CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 23-0005

A Phase 1, Placebo-Controlled, Double-Blinded Study to Assess the Safety and Pharmacokinetics of Single Ascending Doses of EV68-228-N in Healthy Adult Volunteers

NCT06444048

Version 2.0

DATE: 21AUG2025

RESTRICTED

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 23-0005**
Development Phase:	Phase 1
Products:	EV68-228-N
Form/Route:	Intravenous (IV) infusion
Indication Studied:	Acute Flaccid Myelitis
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	18JUN2024
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	21AUG2025
Version Number:	2.0

This study was performed in compliance with Good Clinical Practice.

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VERSION HISTORY

Version	Date	Change	Rationale
1.0	21JUL2025	Not Applicable	Original version
2.0	21AUG2025	Page 80, Table # and title updated	In v1.0, continuation of Table 34 onto next page had incorrect table number and title in error.

List of Abbreviations *(continued)*

LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibodies
AE	Adverse Event
AFM	Acute Flaccid Myelitis
ALT	Alanine Aminotransferase
AUC	Area under the serum concentration-time curve
$AUC_{0-\infty}$	AUC from time 0 to infinity
AUC_{0-t}	AUC from time 0 to time t
AUC_{0-48}	AUC from time 0 to 48 hours post dose
AUC_{0-last}	AUC from time 0 to the time of the last quantifiable concentration
BQL	Below the Quantitation Level
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CL	Total serum clearance
C_{max}	Maximum observed serum concentration
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DMPA	Depot Medroxyprogesterone Acetate

List of Abbreviations *(continued)*

ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECL	Electrochemilumnescence Immunoassay
eCRF	Electronic Case Report Form
EV-D68	Enterovirus D68
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
GM	Geometric Mean
GMT	Geometric Mean Titer
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
IV	Intravenous
IVIg	Intravenous Immunoglobulin
LARC	Long-acting Reversible Contraception
MAAE	Medically Attended Adverse Event
mAb	Monoclonal Antibody
MedDRA®	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MSD	Meso Scale Discovery
MRI	Magnetic Resonance Imaging
N	Number (typically refers to participants)
NCA	Noncompartmental Analysis

List of Abbreviations *(continued)*

NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NOCMC	New Onset Chronic Medical Condition
NRR	"No Recorded Result"
PI	Principal Investigator
PK	Pharmacokinetics
Plt	Platelet
PSRT	Protocol Safety Review Team
PT	Preferred Term
RAMP	Rapid Antibody Manufacturing Platform
RNA	Ribonucleic Acid
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
$t_{1/2}$	Apparent serum terminal elimination half-life
T bili	Total Bilirubin
T_{max}	Time of the maximum observed serum concentration
US	United States
VS	Vital Signs
VTEU	Vaccine Treatment and Evaluation Unit
Vz	Volume of distribution during the terminal phase
WBC	White Blood Cells
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 1, Placebo-Controlled, Double-Blinded Study to Assess the Safety and Pharmacokinetics of Single Ascending Doses of EV68-228-N in Healthy Adult Volunteers" (DMID Protocol 23-0005) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International 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 contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for pharmacokinetics (PK) and safety outcomes, and (4) a list of proposed tables and figures. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

Enterovirus D68 (EV-D68) is a re-emerging picornavirus associated with severe respiratory infections and neurologic diseases, such as acute flaccid myelitis (AFM). AFM is a subtype of myelitis characterized by flaccid weakness in at least one limb and magnetic resonance imaging (MRI) changes in grey matter indicating demyelination within the spinal cord. AFM occurs in ~1% of EV-D68 infections in children with an average age of onset of 5-7 years (1, 2). A majority of AFM patients experience other symptoms of upper respiratory illness within 5-10 days prior to onset of limb weakness, and neurological sequelae typically peak within several days (≤10) of onset (1, 3). Studies have identified enterovirus antibodies in the cerebrospinal fluid of patients with AFM, and more recently EV-D68 ribonucleic acid (RNA) and protein were identified in anterior horn motor neurons of the cervical spinal cord from a 5-year-old boy who died of an AFM-like illness in 2008 (4).

