CLINICAL RESEARCH IN INFECTIOUS DISEASES

SAFETY STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 17-0107

Study Title:

A Phase I, Open-Label Study in Health Adults to Evaluate the Safety and Pharmacokinetics of AVYCAZ® in Combination with Aztreonam (COMBINE)

NCT03978091

Version 1.0

DATE: 20JUL2020

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STUDY TITLE

Protocol Number Code:	**DMID Protocol: 17-0107**
Development Phase:	Phase 1
Products:	AVYCAZ® and Aztreonam (ATM)
Form/Route:	Intravenous (IV) Infusion
Indication Studied:	Infection with MBL-producing Gram-negative bacteria
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	14JUN2019
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	20JUL2020
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
ATM	Aztreonam
AV	Atrioventricular
AVI	Avibactam
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
°C	Degrees Celsius
CAZ	Ceftazidime
CI	Continuous Infusion
C.I.	Confidence Interval
CS	Clinically Significant
CSR	Clinical Study Report
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FEV1	Forced Expiratory Volume in 1 Second
°F	Degrees Fahrenheit
G	Gram
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
hCG	Human Chorionic Gonadotropin
HFIM	Hollow Fiber Infection Model
HIV	Human Immunodeficiency Virus
HLT	High Level Term
IDES	Internet Data Entry System

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List of Abbreviations *(continued)*

IV	Intravenous
kg	Kilogram
L	Liters
LCE	Leukocyte Esterase
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
MBL	Metallo-β-Lactamase
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mmHg	Millimeter of Mercury
msec	Millisecond
N	Number (typically refers to subjects)
NCS	Not Clinically Significant
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
PE	Physical Examination
pH	Potential of Hydrogen
PI	Principal Investigator
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics
PR	Period of ECG extending from beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex
PT	Preferred Term
PTT	Partial Thromboplastin Time
QT	Period of ECG extending from the beginning of the QRS complex to the end of the T wave
QTcF	QT duration corrected for heart rate by Fridericia's formula
RBC	Red Blood Cell
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction

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List of Abbreviations *(continued)*

U	Units
ULN	Upper Limit of Normal
USP	United States Pharmacopeia
WBC	White Blood Cell
WHO	World Health Organization

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1. PREFACE

The Safety Statistical Analysis Plan (SAP) for "A Phase 1, Open-Label Study in Healthy Adults to Evaluate the Safety and Pharmacokinetics of AVYCAZ® in Combination with Aztreonam (COMBINE)" (DMID Protocol 17-0107) describes and expands upon the statistical information presented in the protocol. The main text of this Safety SAP discusses analyses of safety endpoints for the study. Analysis of all Pharmacokinetic (PK) endpoints is presented in the PK SAP.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, figures, and listings 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), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

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

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2. INTRODUCTION

This is a Phase I, open-label, single center trial studying the safety and PK of ceftazidime-avibactam (AVYCAZ®) combined with aztreonam (ATM), AVYCAZ® alone, and ATM alone in 48 healthy adult male and female subjects (6 cohorts of 8 subjects). Cohorts 1-4 are the single drug administration treatment cohorts, including the administration of AVYCAZ® and ATM per dosing label and as a continuous infusion (CI). The AVYCAZ® and ATM combination treatment regimens will be administered to Cohorts 5-6. Study safety will be monitored using assessments of adverse events (AEs), physical examinations (PEs), vital signs, clinical laboratory safety tests, and electrocardiogram (ECG) tests. Subjects who received any study product (started the first infusion) will be included in the Safety Population and used for all safety analyses.

2.1. Purpose of the Analyses

The main text of this Safety SAP discusses analyses of the safety endpoints collected to assess the safety of AVYCAZ® combined with ATM, AVYCAZ® alone, and ATM alone. Analysis of all PK objectives and associated endpoints are described in the PK SAP. Both safety and PK endpoints will be presented in the clinical study report (CSR) after completion of the study.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

- Describe the safety of two dosing regimens of AVYCAZ® combined with ATM relative to AVYCAZ® alone, and ATM alone in healthy adult subjects.

3.1.2. Secondary Objectives

- Characterize the PK profiles of two dosing regimens of AVYCAZ® combined with ATM, AVYCAZ® alone, and ATM alone at the population level in healthy adult subjects.
- Characterize the PK profiles of two dosing regimens of AVYCAZ® combined with ATM, AVYCAZ® alone, and ATM alone following initiation of dosing on day 1 in healthy adult subjects.
- Characterize the PK profiles of two dosing regimens of AVYCAZ® combined with ATM, AVYCAZ® alone, and ATM alone following multiple daily dosing in healthy adult subjects.

3.1.3. Exploratory Objectives

- Predict the distribution of plasma concentration-time profiles observed with two dosing regimens of AVYCAZ® combined with ATM, AVYCAZ® alone, and ATM alone in health adult subjects via simulations.
- Predict the distribution of urine cumulative urine amount-time profiles observed with two dosing regimens AVYCAZ® combined with ATM, AVYCAZ® alone, and ATM alone in healthy adult subjects via simulations.
- Examine the associations between the plasma concentration-time profiles of AVYCAZ® combined with ATM, AVYCAZ® alone, and ATM alone and occurrence of Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) elevations.

3.2. Endpoints

3.2.1. Primary Endpoints

- Number of subjects in each treatment cohort with at least one Grade 2 or higher treatment-emergent AE from first dose through follow-up period.

3.2.2. Secondary Endpoints

- Incidence and severity of all treatment-emergent AEs in each treatment cohort from first dose through follow-up period.
- Population mean PK parameter estimates and the magnitude of the associated inter-individual variability for AVYCAZ® and ATM, when given alone and in combination.
- Individual post-hoc PK parameter estimates and calculated exposure measures in plasma for AVYCAZ® and ATM, when given alone and in combination following initial dosing on Day 1.

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- Individual post-hoc PK parameter estimates and calculated exposure measures in urine for AVYCAZ® and ATM, when given alone and in combination following initial dosing on Day 1.
- Individual post-hoc PK parameter estimates and calculated exposure measures in plasma for AVYCAZ® and ATM, when given alone and in combination following multiple daily dosing.
- Individual post-hoc PK parameter estimates and calculated exposure measures in urine for AVYCAZ® and ATM, when given alone and in combination following multiple daily dosing.

3.2.3. Exploratory Endpoints

- Distribution of simulated plasma concentration-time profiles associated with each treatment cohort.
- Distribution of simulated urine concentration-time profiles associated with each treatment cohort.
- Occurrence of ALT and AST elevations ≥ 3 times the upper limit of normal (ULN) from first dose of study product through follow-up period.
- Occurrence of ALT and AST elevations ≥ 5 times the ULN from first dose of study product through follow-up period.
- Changes in ALT and AST from first dose of study product through follow-up period.

3.3. Study Definitions and Derived Variables

3.3.1. Cohort

Forty-eight (48) subjects will be enrolled in the study with eight (8) subjects in each of the following 6 cohorts. In each cohort, subjects will receive either AVYCAZ® alone, ATM alone, or AVYCAZ® combined with ATM:

- Cohort 1: AVYCAZ® 2.5 g IV as a 2-hour infusion every 8 hours for 7 days (19 total doses)
- Cohort 2: AVYCAZ® 2.5 g IV as a 2-hour infusion x 1, then 0.32 g per hour IV daily as a CI (7.5 g/day) for 7 days (20 total doses, IV bag changes every 8 hours for CI)
- Cohort 3: ATM 2 g IV as a 2-hour infusion every 6 hours for 7 days (25 total doses)
- Cohort 4: ATM 2 g IV as a 2-hour infusion x 1, then 0.33 g per hour IV daily as a CI (8 g/day) for 7 days (14 total doses, IV bag changes every 12 hours for CI)
- Cohort 5: AVYCAZ® 2.5 g IV as a 2-hour infusion every 8 hours for 7 days and ATM 1.5 g IV as a 2-hour infusion every 6 hours for 7 days (AVYCAZ® 19 total doses; ATM 25 total doses)
- Cohort 6*: AVYCAZ® 2.5 g IV as a 2-hour infusion every 8 hours for 7 days and ATM 2 g IV as a 2-hour infusion every 6 hours for 7 days (AVYCAZ® 19 total doses; ATM 25 total doses)

*A SMC meeting will be convened after completion of Cohort 5 to assess whether the study may proceed to Cohort 6.

3.3.2. Adverse Events

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. FDA

defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs, including local (infusion site) and systemic reactions, will be captured on the appropriate data collection form and electronic case report form (eCRF). Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator), date of resolution, seriousness and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution, return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition worsens, it should be recorded as an AE.

All AEs (laboratory and clinical symptoms) will be graded for severity (Table 4 and Table 5) and assessed for relationship to study product (see definitions below). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF.

Severity of Event

AEs will be assessed by the investigator using the protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity.

- Mild (Grade 1): Events that are usually transient (less than 48 hours) and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention (use of non-narcotic pain reliever or over-the-counter medication). The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention (requires prescription medication, or IV fluids or medical procedure). Severe events are usually incapacitating.

Relationship to Study Product

The assessment of the AE's relationship to study product will be done by the licensed study physician indicated on the Form FDA 1572 and the assessment will be part of the documentation process. Whether the AE is related or not to the study product, is not a factor in determining what is or is not recorded in the eCRF in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded in the eCRF.

In a clinical trial, the study product must always be suspect. The relationship to study product will be assessed for AEs using the terms related or not related:

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

3.3.3. Serious Adverse Events (SAEs)

An AE is considered an SAE if, in the view of either the site PI or sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening AE
  - An AE is considered "life-threatening" if, in the view of either the site PI or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect,
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 or by the Institution as the site PI or Sub-Investigator.
- Recorded on the appropriate SAE data collection form and eCRF.

Followed through resolution or stabilization, even if this extends beyond the study-reporting period, by a licensed study physician (for Investigational New Drug Application (IND) studies, a physician listed on the Form FDA 1572 as the site PI or Sub-Investigator).

- Reviewed and evaluated by DMID, an Independent Safety Monitor (ISM) (as deemed necessary) or Safety Monitoring Committee (SMC) (periodic review unless related), and the IRB/IEC.

For additional study definitions and derived variables related to PK endpoints, refer to the PK SAP.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 1, open-label, single center study in 48 healthy adult male and female subjects age 18-45 years old (6 cohorts of 8 subjects) to investigate the safety and PK of AVYCAZ® combined with ATM, AVYCAZ® alone, and ATM alone. Following subject screening, eligible subjects will be assigned into one of the 6 dosing cohorts (see Table 1). Four treatment cohorts (Cohorts 1-4) are single agent dosing cohorts and will include AVYCAZ® per label dosing, AVYCAZ® as a CI, ATM per label dosing, and ATM as a CI. The remaining two cohorts (Cohorts 5-6) are two AVYCAZ® combined with ATM regimens. Cohorts 1-4 will be completed prior to Cohorts 5 and 6.

Subjects will be admitted to the study site on Day -1 for evaluations to confirm they continue to meet the eligibility criteria, after which they will be admitted to the study site for dosing and observation. Subjects will stay for a minimum of 7 nights and 8 days. Study safety will be closely monitored using daily assessment of AEs, vital signs, and clinical laboratory safety tests. Vital signs will be collected on all study days. Clinical laboratory safety tests will be collected at Screening and on Day -1, Days 2, 4, 6, and Day 8 (prior to discharge from the study site). Liver function tests (LFTs) will be obtained daily beginning on Day 4 until a subject completes dosing. The Final Visit (Day 11 + 3) will be scheduled with each subject for a final safety evaluation and collection of clinical laboratory safety tests. A schedule of all study events can be found in Table 2.

The study will run between approximately 12-15 months.

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

As the main focus of this study is to investigate the safety and PK of AVYCAZ® combined with ATM, AVYCAZ® alone, and ATM alone, there is no control group and all subjects within a cohort will receive the same dosing regimen. The single agent dosing cohorts (Cohorts 1-4) will be completed before the combination dosing cohorts (Cohorts 5-6) because although AVYCAZ® and ATM appear to be safe and well-tolerated as standalone products, there is no available data on safety when these antibiotics are used in combination.

4.3. Selection of Study Population

The study will be conducted using 48 healthy volunteers aged 18-45 years old enrolled into 6 cohorts to observe the safety and PK of the two optimal combination regimens of AVYCAZ® with ATM. Safety and PK of combination regimes will be compared to AVYCAZ® and ATM dosing regimens given alone. This is a single center study being conducted in the United States. The study site will determine the most effective procedures to identify potential eligible subjects from the general public for this study.

Only subjects who meet all of the inclusion and none of the exclusion criteria will be eligible for enrollment into this study. No exemptions are granted on Inclusion/Exclusion Criteria in DMID-sponsored studies.

Eligibility criteria from version 3.0 of the protocol are listed below:

4.3.1. Inclusion Criteria

A subject must meet all the following criteria to be considered eligible for inclusion in the study.

1. Provide a signed and dated written informed consent.

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2. Be able to understand and willing to comply with study procedures, restrictions, and requirements, as determined by the Principal Investigator (PI).
3. Male and female volunteers aged 18 to 45 years inclusive.
4. Suitable veins for cannulation or repeated venipuncture.
5. Subject must be in good general health as judged by the investigator as determined by medical history, vital signs[1], body mass index (BMI) and body weight[2], clinical laboratory values[3], and physical examination (PE).

   [1] Oral temp <38.0°C/100.4°F; pulse 50 to 100 bpm; systolic blood pressure 90 to 140 mmHg, and diastolic blood pressure 55 to 90 mmHg.

   [2] BMI between 19-33 kg/m^2 and body weight ≥ 50 kg

   [3] Clinical chemistry, hematology, coagulation and urinalysis results within the clinical laboratory reference ranges; clinical laboratory values outside these ranges, if considered by the site investigator to be clinically insignificant, are also acceptable
6. Sexually active female subjects must be of non-childbearing potential[4] or must use a highly effective method of birth control[5].

   [4] Non-childbearing potential is defined as being post-menopausal for at least 18 months or surgically sterile via hysterectomy, bilateral oophorectomy, or tubal sterilization.

   [5] Sexually active female subjects of childbearing potential must avoid becoming pregnant by using one of the following acceptable methods of birth control for 30 days prior to study product dosing and must be maintained for 30 days after last dose of the study product:

   - *Intrauterine contraceptive device; OR*
   - *Approved hormonal contraceptives (such as birth control pills, skin patches, Implanon®, Nexplanon®, DepoProvera®, or NuvaRing®*

   Birth control must be captured on the appropriate date collection form.
7. Sexually active male subjects must be vasectomized or agree to use barrier contraception (condom with spermicide) from first dose of study product until 30 days following the dose of study product.
8. Nonsmokers defined as abstinence from cigarette smoking or use of nicotine-containing products for 6 months prior to enrollment into the study.

4.3.2. Exclusion Criteria

A subject must not meet any of the following criteria to be considered eligible for inclusion in the study.

1. History of any clinically significant (CS) disease or disorder, medical/surgical procedure, or trauma within 4 weeks prior to the first administration of study product(s)[6].

   [6] In opinion of the PI, may either put the volunteer at risk because of participation in the study, or influence the results of the volunteer's ability to participate in the study.
2. History or presence of gastrointestinal, hepatic, or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
3. Known history of a clinically important allergy/hypersensitivity to avibactam (AVI), any monobactam, and beta-lactam and/or L-arginine.

4. Receipt of probenecid or furosemide within 14 days prior to study enrollment.
5. Receipt of any antibiotics within 14 days prior to study enrollment.
6. Receipt of prescription medications (except birth control pills or hormone replacement in females) within 14 days prior to study enrollment, unless in the opinion of site investigator the medication will not interfere with the study procedures or impact subject safety.
7. Receipt of non-antibiotic medications that interacts with OAT3[7] within 14 days prior to study enrollment.

   [7] *Adefovir, Anagliptin, Baricitinib, Cefaclor, Cimetidine, Ciprofloxacin (Systemic), Clofarabine, Eluxadoline, Empagliflozin, Furosemide, Ketoprofen, Methotrexate, Mycophenolate, PEMEtrexed, Penicillin G (Parenteral/Aqueous), Penicillin G Benzathine, Penicillin G Procaine, Penicillin V Benzathine, Penicillin V Potassium, Zidovudine*
8. Receipt of herbal and dietary supplements (including St. John's Wort) within 14 days prior to study enrollment.
9. ALT or AST laboratory value above the ULN as defined in the toxicity table in Table 5.
10. Prolonged QT duration corrected for heart rate by Fridericia's formula (QTcF) (> 450 msec) or shortened QTcF (< 340 msec) or family history of long QT syndrome. Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG[8].

    [8] *Abnormalities that may interfere with interruption of QTc interval changes per the medical judgement of the PI.*
11. Any positive result on screening for human immunodeficiency virus (HIV), serum hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) antibody.
12. Creatinine clearance equal or less than 80 mL/minute (measured by Cockcroft-Gault method) [1].
13. History of *Clostridium difficile* infection in past 90 days.
14. Known or suspected history of drug or alcohol abuse within the last 5 years, as judged by the PI.
15. Positive screen for drugs of abuse, cotinine (nicotine), or alcohol at screening and at admission to the study site prior to the first administration of the study product(s).
16. Received a new chemical entity (compound not approved for marketing) or participated in a study that included drug treatment within 1 month of the first dose of study product(s) for study.[9]

    Note: subjects consented and screened, but not dosed in this study or a previous Phase I study will not be excluded

    [9] *Period of exclusion begins at the time of the last visit of the prior study.*
17. Previous participation in the present study.
18. Involvement in the planning and/or conduct of the study.
19. Any ongoing/recent (during screening) medical complaints that may interfere with analysis of study data or are considered unlikely to comply with study procedures, restrictions, and requirements.[10]

    [10] *Judgment by the PI that the subject should not participate in the study.*
20. Known history of past or current epilepsy or seizure disorders, excluding febrile seizures of childhood.

4.4. Treatments

4.4.1. Treatments Administered

Subjects will receive infusions of either AVYCAZ® (2.5 g IV) combined with ATM (1.5 g or 2 g IV), AVYCAZ® alone, or ATM alone for 7 days. The single dosing cohorts will receive the study drug per label dosing or as a CI.

4.4.2. Identity of Investigational Product(s)

AVYCAZ® (ceftazidime-avibactam)

AVYCAZ® 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) for injection is a white to yellow sterile powder for constitution consisting of ceftazidime pentahydrate and avibactam sodium packaged in glass vials. The formulation also contains sodium carbonate [2].

Each AVYCAZ® 2.5 grams single-dose vial contains ceftazidime 2 grams (equivalent to 2.635 grams sterile ceftazidime pentahydrate/sodium carbonate) and avibactam 0.5 grams (equivalent to 0.551 grams sterile avibactam sodium). The sodium carbonate content of the mixture is 239.6 mg/vial. The total sodium content of the mixture is approximately 146 mg (6.4 mEq)/vial.

AZACTAM® (aztreonam for injection, USP)

AZACTAM® (aztreonam for injection, USP) is a sterile, non-pyrogenic, sodium-free, white powder containing approximately 780 mg arginine per gram of ATM. Following constitution, the product is for intramuscular or intravenous use. Aqueous solutions of the product have a pH in the range of 4.5 to 7.5.

The study product vials will be labeled according to manufacturer or regulatory specifications. The dispensed study product (IV bags) will be labeled with the cautionary statement “For Investigational Use Only.”

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

This is an open-label study and randomization procedures are not required. Subjects will be enrolled online though the enrollment module of Advantage eClinical®, Emmes’ Internet Data Entry System (IDES).

4.4.4. Selection of Doses in the Study

Although AVYCAZ® combined with ATM has been shown to be efficacious against MBL-producing GNB in pre-clinical studies and clinical case reports, optimal dosing remains unknown. Hollow fiber infection model (HFIM) studies using *E. coli* ARLG-1013 ($bla_{\text{NDM-1}}$, $bla_{\text{CTX-M}}$, bla_{CMY}, bla_{TEM}) and *K. pneumoniae* ARLG-1002 ($bla_{\text{NDM-1}}$, $bla_{\text{CTXM-15}}$, bla_{DHA}, bla_{SHV}, bla_{TEM}) were conducted to identify AVYCAZ® combined with ATM regimens that result in maximal bacterial kill and resistance suppression [1]. In these HFIM experiments, a number of FDA-approved ATM 6-8 grams/day regimens were evaluated in combination with FDA-approved AVYCAZ® dosing (2.5 g IV as a 2-hour infusion every 8 hours) and CI AVYCAZ® (7.5 g IV daily) [2 and 3]. It was anticipated that administration of AVYCAZ® as a CI combined with ATM would outperform FDA-approved AVYCAZ® dosing combined with ATM. Continuous infusion administration maximizes the pharmacokinetics/pharmacodynamics (PK/PD) of AVYCAZ® and it was anticipated that this would result in enhanced bacterial killing and resistance suppression [4, 5, and 6]. Since it is not practical for all institutions to infuse AVYCAZ® as a CI, HFIM experiments were also conducted to identify the optimal dosing of AVYCAZ® combined with ATM using FDA-approved dosing regimens of each antibiotic. In these HFIM experiments, maximal daily dose of AVYCAZ® combined with 8g/day ATM regimens were found to

be optimal. Specifically, the two combination regimens that showed maximal bacterial killing and resistance suppression over 7 days were:

- AVYCAZ® 2.5 g IV as a 2-hour infusion every 8 hours combined with ATM 2 g IV as a 2-hour infusion every six hours, and
- AVYCAZ® combined with ATM, each administered as a CI (AVYCAZ® 7.5 g/day CI combined with ATM 8 g/day CI) [1].

While the initial intent was to examine the two optimal AVYCAZ® and ATM regimens identified in the HFIM experiments, two subjects who received ATM 8 g/day CI alone in Cohort 4 experienced grade 3 AST/ALT elevations. Despite having AST/ALT elevations >10 times the ULN, the two subjects were asymptomatic and there were no clinical findings suggestive of liver necrosis or jaundice.

