and "Condition End Day" are relative to date of treatment administration (which is Day 1, day before treatment administration 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

Sort order: Cohort, Participant ID, MH Number.]

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

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

Listing 7: Treatment Administration

[Implementation Note: Sort order: Cohort, Participant ID.]

Cohort	Participant ID	Planned Dose (mg)	Volume Administered (mL)	Actual Dose Administered (mg)	Infusion Date	Infusion Start Time (hh:mm)	Infusion End Time (hh:mm)	Interruptions in study product administration?	Interruption Start Time (hh:mm)	Interruption End Time (hh:mm)
					ddMMMyyyy	hh:mm	hh:mm	Yes/No		

16.2.7 Adverse Events

Listing 8: Treatment Emergent Adverse Events

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" in the duration column. This listing includes all treatment emergent adverse events. Sort order: Cohort, Participant ID, AE Number.]

Adverse Event	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Study Day of AE Onset	Duration (Days)	Severity	SAE?	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome
Cohort: , Participant ID: , AE Number:												
Comments:												
Cohort: , Participant ID: , AE Number:												
Comments:												

16.2.8 Individual Laboratory Measurements

Listing 9: Clinical Laboratory Results – Chemistry

[Implementation Note: These listings (for hematology, chemistry, coagulation, and urinalysis) include all laboratory results, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., "16.2 (Mild)". Results outside 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 (same order described in Section 9.6), Cohort, Participant ID, and Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range

Listing 10: Clinical Laboratory Results – Hematology

[Implementation Note: Sort Order: Parameter, Cohort, Participant ID, and Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range

Listing 11: Clinical Laboratory Results – Coagulation

[Implementation Note: Sort Order: Parameter, Cohort, Participant ID, and Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range

Listing 12: Clinical Laboratory Results – Urinalysis

[Implementation Note: Sort Order: Parameter, Cohort, Participant ID, and Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range

Listing 13: Kidney Function Biomarker Results – Cystatin C and KIM-1

[Implementation Note: Sort Order: Parameter, Cohort, Participant ID, and Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result	Change from Baseline

Listing 14: Screening Laboratory Results – Serology

[Implementation Note: Sort Order: Cohort, Participant ID.]

Cohort	Participant ID	Timepoint	Actual Study Day	HBsAg	HCV Antibodies	HIV Antibodies

Listing 15: Screening Laboratory Results – Urine Drug and Cotinine and Alcohol Breathalyzer

[Implementation Note: Sort Order: Cohort, Participant ID, and Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Drug	Result
				Amphetamines	Positive/Negative
				Barbiturates	
				Benzodiazepines	

Listing 16: Screening Laboratory Results – Pregnancy and FSH

[Implementation Note: Sort Order: Cohort, Participant ID, and Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Urine Pregnancy Result	Serum HCG Result	FSH Test Result

16.2.9 Vital Signs and Physical Exam Findings

Listing 17: Vital Signs

[Implementation Note: This listing includes all vital signs assessments, scheduled and unscheduled. All height, weight, and BMI measurements will be included in this listing as well. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal assessments, e.g., "100.7 (Mild)". Sort order: Cohort, Participant ID, Parameter (same order described in Section 9.6), Date of Assessment, Time of Assessment.]

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

Listing 18: Abnormal 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 Number in parenthesis, e.g., "Yes (7)". Sort order: Cohort, Participant ID, Date of Assessment, Time of Assessment, Body System, Abnormal Finding.]

Cohort	Participant ID	Timepoint	Actual Study Day	Date of Assessment	Time of Assessment	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)
				ddMMMyyyy	hh:mm			

16.2.10 ECG Results and Findings

Listing 19: Listing of ECG Interval Measurements

[Implementation Note: This listing includes all ECG assessments, scheduled or unscheduled. These listings are not color-coded, but the severity should be included in parentheses for abnormal assessment, e.g., "500 (Mild)". For the mean of the triplicate readings, no assessment time should be presented, and the replicate number should specify "Mean". Sort order: Cohort, Participant ID, Parameter, Date of Assessment, Time of Assessment.]

Cohort	Participant ID	Timepoint	Actual Study Day	Date of Assessment	Time of Assessment	Sex	Parameter (Units)	Replicate Number	Result (Severity)	Pre-Dose Change from Baseline	Time-Matched Change from Baseline
				ddMMMyyyy	hh:mm						
Notes: Pre-Dose Baseline = The most recent measurement prior to start of infusion. Time-Matched Baseline = The measurement recorded on the matching timepoint on Day -1.											