AFM outbreaks have occurred worldwide and have been well characterized in the U.S., with peaks in incidence occurring in August through October every other year since 2014. The outbreak in 2014 remains the largest ever recorded EV-D68 outbreak, with 1,152 confirmed cases spanning all states except for Alaska. Over half of the hospitalized patients with respiratory disease were admitted to intensive care units, with 80% receiving supplemental oxygen, 23% requiring non-invasive ventilation, 8% requiring intubation and mechanical ventilation, and 1% died (3). Since that time, incidence has steadily increased. The biennial domestic AFM outbreaks have been associated with EV-D68 circulation, and there is now strong evidence of causality for enteroviruses and AFM. In 2020 and 2022, AFM incidence was lower than in previous years (5), likely due to social distancing measures from the ongoing COVID pandemic; however, it is likely that EV-D68 will re-emerge in years to come, leading to sustained AFM incidence.

Currently, no agent is approved in the U.S. for the treatment of severe EV-D68 infection or AFM, and the current standard of care is limited to supportive treatment and polyclonal intravenous immunoglobulin (IVIg). Commercial lots of IVIg contain varying levels of antibodies to EV-D68, and the efficacy of IVIg administration is unknown.

The human monoclonal antibody 228 was derived from patients recovering from EV-D68 infection (6). This monoclonal antibody (mAb) was found to have potent in vitro neutralizing activity against multiple clinical EV-D68 strains across multiple years (2014, 2016, and 2018 epidemic years). The 228 antibody has subsequently been produced by KBio, Inc., using genetically engineered plasmids in a Nicotiana benthamiana (tobacco plant) based rapid antibody manufacturing platform (RAMP) (product name: EV68-228-N) (7). It has been tested against EV-D68 in vitro and in vivo and has demonstrated therapeutic effects when administered soon after the onset of neurological symptoms in a murine model of EV-D68 infection.

In a murine neurologic model of infection that mimics human AFM, mAb EV68-228-N treatment eliminated detectable virus from the blood within 24 hours of administration; improved survival and neurologic disease when given up to 48 hours after infection; and improved clinical response when given as late as 72 hours after infection. In a separate in vivo murine model of EV-D68 induced AFM, mAb EV68-228-N treatment effectively prevented progression of paralysis and improved histopathologic evidence of disease in tissues of the central nervous system (CNS) when treatment was initiated after the onset of limb weakness; most critically, EV68-228-N treatment conferred a protective effect on CNS motor neurons following EV-D68-infection induced paralysis. These data support the hypothesis that mAb EV68-228-N is a potent neutralizing antibody in vivo and can result in clinical improvement in murine models of EV-D68 infection, even when administered after the onset of neurologic disease (7).

While the pathogenesis of AFM is incompletely understood, targeting the replicating virus with a neutralizing monoclonal antibody appears to be a reasonable next step based on recent human data. Vogt, Wright, and Hickey reported on a 5-year-old boy who died of an AFM-like illness in 2008 (4). EV-D68 was detected in the cerebrospinal fluid (CSF) and using preserved formalin-fixed and paraffin-embedded autopsy tissue, the authors were able to detect EV-D68 RNA and protein in anterior horn motor neurons and their axons using in situ hybridization and immuno-histochemistry. In addition, Vogt et al identified CD8+ T-cell and CD68+ macrophage infiltration in EV-D68-infected regions along with up-regulated inflammatory gene transcripts in inflamed tissues. Not only do these data support the causal association between EV-D68 and AFM, but they also support the hypothesis that the clinical presentation of AFM includes a combination of the direct effects of viral infection of spinal cord motor neurons and damage resulting from local inflammation. Taken together, the data supports ongoing efforts to develop antiviral and neutralizing monoclonal antibody treatment options that may aid in viral clearance and possible immunomodulation.