In response to the occurrence of two grade 3 AEs that were related to study product and of the same type [High Level Term (HLT)], the study was halted, and a SMC meeting was convened. The SMC recommended to continue the study but reduce the dose of ATM in Cohort 5 to ATM 1.5 g IV as a 2-hour infusion every 6 hours (ATM 6 g/daily) and to administer it in combination with AVYCAZ 2.5 g IV as a 2-hour infusion every 8 hours. Furthermore, the SMC recommended that a SMC meeting be convened after completion of Cohort 5. If no halting rules are met and there are no other safety concerns, the SMC recommended administering ATM 2 g IV as a 2-hour infusion every 6 hours (ATM 8 g/daily) in combination with AVYCAZ® 2.5 g IV as a 2-hour infusion every 8 hours in Cohort 6. The SMC was in favor of escalating the ATM dose in Cohort 6 if no halting rules are met as the HFIM experiments showed increased bacterial killing with 8 g/day vs 6 g/day combination regimens. Since the safety of ATM CI was not established in this study, the SMC was opposed to administering ATM as a CI in any subsequent cohorts. As an additional safeguard, the SMC also recommended that more intensive LFT monitoring be performed.

4.4.5. Selection and Timing of Dose for Each Subject

Administration of the study products to subjects will occur over a period of 7 days, with dosing being completed the morning of Day 7 for all cohorts.

Each subject will receive doses of AVYCAZ® alone, ATM alone, or a combination of AVYCAZ® and ATM depending on the cohort. The dosing schedules for each cohort can be found in Table 1. Refer to Section 4.4.4 for additional details regarding the selection of the dose timing schedule.

4.4.6. Blinding

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

4.4.7. Prior and Concomitant Therapy

Use of concomitant medications (probenecid and furosemide) that are contraindicated in the AVYCAZ® and ATM package inserts will be not permitted [2 and 3]. Subjects taking such medications will be not eligible for the study.

Patients who received antibiotics within 14 days prior to study enrollment will not be eligible for the study.

Patients receiving a non-antibiotic medication that interacts with OAT3 (e.g., Adefovir, Anagliptin, Baricitinib, Cefaclor, Cimetidine, Ciprofloxacin (Systemic), Clofarabine, Eluxadoline, Empagliflozin, Furosemide, Ketoprofen, Methotrexate, Mycophenolate, PEMEtrexed, Penicillin G (Parenteral/Aqueous), Penicillin G Benzathine, Penicillin G Procaine, Penicillin V Benzathine, Penicillin V Potassium, Zidovudine) will not be included [7 and 8].

In addition, no prescription (except birth control pills or hormone replacement in females) or non-prescription drugs will be permitted, unless in the opinion of site investigator the medication will not interfere with the study procedures or impact subject safety. The use of herbal and dietary supplements (including St. John's Wort) will not be permitted during the study.

4.4.8. Treatment Compliance

The Investigational Pharmacist or designee is responsible for the reconstitution and labeling of the study products. Study products will be administered via IV infusion by a member of the clinical research team who is licensed to administer the study products. Administration will be documented on the source document and entered into the eCRF.

Study product compliance including start and stop time of infusion, volume administered, and the occurrence of any infusion interruptions (greater than 10 minutes) will be captured in the source documents.

4.5. Safety Variables

The following section describes the variables related to the safety endpoints, safety related variables collected throughout the study. For a detailed schedule of events refer to Table 2.

The type, incidence, relatedness, and severity of AEs and SAEs will be recorded from start of infusion of the first dose of study product on Day 1 through the final Study Visit of Day 11 + 3. Refer to Section 3.3 for definitions of AEs, SAEs, severity, and relatedness.

The following safety laboratory parameters and vital signs will be summarized for baseline and each post-dose time point collected. For continuous parameters, change from baseline will be summarized for all post dose time points. Assessments at Day -1 will serve as baseline values for all laboratory parameters.

Serum Chemistry:

- Sodium, Potassium, Chloride, Bicarbonate, Blood Urea Nitrogen (BUN), Creatinine, Glucose (Fasting and Non-Fasting), Albumin, Total Protein, and Lactate Dehydrogenase (LDH) will be collected at Screening, Day -1, and Days 2, 4, 6, 8, and 11 (+3).
- Liver function tests ALT, AST, Alkaline Phosphatase (ALP), and Total Bilirubin will be collected at Screening, Day -1, Day 2, Days 4-8, and Day 11 (+3). Days 5 and 7 are collected for Cohorts 5 and 6 only.

Hematology:

- Hemoglobin, Hematocrit, White Blood Cell Count (WBC), WBC differential, Red Blood Cell Count (RBC), and Platelets will be collected at Screening, Day -1, and Days 2, 4, 6, 8, and 11 (+3).
- Coombs tests will be conducted at Screening and Day 8.

Coagulation:

- Prothrombin Time and Partial Thromboplastin Time (PTT) will be collected at Screening, Day -1, and Days 2, 4, 6, 8, and 11 (+3).

Urinalysis

- Dipstick urinalysis, including Protein, Glucose, Ketones, Bilirubin, Blood, Nitrites, Leukocyte Esterase (LCE), Urobilinogen, Specific Gravity, and pH, will be collected at Screening, Day -1, and Days 4, 8, and 11 (+3).

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Vital signs including Systolic Blood Pressure (BP), Diastolic BP, Pulse Rate, Respiratory Rate, and Body Temperature will be obtained at Screening, Day -1, prior to dosing on Day 1, 1 hour after first dose on Day 1, Days 2-8, and Day 11 (+3). Change from baseline will be summarized for all post dose time points. The measurements obtained on Day -1 will serve at the baseline measurement.

ECGs including QTc Interval and PR Interval will be obtained at Screening and on Days -1 (baseline), 8, and 11 (+3). ECGs will be done in triplicate at Screening only. Single ECGs will be recorded on Days -1, 8, and 11 (+3). In case of premature discontinuation of study drug, ECG will be performed before discharge. Overall ECG assessment and change from baseline will be summarized for all post dose time points.

A complete physical examination will be completed at Screening and on Days -1, 8, and 11 (+3). Height and Weight will be measured at Screening and Day -1, and BMI will be calculated from the Day -1 measurements.

5. SAMPLE SIZE CONSIDERATIONS

This is a Phase 1 study to investigate the safety and PK of AVYCAZ® combined with ATM. The sample size was chosen to obtain reasonable evidence of safety without exposing undue numbers of healthy subjects to combination of AVYCAZ® and ATM at this phase of clinical evaluation. Previous experience in Phase I studies has shown that the sample size being proposed is sufficient to fulfil the primary and secondary objectives of the study.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: N (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. When 95% confidence intervals (C.I.s) are given for a percent, exact (Clopper-Pearson) C.I.s will be used unless otherwise noted.

In general, all data will be listed, sorted by treatment and subject, and when appropriate by visit number within subject. All summary tables will be annotated with the total population size relevant to that table, including any missing observations.

6.2. Timing of Analyses

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

6.3. Analysis Populations

6.3.1. Safety Population

All subjects who receive any amount of study product (start first infusion) will be included in the Safety Population.

6.3.2. PK Population

All subjects who receive at least one dose of study drug and have at least one quantifiable plasma or urine concentration of ceftazidime (CAZ), AVI, or ATM measurement will be included in the PK Population.

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 any data per protocol. No imputation will be performed for missing safety values and outliers will not be excluded from the safety analysis. The amount of missing data and reasons for missingness if available will be summarized in the body of the CSR.

6.6. Interim Analyses and Data Monitoring

A safety summary report will be generated for review by the SMC if a halting rule (see Protocol v3.0 Section 8.6) is met. No formal interim analyses were planned. However, in response to the occurrence of two grade 3 AEs of the same HLT in Cohort 4, a SMC meeting will be convened after the completion of Cohort 5 to assess patient profiles for subjects with elevated liver function tests from Cohorts 1-5 and determine if the study should proceed to Cohort 6.

6.7. Multicenter Studies

DMID Protocol 17-0107 is a single center study.

6.8. Multiple Comparisons/Multiplicity

The safety data summarized in these analyses will not be adjusted for multiple comparisons.

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7. STUDY SUBJECTS

7.1. Disposition of Subjects

The disposition of subjects in the study will be tabulated for all subjects and by treatment cohort (Table 6). The table shows the total number of subjects who were screened, were enrolled, started treatment on Day 1, completed treatment on Day 7, completed discharge on Day 8, received all scheduled treatments, received partial dose of study product, completed all blood draws and urine collections related to the safety endpoints, and completed the follow-up visit on Day 11 (+3).

A flowchart showing the disposition of study subjects will be presented in Figure 1. This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed. A listing of subjects who did not receive all infusions or terminated from study follow-up, including the reason for treatment discontinuation or termination, will be included in Listing 1.

The composition of the analysis populations, including the reason for subject exclusion, is presented in Table 7. Subjects who were excluded from the analysis populations will be listed along with reason for exclusion (Listing 4).

Table 9 will present a summary of the reasons that subjects were screened but not enrolled summarized by inclusion and exclusion criteria.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviations and the deviation category for all subjects (Table 3). This table will provide both the number of subjects and the number of deviations for each category. All subject-specific protocol deviations and non-subject specific protocol deviations will be included in Appendix 3 as data listings (Listing 2 and Listing 3, respectively).

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8. EFFICACY EVALUATION

There are no efficacy endpoints for this protocol.

9. SAFETY EVALUATION

All safety analyses will be presented using the Safety Population.

When calculating the incidence of AEs (i.e., on a per subject basis), each subject will be counted once and any repetitions within a subject will be ignored for events coded in the same category by the Medical Dictionary for Regulatory Activities (MedDRA®). The denominators for percent values will be indicated within the table or table header and will consist of the maximal size of the Safety Population in the indicated observation period. All C.I.s for proportions will be computed using the exact (Clopper-Pearson) method. Toxicity grading scales are provided in Table 4 and Table 5.

9.1. Demographic and Other Baseline Characteristics

Summaries of age, weight, height, BMI, sex, ethnicity, and race will be presented by treatment cohort and for all subjects (Table 10 and Table 11). Ethnicity will be categorized as Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual subject listings will be presented for all demographics (Listing 5).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be coded using MedDRA® dictionary version 20.1 or higher. Summaries of subjects' pre-existing medical conditions by MedDRA® system organ class (SOC) will be presented by treatment cohort and overall (Table 12). Individual subject listings will be presented for all medical conditions (Listing 6).

9.1.2. Prior and Concomitant Medications

Prior (30 days before administration of the first dose of study product) and concomitant medications will be coded to the Anatomical Therapeutic Classification (ATC) using the WHO Drug Dictionary. The use of prior or concomitant medications during the study will be summarized by ATC1 and ATC2 codes and treatment cohort for the Safety Population (Table 108). Individual subject listings will be presented for all prior and concomitant medications (Listing 20).

9.2. Measurements of Treatment Compliance

The number of enrolled subjects who started the first infusion of study product will be reported by treatment cohort and time period (Table 8).

Dates and times for the start and end of infusion, dose number, whether the dose was interrupted, start and end times of dose interruption, dose duration, and actual dose received are listed for subjects who did not receive the full dose of study product or whose dose was interrupted for one of their scheduled doses in Listing 7.

9.3. Adverse Events

AEs will be collected after starting infusion on the first dose of study product on Day 1 through the final Study Visit on Day 11 +3. When calculating the incidence of AEs (i.e., on a per subject basis), each subject will only be counted once at the highest severity recorded and any repetitions of AEs within a subject will be ignored. Denominators for percentages are the number of subjects in the Safety Population. All AEs reported will be included in the summaries and analyses.

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Laboratory abnormalities reported as an AE will be included in summary tables together with all other AEs. Additionally, all laboratory abnormalities will be summarized by laboratory parameter. Refer to Protocol v3.0 Section 8.5 for abnormal laboratory values that are reported as AEs.

9.3.1. Solicited Events and Symptoms

No solicited events or symptoms will be collected in this study.

9.3.2. Unsolicited Adverse Events

The proportion of subjects reporting at least one unsolicited AE will be summarized by MedDRA® SOC, preferred term (PT), and HLT. Denominators for percentages are the number of subjects in the Safety Population.

A brief overall summary of AEs will be shown in Table 13, including the number of subjects with at least one AE of any severity, the number of subjects with at least one related and unrelated AE of each severity, the number of subjects with at least one SAE, the number of subjects with at least one AE leading to early termination, and number of subjects with at least one SUSAR. The number of AEs reported for each subject will be presented in Table 14 by severity and overall.

The following summaries for unsolicited AEs will be summarized by MedDRA® SOC, MedDRA® PT, and MedDRA® HLT, and by treatment cohort or treatment (AVYCAZ®, ATM, or Combination):

- Frequency (number and percent of subjects with an AE of mild severity or greater) and the number of events by relationship to study product and seriousness, regardless of severity, for AEs occurring in 10% of subjects in any treatment cohort (Table 15 by treatment cohort and Table 16 by treatment);
- Frequency and the number of events, regardless of severity or relationship to study product. 95% C.I.s will be presented for proportions (Table 17 by treatment cohort and Table 18 by treatment);
- Frequency of AEs by severity and relationship to study product. 95% C.I.s will be presented for proportions (Table 19 by treatment cohort and Table 20 by treatment);
- Bar chart displaying the frequency (number of events) of related AEs by severity, MedDRA® SOC, and treatment cohort (Figure 2 by treatment cohort and Figure 3 by treatment);
- Bar chart displaying the incidence (number of occurrences) of related AEs by severity, MedDRA® SOC, and treatment cohort (Figure 4 by treatment cohort and Figure 5 by treatment).

AEs by subject will be presented in Listing 8. A subject listing of non-serious AEs of moderate or greater severity will be presented in Table 22. For Listing 8 and Table 22, all related AEs will be listed before unrelated AEs.

9.4. Deaths, Serious Adverse Events and other Adverse Events

A listing of SAEs by subject will be presented in Table 21. The listing will include Subject ID, treatment cohort, AE description, dose number, duration, reason reported as an SAE, relationship to study product, alternate etiology if not related, action taken with study product, whether the subject discontinued due to the AE, outcome, whether the AE was a suspected unexpected serious adverse reaction (SUSAR), MedDRA® SOC, MedDRA® PT, and MedDRA® HLT.

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9.5. Birth Control and Pregnancies

For any subjects in the Safety Population who become pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. If any pregnancies occur, listings of pregnancies and outcomes will be presented (Listing 21, Listing 22, Listing 23, Listing 24, and Listing 25).

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

9.6. Clinical Laboratory Evaluations

Chemistry, Hematology, Coagulation, and Urinalysis laboratory parameters will be collected as described in Section 4.5. Toxicity grading criteria for the clinical laboratory evaluations can be found in Table 5. Unscheduled tests for medical or safety reasons will be listed but excluded from tabular and graphical summaries, except when calculating the maximum severity post-baseline. Assessments at Day -1 will serve as baseline values for all laboratory parameters.

The following laboratory parameters will be presented:

- Chemistry: Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, Glucose (Fasting and Non-Fasting), Albumin, Total Protein, LDH, ALT, AST, ALP, and Total Bilirubin

  Note: Unknown Glucose is reported as Non-Fasting Glucose

- Hematology: Hemoglobin, Hematocrit, WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, RBC, Platelets, and Coombs test
- Coagulation: Prothrombin Time and PTT
- Urinalysis: Protein, Glucose, Ketones, Bilirubin, Blood, Nitrites, LCE, Urobilinogen, Specific Gravity, and pH

Laboratory parameters will be summarized by treatment cohort and parameter for change in severity from Baseline to all post-dose time points (including early terminations and maximum severity post-baseline). Only laboratory parameters that have a grading listed in Table 5 will be summarized. All baseline and post-dose measurements will be summarized according to the grading scale in Table 5. If any post-dose measurement is outside the normal range but did not meet the definition for an AE based on the grading in Table 5, it will be categorized as "Outside Normal Range." Laboratory measurements collected that have a mild grading but are not clinically significant will be included in these tables. Additionally, laboratory parameters that have grading criteria for both high (results higher than normal range) and low (results lower than normal range) will be summarized separately.

Frequencies (numbers and percentages) of the change in severity from Baseline to all scheduled post-dose time points for all Chemistry parameters, not including Bicarbonate, Chloride, Albumin, and LDH, will be summarized in Table 27. Frequencies of individual parameters, excluding the same parameters from Table 27, will be summarized starting at Table 28 and continuing through Table 38. Frequencies of the change in severity from Baseline to all scheduled post-dose time points for all Hematology parameters, not including Hematocrit, Monocytes, Basophils, and RBC, will be summarized in Table 55. Frequencies of individual parameters, excluding the same parameters from Table 55, will be summarized starting at Table 56 and continuing through Table 61. Frequencies of the change in severity from Baseline to all scheduled post-dose time points for all Coagulation parameters will be summarized in Table 74. Frequencies of individual parameters will be summarized in Table 75 and Table 76. Frequencies of the change in severity from Baseline

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to all scheduled post-dose time points for all Urinalysis parameters, not including Ketones, Bilirubin, Nitrites, LCE, Urobilinogen, Specific Gravity, and pH will be summarized in Table 80. Frequencies of individual parameters, excluding the same parameters from Table 80, will be summarized in Table 81 and Table 82.

Abnormal laboratory results (graded mild, moderate, or severe, or outside of reference range) for Chemistry, Hematology, Coagulation, and Urinalysis parameters will be listed in Table 23, Table 24, Table 25, and Table 26, respectively. Abnormal laboratory results that are reported as AEs and are related to the study product will be summarized for Chemistry, Hematology, Coagulation, and Urinalysis parameters by severity for all post-dose time points (Table 39, Table 62, Table 77, and Table 83, respectively). Refer to Protocol v3.0 Section 8.5 for abnormal laboratory values that are reported as AEs.

For continuous laboratory parameters, descriptive statistics, including mean, standard deviation, median, minimum, and maximum values by time point and change from baseline for all post-dose measurements will be presented by laboratory parameter and treatment cohort. Chemistry parameters will be presented beginning at Table 40 and continuing through Table 54. Hematology parameters will be presented beginning at Table 63 and continuing through Table 72. Results from Coombs tests will be presented for Screening and Day 8 by treatment cohort in Table 73. Coagulation parameters will be presented in Table 78 and Table 79. Urinalysis parameters (Specific Gravity and pH) will be presented in Table 84 and Table 85. Categorical urinalysis parameters (protein, glucose, ketones, bilirubin, blood, nitrites, leukocyte esterase, and urobilinogen) will be presented for baseline and all post-dose measurements by treatment cohort beginning at Table 86 and continuing through Table 93.

Line plots showing individual subject and mean values at baseline and all scheduled post-dose time points will be presented by laboratory parameter and treatment cohort. Chemistry parameters will be presented in Figure 6 through Figure 21. Hematology parameters will be presented in Figure 37 through Figure 47. Coagulation parameters will be presented in Figure 58 and Figure 59. Urinalysis parameters will be presented in Figure 62 and Figure 63. Line plots with standard error bars showing the mean change from baseline at each scheduled post-dose time point will be presented by laboratory parameter and treatment cohort. Chemistry parameters will be presented beginning at Figure 22 and continuing through Figure 36. Hematology parameters will be presented beginning at Figure 48 and continuing through Figure 57. Coagulation parameters will be presented in Figure 60 and Figure 61. Urinalysis parameters will be presented in Figure 64 and Figure 65. Laboratory parameters that have grading criteria for both males and females will be presented separately.

Listing 9, Listing 10, Listing 11, and Listing 12 will provide a complete listing of individual clinical laboratory results with applicable reference ranges. Serology screening, Coombs test, urine cotinine, urine toxicology and alcohol screening, and pregnancy test results will be provided in Listing 13, Listing 14, Listing 15, and Listing 16, respectively.

9.7. Vital Signs and Physical Evaluations

Vital sign measurements include pulse rate, systolic BP, diastolic BP, oral temperature, and respiratory rate. Vital signs will be assessed at Screening, Day -1, prior to dosing and 1 hour after starting the first dose on Day 1, and on Days 2-8. Assessments at Day -1 will serve as baseline values for all vital sign measurements.

The grading scale for vital sign evaluations is presented in Table 5. Summaries of vital signs by severity will be tabulated by time point and treatment cohort and presented for all parameters in Table 94 and by parameter in Table 95, Table 96, Table 97, Table 98, and Table 99. Vital signs that have grading criteria for both decreases (results lower than normal range) and increases (result higher than normal range) will be summarized separately.

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Descriptive statistics including mean, standard deviation, median, minimum, and maximum values by time point and change from baseline for all post-dose measurements (including early terminations and max severity post-baseline) will be presented in Table 100, Table 101, Table 102, Table 103, and Table 104.

Line plots showing individual subject and mean values at baseline and all scheduled post-dose time points will be presented by vital sign and treatment cohort (Figure 66, Figure 67, Figure 68, Figure 69, and Figure 70). Line plots with standard error bars showing the mean change from baseline at each scheduled post-dose time point will be presented by vital sign and treatment cohort (Figure 71, Figure 72, Figure 73, Figure 74, and Figure 75).

Vital signs will be listed (Listing 17). Unplanned vital signs measurements will be included in the listing, but excluded from tabular and graphic summaries, except when calculating the maximum severity post-baseline.

A physical exam will be performed at Screening and on Days -1, 8, and 11 (+3) as described in Section 4.5, as well as SAE follow-up as needed. Results of physical examinations, scheduled and unscheduled, will be presented in Listing 18.

9.8. ECG Assessments

ECG measurements include QTcF Interval and PR Interval. ECGs will be performed at Screening and on Days -1 (baseline), 8, and 11 (+3). The grading scale for ECG evaluations is presented in Table 4.

ECG change in overall interpretation from Baseline to all scheduled post-dose time points by treatment cohort will be shown in Table 105. Summaries of ECG results will be tabulated by treatment cohort, severity grading, and time point (Table 106).

Descriptive statistics including mean, standard deviation, median, minimum, and maximum values by time point and change from baseline will be tabulated and presented for baseline and each scheduled post-dose time point in Table 107. The baseline measurement used for all post-dose time points will be the measurements taken on Day -1.

Line plots showing individual subject and mean values at baseline and all scheduled post-dose time points will be presented by ECG measurement and treatment cohort (Figure 76 and Figure 78). Line plots with standard error bars showing the mean change from baseline at each scheduled post-dose time point will be presented by ECG measurement and treatment cohort (Figure 77 and Figure 79).

Individual data listings of ECG results will be listed (Listing 19). ECGs will be done in triplicate at Screening, and the individual results along with the mean of the three measurements will be included in the listing.

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10. PHARMACOKINETICS

PK analysis will be described in the PK SAP.

Listings of subject level concentrations of CAZ, AVI, and ATM in plasma and urine will be presented in Listing 27 and Listing 28, respectively. Listings of subject-specific PK parameters from non-compartmental plasma and urine PK analyses will be presented for CAZ, AVI, and ATM in Listing 29 and Listing 30. Subject-specific PK parameters from the population PK analysis will be listed in Listing 31.