Listing 20: Listing of ECG Overall Interpretation and Change from Baseline

[Implementation Note: This listing includes all ECG assessments, scheduled or unscheduled. Sort order: Cohort, Participant ID, Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Date of Assessment	Sex	Interpretation	Change from Baseline	Comments
				ddMMMyyyy				

16.2.11 Otoacoustic Test Results

Listing 21: Otoacoustic Test Results – Ear Otoscopy

[Implementation Note: This listing includes all ear otoscopy assessment, scheduled and unscheduled. Sort order: Cohort, Participant ID, Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Date of Assessment	Right Ear Result	Left Ear Result

Listing 22: Otoacoustic Test Results – Pure-Tone Audiometry

[Implementation Note: This listing includes all pure-tone audiometry results, scheduled and unscheduled. Sort order: Cohort, Participant ID, Timepoint, and Frequency.]

Cohort	Participant ID	Timepoint	Actual Study Day	Date of Assessment	Frequency (kHz)	Threshold (dB)		Change from Baseline (dB)	
						Right Ear	Left Ear	Right Ear	Left Ear

Listing 23: Otoacoustic Test Results – DPOAE

[Implementation Note: This listing includes all pure-tone audiometry results, scheduled and unscheduled. "Change from Baseline" will be missing for categorical results. Sort order: Cohort, Participant ID, Timepoint, Parameter, and Frequency.]

Cohort	Participant ID	Timepoint	Actual Study Day	Date of Assessment	Parameter	Frequency (kHz)	Result		Change from Baseline	
							Right Ear	Left Ear	Right Ear	Left Ear
					DPOAE, SNR, Result					

Listing 24: Screening Otoacoustic Test Results – Valsalva

[Implementation Note: Sort Order: Cohort, Participant ID, Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Date of Assessment	Result
					Normal/Abnormal

Listing 25: Screening Otoacoustic Test Results – Tympanometry

[Implementation Note: Sort Order: Cohort, Participant ID, Timepoint.]

Cohort	Participant ID	Timepoint	Actual Study Day	Date of Assessment	Peak Pressure (Positive/Negative)		Peak Pressure (daPa)		Result	
					Right Ear	Left Ear	Right Ear	Left Ear	Right Ear	Left Ear
									Normal/Abnormal	Normal/Abnormal

Listing 26: Screening Otoacoustic Test Results – Stapedial Reflexes

[Implementation Note: Sort Order: Cohort, Participant ID, Timepoint, Frequency.]

Cohort	Participant ID	Timepoint	Actual Study Day	Date of Assessment	Frequency (kHz)	Ipsilateral Reflex		Contralateral Reflex	
						Right Ear	Left Ear	Right Ear	Left Ear
					0.5, 1.0, 2.0, 4.0	Present/Absent	Present/Absent	Present/Absent	Present/Absent

16.2.12 Concomitant Medications

Listing 27: Prior Medications

[Implementation Note: Include prior medications (medications with an end date prior to dosing) only. If start date is more than 30 days before enrollment, then categorize as follows:

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

If taken for MH, display "Yes" with the MH Number in parentheses, e.g., "Yes (7)". Sort order: Cohort, Participant ID, and CM Number.]

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

Listing 28: Concurrent Medications

[Implementation Note: Include concomitant medications (medications that are ongoing or have an end date after date of infusion) only. "Medication Start Day" and "Medication End Day" are relative to date of infusion (which is Day 1, day before date of treatment administration is Day -1). For medication start dates that are > 30 days prior to enrollment, rather than use the exact study days, categorize as follows:

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

If ongoing, display "Ongoing" in the "Medication End Day" column. If taken for an AE or MH, display "Yes" with the AE or MH Number in parentheses, e.g., "Yes (7)". Sort order: Cohort, Participant ID, CM Number.]

Cohort	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)	Authorized as medically indicated/ Immediately necessary by study clinician?	ATC Level 1 (ATC Level 2)

16.2.13 Pregnancy Reports

Listing 29: Pregnancy Reports – Maternal Information

Cohort	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 30: Pregnancy Reports – Gravida and Para

				Live Births												
Cohort	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 31: Pregnancy Reports – Live Birth Outcomes

Cohort	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 32: Pregnancy Reports – Still Birth Outcomes

Cohort	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?
		ddMMMyyyy										

Listing 33: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Cohort	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
		ddMMMyyyy					

Listing 34: Birth Control Listing

[Implementation Note: If participant is not of childbearing potential, indicate the reason the subject is not of childbearing potential in parentheses in the "Childbearing Potential" column. Sort order: Cohort, Participant ID, Birth Control Start Day.]

Cohort	Participant ID	Sex	Childbearing Potential	Birth Control Method	Birth Control Start Day	Birth Control End Day
					ddMMMyyyy	ddMMMyyyy

16.2.6 Individual Pharmacokinetic Data

Listing 35: Participant Level Total Apramycin Concentrations in Plasma

[Implementation Note: 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 Concentrations will report the value exactly 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: Cohort, Participant ID, Actual Time.]