Given the therapeutic potential of EV68-228-N and the exceptional safety profile of fully human monoclonal antibodies, further development is warranted. This Phase 1 clinical trial will evaluate the safety and PK of EV68-228-N in healthy adult volunteers to support future evaluations of its efficacy as a treatment for AFM in pediatric patients.

2.1. Purpose of the Analyses

These analyses will assess the safety and PK of EV68-228-N after a single IV infusion in healthy adult male and female volunteers. Safety and PK data from the Phase 1 study of EV68-228-N will be used to support identification of a target dose for future efficacy trials in AFM patients.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary

- To evaluate the safety of a single IV infusion of either 3, 10, or 30 mg/kg of EV68-228-N when administered to healthy adults.

3.1.2. Secondary

- To characterize the PK of single ascending doses of EV68-228-N for approximately four months following the infusion.
- To measure the occurrence of Anti-Drug Antibodies (ADAs) elicited following a single IV infusion of EV68-228-N in healthy adults.

3.2. Outcome Measures

3.2.1. Primary

- Proportion of participants experiencing solicited adverse events (AEs) through 48 hours post-infusion.
- Proportion of participants experiencing unsolicited AEs – including clinical and laboratory AEs – through Day 29.
- Proportion of participants experiencing serious AEs (SAEs), medically attended AEs (MAAEs), and new onset chronic medical conditions (NOCMCs) through the end of the study.

3.2.2. Secondary

After a single IV infusion of EV68-228-N:

- EV68-228-N concentrations in serum will be determined with a validated assay. The PK parameters will be estimated based on the concentration-time data, including area under the serum concentration-time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$), AUC from time 0 to 48 hours post dose (AUC_{0-48}), AUC from time 0 to the time of the last quantifiable concentration (AUC_{0-last}), maximum observed serum concentration (C_{max}), time of the C_{max} (T_{max}), apparent serum terminal elimination half-life ($t_{1/2}$), total serum clearance (CL), and volume of distribution during the terminal phase (Vz) calculated from serum EV68-228-N levels.
- Incidence of anti-EV68-228-N antibodies as measured by the proportion of participants with detectable anti-EV68-228-N antibodies in serum.

3.3. Study Definitions and Derived Variables

3.3.1. Baseline

For clinical laboratory and serological and electrocardiogram (ECG) measurements, the last value recorded prior to administration of study drug will be considered as baseline. For vital signs (VS) measurements, generally the last value recorded prior to administration of study drug will also be considered as baseline, but

if repeat measurements are collected at the baseline visit, the rules in Section 9.7 will be used to determine which result will be used as the actual baseline value.

Baseline height was obtained at screening. Weight was obtained at both screening and Day 1 prior to dosing; the baseline weight will be the one obtained at Day 1. Baseline body mass index (BMI) will be calculated using the height measure at screening and the weight measure at Day 1. Age will be based on age at the time of enrollment.

3.3.2. Study Day

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

Participation for an individual participant will be approximately four to six months, which includes a 1 to 28-day screening period, infusion on Day 1, and follow-up visits on Day 2, 3, 8, 15, 29, 61, 91, and 121.

3.3.3. Detectable Anti-Drug Antibody

There are three steps in the Meso Scale Discovery (MSD) Electrochemiluminescent (ECL) assay: screening assay, confirmatory assay, and titer assay. The screening assay will have qualitative results of negative (NEG), potential positive screening (PPS) and no recorded result (NRR).

An ADA confirmatory assay will be performed for specimens with PPS screening results. The result of the confirmatory assay is qualitative, NEG, NRR, or positive (POS).

A detectable ADA is defined when the confirmatory assay result is POS.