11. IMMUNOGENICITY

There are no immunogenicity endpoints for this protocol.

12. OTHER ANALYSES

There are no other analyses.

13. REPORTING CONVENTIONS

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

Listings of individual subject data include a Subject ID column. The subject identifiers assigned by site staff are replaced throughout this report with the 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 eClinical platform code followed by a numeric identifier assigned chronologically to enrolled subjects as well as screening failures across all sites and protocol in the eClinical platform. Any data sharing activities will include the USUBJID and not the subject identifiers assigned at the site.

14. TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures, and listings.

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

In response to the occurrence of two grade 3 AEs that were related to study product and of the same HLT in Cohort 4, the dose of ATM in Cohort 5 was reduced to 1.5 g IV as a 2-hour infusion every 6 hours (ATM 6 g/daily) and will be administered in combination with AVYCAZ® 2.5 g IV as a 2-hour infusion every 8 hours. A SMC meeting will be convened after the completion of Cohort 5, and if no halting rules are met or there are no other safety concerns, the dose of ATM in Cohort 6 will be 2 g IV as a 2-hour infusion every 6 hours (ATM 8 g/daily) and administered in combination with AVYCAZ® 2.5 g IV as a 2-hour infusion every 8 hours.

More intensive LFT monitoring will be performed in Cohorts 5 and 6 with additional collection of LFTs on Days 5 and 7.

16. REFERENCES

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17. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

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9.1 Overall Study Design and Plan Description

Table 1: Treatment Cohorts

Cohort Number	Cohort Name	No. of Subjects	Treatment
Cohort 1	AVYCAZ IV	8	AVYCAZ® 2.5 g IV as 2-hour infusion every 8 hours for 7 days (19 total doses)
Cohort 2	AVYCAZ CI	8	AVYCAZ® 2.5 g IV as a 2-hour infusion x 1, then 0.32 g per hour IV daily as a Continuous Infusion (CI) (7.5 g/day) for 7 days (20 total doses, IV bag changes every 8 hours for CI)
Cohort 3	ATM IV	8	ATM 2 g IV as 2-hour infusion every 6 hours for 7 days (25 total doses)
Cohort 4	ATM CI	8	ATM 2 g IV as a 2-hour infusion x 1, then 0.33 g per hour IV daily as a CI (8 g/day) for 7 days (14 total doses, IV bag changes every 12 hours for CI)
Cohort 5	AVYCAZ IV + ATM (1.5) IV	8	AVYCAZ® 2.5 g IV as 2-hour infusion every 8 hours for 7 days and ATM 1.5 g IV as a 2-hour infusion every 6 hours for 7 days (AVYCAZ® 19 total doses; ATM 25 total doses)
Cohort 6	AVYCAZ IV + ATM (2.0) IV	8	AVYCAZ® 2.5 g IV as a 2-hour infusion every 8 hours for 7 days and ATM 2 g IV as a 2-hour infusion every 6 hours for 7 days (AVYCAZ® 19 total doses; ATM 25 total doses)

9.5.1 Efficacy/Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 2: Schedule of Study Procedures

[Note: This table will be taken from the current version of the protocol at the time of the CSR.]

10.2 Protocol Deviations

Table 3: Distribution of Protocol Deviations by Category, Type, and Treatment Cohort

Category	Deviation Type	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		Cohort 6 (N=X)		All Subjects (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.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type														
	Did not meet inclusion criterion														
	Met exclusion criterion														
	Incorrect version of ICF signed														
	ICF not signed prior to study procedures														
	Other														
Treatment administration schedule	Any type														
	Out of window visit														
	Missed visit/visit not conducted														
	Missed treatment administration														
	Delayed treatment administration														
	Other														
Follow-up visit schedule	Any type														
	Out of window visit														
	Missed visit/visit not conducted														
	Other														
Protocol procedure/assessment	Any type														
	Blood not collected														
	Urine not collected														
	Too few aliquots obtained														
	Specimen result not obtained														

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Table 3: Distribution of Protocol Deviations by Category, Type, and Treatment Cohort *(continued)*

Category	Deviation Type	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		Cohort 6 (N=X)		All Subjects (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.	No. of Subj.	No. of Dev.
	Required procedure not conducted														
	Required procedure done incorrectly														
	Study product temperature excursion														
	Specimen temperature excursion														
	Other														
Treatment administration	Any type														
	Missed treatment administration														
	Delayed treatment administration														
	Required procedure done incorrectly														
	Study product temperature excursion														
	Other														

Note: N = Number of Subjects Enrolled

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12.2.2 Displays of Adverse Events

Table 4: Adverse Event Definitions

[Note: This table will be taken from the current version of the protocol at the time of the CSR.]

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 5: Laboratory and Vital Signs Reference Ranges, Eligibility Ranges, and Toxicity Grading

[Note: This table will be taken from the current version of the protocol at the time of the CSR.]

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 6: Subject Disposition by Treatment Cohort – All Enrolled Subjects

[Implementation Note: Blood Draws include hematology, chemistry, coagulation measurements that relate to the safety endpoints. Urine Collections include urine dipstick that relate to the safety endpoints.]

Subject Disposition	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		Cohort 6 (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Screened	-	-	-	-	-	-	-	-	-	-	-	-	x	-
Enrolled	x	100	x	100	x	100	x	100	x	100	x	100	x	100
Started Treatment on Day 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Treatment on Day 7														
Completed Discharge on Day 8														
Received All Scheduled Treatments[a]														
Received Partial Dose of Study Product														
Completed All Safety Blood Draws[b]														
Completed All Safety Urine Collections[b]														
Completed Follow-up (Study Day 11)[a]														

Note: N = Number of Subjects Enrolled. n = Number of Subjects who fall into each category.
[a] Refer to Listing 1 for reasons subjects discontinued or terminated early
[b] Blood Draws and Urine Collections include all measurements that are related to the safety endpoints.

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Table 7: Analysis Population Exclusions by Treatment Cohort – All Enrolled Subjects

Analysis Populations	Reason Subjects Excluded	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		Cohort 6 (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Safety Population	Any Reason	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Did not receive any dose of study product(s)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
PK Population	Any Reason	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Did not receive any dose of study product(s)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Did not have any quantifiable plasma or urine concentration of CAZ, AVI, or ATM	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Note: N = Number of Subjects Enrolled. n = Number of Subjects who were excluded for each reason.

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Table 8: Dates of First Treatment by Treatment Cohort

[Implementation Note: Dosing dates should be categorized monthly. For June 2019, month should start on 14JUN2019 instead of 01JUN2019 to account for study start date.]

Dates of Dosing	Cohort 1 (N=X)	Cohort 2 (N=X)	Cohort 3 (N=X)	Cohort 4 (N=X)	Cohort 5 (N=X)	Cohort 6 (N=X)	All Subjects (N=X)
Total (Entire period of enrollment)	x	x	x	x	x	x	x
14JUN2019 – 30JUN2019	x	x	x	x	x	x	x
01JUL2019 – 31JUL2019							
01AUG2019 – 31AUG2019							
…							

Note: N = Number of Subjects in Safety Population

Table 9: Ineligibility Summary of Screen Failures

[Implementation Note: Although all I/E criteria are included in the shell, only criteria that are reported as reasons for screen failures will be included.]

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	xx
	Provide a signed and dated written informed consent	x	xx
	Be able to understand and willing to comply with study procedures, restriction, and requirements, as determined by the PI	x	xx
	Males and females volunteer aged 18 to 45 inclusion	x	xx
	Suitable veins for cannulation or repeated venipuncture	x	xx
	Subject must be in good general health as judged by the investigator as determined by medical history, vital signs, body mass index (BMI) and body weight, clinical laboratory values, and physical examination (PE)	x	xx
	Sexually active female subjects must be of non-childbearing potential or must use a highly effective method of birth control	x	xx
	Sexually active male subjects must be vasectomized or agree to use barrier contraception (condom with spermicide) from first dose of study product until 30 days following last dose of study product	x	xx
	Nonsmokers defined as abstinence from cigarette smoking or use of nicotine-containing products for 6 months prior to enrollment into the study	x	xx
Exclusion	Any exclusion criterion	x	xx
	History of any clinically significant (CS) disease or disorder, medical/surgical procedure, or trauma within 4 weeks prior to the first administration of study product(s)	x	xx
	History or presence of gastrointestinal, hepatic, or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs	x	xx
	Known history of a clinically important allergy/hypersensitivity to avibactam (AVI), any monobactam, any beta-lactam and/or L-arginine	x	xx
	Receipt of probenecid or furosemide within 14 days prior to study enrollment	x	xx
	Receipt of any antibiotics within 14 days prior to study enrollment	x	xx
	Receipt of prescription medication (except birth control pills or hormone replacement in females) within 14 days prior to study enrollment, unless in the opinion of site investigator the medication will not interfere with the study procedures or impact study safety	x	xx
	Receipt of non-antibiotic medications that interacts with OAT3 within 14 days prior to study enrollment	x	xx
	Receipt of herbal and dietary supplements (including St. John's Wort) within 14 days prior to study enrollment	x	xx
	Alkaline transaminase (ALT) or aspartate aminotransferase (AST) laboratory value above the ULN as defined in Table 5	x	xx

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Table 9: Ineligibility Summary of Screen Failures *(continued)*

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
	Prolonged QTcF (> 450 msec) or shortened QTcF (< 340 msec) or family history of long QT syndrome. Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG	x	xx
	Any positive result on screening for human immunodeficiency virus (HIV) serum hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) antibody	x	xx
	Creatinine clearance equal or less than 80 mL/minute (measured by Cockcroft-Gault method)	x	xx
	History of *Clostridium difficile* infection in past 90 days	x	xx
	Known or suspected history of drug or alcohol abuse within the last 5 years, as judged by the PI	x	xx
	Positive screen for drugs of abuse, cotinine (nicotine), or alcohol at screening and at admission to the study site prior to the first administration of the study products(s)	x	xx
	Received a new chemical entity (compound not approved for marketing) or participated in a study that included drug treatment within 1 month of the first dose of study product(s) for study	x	xx
	Previous participation in the present study	x	xx
	Involvement in the planning and/or conduct of the study	x	xx
	Any ongoing/recent (during screening) medical complaints that may interfere with analysis of study data or are considered unlikely to comply with study procedures, restrictions, and requirements	x	xx
	Known history of past or current epilepsy or seizure disorders, excluding febrile seizures of childhood	x	xx

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

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14.1.2 Demographic Data by Study Group

Table 10: Summary of Categorical Demographic and Baseline Characteristics by Treatment Cohort

Demographic Category	Characteristic	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		Cohort 6 (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Female														
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Hispanic or Latino														
	Not Reported														
	Unknown														
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Asian														
	Native Hawaiian or Other Pacific Islander														
	Black or African American														
	White														
	Multi-Racial														
	Unknown														

Note: N = Number of Subjects in Safety Population

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Table 11: Summary of Continuous Demographic and Baseline Characteristics by Treatment Cohort

[Implementation Note: Use height and weight measurements from Day -1.]

Variable	Statistic	Cohort 1 (N=X)	Cohort 2 (N=X)	Cohort 3 (N=X)	Cohort 4 (N=X)	Cohort 5 (N=X)	Cohort 6 (N=X)	All Subjects (N=X)
Age	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x
BMI (kg/m^2)	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Standard Deviation	x.xx	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	x.xx
	Minimum	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Height (cm)[a]	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Standard Deviation	x.xx	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	x.xx
	Minimum	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Weight (kg)[a]	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Standard Deviation	x.xx	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	x.xx
	Minimum	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x	x.x	x.x	x.x	x.x

Notes: N = Number of Subjects in Safety Population; Age is rounded down to the nearest whole number; BMI = Weight (kg) / Height $(m)^2$

[a] The height and weight measurements from Day -1 were used for each subject.

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14.1.3 Prior and Concurrent Medical Conditions

Table 12: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Cohort

[Implementation Note: SOC will be ordered alphabetically.]

MedDRA System Organ Class	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		Cohort 6 (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]														
[SOC 2]														

Notes: N = Number of Subjects in Safety Population; n = Number of Subjects reporting medical history within the specified SOC. A subject is only counted once per SOC; SOC = System Organ Class.

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14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 13: Overall Summary of Adverse Events

	Cohort 1 (N=X)		Cohort 2 (N=X)		Cohort 3 (N=X)		Cohort 4 (N=X)		Cohort 5 (N=X)		Cohort 6 (N=X)		All Subjects (N=X)	
Subjects[a] with	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
At least one AE	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
At least one related AE														
At least one related Mild (Grade 1) AE														
At least one related Moderate (Grade 2) AE														
At least one related Severe (Grade 3) AE														
At least one unrelated AE														
At least one unrelated Mild (Grade 1) AE														
At least one unrelated Moderate (Grade 2) AE														
At least one unrelated Severe (Grade 3) AE														
At least one AE leading to early termination														
At least one SAE[b]														
At least one related SAE														
At least one SUSAR														

Notes: N = Number of Subjects in Safety Population; SAE = Serious Adverse Event (Unsolicited); SUSAR = Suspected Unexpected Severe Adverse Reaction.
[a] Subjects are counted once for each category regardless of the number of events.
[b] A listing of SAEs is included in Table 18.

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Table 14: Number of Adverse Events Experienced by Subject and Severity

[Implementation Note: Order by treatment cohort and descending total number of AEs reported.]

Treatment Cohort	Subject ID	Number of Mild AEs	Number of Moderate AEs	Number of Severe AEs	Total Number of AEs
Cohort 1	XX	2	0	1	3

Table 15: Adverse Events Occurring in 10% of Subjects in Any Treatment Cohort by MedDRA System Organ Class, Preferred Term, High Level Term, Relationship and Treatment Cohort

[Implementation Note: SOC, PT, and HLT will be ordered alphabetically.]

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	Cohort 1 (N=X)			Cohort 2 (N=X)			Cohort 3 (N=X)			Cohort 4 (N=X)			Cohort 5 (N=X)			Cohort 6 (N=X)			All Subjects (N=X)		
			n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
Related																							
Serious Adverse Events																							
Any SOC	Any PT	Any HLT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT																					
	[PT 1]	Any HLT																					
		[HLT 1]																					
Etc.	Etc.																						
Other (Non-serious) Adverse Events																							
Any SOC	Any PT	Any HLT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT																					
	[PT 1]	Any HLT																					
		[HLT 1]																					
Etc.	Etc.																						
Unrelated																							
Serious Adverse Events																							
Any SOC	Any PT	Any HLT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT																					
	[PT 1]	Any HLT																					
		[HLT 1]																					
Etc.	Etc.																						

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Table 15: Adverse Events Occurring in 10% of Subjects in Any Treatment Cohort by MedDRA System Organ Class, Preferred Term, High Level Term, Relationship and Treatment Cohort *(continued)*

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	Cohort 1 (N=X)			Cohort 2 (N=X)			Cohort 3 (N=X)			Cohort 4 (N=X)			Cohort 5 (N=X)			Cohort 6 (N=X)			All Subjects (N=X)		
			n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
Other (Non-serious) Adverse Events																							
Any SOC	Any PT	Any HLT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT																					
	[PT 1]	Any HLT																					
		[HLT 1]																					
Etc.	Etc.																						

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects Reporting Event. Events = Total Frequency of Events Reported. SOC = System Organ Class. PT = Preferred Term. HLT = High Level Term.

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Table 16: Adverse Events Occurring in 10% of Subjects in Any Treatment Cohort by MedDRA System Organ Class, Preferred Term, High Level Term, Relationship and Treatment

[Implementation Note: SOC, PT, and HLT will be ordered alphabetically.]

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	AVYCAZ (N=X)			ATM (N=X)			Combination (N=X)		
			n	%	Events	n	%	Events	n	%	Events
Related											
Serious Adverse Events											
Any SOC	Any PT	Any HLT	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT									
	[PT 1]	Any HLT									
		[HLT 1]									
Etc.	Etc.										
Other (Non-serious) Adverse Events											
Any SOC	Any PT	Any HLT	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT									
	[PT 1]	Any HLT									
		[HLT 1]									
Etc.	Etc.										
Unrelated											
Serious Adverse Events											
Any SOC	Any PT	Any HLT	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT									
	[PT 1]	Any HLT									
		[HLT 1]									

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Table 16: Adverse Events Occurring in 10% of Subjects in Any Treatment Cohort by MedDRA System Organ Class, Preferred Term, High Level Term, Relationship and Treatment *(continued)*

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	AVYCAZ (N=X)			ATM (N=X)			Combination (N=X)		
			n	%	Events	n	%	Events	n	%	Events
Other (Non-serious) Adverse Events											
Etc.	Etc.										
Any SOC	Any PT	Any HLT	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT									
	[PT 1]	Any HLT									
		[HLT 1]									
Etc.	Etc.										

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects Reporting Event. Events = Total Frequency of Events Reported. SOC = System Organ Class. PT = Preferred Term. HLT = High Level Term. AVYCAZ = Cohort 1 and Cohort 2. ATM = Cohort 3 and Cohort 4. Combination = Cohort 5 and Cohort 6.

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14.3.1.2 Unsolicited Adverse Events

Table 17: Number and Percentage of Subjects Experiencing Unsolicited Events with 95% Confidence Intervals by MedDRA System Organ Class, Preferred Term, High Level Term, and Treatment Cohort

[Implementation Note: SOC, PT, and HLT will be ordered alphabetically.]

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	Any Time Post Dose			
			n	%	95% C.I.[a]	Events
All Subjects (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				
Cohort 1 (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				
Cohort 2 (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				
Cohort 3 (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				
Cohort 4 (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				
Cohort 5 (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				

Table 17: Number and Percentage of Subjects Experiencing Unsolicited Events with 95% Confidence Intervals by MedDRA System Organ Class, Preferred Term, High Level Term, and Treatment Cohort *(continued)*

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	Any Time Post Dose			
			n	%	95% C.I.[a]	Events
Cohort 6 (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				

Notes: N = Number of Subjects in Safety Population; n = Number of Subjects Reporting Event; Events = Total Frequency of Events Reported; SOC = System Organ Class; PT = Preferred Term; HLT = High Level Term.
This table presents number and percentages of subjects, as well as the number of events. A subject is only counted once per PT.
[a] Calculated using the exact (Clopper-Pearson) method.

Table 18: Number and Percentage of Subjects Experiencing Unsolicited Events with 95% Confidence Intervals by MedDRA System Organ Class, Preferred Term, High Level Term, and Treatment

[Implementation Note: SOC, PT, and HLT will be ordered alphabetically.]

			Any Time Post Dose			
MedDRA System Organ Class	**MedDRA Preferred Term**	**MedDRA High Level Term**	**n**	**%**	**95% C.I.[a]**	**Events**
All Subjects (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				
AVYCAZ (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				
ATM (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				
Combination (N=X)						
Any SOC	Any PT	Any HLT	x	x	(x, x)	x
[SOC 1]	Any PT	Any HLT	x	x	(x, x)	x
	[PT 1]	Any HLT				
	[PT 1]	[HLT 1]				

Notes: N = Number of Subjects in Safety Population; n = Number of Subjects Reporting Event; Events = Total Frequency of Events Reported; SOC = System Organ Class; PT = Preferred Term; HLT = High Level Term. AVYCAZ = Cohort 1 and Cohort 2. ATM = Cohort 3 and Cohort 4. Combination = Cohort 5 and Cohort 6.
This table presents number and percentages of subjects, as well as the number of events. A subject is only counted once per PT.
[a] Calculated using the exact (Clopper-Pearson) method.

Table 19: Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and High Level Term, Maximum Severity, Relationship, and Treatment Cohort

[Implementation Note: SOC, PT, and HLT will be ordered alphabetically. Rows for Mild, Moderate, and Severe will only be shown for non-zero counts.]

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	Severity	Related		Not Related		Total	
				n	%	n	%	n	%
All Subjects (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
	[PT 1]	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
Cohort 1 (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
	[PT 1]	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
Cohort 2 (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x

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Table 17: Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and High Level Term, Maximum Severity, Relationship, and Treatment Cohort *(continued)*

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	Severity	Related		Not Related		Total	
				n	%	n	%	n	%
[SOC 1]	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
	[PT 1]	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
Cohort 3 (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
	[PT 1]	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
Cohort 4 (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
	[PT 1]	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x

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Table 17: Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and High Level Term, Maximum Severity, Relationship, and Treatment Cohort *(continued)*

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	Severity	Related		Not Related		Total	
				n	%	n	%	n	%
Cohort 5 (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
	[PT 1]	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
Cohort 6 (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
	[PT 1]	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x

Notes: N = Number of Subjects in Safety Population; SOC = System Organ Class; PT = Preferred Term; HLT = High Level Term. A subject is only counted once per PT/severity.

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Table 20: Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and High Level Term, Maximum Severity, Relationship, and Treatment

[Implementation Note: SOC, PT, and HLT will be ordered alphabetically. Rows for Mild, Moderate, and Severe will only be shown for non-zero counts.]

MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Term	Severity	Related		Not Related		Total	
				n	%	n	%	n	%
All Subjects (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
	[PT 1]	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
AVYCAZ (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
[SOC 1]	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
	[PT 1]	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x
ATM (N=X)									
Any SOC	Any PT	Any HLT	Any Severity	x	x	x	x	x	x
			Mild	x	x	x	x	x	x
			Moderate	x	x	x	x	x	x
			Severe	x	x	x	x	x	x

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Table 20: Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and High Level Term, Maximum Severity, Relationship, and Treatment *(continued)*

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

Notes: N = Number of Subjects in Safety Population; SOC = System Organ Class; PT = Preferred Term; HLT = High Level Term. A subject is only counted once per PT/severity. AVYCAZ = Cohort 1 and Cohort 2. ATM = Cohort 3 and Cohort 4. Combination = Cohort 5 and Cohort 6.

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14.3.2 Listing of Deaths and Other Serious Adverse Events

Table 21: Listing of Serious Adverse Events

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

Table 22: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

[Implementation Note: Sort by Relatedness (related then unrelated), Treatment Cohort, Subject ID.]

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

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14.3.3 Narratives of Deaths and Other Serious Adverse Events

Not included in SAP, but this is a placeholder for the CSR.

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 23: Listing of Abnormal Laboratory Results – Chemistry

[Implementation Note: This table will report all lab results that are outside the reference range, including results that are not graded.]