Cohort	Participant ID	Nominal Time[a] (h)	Actual Time[a] (h)	Laboratory Reported Concentration (µg/mL)	Analysis Concentration (µg/mL)	Used in K_e Calculations

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

Listing 36: Participant Level Free Apramycin Concentrations in Plasma

[Implementation Note: 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 Concentrations will report the value exactly 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: Cohort, Participant ID, Actual Time.]

Cohort	Participant ID	Nominal Time[a] (h)	Actual Time[a] (h)	Laboratory Reported Concentration (µg/mL)	Analysis Concentration (µg/mL)

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

Listing 37: Participant Level Free Portion of Plasma Apramycin

[Implementation Note: 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: Cohort, Participant ID, Actual Time.]

Cohort	Participant ID	Nominal Time[a] (h)	Actual Time[a] (h)	Free Portion (fu, % Unbound)

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

Listing 38: Participant Specific Total Apramycin in Plasma PK Parameters

[Implementation Note: Sort order: Cohort, Participant ID, Actual Time.]

Cohort	Participant ID	C_{max} (µg/mL)	T_{max} (h)	$AUC_{(0-24)}$ (µg*h/mL)	$AUC_{(0-last)}$ (µg*h/mL)	$AUC_{(0-\infty)}$ (µg*h/mL)	K_e (1/h)	$t_{1/2}$ (h)	CL (L/h)	V_d (L)	Lambda Z Acceptance Criteria Met?	$\%AUC_{ex}$ Criteria Met?
											Yes/No	Yes/No

Listing 39: Participant Level Apramycin Concentrations in ELF

[Implementation Note: 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 Concentrations will report the value exactly 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 columns, 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: Cohort, Participant ID.]

Cohort	Participant ID	Nominal Time[a] (h)	Actual Time of BAL (h)	Actual Time of Urea Collection (h)	Volume of BAL Supernatant (Volume BAL SUP) (mL)	Urea Concentration in Plasma (Urea Plasma) (µg/mL)	Urea Concentration in BAL Supernatant (Urea BAL SUP) (µg/mL)	Volume of ELF[b] (Volume ELF) (mL)	Apramycin Concentration in BAL Supernatant (Apramycin BAL SUP) (µg/mL)	Apramycin Concentration in ELF[c,d] (Apramycin ELF) (µg/mL)

Note: BQL = Below the Quantification Limit.
[a] Times are relative to time of dosing. For actual time, out of window times are indicated by an asterisk (*), substantially out of window times are indicated by two asterisks (**), and imputed times are indicated by three asterisks (***).
[b] Volume ELF = Volume BAL SUP * (Urea BAL SUP / Urea Plasma).
[c] Apramycin ELF = Apramycin BAL SUP x (Volume BAL SUP / Volume ELF).
[d] Apramycin ELF = Apramycin BAL SUP * (Urea Plasma / Urea BAL SUP).

Listing 40: Participant Level Apramycin Concentrations in AM

[Implementation Note: 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 Concentrations will report the value exactly 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: Cohort, Participant ID.]

Cohort	Participant ID	Nominal Time[a] (h)	Apramycin Concentration in BAL Pellet (Concentration BAL AC) (µg/mL)	Total Volume of BAL Pellet in Suspension (µL)	Number of Alveolar Cells per mL BAL Volume (BAL AC) (10^6/mL)	Total BAL Volume (BAL Volume) (mL)	Percent of Macrophages in BAL Pellet (% AM) (%)	Amount of Apramycin in Total Volume of Alveolar Cells[b] (Apramycin BAL AC) (µg)	Total Volume of AM in BAL Pellet[c] (Volume AM) (mL)	Apramycin Concentration in AM[d] (Apramycin AM) (µg/mL)

Note: BQL = Below the Quantification Limit.
[a] Times are relative to time of dosing.
[b] Apramycin BAL AC = Concentration BAL AC * Total Volume of BAL Pellet in Suspension.
[c] Volume AM = BAL AC * BAL Volume * % AM * 2.42 µL/10^6 cells.
[d] Apramycin AM = Apramycin BAL AC / Volume AM.

Listing 41: Apramycin in ELF and AM to Total Apramycin in Plasma Concentration Ratios

[Implementation Note: Sort order: Cohort, Participant ID.]

Cohort	Participant ID	Timepoint	Apramycin in ELF to Total Apramycin in Plasma Concentration Ratio	Apramycin in AM to Total Apramycin in Plasma Concentration Ratio

Listing 42: Bronchoalveolar Lavage Cell Counts

[Implementation Note: Sort order: Cohort, Participant ID.]

Cohort	Participant ID	Timepoint	Total Cell Count (10^3/mL)	WBC Count (10^3/mL)	Macrophages (%)	Neutrophils (%)	Eosinophils (%)	Lymphocytes (%)	Epithelial Cells (%)	Other Cells (%)	If other cells observed, specify