3.3.4. Pharmacokinetic Parameters

$AUC_{0-\infty}$ is defined as the AUC from the time of dosing extrapolated to time infinity based on the last observed concentration (C_{last}) and the elimination rate constant (λz), where C_{last} is defined as the last observed positive concentration above the lower limit of quantitation (LLOQ) and λz is defined as the first-order rate constant associated with the terminal (log-linear) portion of the curve describing the rate of elimination from serum. Estimated by linear regression of time vs. log concentration. $AUC_{0-\infty}$ will be computed by adding AUC_{0-last} to an area extrapolated by C_{last} divided by λz, as shown below:

$$AUC_{0-\infty} = AUC_{0-last} + \frac{C_{last}}{\lambda_z}$$

AUC_{0-last} is defined as the AUC from the time of dosing to the time of the last quantifiable concentration above the LLOQ based on observed concentrations.

AUC_{0-48} is defined as the AUC from the time of dosing to the time of the last quantifiable concentration above the LLOQ up to and including the nominal 48 hr time point based on observed concentrations.

Maximum serum concentration (C_{max}) is defined as the maximum observed concentration, occurring the time of maximal serum concentration (T_{max}), in serum following the first dose of EV68-228-N.

T_{max} is defined as the time at which the maximum observed serum concentration occurs. Because non-steady-state data is collected, the entire curve is considered. If the maximum observed concentration is not unique, then the first maximum is used.

The terminal elimination half-life ($t_{1/2}$) is defined as the time it takes serum concentrations to reduce by 50% during the terminal elimination phase and will be estimated by the natural logarithm of 2 (ln(2)) divided by λz.

Total serum clearance (CL) is defined as the total clearance and represents a volume that is cleared of the molecule of interest per hour. It will be calculated as the dose divided by the $AUC_{0-\infty}$, as shown below:

$$CL = \frac{Dose}{AUC_{0-\infty}}$$

The volume of distribution during the terminal phase (V_z) is defined as the theoretical volume that the total amount of the molecule of interest would occupy if uniformly distributed at the concentration observed in serum. If the terminal phase has been adequately captured, this value should approximate the volume of distribution at steady state and is calculated as shown below:

$$V_z = \frac{Dose}{\lambda_z \times AUC_{0-\infty}} = \frac{CL}{\lambda_z}$$

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 1, randomized, placebo-controlled, double-blinded study to assess the safety and PK of single IV administrations of EV68-228-N in healthy adult volunteers.

Three doses (3, 10 and 30 mg/kg) of EV68-228-N will be evaluated in three separate, sequential cohorts (N = 12, each cohort) in this single dose escalation study. The cohorts will be randomized in a 5:1 randomization scheme for EV68-228-N and placebo. The first two participants in each cohort will serve as sentinels. Sentinel participants may be located at different sites. Sentinel safety data will be collected through Day 3 before submitting to the Protocol Review Safety Team (PSRT) for review. The PSRT is comprised of the Principal Investigator (PI), the DMID Medical Monitor, and the DMID Medical Officer.

Data to be reviewed will include clinical data collected from Visits 1, 2 and 3, the results of laboratory testing conducted at these visits, solicited AEs and the passive reporting of AEs through Day 3. From the time of infusion of the sentinels to at least 48 hours after infusion, no new participants will be given study product or placebo, but screening may continue. If no safety signal is detected in the sentinel group, and after approval from the DMID Medical Monitor, the remaining 10 participants in the cohort will be dosed following the overall 5:1 randomization scheme.

All participants will be actively monitored for AEs and safety laboratory data following dosing through Day 8. Data will be reviewed by the PSRT and discussed with the SMC for their concurrence before advancing to the next cohort. Electronic review of the safety data by the SMC is required prior to the cohort dose escalation when halting rules are met or there are any safety concerns.

Assuming no safety concerns are identified after review of the first cohort safety data through Day 8, enrollment of Cohort 2 will begin. The dose of EV68-228-N will be increased to 10 mg/kg for the second cohort. The same sentinel design and safety plan will be used to evaluate sentinel participants in Cohort 2 and determine whether to enroll the remaining participants in Cohort 2. In addition, the same sentinel design and safety plan will be used for Cohort 3, which will evaluate the 30 mg/kg dose.