Subject ID	Treatment Cohort	Sex	Age (years)	Planned Study Day	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

Table 24: Listing of Abnormal Laboratory Results – Hematology

[Implementation Note: This table will report all lab results that are outside the reference range, including results that are not graded.]

Subject ID	Treatment Cohort	Sex	Age (years)	Planned Study Day	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

Table 25: Listing of Abnormal Laboratory Results – Coagulation

[Implementation Note: This table will report all lab results that are outside the reference range, including results that are not graded.]

Subject ID	Treatment Cohort	Sex	Age (years)	Planned Study Day	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

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Table 26: Listing of Abnormal Laboratory Results – Urinalysis

[Implementation Note: This table will report all lab results that are outside the reference range, including results that are not graded.]

Subject ID	Treatment Cohort	Sex	Age (years)	Planned Study Day	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 27: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Any Chemistry Parameter

[Implementation Note: Only includes chemistry parameters that have gradings (Sodium, Potassium, BUN, Serum Creatinine, Fasting Glucose, Non-Fasting (Unknown) Glucose, Total Protein, Total Bilirubin, ALT, AST, and ALP). If no results are missing for any time point, then this column can be removed from the table. If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table. Day 5 and 7 are only applicable to Cohorts 5 and 6; ALT, AST, ALP, and total bilirubin.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Outside Normal Range												
		Mild												
		Moderate												
		Severe												
		Missing												
	Cohort 1 (N=X)	None												
		Outside Normal Range												
		Mild												
		Moderate												
		Severe												
		Missing												
	Cohort 2 (N=X)	None												
		Outside Normal Range												
		Mild												
		Moderate												

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Table 27: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Any Chemistry Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
		Severe												
		Missing												
	Cohort 3 (N=X)	None												
		Outside Normal Range												
		Mild												
		Moderate												
		Severe												
		Missing												
	Cohort 4 (N=X)	None												
		Outside Normal Range												
		Mild												
		Moderate												
		Severe												
		Missing												
	Cohort 5 (N=X)	None												
		Outside Normal Range												
		Mild												
		Moderate												
		Severe												
		Missing												
	Cohort 6 (N=X)	None												
		Outside Normal Range												
		Mild												

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Table 27: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Any Chemistry Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
		Moderate												
		Severe												
		Missing												
Day 4	All Subjects (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 1 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 2 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 3 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 4 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 5 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 6 (N=X)	None												
		Outside Normal Range												

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Table 27: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Any Chemistry Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
		…												
Day 5	Cohort 5 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 6 (N=X)	None												
		Outside Normal Range												
		…												
Day 6	All Subjects (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 1 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 2 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 3 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 4 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 5 (N=X)	None												

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Table 27: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Any Chemistry Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
		Outside Normal Range												
		…												
	Cohort 6 (N=X)	None												
		Outside Normal Range												
		…												
Day 7	Cohort 5 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 6 (N=X)	None												
		Outside Normal Range												
		…												
Day 8	All Subjects (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 1 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 2 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 3 (N=X)	None												
		Outside Normal Range												
		…												

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Table 27: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Any Chemistry Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	Cohort 4 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 5 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 6 (N=X)	None												
		Outside Normal Range												
		…												
Day 11	All Subjects (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 1 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 2 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 3 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 4 (N=X)	None												
		Outside Normal Range												

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Table 27: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Any Chemistry Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
		…												
	Cohort 5 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 6 (N=X)	None												
		Outside Normal Range												
		…												
Early Termination Visit	All Subjects (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 1 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 2 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 3 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 4 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 5 (N=X)	None												

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Table 27: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Any Chemistry Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
		Outside Normal Range												
		…												
	Cohort 6 (N=X)	None												
		Outside Normal Range												
		…												
Max Severity Post Baseline	All Subjects (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 1 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 2 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 3 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 4 (N=X)	None												
		Outside Normal Range												
		…												
	Cohort 5 (N=X)	None												
		Outside Normal Range												
		…												

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Table 27: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Any Chemistry Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	Cohort 6 (N=X)	None												
		Outside Normal Range												
		…												

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. Only includes Chemistry parameters that have a grading provided: sodium, potassium, BUN, serum creatinine, fasting glucose, non-fasting (unknown) glucose, total protein, total bilirubin, ALT, AST, and ALP

[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

Table 28: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Sodium

[Implementation Note: If no results are missing for any subject at any time point, then this column can be removed from the table.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild (Low)																
		Mild (High)																
		Moderate (Low)																
		Moderate (High)																
		Severe (Low)																
		Severe (High)																
		Missing																
	Cohort 1 (N=X)	None																
		Mild (Low)																
		…																
	Cohort 2 (N=X)	None																
		Mild (Low)																
		…																
	…																	
Day 4	All Subjects (N=X)	None																
		Mild (Low)																
		…																
	Cohort 1 (N=X)	None																
		Mild (Low)																
		…																

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Table 28: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Sodium *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Cohort 2 (N=X)	None																
		Mild (Low)																
		…																
	…																	
Day 6	All Subjects (N=X)	None																
		Mild (Low)																
		…																
	Cohort 1 (N=X)	None																
		Mild (Low)																
		…																
	Cohort 2 (N=X)	None																
		Mild (Low)																
		…																
	…																	
Day 8	All Subjects (N=X)	None																
		Mild (Low)																
		…																
	Cohort 1 (N=X)	None																
		Mild (Low)																
		…																
	Cohort 2 (N=X)	None																
		Mild (Low)																

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Table 28: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Sodium *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
		…																
	…																	
Day 11	All Subjects (N=X)	None																
		Mild (Low)																
		…																
	Cohort 1 (N=X)	None																
		Mild (Low)																
		…																
	Cohort 2 (N=X)	None																
		Mild (Low)																
		…																
	…																	
Early Termination Visit	All Subjects (N=X)	None																
		Mild (Low)																
		…																
	Cohort 1 (N=X)	None																
		Mild (Low)																
		…																
	Cohort 2 (N=X)	None																
		Mild (Low)																
		…																
	…																	

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Table 28: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Sodium *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	All Subjects (N=X)	None																
		Mild (Low)																
		…																
	Cohort 1 (N=X)	None																
		Mild (Low)																
		…																
	Cohort 2 (N=X)	None																
		Mild (Low)																
		…																
	…																	

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurement from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point past baseline, including unscheduled assessments.

Tables with similar format:

Table 29: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Potassium

Table 30: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Fasting Glucose

Table 31: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Non-Fasting Glucose

[Implementation Note: If no results are missing for any subject at any time point, then this column can be removed from the table.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	
Day 4	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	
Day 6	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	

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Table 31: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Non-Fasting Glucose *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 8	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	
Day 11	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	
Early Termination Visit	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	
Max Severity Post Baseline	All Subjects (N=X)	None																

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Table 31: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Non-Fasting Glucose *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point past baseline, including unscheduled assessments. Unknown Glucose status was reported as Non-Fasting Glucose.

Table 32: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Blood Urea Nitrogen

[If no results are missing for any subjects at any time point, then this column can be removed from the table. If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table. Tables 34, 35, and 36 will have entries for Day 5 and 7 for cohorts 5 and 6.]

			Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
Time Point	Treatment Cohort	Baseline Severity	n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 4	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 6	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												

Table 32: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Blood Urea Nitrogen *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	…													
Day 8	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 11	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Early Termination Visit	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Max Severity Post Baseline	All Subjects (N=X)	None												

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Table 32: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Blood Urea Nitrogen *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

Tables with similar format:

Table 33: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Serum Creatinine

Table 34: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Total Bilirubin

Table 35: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Aspartate Aminotransferase

Table 36: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Alkaline Phosphatase

Table 37: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Alanine Aminotransferase

[If no results are missing for any subjects at any time point, then this column can be removed from the table. If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table. Days 5 and 7 are only applicable to cohorts 5 and 6.]

			Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
Time Point	Treatment Cohort	Baseline Severity	n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 4	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 5	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												

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Table 37: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Alanine Aminotransferase *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 6	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 7	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												
Day 8	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 11	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												

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Table 37: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Alanine Aminotransferase *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
		…												
	…													
Early Termination Visit	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Max Severity Post Baseline	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

Table 38: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Total Protein

[If no results are missing for any subjects at any time point, then this column can be removed from the table. If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (Low)		Moderate/ Grade 2 (Low)		Severe/ Grade 3 (Low)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 4	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 6	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												

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Table 38: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Total Protein *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (Low)		Moderate/ Grade 2 (Low)		Severe/ Grade 3 (Low)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	…													
Day 8	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 11	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Early Termination Visit	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

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Table 38: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Chemistry – Total Protein *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (Low)		Moderate/ Grade 2 (Low)		Severe/ Grade 3 (Low)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

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Table 39: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Any Chemistry Parameter

[Implementation Note: Only includes chemistry parameters that have gradings (Sodium, Potassium, BUN, Serum Creatinine, Fasting Glucose, Non-Fasting (Unknown) Glucose, Total Protein, Total Bilirubin, ALT, AST, and ALP). If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table. Days 5 and 7 are only applicable to Cohorts 5 and 6.]

Time Point	Treatment Cohort	N	Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
Day 2	All Subjects	x	x	xx	x	xx	x	xx	x	xx
	Cohort 1									
	Cohort 2									
	…									
Day 4	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Day 5	Cohort 5									
	Cohort 6									
Day 6	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Day 7	Cohort 5									
	Cohort 6									
Day 8	All Subjects									
	Cohort 1									
	Cohort 2									
	…									

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Table 39: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Any Chemistry Parameter *(continued)*

Time Point	Treatment Cohort	N	Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Early Termination Visit	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Max Severity Post Baseline	All Subjects									
	Cohort 1									
	Cohort 2									
	…									

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. The "Max Post Baseline" rows indicate the maximum severity of abnormal laboratory results related to study treatment experienced by each subject at any time point post baseline, including unscheduled assessments. Only includes Chemistry parameters that have a grading provided: sodium, potassium, BUN, serum creatinine, fasting glucose, non-fasting (unknown) glucose, total protein, total bilirubin, ALT, AST, and ALP.
[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

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Table 40: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Sodium (mEq/L)

[Implementation Note: Min and Max will be reported using the minimum number of significant figures of what is collected. Mean, Std. Dev., and Median will be reported using the maximum number of significant figures + 1 of what is collected. For example, sodium is reported as XX, so the Min and Max will be reported as XX, and Mean, Std. Dev., and Median will be reported as XX.X. This applies to all the lab tables (Chemistry, Hematology, Coagulation, and Urinalysis). Tables 51, 52, and 53 will have rows for Days 5 and 7 applicable to Cohorts 5 and 6 only.]

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Baseline	All Subjects	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Cohort 1	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Cohort 2	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Cohort 3	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Cohort 4	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Cohort 5	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
	Cohort 6	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
Day 2	All Subjects	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Cohort 1	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Cohort 2	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Cohort 3	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Cohort 4	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Cohort 5	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
	Cohort 6	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx.x, xx.x
Day 4	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

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Table 40: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Sodium (mEq/L) *(continued)*

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Day 6	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 8	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

Note: N = Number of Subjects in Safety Population with the laboratory result assessed at the respective time point. Baseline = Measurements from Day -1.

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Tables with similar format:

Table 41: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Potassium (mEq/L)

Table 42: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Chloride (mmol/L)

Table 43: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Bicarbonate (mmol/L)

Table 44: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Blood Urea Nitrogen (mg/dL)

Table 45: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Serum Creatinine (mg/dL)

Table 46: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Fasting Glucose (mg/dL)

Table 47: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Non-Fasting Glucose (mg/dL)

Table 48: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Total Protein (g/dL)

Table 49: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Lactate Dehydrogenase (U/L)

Table 50: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Albumin (g/dL)

Table 51: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Total Bilirubin (mg/dL)

Table 52: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Aspartate Aminotransferase (U/L)

Table 53: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Chemistry – Alkaline Phosphatase (U/L)

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Table 54: Laboratory Summary Statistics by Parameter, Time Point, Gender, and Treatment Cohort – Chemistry – Alanine Aminotransferase (U/L)

[Implementation Note: Days 5 and 7 are applicable to Cohorts 5 and 6 only.]

				Measurement				Change from Baseline			
Time Point	**Gender**	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Baseline	Male	All Subjects	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		Cohort 1	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		Cohort 2						-	-	-	-
		…						-	-	-	-
	Female	All Subjects	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		Cohort 1	x	xx.x	xx.x	xx.x	xx, xx	-	-	-	-
		Cohort 2						-	-	-	-
		…						-	-	-	-
Day 2	Male	All Subjects	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
		Cohort 1	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
		Cohort 2									
		…									
	Female	All Subjects	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
		Cohort 1	x	xx.x	xx.x	xx.x	xx, xx	xx.x	xx.x	xx.x	xx, xx
		Cohort 2									
		…									
Day 4	Male	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
	Female	All Subjects									
		Cohort 1									
		Cohort 2									
		…									

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Table 54: Laboratory Summary Statistics by Parameter, Time Point, Gender, and Treatment Cohort – Chemistry – Alanine Aminotransferase (U/L)
(continued)

				Measurement				Change from Baseline			
Time Point	**Gender**	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Day 5	Male	All Subjects									
		Cohort 5									
		Cohort 6									
	Female	All subjects									
		Cohort 5									
		Cohort 6									
Day 6	Male	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
	Female	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
Day 7	Male	All Subjects									
		Cohort 5									
		Cohort 6									
	Female	All Subjects									
		Cohort 5									
		Cohort 6									
Day 8	Male	All Subjects									
		Cohort 1									
		Cohort 2									
		…									

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Table 54: Laboratory Summary Statistics by Parameter, Time Point, Gender, and Treatment Cohort – Chemistry – Alanine Aminotransferase (U/L)
(continued)

				Measurement				Change from Baseline			
Time Point	**Gender**	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
	Female	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
Day 11	Male	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
	Female	All Subjects									
		Cohort 1									
		Cohort 2									
		…									

Note: N = Number of Subjects in Safety Population with the laboratory result assessed at the respective time point. Baseline = Measurements from Day -1.

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14.3.5.2 Hematology Results

Table 55: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Any Hematology Parameter

[Implementation Note: Only include hematology parameters that are graded (hemoglobin, WBC, neutrophils, lymphocytes, eosinophils, and platelets). If no results are missing for any time point, then this column can be removed from the table. If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												
Day 4	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												

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Table 55: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Any Hematology Parameter (U/L)
(continued)

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												
Day 6	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												

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Table 55: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Any Hematology Parameter (U/L)
(continued)

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	Cohort 6 (N=X)	None												
		…												
Day 8	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												
Day 11	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												

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Table 55: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Any Hematology Parameter (U/L)
(continued)

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												
Early Termination Visit	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												

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Table 55: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Any Hematology Parameter (U/L)
(continued)

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. Only includes Hematology parameters that have a grading provided: hemoglobin, WBC, neutrophils, lymphocytes, eosinophils, and platelets.

[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

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Table 56: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – White Blood Cell Count

[Implementation Note: If no results are missing for any time point, then this column can be removed from the table.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	
Day 4	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	
Day 6	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																

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Table 56: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – White Blood Cell Count *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	…																	
Day 8	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	
Day 11	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	
Early Termination Visit	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	

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Table 56: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – White Blood Cell Count *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity															
			None		Mild/ Grade 1 (Low)		Mild Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	All Subjects (N=X)	None																
		…																
	Cohort 1 (N=X)	None																
		…																
	Cohort 2 (N=X)	None																
		…																
	…																	

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Table 57: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Eosinophils

[Implementation Note: If no results are missing for any time point, then this column can be removed from the table. If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 4	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 6	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												

Table 57: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Eosinophils *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	…													
Day 8	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 11	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Early Termination Visit	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

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Table 57: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Eosinophils *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

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Table 58: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Neutrophils

[Implementation Note: If no results are missing for any time point, then this column can be removed from the table. If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (Low)		Moderate/ Grade 2 (Low)		Severe/ Grade 3 (Low)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 4	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 6	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												

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Table 58: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Neutrophils *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (Low)		Moderate/ Grade 2 (Low)		Severe/ Grade 3 (Low)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	…													
Day 8	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 11	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Early Termination Visit	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

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Table 58: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Neutrophils *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (Low)		Moderate/ Grade 2 (Low)		Severe/ Grade 3 (Low)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

Tables with similar format:

Table 59: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Lymphocytes

Table 60: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Platelets

Table 61: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Hemoglobin

[Implementation Note: If no results are missing for any time point, then this column can be removed from the table. If there are no results that meet the criteria for "Outside Normal Range", then these columns and corresponding footnote can be removed from the table.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (Low)		Moderate/ Grade 2 (Low)		Severe/ Grade 3 (Low)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 4	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 6	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

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Table 61: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Hemoglobin *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (Low)		Moderate/ Grade 2 (Low)		Severe/ Grade 3 (Low)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 8	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Day 11	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													
Early Termination Visit	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

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Table 61: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Hematology – Hemoglobin *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (Low)		Moderate/ Grade 2 (Low)		Severe/ Grade 3 (Low)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	…													

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

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Table 62: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Any Hematology Parameter

[Implementation Note: Only include hematology parameters that are graded (hemoglobin, WBC, neutrophils, lymphocytes, eosinophils, and platelets). If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table.]

Time Point	Treatment Cohort	N	Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
Day 2	All Subjects	x	x	xx	x	xx	x	xx	x	xx
	Cohort 1									
	Cohort 2									
	…									
Day 4	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Day 6	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Day 8	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Early Termination Visit	All Subjects									

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Table 62: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Any Hematology Parameter *(continued)*

Time Point	Treatment Cohort	N	Outside Normal Range[a]		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
	Cohort 1									
	Cohort 2									
	…									
Max Severity Post Baseline	All Subjects									
	Cohort 1									
	Cohort 2									
	…									

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. The "Max Post Baseline" rows indicate the maximum severity of abnormal laboratory results related to study treatment experienced by each subject at any time point post baseline, including unscheduled assessments. Only includes Hematology parameters that have a grading provided: hemoglobin, WBC, neutrophils, lymphocytes, eosinophils, and platelets.

[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

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Table 63: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – Hematocrit (%)

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Baseline	All Subjects	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 1	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 2	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 3	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 5	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 6	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
Day 2	All Subjects	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 1	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 2	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 3	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 5	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 6	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 4	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

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Table 63: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – Hematocrit (%) *(continued)*

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Day 6	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 8	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

Note: N = Number of Subjects in Safety Population with the laboratory result assessed at the respective time point. Baseline = Measurements from Day -1.

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Tables with similar format:

Table 64: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – White Blood Cell Count (10^9/L)

Table 65: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – Neutrophils (10^9/L)

Table 66: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – Lymphocytes (10^9/L)

Table 67: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – Monocytes (10^9/L)

Table 68: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – Eosinophils (10^9/L)

Table 69: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – Basophils (10^9/L)

Table 70: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – Red Blood Cell Count (10^12/L)

Table 71: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Hematology – Platelets (10^9/L)

Table 72: Laboratory Summary Statistics by Parameter, Time Point, Gender, and Treatment Cohort – Hematology – Hemoglobin (g/dL)

				Measurement				Change from Baseline			
Time Point	**Gender**	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Baseline	Male	All Subjects	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
		Cohort 1	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
		Cohort 2						-	-	-	-
		…						-	-	-	-
	Female	All Subjects	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
		Cohort 1	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
		Cohort 2						-	-	-	-
		…						-	-	-	-
Day 2	Male	All Subjects	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
		Cohort 1	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
		Cohort 2									
		…									
	Female	All Subjects	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
		Cohort 1	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
		Cohort 2									
		…									
Day 4	Male	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
	Female	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
Day 6	Male	All Subjects									

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Table 72: Laboratory Summary Statistics by Parameter, Time Point, Gender, and Treatment Cohort – Hematology – Hemoglobin (g/dL) *(continued)*

				Measurement				Change from Baseline			
Time Point	**Gender**	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
		Cohort 1									
		Cohort 2									
		…									
	Female	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
Day 8	Male	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
	Female	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
Day 11	Male	All Subjects									
		Cohort 1									
		Cohort 2									
		…									
	Female	All Subjects									
		Cohort 1									
		Cohort 2									
		…									

Note: N = Number of Subjects in Safety Population with the laboratory result assessed at the respective time point. Baseline = Measurements from Day -1.

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Table 73: Laboratory Results by Parameter, Time Point, and Treatment Cohort – Hematology – Coombs Test

Time Point	Treatment Cohort		Positive		Negative	
		N	n	%	n	%
Screening	All Subjects	x	x	xx	x	xx
	Cohort 1					
	Cohort 2					
	…					
Day 8	All Subjects					
	Cohort 1					
	Cohort 2					
	…					

Note: N = Number of Subject in Safety Population. n = Number of Subjects with each result.

14.3.5.3 Coagulation Results

Table 74: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Coagulation – Any Coagulation Parameter

[Implementation Note: If no results are missing for any time point, then this column can be removed from the table. If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table.]

			Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
Time Point	Treatment Cohort	Baseline Severity	n	%	n	%	n	%	n	%	n	%	n	%
Day 2	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												
Day 4	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												

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Table 74: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Coagulation – Any Coagulation Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												
Day 6	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												

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Table 74: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Coagulation – Any Coagulation Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	Cohort 6 (N=X)	None												
		…												
Day 8	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												
Day 11	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												

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Table 74: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Coagulation – Any Coagulation Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												
Early Termination Visit	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												

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Table 74: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Coagulation – Any Coagulation Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity											
			None		Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	All Subjects (N=X)	None												
		…												
	Cohort 1 (N=X)	None												
		…												
	Cohort 2 (N=X)	None												
		…												
	Cohort 3 (N=X)	None												
		…												
	Cohort 4 (N=X)	None												
		…												
	Cohort 5 (N=X)	None												
		…												
	Cohort 6 (N=X)	None												
		…												

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

Tables with similar format:

Table 75: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Coagulation – Prothrombin Time

Table 76: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Coagulation – Partial Thromboplastin Time

Table 77: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Any Coagulation Parameter

[Implementation Note: If there are no results that meet the criteria for "Outside Normal Range", then this column and corresponding footnote can be removed from the table.]

Time Point	Treatment Cohort	N	Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)	
			n	%	n	%	n	%	n	%
Day 2	All Subjects	x	x	xx	x	xx	x	xx	x	xx
	Cohort 1									
	Cohort 2									
	…									
Day 4	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Day 6	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Day 8	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	…									

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Table 77: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Any Coagulation Parameter *(continued)*

Time Point	Treatment Cohort	N	Outside Normal Range[a]		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)	
			n	%	n	%	n	%	n	%
Early Termination Visit	All Subjects									
	Cohort 1									
	Cohort 2									
	…									
Max Severity Post Baseline	All Subjects									
	Cohort 1									
	Cohort 2									
	…									

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. The "Max Post Baseline" rows indicate the maximum severity of abnormal laboratory results related to study treatment experienced by each subject at any time point, including unscheduled assessments.
[a] Measurements that were outside the normal range but did not meet the definition for an AE will be categorized as "Outside Normal Range".

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Table 78: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Coagulation – Prothrombin Time (seconds)

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Baseline	All Subjects	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 1	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 2	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 3	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 5	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
	Cohort 6	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
Day 2	All Subjects	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 1	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 2	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 3	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 5	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Cohort 6	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 4	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 6	All Subjects									
	Cohort 1									
	Cohort 2									

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Table 78: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Coagulation – Prothrombin Time (seconds) *(continued)*

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 8	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

Note: N = Number of Subjects in Safety Population with the laboratory result assessed at the respective time point. Baseline = Measurements from Day -1.

Table with similar format:

Table 79: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Coagulation – Partial Thromboplastin Time (seconds)

14.3.5.4 Urinalysis Results

Table 80: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Urinalysis – Any Urinalysis Parameter

[Implementation Note: Only include urinalysis variables that are graded (Protein, Glucose). If no results are missing for any time point, then the column can be removed from the table.]

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity									
			None		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%
Day 4	All Subjects (N=X)	None	x	xx	x	xx	x	xx	x	xx	x	xx
		…										
	Cohort 1 (N=X)	None										
		…										
	Cohort 2 (N=X)	None										
		…										
	Cohort 3 (N=X)	None										
		…										
	Cohort 4 (N=X)	None										
		…										
	Cohort 5 (N=X)	None										
		…										
	Cohort 6 (N=X)	None										
		…										
Day 8	All Subjects (N=X)	None										
		…										
	Cohort 1 (N=X)	None										
		…										

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Table 80: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Urinalysis – Any Urinalysis Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity									
			None		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%
	Cohort 2 (N=X)	None										
		…										
	Cohort 3 (N=X)	None										
		…										
	Cohort 4 (N=X)	None										
		…										
	Cohort 5 (N=X)	None										
		…										
	Cohort 6 (N=X)	None										
		…										
Day 11	All Subjects (N=X)	None										
		…										
	Cohort 1 (N=X)	None										
		…										
	Cohort 2 (N=X)	None										
		…										
	Cohort 3 (N=X)	None										
		…										
	Cohort 4 (N=X)	None										
		…										
	Cohort 5 (N=X)	None										
		…										

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Table 80: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Urinalysis – Any Urinalysis Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity									
			None		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%
	Cohort 6 (N=X)	None										
		…										
Early Termination Visit	All Subjects (N=X)	None										
		…										
	Cohort 1 (N=X)	None										
		…										
	Cohort 2 (N=X)	None										
		…										
	Cohort 3 (N=X)	None										
		…										
	Cohort 4 (N=X)	None										
		…										
	Cohort 5 (N=X)	None										
		…										
	Cohort 6 (N=X)	None										
		…										
Max Severity Post Baseline	All Subjects (N=X)	None										
		…										
	Cohort 1 (N=X)	None										
		…										
	Cohort 2 (N=X)	None										
		…										

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Table 80: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Urinalysis – Any Urinalysis Parameter *(continued)*

Time Point	Treatment Cohort	Baseline Severity	Post-Baseline Severity									
			None		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%
	Cohort 3 (N=X)	None										
		…										
	Cohort 4 (N=X)	None										
		…										
	Cohort 5 (N=X)	None										
		…										
	Cohort 6 (N=X)	None										
		…										

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. Only includes Urinalysis parameters that have a grading provided: protein and glucose.

Tables with similar format:

Table 81: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Urinalysis – Protein

Table 82: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Urinalysis – Glucose

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Table 83: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Cohort – Any Urinalysis Parameter

Time Point	Treatment Cohort	N	Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)	
			n	%	n	%	n	%
Day 4	All Subjects	x	x	xx	x	xx	x	xx
	Cohort 1							
	Cohort 2							
	…							
Day 8	All Subjects							
	Cohort 1							
	Cohort 2							
	…							
Day 11	All Subjects							
	Cohort 1							
	Cohort 2							
	…							
Early Termination Visit	All Subjects							
	Cohort 1							
	Cohort 2							
	…							
Max Severity Post Baseline	All Subjects							
	Cohort 1							
	Cohort 2							
	…							

Notes: N = Number of Subjects in Safety Population. n = Number of Subjects who experience each AE grading. The "Max Post Baseline" rows indicate the maximum severity of abnormal laboratory results related to study treatment experienced by each subject at any time point, including unscheduled assessments. Only includes Urinalysis parameters that have a grading provided: protein and glucose.

Table 84: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Urinalysis – Specific Gravity

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Baseline	All Subjects	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	-	-	-	-
	Cohort 1	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	-	-	-	-
	Cohort 2	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	-	-	-	-
	Cohort 3	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	-	-	-	-
	Cohort 4	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	-	-	-	-
	Cohort 5	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	-	-	-	-
	Cohort 6	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	-	-	-	-
Day 4	All Subjects	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx
	Cohort 1	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx
	Cohort 2	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx
	Cohort 3	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx
	Cohort 4	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx
	Cohort 5	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx
	Cohort 6	x	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx	x.xxxx	x.xxxx	x.xxxx	x.xxx, x.xxx
Day 8	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

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Table 84: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Urinalysis – Specific Gravity *(continued)*

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

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

Table with similar format:

Table 85: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Cohort – Urinalysis – pH

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Table 86: Laboratory Results by Parameter, Time Point, and Treatment Cohort – Urinalysis – Protein

Time Point	Treatment Cohort		Negative		Trace		1+		2+		3+		4+	
		N	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	All Subjects	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 1													
	Cohort 2													
	…													
Day 4	All Subjects													
	Cohort 1													
	Cohort 2													
	…													
Day 8	All Subjects													
	Cohort 1													
	Cohort 2													
	…													
Day 11	All Subjects													
	Cohort 1													
	Cohort 2													
	…													

Notes: N = Number of subjects in Safety Population. Baseline = Measurements from Day -1.

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Tables with similar format:

Table 87: Laboratory Results by Parameter, Time Point, and Treatment Cohort – Urinalysis – Glucose

Table 88: Laboratory Results by Parameter, Time Point, and Treatment Cohort – Urinalysis – Ketones

Table 89: Laboratory Results by Parameter, Time Point, and Treatment Cohort – Urinalysis – Bilirubin

Table 90: Laboratory Results by Parameter, Time Point, and Treatment Cohort – Urinalysis – Blood

Table 91: Laboratory Results by Parameter, Time Point, and Treatment Cohort – Urinalysis – Nitrites

Table 92: Laboratory Results by Parameter, Time Point, and Treatment Cohort – Urinalysis – Leukocyte Esterase

Table 93: Laboratory Results by Parameter, Time Point, and Treatment Cohort – Urinalysis – Urobilinogen

Time Point	Treatment Cohort		Positive		Negative	
		N	n	%	n	%
Baseline	All Subjects	x	x	xx	x	xx
	Cohort 1					
	Cohort 2					
	…					
Day 4	All Subjects					
	Cohort 1					
	Cohort 2					
	…					
Day 8	All Subjects					
	Cohort 1					
	Cohort 2					
	…					
Day 11	All Subjects					
	Cohort 1					
	Cohort 2					
	…					

Notes: N = Number of Subjects in Safety Population. Baseline = Measurements from Day -1.

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14.3.6 Displays of Vital Signs

Table 94: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Any Assessment

[If no results are missing for any subject at any time point, then is column can be removed from the table.]

Time Point	Treatment Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	All Subjects	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 1	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 2	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											

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Table 94: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Any Assessment *(continued)*

Time Point	Treatment Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Day 3	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 4	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 5	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 6	All Subjects											
	Cohort 1											
	Cohort 2											

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Table 94: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Any Assessment *(continued)*

Time Point	Treatment Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 7	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 8	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 11	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											

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Table 94: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Any Assessment *(continued)*

Time Point	Treatment Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Early Termination Visit	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Max Severity Post Baseline	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											

Notes: N = Number of Subjects in Safety Population. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

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Table 95: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Pulse Rate

[If no results are missing for any subject at any time point, then the column can be removed from the table.]

Time Point	Treatment Cohort	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	All Subjects	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	Xx
	Cohort 1																	
	Cohort 2																	
	…																	
Day 1	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	
Day 2	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	
Day 3	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	
Day 4	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	

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Table 95: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Pulse Rate *(continued)*

Time Point	Treatment Cohort	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 5	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	
Day 6	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	
Day 7	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	
Day 8	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	
Day 11	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	

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Table 95: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Pulse Rate *(continued)*

Time Point	Treatment Cohort	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Early Termination Visit	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	
Max Severity Post Baseline	All Subjects																	
	Cohort 1																	
	Cohort 2																	
	…																	

Notes: N = Number of Subjects in Safety Population. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Table with similar format:

Table 96: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Systolic Blood Pressure

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Table 97: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Diastolic Blood Pressure

[If no results are missing for any subject at any time point, then this column can be removed from the table.]

Time Point	Treatment Cohort	N	None		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	All Subjects	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 1											
	Cohort 2											
	…											
Day 1	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 2	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 3	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 4	All Subjects											
	Cohort 1											
	Cohort 2											
	…											

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Table 97: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Diastolic Blood Pressure *(continued)*

Time Point	Treatment Cohort	N	None		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%
Day 5	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 6	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 7	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 8	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 11	All Subjects											
	Cohort 1											
	Cohort 2											
	…											

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Table 97: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Diastolic Blood Pressure *(continued)*

Time Point	Treatment Cohort	N	None		Mild/ Grade 1 (High)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%
Early Termination Visit	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Max Severity Post Baseline	All Subjects											
	Cohort 1											
	Cohort 2											
	…											

Notes: N = Number of Subjects in Safety Population. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Table with similar format:

Table 98: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Oral Temperature

Table 99: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Respiratory Rate

[If no results are missing for any subject at any time point, then this column can be removed from the table.]

Time Point	Treatment Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	All Subjects	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 1											
	Cohort 2											
	…											
Day 1	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 2	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 3	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 4	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 5	All Subjects											
	Cohort 1											
	Cohort 2											
	…											

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Table 99: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Cohort – Respiratory Rate *(continued)*

Time Point	Treatment Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Day 6	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 7	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 8	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Day 11	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Early Termination Visit	All Subjects											
	Cohort 1											
	Cohort 2											
	…											
Max Severity Post Baseline	All Subjects											
	Cohort 1											
	Cohort 2											
	…											

Notes: N = Number of Subjects in Safety Population. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

PRIVILEGED AND CONFIDENTIAL COMMUNICATION

Table 100: Vital Signs Summary Statistics by Assessment, Time Point, and Treatment Cohort – Pulse Rate (beats/minute)

[Implementation Note: Min and Max will be reported using the minimum number of significant figures of what is collected. Mean, Std. Dev., and Median will be reported using the maximum number of significant figures + 1 of what is collected. For example, Pulse Rate is reported as XX, so the Min and Max will be reported as XX, and Mean, Std. Dev., and Median will be reported as XX.X. This applies to all the vital signs tables.]

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Baseline	All Subjects	x	xx.x	xx.x	xx.x	xxx, xxx	-	-	-	-
	Cohort 1	x	xx.x	xx.x	xx.x	xxx, xxx	-	-	-	-
	Cohort 2						-	-	-	-
	Cohort 3						-	-	-	-
	Cohort 4						-	-	-	-
	Cohort 5						-	-	-	-
	Cohort 6						-	-	-	-
Day 1	All Subjects	x	xx.x	xx.x	xx.x	xxx, xxx	xxx	xxx	xxx	xxx, xxx
	Cohort 1	x	xx.x	xx.x	xx.x	xxx, xxx	xxx	xxx	xxx	xxx, xxx
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 2	All Subjects	x	xx.x	xx.x	xx.x	xx.x, xx.x	xxx	xxx	xxx	xxx, xxx
	Cohort 1	x	xx.x	xx.x	xx.x	xx.x, xx.x	xxx	xxx	xxx	xxx, xxx
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

Table 100: Vital Signs Summary Statistics by Assessment, Time Point, and Treatment Cohort – Pulse Rate (beats/minute) *(continued)*

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
Day 3	All Subjects	x	xx.x	xx.x	xx.x	xx.x, xx.x	xxx	xxx	xxx	xxx, xxx
	Cohort 1	x	xx.x	xx.x	xx.x	xx.x, xx.x	xxx	xxx	xxx	xxx, xxx
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 4	All Subjects	x	xx.x	xx.x	xx.x	xx.x, xx.x	xxx	xxx	xxx	xxx, xxx
	Cohort 1	x	xx.x	xx.x	xx.x	xx.x, xx.x	xxx	xxx	xxx	xxx, xxx
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 5	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 6	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									

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Table 100: Vital Signs Summary Statistics by Assessment, Time Point, and Treatment Cohort – Pulse Rate (beats/minute) *(continued)*

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
	Cohort 5									
	Cohort 6									
Day 7	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 8	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

Note: N = Number of Subjects in Safety Population with the laboratory result assessed at the respective time point. Baseline = Measurements from Day -1.

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Tables with similar format:

Table 101: Vital Signs Summary Statistics by Assessment, Time Point, and Treatment Cohort – Systolic Blood Pressure (mmHg)

Table 102: Vital Signs Summary Statistics by Assessment, Time Point, and Treatment Cohort – Diastolic Blood Pressure (mmHg)

Table 103: Vital Signs Summary Statistics by Assessment, Time Point, and Treatment Cohort – Oral Temperature (°C)

Table 104: Vital Signs Summary Statistics by Assessment, Time Point, and Treatment Cohort – Respiratory Rate (breaths/minute)

14.3.7 Displays of ECG Measurements

Table 105: ECG Overall Interpretations Compared to Baseline by Post-Baseline Time Point and Treatment Cohort

		ECG Interpretation Compared to Baseline (N = X)								
Time Point	Treatment Cohort	Normal at Both Times n (%)	Normal to Abnormal, NCS n (%)	Normal to Abnormal, CS n (%)	Normal to Other[a] n (%)	Abnormal, NCS at Both Times n (%)	Abnormal, NCS to Abnormal, CS n (%)	Abnormal, NCS to Normal n (%)	Abnormal, NCS to Other[a] n (%)	Missing n (%)
Day 8	All Subjects	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

Notes: N = Number of Subjects in Safety Population with the ECG measurement at the visit indicated above. CS = Clinically Significant. NCS = Not Clinically Significant.
[a] See Listing 18 for details about ECG Overall Interpretations classified as "Other"

Table 106: ECG Results by Parameter, Severity, Time Point, and Treatment Cohort – QTcF/PR Interval

[If no results are missing for any subject at any time point, then this column can be removed from the table.]

Time Point	Treatment Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
QTcF Interval (msec)												
Baseline	All Subjects	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 8	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 11	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Early Termination Visit	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											

Table 106: ECG Results by Parameter, Severity, Time Point, and Treatment Cohort – QTcF/PR Interval
(continued)

Time Point	Treatment Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
PR Interval (msec)												
Baseline	All Subjects	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 8	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Day 11	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											
Early Termination Visit	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											

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Table 106: ECG Results by Parameter, Severity, Time Point, and Treatment Cohort – QTcF/PR Interval
(continued)

Time Point	Treatment Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
	Cohort 5											
	Cohort 6											
Max Severity Post Baseline	All Subjects											
	Cohort 1											
	Cohort 2											
	Cohort 3											
	Cohort 4											
	Cohort 5											
	Cohort 6											

Notes: N = Number of Subjects in Safety Population. Baseline = Measurements from Day -1. The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Table 107: ECG Summary Statistics by Parameter, Time Point, and Treatment Cohort

[Implementation Note: Use the QTcF and PR Intervals from the most recent measurement prior to first study product administration. If using measurements from Screening Visit (visit 00), use the average of the measurements taken.]

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
QTcF Interval (msec)										
Baseline	All Subjects	x	xx.x	xx.x	xx.x	xx.x, xx.x	-	-	-	-
	Cohort 1	x	xx.x	xx.x	xx.x	xx.x, xx.x	-	-	-	-
	Cohort 2						-	-	-	-
	Cohort 3						-	-	-	-
	Cohort 4						-	-	-	-
	Cohort 5						-	-	-	-
	Cohort 6						-	-	-	-
Day 8	All Subjects	x	xx.x	xx.x	xx.x	xx.x, xx.x	xx.x	xx.x	xx.x	xx.x, xx.x
	Cohort 1	x	xx.x	xx.x	xx.x	xx.x, xx.x	xx.x	xx.x	xx.x	xx.x, xx.x
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 11	All Subjects	x	xx.x	xx.x	xx.x	xx.x, xx.x	xx.x	xx.x	xx.x	xx.x, xx.x
	Cohort 1	x	xx.x	xx.x	xx.x	xx.x, xx.x	xx.x	xx.x	xx.x	xx.x, xx.x
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

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Table 107: ECG Summary Statistics by Parameter, Time Point, and Treatment Cohort *(continued)*

			Measurement				Change from Baseline			
Time Point	**Treatment Cohort**	**N**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**	**Mean**	**Std. Dev.**	**Median**	**Min, Max**
PR Interval (msec)										
Baseline	All Subjects	x	xx.x	xx.x	xx.x	xx.x, xx.x	-	-	-	-
	Cohort 1	x	xx.x	xx.x	xx.x	xx.x, xx.x	-	-	-	-
	Cohort 2						-	-	-	-
	Cohort 3						-	-	-	-
	Cohort 4						-	-	-	-
	Cohort 5						-	-	-	-
	Cohort 6						-	-	-	-
Day 8	All Subjects	x	xx.x	xx.x	xx.x	xx.x, xx.x	xx.x	xx.x	xx.x	xx.x, xx.x
	Cohort 1	x	xx.x	xx.x	xx.x	xx.x, xx.x	xx.x	xx.x	xx.x	xx.x, xx.x
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									
Day 11	All Subjects									
	Cohort 1									
	Cohort 2									
	Cohort 3									
	Cohort 4									
	Cohort 5									
	Cohort 6									

Notes: N = Number of Subjects in Safety Population. Baseline = Measurements from Day -1.

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14.4 Summary of Prior and Concomitant Medications

Table 108: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Cohort

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)		Cohort 6 (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	N	%	n	%
Any Level 1 Codes	Any Level 2 Codes														
[ATC Level 1 – 1]	Any [ATC 1 – 1]														
	[ATC 2 – 1]														
	[ATC 2 – 2]														
	[ATC 2 – 3]														
[ATC Level 1 – 2]	[ATC 2 – 1]														
	[ATC 2 – 2]														
	[ATC 2 – 3]														

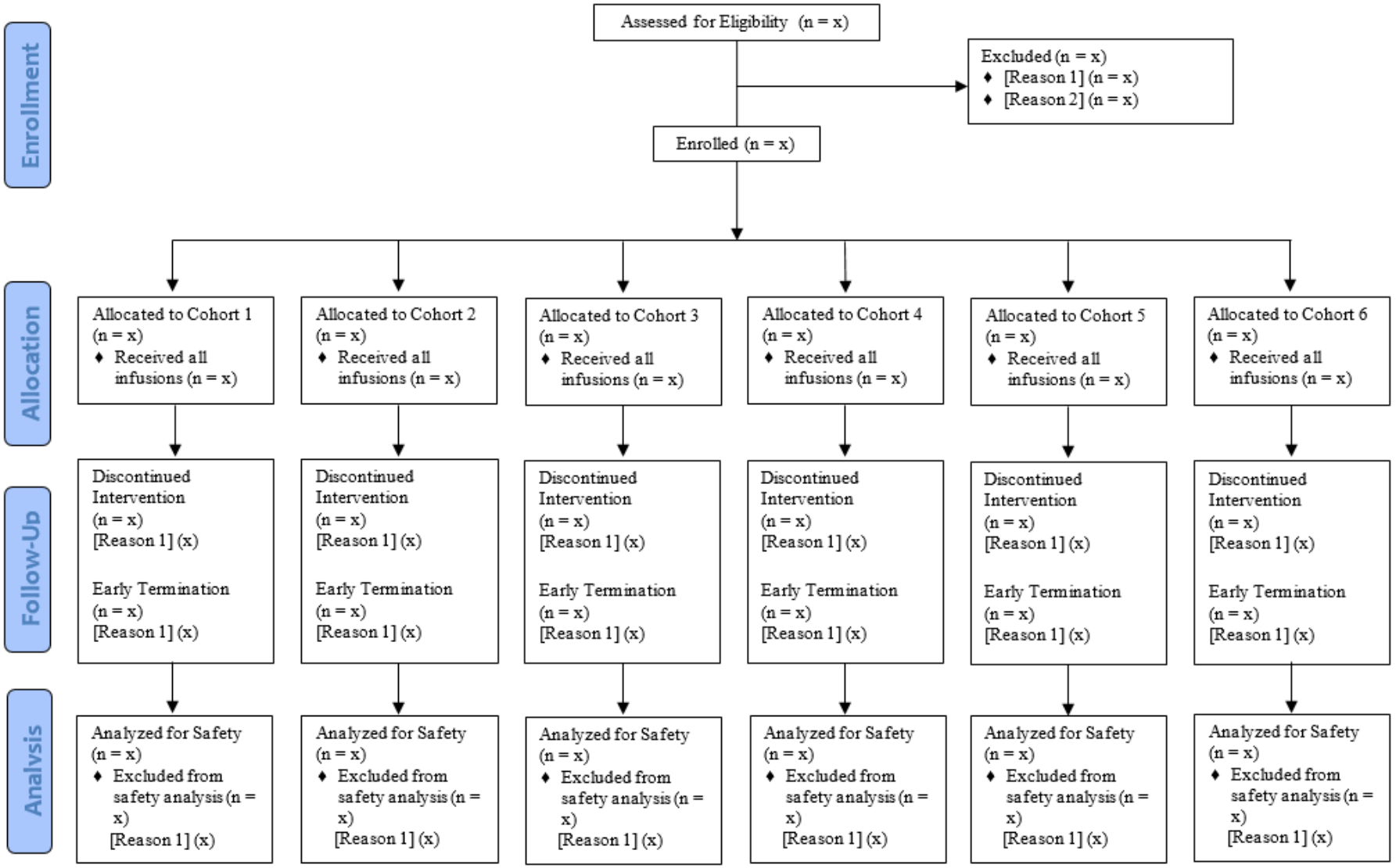
Note: N = Number of Subjects in Safety Population. N = Number of Subjects reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram



14.3.1.2 Unsolicited Adverse Events

Figure 2: Frequency of Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Cohort

[Implementation Note: A generic figure is shown below. This figure includes all unsolicited events across all treatment cohorts. A horizontal bar chart should be presented in 1 image file with separate panels for each study arm (6 panels in total – Top Row: Cohort 1, Cohort 2, Cohort 3; Bottom Row: Cohort 4, Cohort 5, Cohort 6(2.0) IV). The study arms should be indicated in panel headers including "(N=X)", where N=Number of Subjects in the Safety Population. Axes should be labeled as follows – y-axis: "System Organ Class"; x-axis: "Number of Events". The y-axis should present all SOCs reported by at least one subject as well as an "Any SOC" category. The Y-axis should be sorted with "Any SOC" first, then in decreasing order of total frequency.]