Following informed consent, participants will be screened for eligibility, including medical history, physical examination, weight and height measurements, VS, screening laboratory tests, and a 12-lead ECG. Within 28 days of screening, eligible participants will be seen at the clinical research unit (Day 1) and be randomized to receive either a single IV dose of EV68-228-N or placebo (formulation buffer alone). Participants will remain in the unit for at least 5 hours following infusion and return for assessments on Day 2 and Day 3. Participants will have subsequent follow-up clinic visits on Days 8, 15, 29, 61, 91, and 121.

Participants will be monitored and assessed for safety and the incidence of AEs at all visits beginning with the dosing visit. An electronic memory aid will be utilized from Day 1 through Day 3 to assist with collecting solicited AEs. Safety laboratory studies will be collected at screening and on Days 1, 2, 3, 8, and 29. Concomitant medications taken 28 days before and after dosing will be recorded.

PK samples will be collected prior to infusion, at the end of infusion, at 1, 3, 5, 24 and 48 hours after end of infusion; and on Days 8, 15, 29, 61, 91, and 121. The single dose PK parameters to be estimated include C_{max}, T_{max}, - AUC_{0-48}, AUC_{0-last}, and $AUC_{0-\infty}$, $t_{1/2}$, CL, and Vz. PK parameters will be calculated from serum EV68-228-N levels measured using a validated ECL assay performed by PPD, Inc..

Samples for serum levels of anti-EV68-228-N antibodies will be collected prior to infusion on Day 1 and on Days 8, 15, 29, 61, 91 and 121.

A sample will be collected pre-infusion on Day 1 for hypersensitivity testing in the event that the participant experiences an infusion reaction. These baseline samples will only be analyzed in the event of a hypersensitivity reaction related to the infusion. If a participant experiences anaphylaxis or an anaphylactoid event related to the infusion, three additional samples will be collected: 1) during onset, 2) 2 or more hours after onset, and 3) after resolution of symptoms.

The study dosing plan is shown in Table 1.

4.2. Discussion of Study Design

This is a Phase 1, randomized, placebo-controlled, double-blinded study to assess the safety and PK of a single IV infusion of EV68-228-N in healthy adult volunteers. All participants will be actively monitored for solicited AE following infusion through Day 3 and clinical and safety laboratory data following dosing through Day 8. Three doses (3, 10 and 30 mg/kg) of EV68-228-N will be evaluated in three separate, sequential cohorts in this single dose escalation study. The cohorts will be randomized in a 5:1 randomization scheme. All placebo participants are analyzed jointly across cohorts. The first two participants in each cohort will serve as sentinels. Sentinel participants may be located at different sites.

4.3. Selection of Study Population

As this is the first time EV68-228-N will be tested in humans, the study population will be comprised of healthy males and non-pregnant, non-lactating females, ages 18-49 years inclusive at the time of consent, regardless of religion, sex, or ethnic background, who meet all of the inclusion and none of the exclusion criteria. The eligibility criteria apply only to enrollment of participants into the study. The focus population should reflect the community at large at the site. Participant Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses. No exemptions are granted on Subject Inclusion/Exclusion Criteria in DMID-sponsored studies. Questions about eligibility will be directed toward the DMID Medical Officer.

4.3.1. Eligibility Criteria

4.3.1.1. Participant Inclusion Criteria

1. Provides written informed consent prior to initiation of any study procedures.
2. Is able to understand and agrees to adhere to planned study procedures and is available for all study visits.
3. Adult volunteers 18 to 49 years of age, inclusive.
4. Females who are of childbearing potential[1] must agree not to become pregnant.