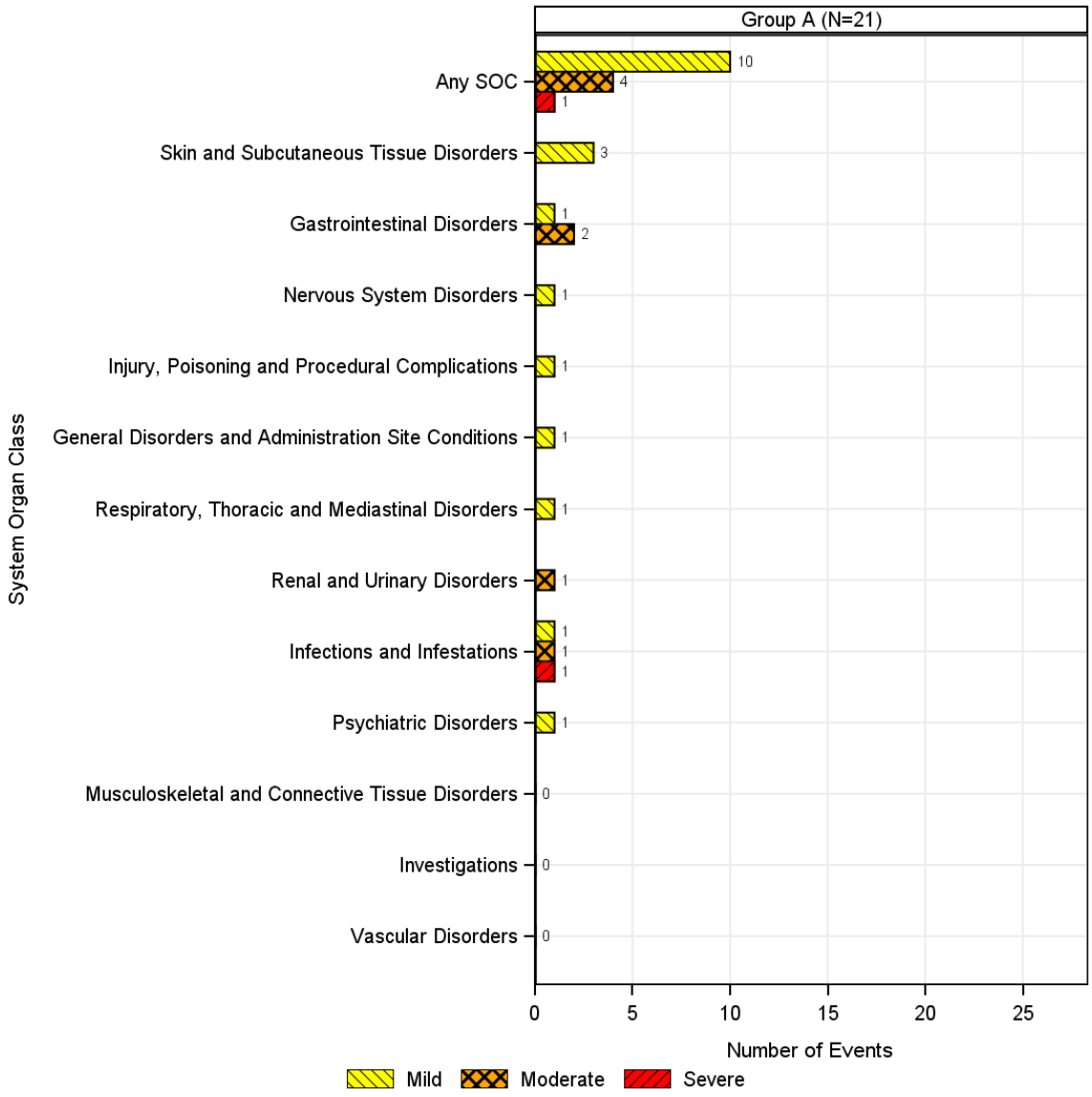


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Figure with Similar Format:

Figure 3: Frequency of Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment

[Implementation Note: A horizontal bar chart should be presented in 1 image file with separate panels for each study treatment (3 panels in total – AVYCAZ, ATM, and Combination (2.0) IV). The treatments should be indicated in panel headers including "(N=X)", where N=Number of Subjects in the Safety Population. Axes should be labeled as follows – y-axis: "System Organ Class"; x-axis: "Number of Events". The y-axis should present all SOCs reported by at least one subject as well as an "Any SOC" category. The Y-axis should be sorted with "Any SOC" first, then in decreasing order of total frequency.]

Figure 4: Incidence of Related Adverse Events by MedDRA System Organ Class, Maximum Severity, and Treatment Cohort

[Implementation Note: A generic figure is shown below. This figure includes all unsolicited events across all treatment cohorts. A horizontal bar chart should be presented in 1 image file with separate panels for each study arm (6 panels in total – Top Row: Cohort 1, Cohort 2, Cohort 3; Bottom Row: Cohort 4, Cohort 5, Cohort 6). The study arms should be indicated in panel headers including "(N=X)", where N=Number of Subjects in the Safety Population in each group. Axes should be labeled as follows – y-axis: "System Organ Class"; x-axis: "Incidence of Events". The y-axis should present all SOCs reported by at least one subject as well as an "Any SOC" category. The Y-axis should be sorted with "Any SOC" first, then in decreasing order of total incidence.]

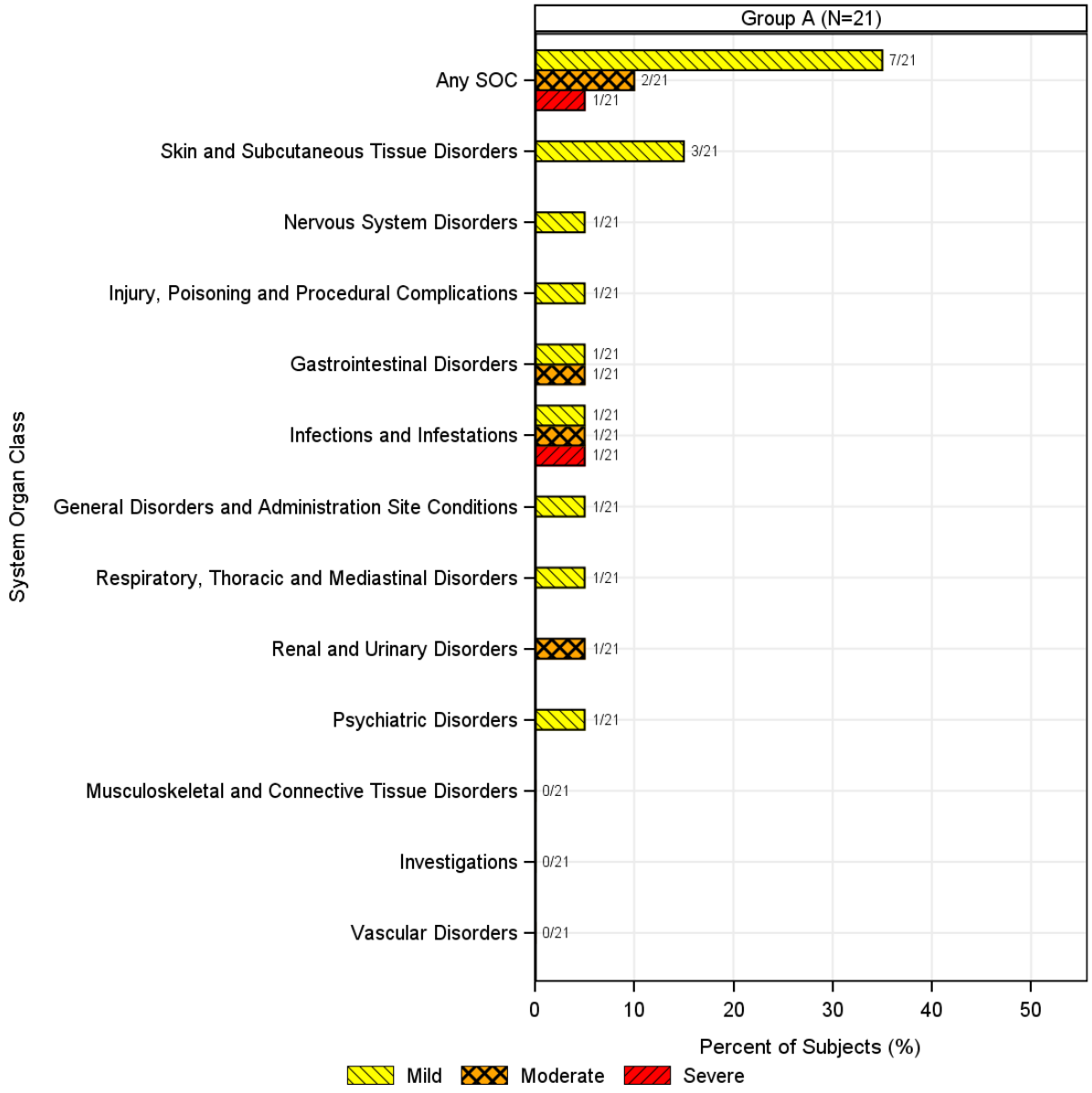


Figure with Similar Format:

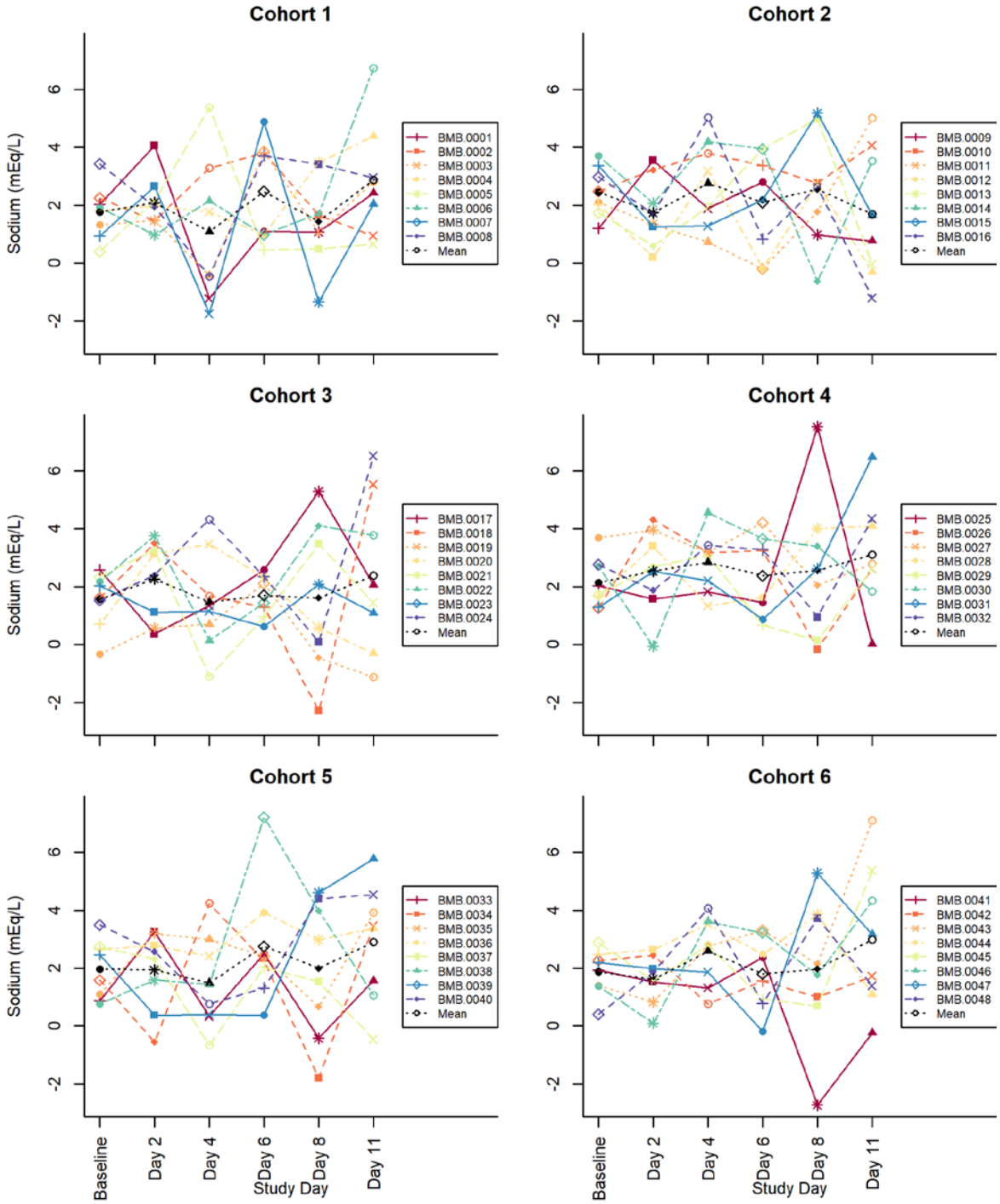
Figure 5: Incidence of Related Adverse Events by MedDRA System Organ Class, Maximum Severity, and Treatment

[Implementation Note: A horizontal bar chart should be presented in 1 image file with separate panels for each study treatment (3 panels in total – AVYCAZ, ATM, and Combination). The treatments should be indicated in panel headers including "(N=X)", where N=Number of Subjects in the Safety Population in each group. Axes should be labeled as follows – y-axis: "System Organ Class"; x-axis: "Incidence of Events". The y-axis should present all SOCs reported by at least one subject as well as an "Any SOC" category. The Y-axis should be sorted with "Any SOC" first, then in decreasing order of total incidence.]

14.3.5 Displays of Laboratory Results

Figure 6: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Sodium (mEq/L)

[Implementation Note: For all individual and mean value figures, the y-axis should match for all cohorts. Additionally, different lines types and markers should be used for each line in each sub-plot.



Figures with Similar Formats:

Figure 7: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Potassium (mEq/L)

Figure 8: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Chloride (mmol/L)

Figure 9: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Bicarbonate (mmol/L)

Figure 10: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Blood Urea Nitrogen (mg/dL)

Figure 11: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Creatinine (mg/dL)

Figure 12: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Fasting Glucose (mg/dL)

Figure 13: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Non-Fasting Glucose (mg/dL)

Figure 14: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Albumin (g/dL)

Figure 15: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Total Protein (g/dL)

Figure 16: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Total Bilirubin (mg/dL)

Figure 17: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Alkaline Aminotransferase, Male (U/L)

Figure 18: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Alkaline Aminotransferase, Female (U/L)

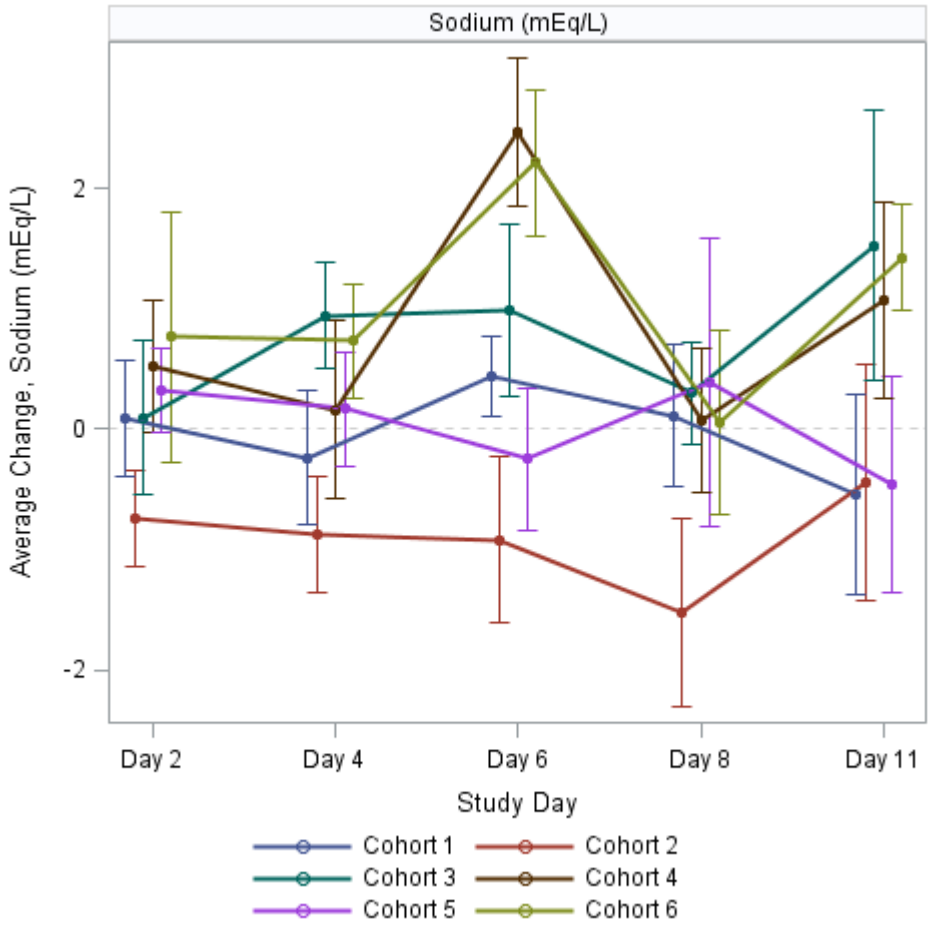
Figure 19: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Aspartate Aminotransferase (U/L)

Figure 20: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Alkaline Phosphate (U/L)

Figure 21: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Chemistry – Lactate Dehydrogenase (U/L)

Figure 22: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Sodium (mEq/L)

[Implementation Note: All change from baseline figures should include the parameter name with units in the figure header. For liver function tests (ALT, AST, ALP, and total bilirubin) that have additional collections in Cohorts 5 and 6, create one image file that contains a panel for cohorts 1-4 (left) and cohorts 5-6 (right). For lab parameters that have gradings that are broken up by gender (Chemistry – ALT and Hematology – Hemoglobin only), create one image file that contains a panel for each gender (Males on top and Females on bottom). ALT will have four panels broken up by gender and cohort based on the above separations.]



Figures with similar format:

Figure 23: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Potassium (mEq/L)

Figure 24: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Chloride (mmol/L)

Figure 25: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Bicarbonate (mmol/L)

Figure 26: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Blood Urea Nitrogen (mg/dL)

Figure 27: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Serum Creatinine (mg/dL)

Figure 28: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Fasting Glucose (mg/dL)

Figure 29: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Non-Fasting Glucose (mg/dL)

Figure 30: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Albumin (g/dL)

Figure 31: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Total Protein (g/dL)

Figure 32: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Total Bilirubin (mg/dL)

Figure 33: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Alkaline Aminotransferase (U/L)

Figure 34: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Aspartate Aminotransferase (U/L)

Figure 35: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Alkaline Phosphate (U/L)

Figure 36: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Chemistry – Lactate Dehydrogenase (U/L)

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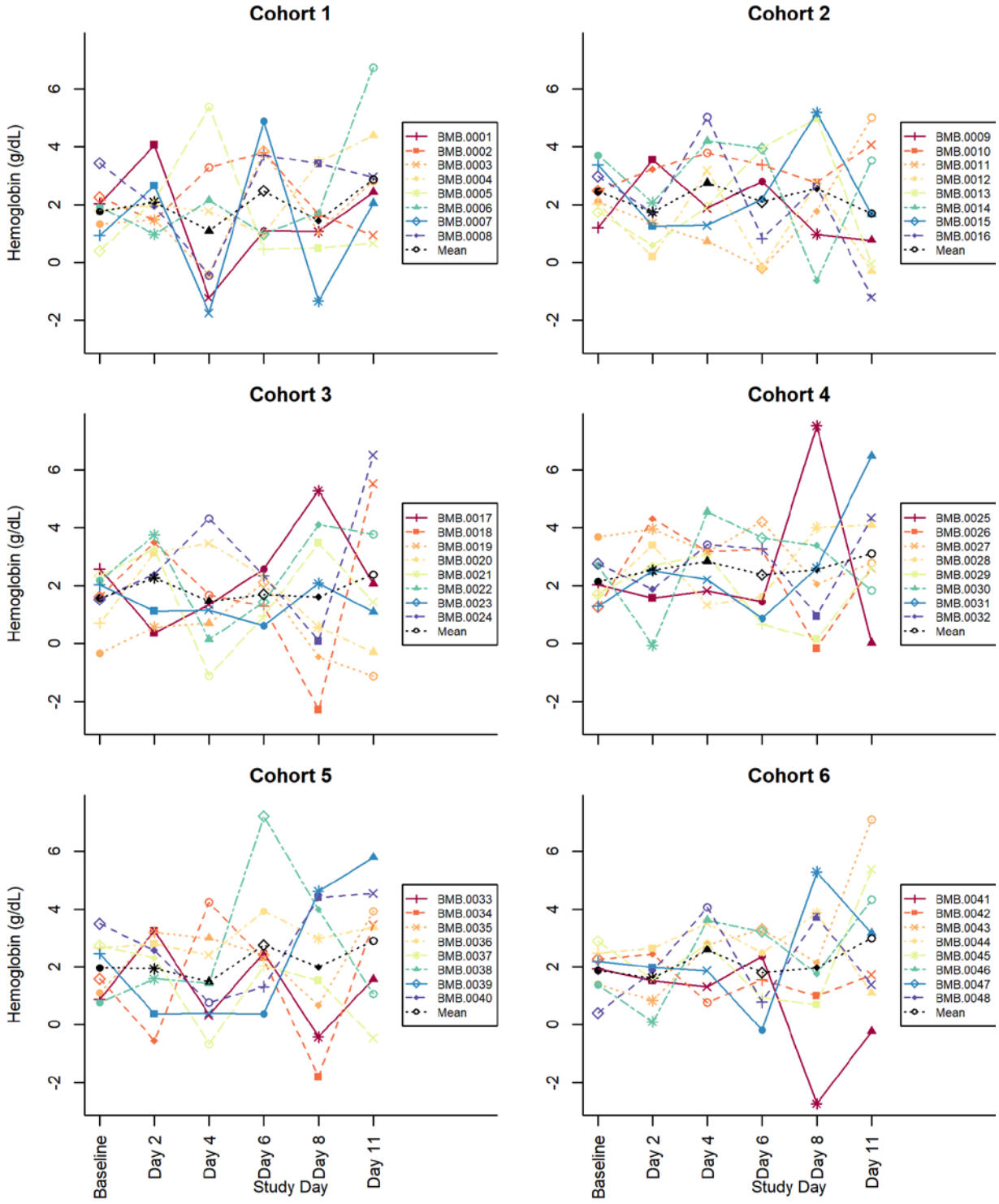
Figure 37: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Hemoglobin, Male (g/dL)



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Figures with similar format:

Figure 38: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Hemoglobin, Female (g/dL)

Figure 39: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Hematocrit (%)

Figure 40: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – White Blood Cells (10^9/L)

Figure 41: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Neutrophils (10^9/L)

Figure 42: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Lymphocytes (10^9/L)

Figure 43: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Monocytes (10^9/L)

Figure 44: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Eosinophils (10^9/L)

Figure 45: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Basophils (10^9/L)

Figure 46: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Red Blood Cells (10^12/L)

Figure 47: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Hematology – Platelets (10^9/L)

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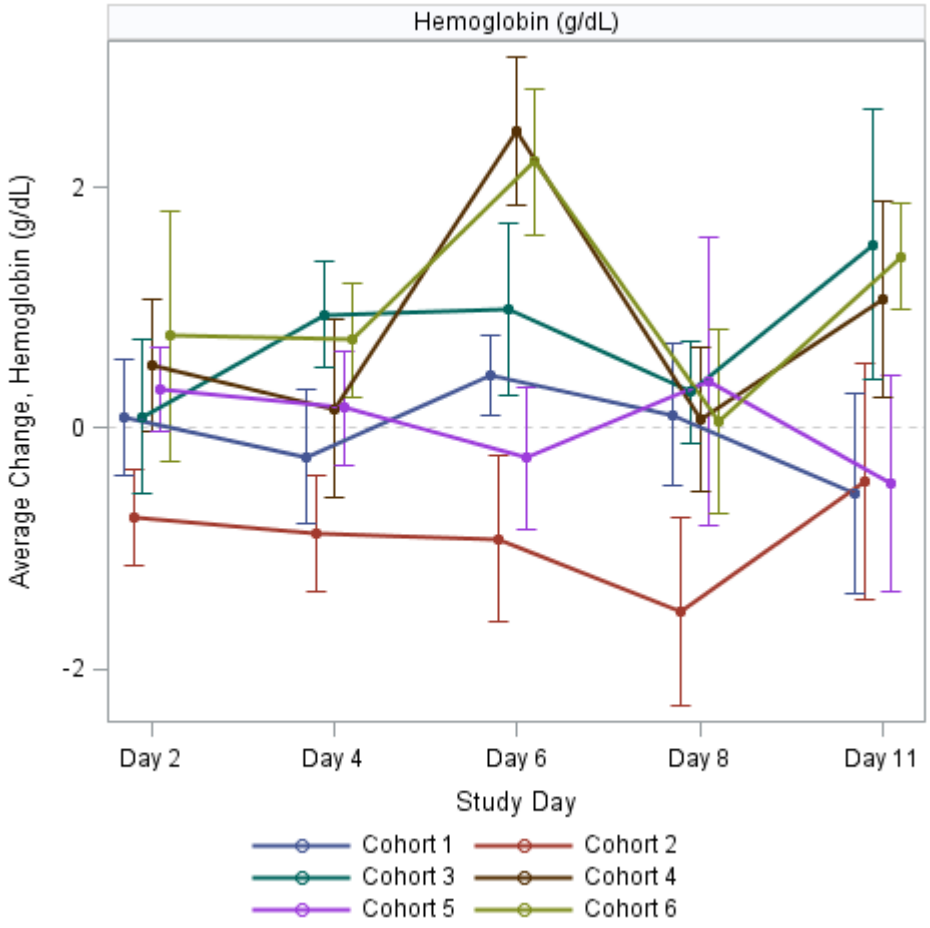
Figure 48: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – Hemoglobin (g/dL)



Figures with similar format:

Figure 49: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – Hematocrit (%)

Figure 50: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – White Blood Cells (10^9/L)

Figure 51: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – Neutrophils (10^9/L)

Figure 52: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – Lymphocytes (10^9/L)

Figure 53: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – Monocytes (10^9/L)

Figure 54: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – Eosinophils (10^9/L)

Figure 55: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – Basophils (10^9/L)

Figure 56: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – Red Blood Cells (10^12/L)

Figure 57: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Hematology – Platelets (10^9/L)

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Figure 58: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Coagulation – Prothrombin Time (seconds)

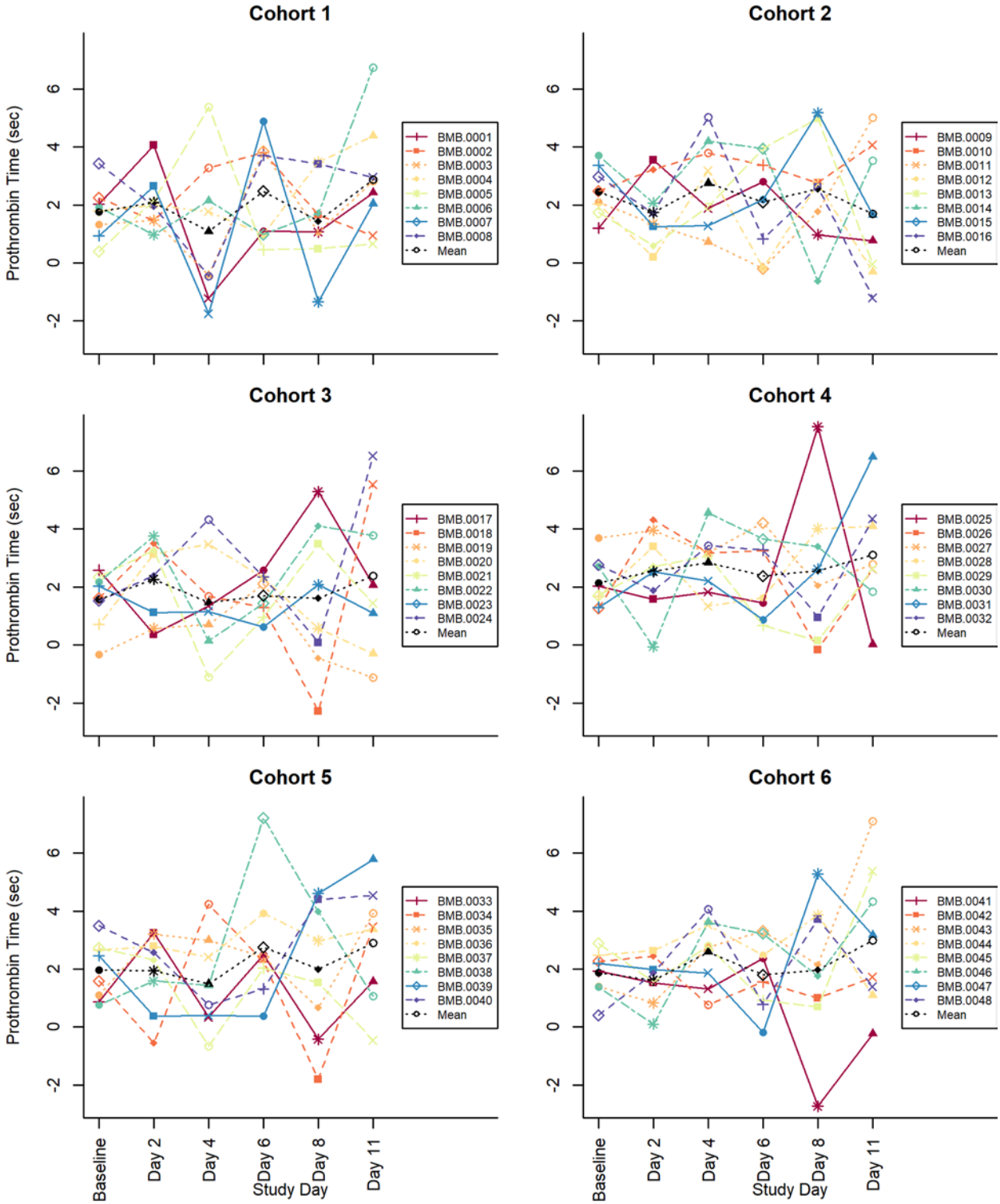


Figure with similar format:

Figure 59: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Coagulation – Partial Thromboplastin Time (seconds)

Figure 60: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Coagulation – Prothrombin Time (sec)

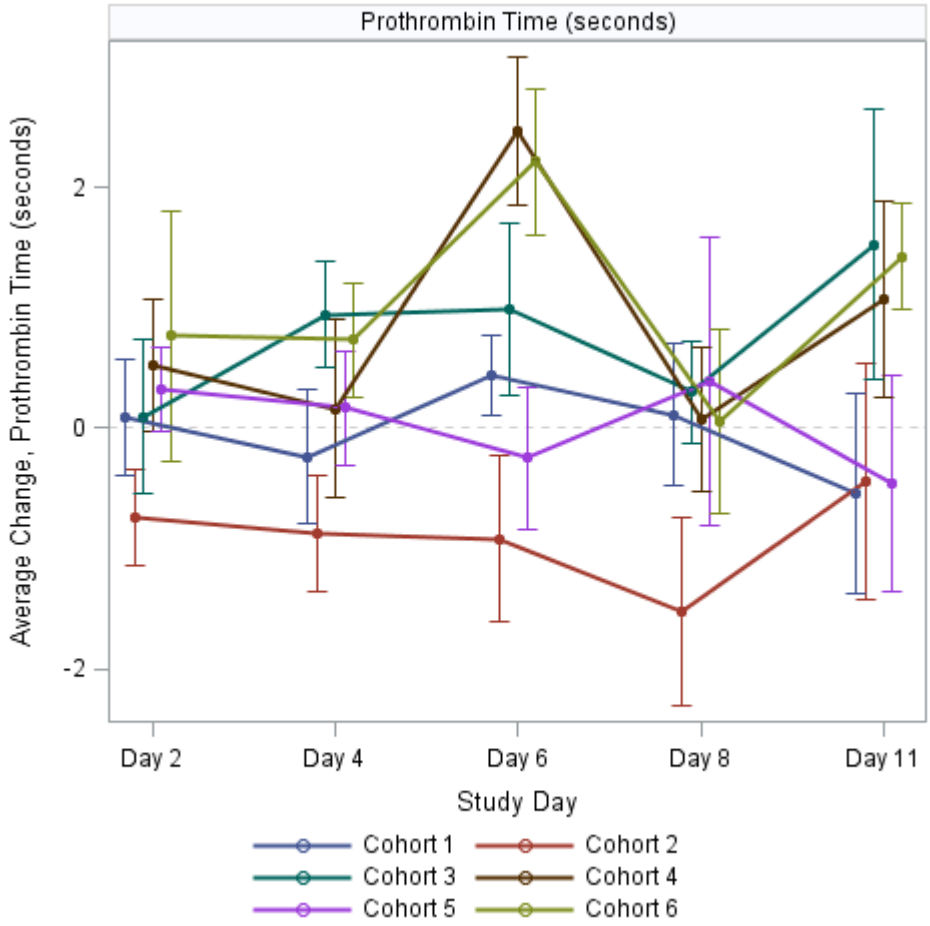


Figure with similar format:

Figure 61: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Coagulation – Partial Thromboplastin Time (sec)

Figure 62: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Urinalysis – Specific Gravity

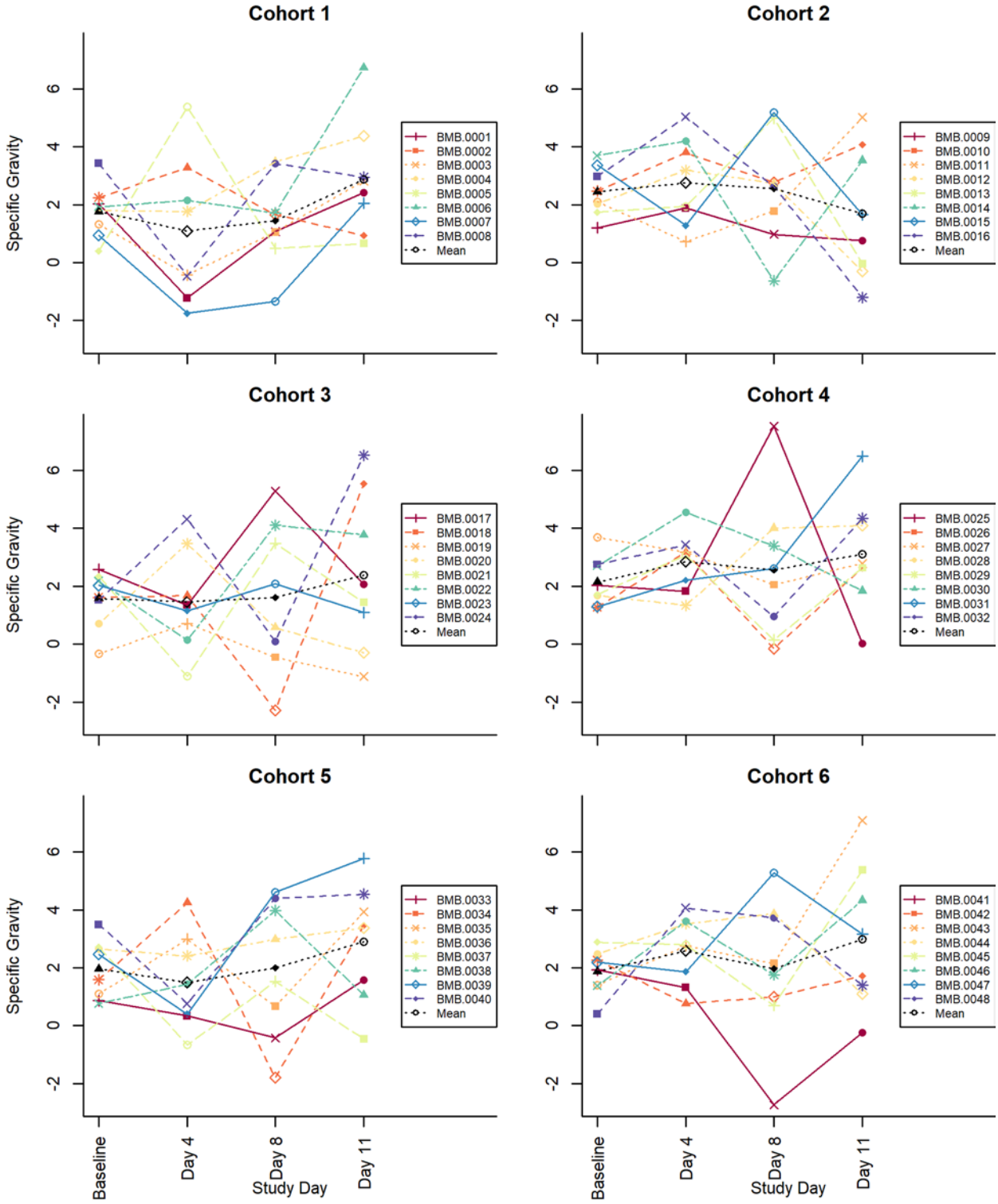


Figure with similar format:

Figure 63: Laboratory Results by Scheduled Visits: Individual and Mean Values by Laboratory Parameter and Treatment Cohort – Urinalysis – pH

Figure 64: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Urinalysis – Specific Gravity

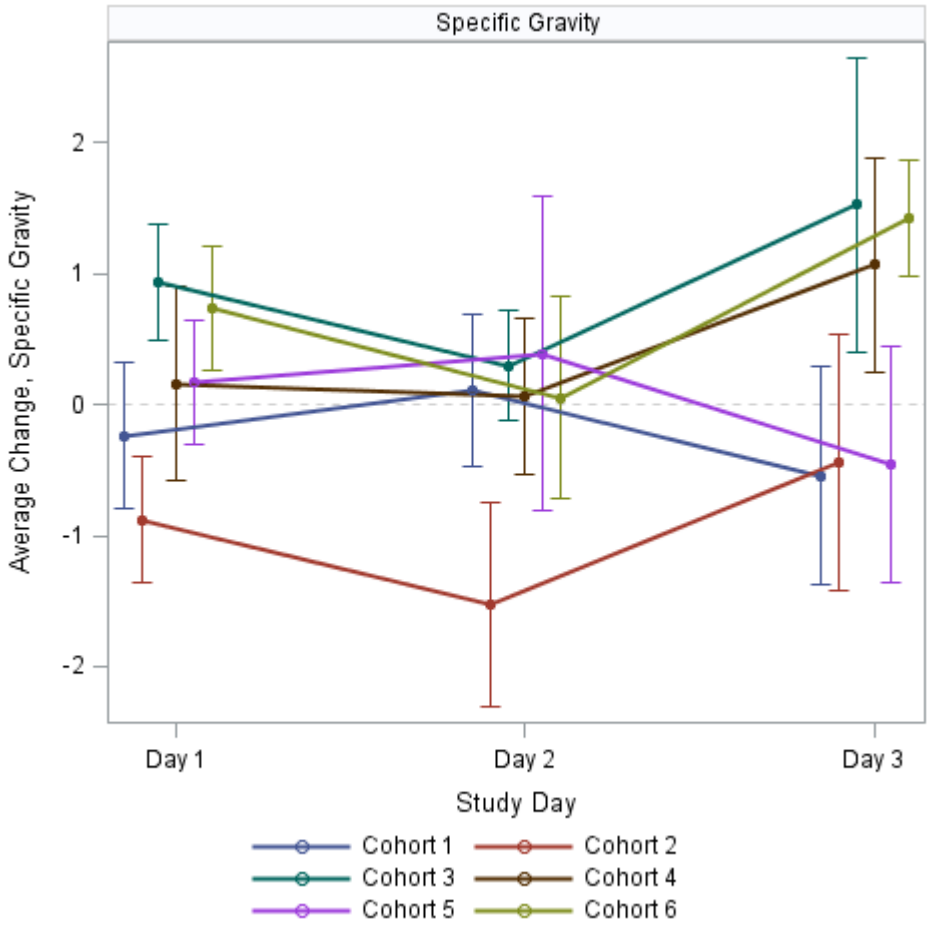
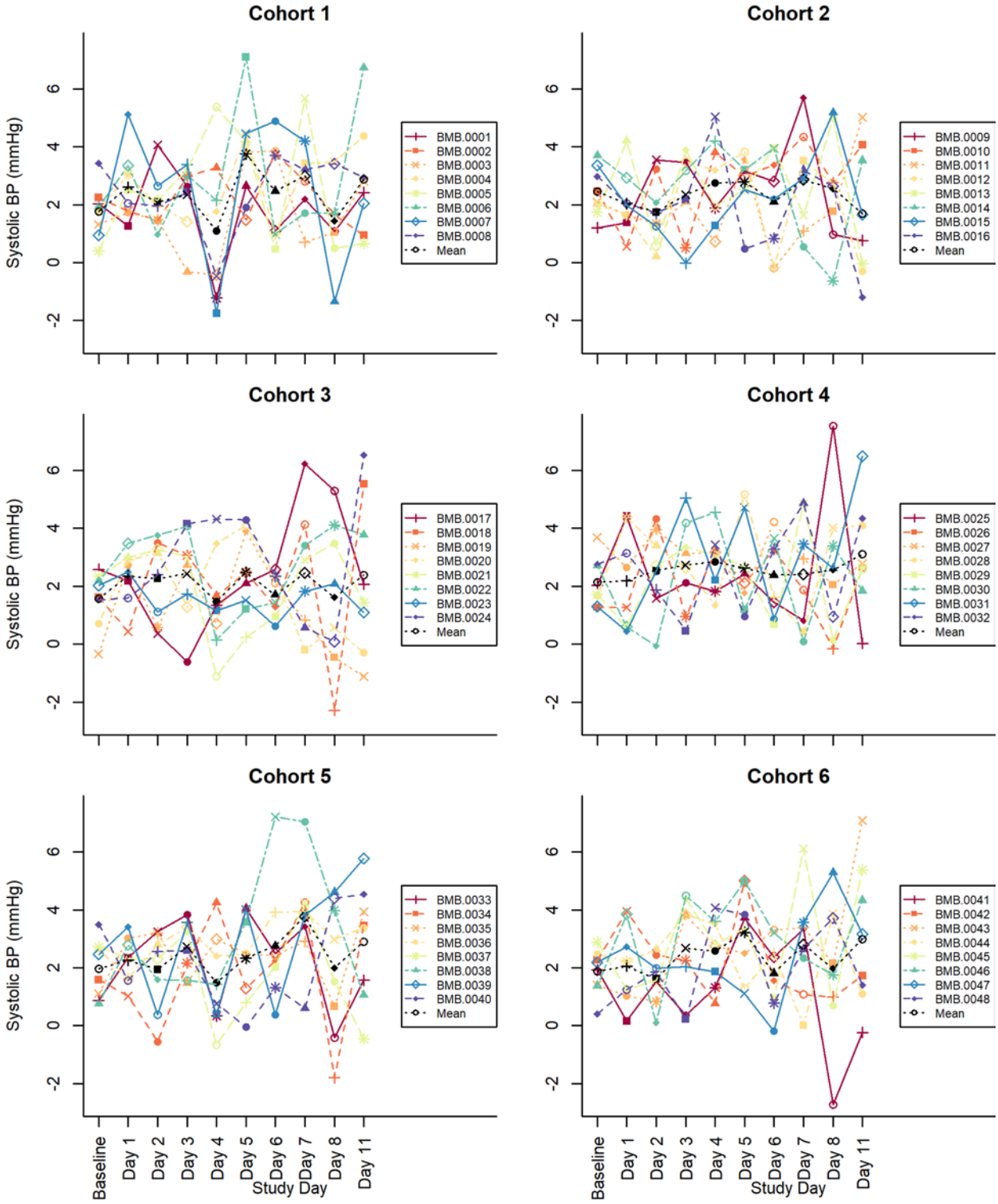


Figure with similar format:

Figure 65: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter and Treatment Cohort – Urinalysis – pH

14.3.6 Displays of Vital Signs

Figure 66: Vital Signs by Scheduled Visits: Individual and Mean Values by Assessment and Treatment Cohort – Systolic Blood Pressure (mmHg)



Figures with similar format:

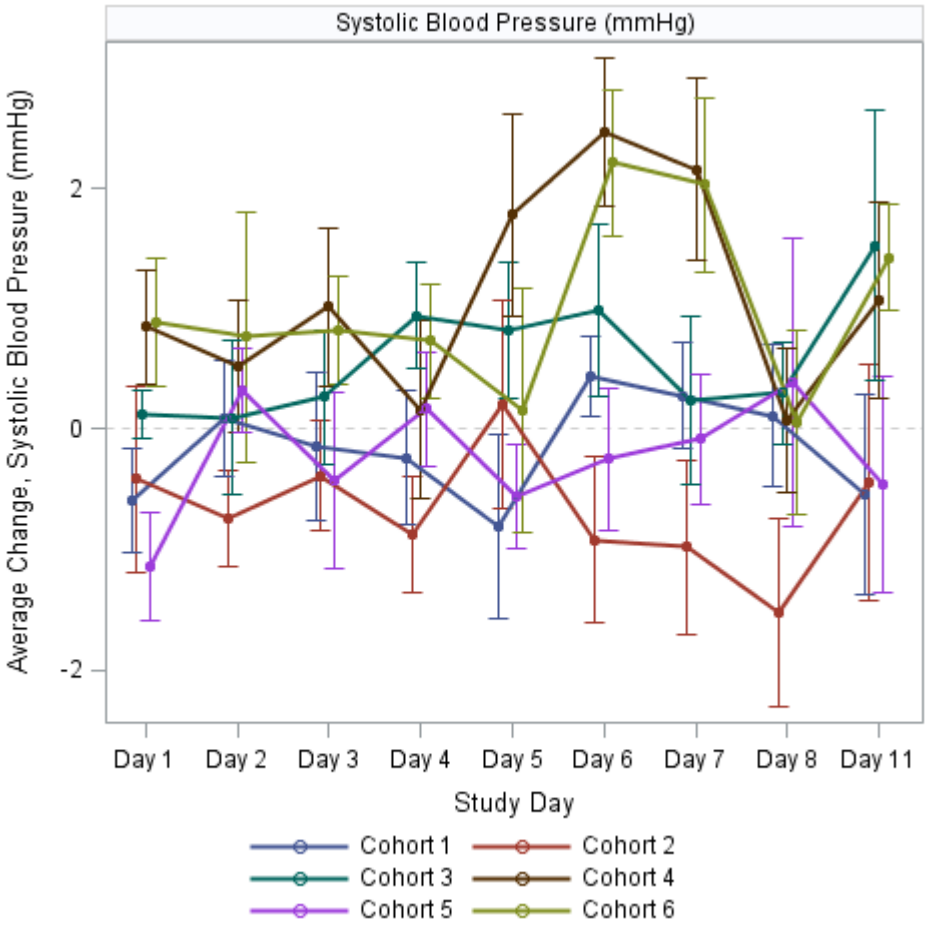
Figure 67: Vital Signs by Scheduled Visits: Individual and Mean Values by Assessment and Treatment Cohort – Diastolic Blood Pressure (mmHg)

Figure 68: Vital Signs by Scheduled Visits: Individual and Mean Values by Assessment and Treatment Cohort – Pulse Rate (beats/minute)

Figure 69: Vital Signs by Scheduled Visits: Individual and Mean Values by Assessment and Treatment Cohort – Respiratory Rate (breaths/minute)

Figure 70: Vital Signs by Scheduled Visits: Individual and Mean Values by Assessment and Treatment Cohort – Oral Temperature (°C)

Figure 71: Vital Signs by Scheduled Visits: Mean Changes from Baseline by Assessment and Treatment Cohort – Systolic Blood Pressure (mmHg)



Figures with similar format:

Figure 72: Vital Signs by Scheduled Visits: Mean Changes from Baseline by Assessment and Treatment Cohort – Diastolic Blood Pressure (mmHg)

Figure 73: Vital Signs by Scheduled Visits: Mean Changes from Baseline by Assessment and Treatment Cohort – Pulse Rate (beats/minute)

Figure 74: Vital Signs by Scheduled Visits: Mean Changes from Baseline by Assessment and Treatment Cohort – Respiratory Rate (breaths/minute)

Figure 75: Vital Signs by Scheduled Visits: Mean Changes from Baseline by Assessment and Treatment Cohort – Oral Temperature (°C)

14.3.7 Displays of ECG Measurements

Figure 76: ECG by Scheduled Visits: Individual and Mean Values by Parameter and Treatment Cohort – QTcF Interval (msec)

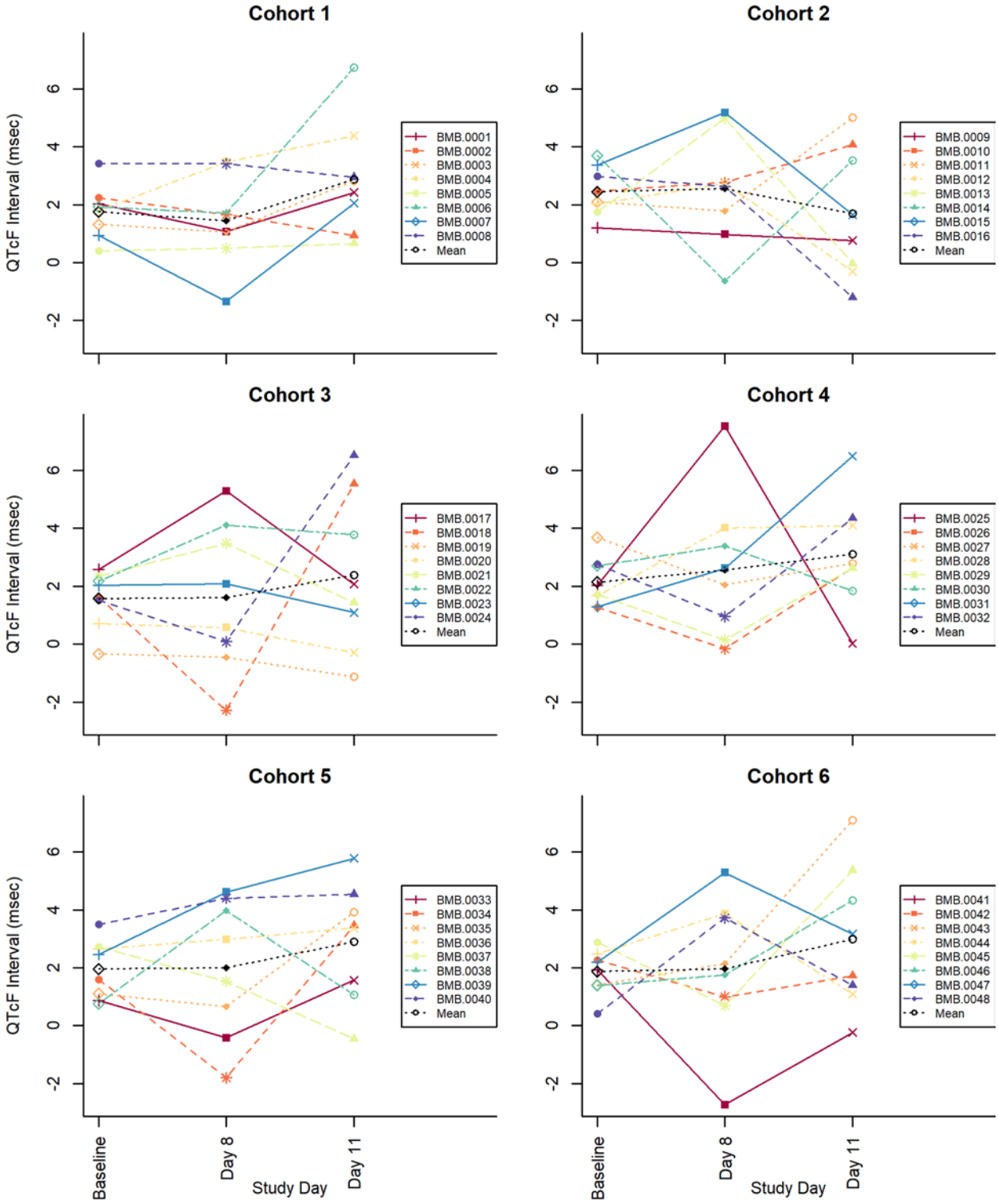


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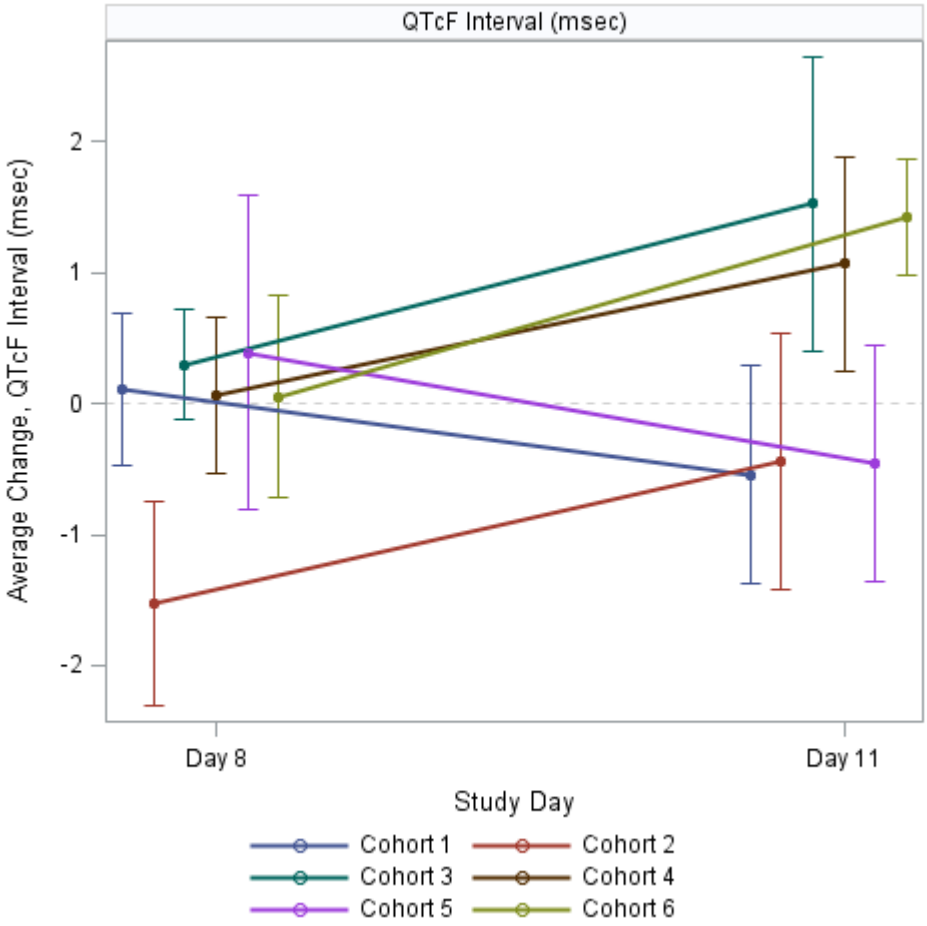
Figure 77: ECG by Scheduled Visits: Mean Changes from Baseline by Parameter and Treatment Cohort – QTcF Interval (msec)



Figures with similar format:

Figure 78: ECG by Scheduled Visits: Individual and Mean Values by Parameter and Treatment Cohort – PR Interval (msec)

[Implementation Note: Similar format to Figure 76.]

Figure 79: ECG by Scheduled Visits: Mean Changes from Baseline by Parameter and Treatment Cohort – PR Interval (msec)

[Implementation Note: Similar format to Figure 77.]

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

PRIVILEGED AND CONFIDENTIAL COMMUNICATION

16.1.6 Listing of Subjects Receiving Investigational Product

Not included in SAP, but this is a placeholder for the CSR.

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 1: 16.2.1: Early Terminations or Discontinued Subjects

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

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16.2.2 Protocol Deviations

Listing 2: 16.2.2.1: Subject-Specific Protocol Deviations

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

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

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

16.2.3 Subjects Excluded from the Analysis Populations

Listing 4: 16.2.3: Subjects Excluded from Analysis Populations

Treatment Cohort	Subject ID	Analyses from which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., Safety, PK]	[e.g., Safety, PK]		

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.

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16.2.4 Demographic Data

Listing 5: 16.2.4.1: Demographic Data

Treatment Cohort	Subject ID	Sex	Age at Enrollment (years)	Ethnicity	Race

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

Treatment Cohort	Subject 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

Listing 7: 16.2.5: Drug Concentration Data for Subjects with an Incomplete or Interrupted Infusion

[Implementation Note: Only include subjects who did not receive the full dose of study product or dose was interrupted for one of their scheduled doses.]

Treatment Cohort	Subject ID	Dose Number	Study Product Administered	Dose Start Date	Dose Taken?	Dose Interrupted?	Dose Start Time	Dose End Time	Interruption Start Time	Interruption End Time	Dose Duration (min)	Actual Dosage Administered (mL)
Cohort 1	XX	XX	AVYCAZ or ATM	ddMMMyyyy	Yes/No	Yes/No	hh:mm	hh:mm	hh:mm	hh:mm	XXX	XX

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16.2.7 Adverse Events

Listing 8: 16.2.7: Unsolicited Adverse Events

[Implementation Note: Sort by relatedness (related then unrelated), Treatment Cohort, Subject ID.]

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

Note: For additional details about SAEs, see Table 18.

16.2.8 Individual Laboratory Measurements

Listing 9: 16.2.8.1: Clinical Laboratory Results – Chemistry

[Implementation Note: If laboratory result is Outside of Normal Range, use 'ONR' as Severity Grade.]

Treatment Cohort	Subject ID	Study Day	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline[a]	Reference Range Low	Reference Range High

[a] Baseline = Measurement from Day -1.

Listing 10: 16.2.8.2: Clinical Laboratory Results – Hematology

[Implementation Note: If laboratory result is Outside of Normal Range, use 'ONR' as Severity Grade.]

Treatment Cohort	Subject ID	Study Day	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline[a]	Reference Range Low	Reference Range High

[a] Baseline = Measurement from Day -1.

Listing 11: 16.2.8.3: Clinical Laboratory Results – Coagulation

[Implementation Note: If laboratory result is Outside of Normal Range, use 'ONR' as Severity Grade.]

Treatment Cohort	Subject ID	Study Day	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline[a]	Reference Range High

[a] Baseline = Measurement from Day -1.

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Listing 12: 16.2.8.4: Clinical Laboratory Results – Urinalysis

[Implementation Note: Change from Baseline row will be N/A for urinalysis parameters that are recorded as Negative/Trace/1+/2+/3+/4+. If laboratory result is Outside of Normal Range, use 'ONR' as Severity Grade.]

Treatment Cohort	Subject ID	Study Day	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline[a]

[a] Baseline = Measurement from Day -1.

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Listing 13: 16.2.8.5: Screening Laboratory Results – Serology

Treatment Cohort	Subject ID	Study Day	Actual Study Day	HIV Antibodies	HBsAg	HCV Antibodies
Cohort 1	XXXX	Screening	-15	Positive/Negative	Positive/Negative	Positive/Negative

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Listing 14: 16.2.8.6: Laboratory Results – Coombs Test

Treatment Cohort	Subject ID	Study Day	Actual Study Day	Coombs Test Result
Cohort 1	XXXX	Screening	-15	Positive/Negative

Listing 15: 16.2.8.7: Laboratory Results – Urine Cotinine, Urine Toxicology, and Alcohol Testing

[Implementation Notes: Listing will include results from urine cotinine, urine toxicology, and alcohol breathalyzer testing.]

Treatment Cohort	Subject ID	Study Day	Actual Study Day	Test	Result
Cohort 1	XXXX	Screening	-15	Barbiturates	Positive/Negative

Listing 16: 16.2.8.8: Laboratory Results – Pregnancy Testing

Treatment Cohort	Subject ID	Study Day	Actual Study Day	Result
Cohort 1	XXXX	Screening	-15	Positive/Negative

16.2.9 Vital Signs and Physical Exam Findings

Listing 17: 16.2.9.1: Vital Signs

Treatment Cohort	Subject ID	Study Day	Actual Study Day	Oral Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse Rate (beats per minute)	Respiratory Rate (breaths per minute)	Weight (kg)	Height (cm)

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Listing 18: 16.2.9.2: Physical Exam Findings

Treatment Cohort	Subject ID	Study Day	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

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Listing 19: 16.2.9.3: Listing of ECG Interval Measurements and Overall Interpretation

						Interval Measurement					
Treatment Cohort	**Subject ID**	**Study Day**	**Actual Study Day**	**Date of Assessment**	**Time of Assessment (hh:mm)**	**QTcF Interval (msec)**	**PR Interval (msec)**	**Replicate Number**	**Change from Baseline[a]**	**Overall Assessment**	**Comments**
Cohort 1	XX	Screening	-15	ddMMMyyyy	hh:mm	395	130	1	-	-	
Cohort 1	XX	Screening	-15	ddMMMyyyy	hh:mm	400	135	2	-	-	
Cohort 1	XX	Screening	-15	ddMMMyyyy	hh:mm	405	140	3	-	-	
Cohort 1	XX	Screening	-15	ddMMMyyyy	Mean	400	135	-	-	Normal	

[a] Baseline = Measurement from Day -1.

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16.2.10 Concomitant Medications

Listing 20: 16.2.10: Concomitant Medications

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

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16.2.11 Pregnancy Reports

Listing 21: 16.2.11.1: Pregnancy Reports – Maternal Information

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

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

Listing 22: 16.2.11.2: Pregnancy Reports – Gravida and Para

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

Note: Gravida includes the current pregnancy, para events do not. Extremely PB = <25 weeks; Very Early PB = 25 0/7 - 31 6/7 weeks; Early PB = 32 0/7 – 33 6/7 weeks; Late PB = 34 0/7 – 36 6/7 weeks; Early TB = 37 0/7 – 38 6/7 weeks; Full TB = 39 0/7 – 40 6/7 weeks; Late TB = 41 0/7 – 41 6/7 weeks; Post TB = >= 42 0/7 weeks.

[a] Preterm Birth

[b] Term Birth

Listing 23: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

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

Note: Congenital Anomalies are included in the AE listing.

Listing 24: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

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

Listing 25: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

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

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Listing 26: Birth Control Listing

Treatment Cohort	Subject ID	Sex	Child Bearing Potential (if Female)	Sexually Active (if Male)	Birth Control Method	Start Date	Start Date Certainty	End Date	End Date Certainty	Ongoing?

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Listing 27: Subject Level CAZ, AVI, and ATM Concentrations in Plasma

[Implementation Note: Out of window blood draws will be marked with an asterisk. If CEF, AVI, or ATM concentration levels are below LLQQ, report as BQL and include footnote "BQL = Below Quantitative Limit". If no levels are BQL, footnote does not need to be included in table.]

Treatment Cohort	Subject ID	Date of Blood Draw (ddMMMyyyy)	Time of Blood Draw (hh:mm)	Nominal Time[a] (hr)	Actual Time[a] (hr)	CEF Concentration in Plasma (µg/mL)	AVI Concentration in Plasma (µg/mL)	ATM Concentration in Plasma (µg/mL)

Note: BQL = Below Quantitative Limit
[a] Times relative to start of study product infusion. For actual time, out of window times are indicated by an asterisk.

Listing 28: Subject Level CAZ, AVI, and ATM Concentrations in Urine

[Implementation Note: Out of window urine collections will be marked with an asterisk.]

Drug	Treatment Cohort	Subject ID	Study Day	Date of Urine Collection (ddMMMyyyy)	Time of Urine Collection (hh:mm)	Nominal Time [a] (hr)	Actual Time [a] (hr)	Volume of Urine (mL)	Drug Concentration in Urine (µg/mL)	Amount of Drug in Urine[b] (µg)

[a] Times relative to start of study product infusion. For actual time, out of window times are indicated by an asterisk.
[b] Amount of Drug in Urine = Volume * Drug Concentration

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Listing 29: Subject-Specific Pharmacokinetic Parameters from Non-Compartmental Plasma Pharmacokinetic Analysis

Drug	Treatment Cohort	Subject ID	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-}Tau,1}$ (µg·hr/mL)	$AUC_{0\text{-}Tau,ss}$ (µg·hr/mL)	C_{min} (µg/mL)	K_{el} (1/hr)	$T_{1/2,kel}$ (hr)	CL_{ss} (L/h)	V_z (L)

Listing 30: Subject-Specific Pharmacokinetic Parameters from Non-Compartmental Urine Pharmacokinetic Analysis

Drug	Treatment Cohort	Subject ID	Day 1 $Ae_{0\text{-}4}$ (µg)	Day 1 $Ae_{0\text{-}8}$ (µg)	Day 1 $Ae_{0\text{-}12}$ (µg)	Day 1 $Ae_{0\text{-}24}$ (µg)	Day 1 $Fe_{0\text{-}24}$	Day 6 $Ae_{0\text{-}4}$ (µg)	Day 6 $Ae_{0\text{-}8}$ (µg)	Day 6 $Ae_{0\text{-}12}$ (µg)	Day 6 $Ae_{0\text{-}24}$ (µg)	Day 6 $Fe_{0\text{-}24}$	CL_R (L/h)

Listing 31: Subject-Specific Pharmacokinetic Parameters from Population Pharmacokinetic Analysis (Final Model)

[Implementation Note: Other Parameters may be added depending on the final model.]

Drug	Treatment Cohort	Subject ID	V (L)	V_p (L)	CL (L/h)	Q (L/h)	$C_{max,\ ss}$ (µg/mL)	$C_{min,\ ss}$ (µg/mL)	$AUC_{0\text{-}24,ss}$ (µg·hr/mL)

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