[1] *Not of childbearing potential includes post-menopausal females (defined as no menses for at least 12 months without an alternative medical cause for amenorrhea) or surgically sterile females with documented history of hysterectomy, bilateral oophorectomy, tubal ligation/salpingectomy, or Essure® placement.*

5. Females who have sexual intercourse with male partners must agree to use at least one acceptable form of contraception for the duration of the study[2,3].

   [2] Acceptable methods of birth control include long-acting reversible contraception (LARC), combined pill, progestin-only pill, hormone-releasing transdermal patch or vaginal ring, and depot medroxyprogesterone acetate (DMPA) injection. Participants who choose to use a licensed hormonal product should use them for a minimum of 28 days prior to study infusion. True sexual abstinence or a monogamous relationship with a vasectomized partner who has been vasectomized for 180 days or more prior to the participant's first infusion are also acceptable contraceptive methods.

   [3] Participants who report practicing true abstinence, defined as no heterosexual vaginal-penile intercourse, need to practice true abstinence at all times during the study. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and the withdrawal method are not acceptable methods of contraception.

6. Females of childbearing potential must agree to not donate ova or oocytes during the study.
7. Participant is in good health[4].

   [4] Good health is defined by the absence of a medical condition described in the exclusion criteria. If the participant has another current, ongoing medical condition, the condition cannot meet any of the following criteria: (1) was first diagnosed within 3 months of enrollment with a clinically significant condition, in the opinion of investigator that has worsened within 3 months of enrollment; (2) had non-elective surgery, clinically significant medical procedure, or hospitalization within 3 months of enrollment; (3) received new prescription for systemic medication within 30 days of enrollment, unless the new prescription is in the same class of agent or a transition from generic to/from brand name equivalent; or (4) takes medication that may pose a risk to participant's safety or impede assessment of adverse events or study endpoints if they participate in the study.

8. Must agree to refrain from donating blood or blood products[5] during the study.

   [5] This includes whole blood cells, red blood cells, platelets, plasma, and plasma derivatives collected and donated outside of the study blood draws.

9. Body mass index (BMI) 18 kg/m^2 to 32 kg/m^2, inclusive, and a weight of 125 kg or less at time of screening.
10. Must have adequate venous access for intravenous (IV) infusion and blood sampling.

4.3.1.2. Participant Exclusion Criteria

All participants meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Positive pregnancy test at screening or prior to infusion.
2. Female participant who is lactating.
3. Presence of significant psychiatric condition, that in the opinion of the site PI or appropriate sub-investigator, precludes study participation.
4. History of drug abuse or alcohol abuse within 6 months of enrollment that, in the opinion of the site PI or appropriate sub-investigator, precludes study participation.
5. Has a significant acute illness (with or without fever), as determined by the site PI or appropriate sub-investigator, within 72 hours prior to infusion[1].

   [1]If the participant meets all other eligibility criteria, they may be enrolled and dosed once they meet this eligibility criterion. If the illness resolves within the 28-day screening window, they do not need to be rescreened, otherwise they will need to be rescreened.

6. Currently enrolled in or plans to participate in another clinical trial with an investigational agent that will be received during the study-reporting period.
7. Has a history of significant hypersensitivity, intolerance, or allergy to any drug compound, vaccine, food, or other substance, unless approved by the Investigator (or designee)[2].

[2]*Sensitivity to glycine, citric acid, trisodium citrate, sorbitol, or polysorbate 80 (components of the study product) is exclusionary.*

8. Any history of an infusion reaction to any biologic product.
9. Receipt of a monoclonal antibody in the 180 days prior to infusion.
10. Receipt of a blood product within 120 days prior to infusion.
11. Received any live-attenuated vaccine in the 28 days prior or any other vaccine in the 14 days prior to infusion.
12. Has used any prohibited medication within 30 days prior to Day 1 or plans to use prohibited medication[3] during the study.

    [3]*Prohibited medications include systemic immunosuppressive drugs, immune modulators (except acetaminophen or non-steroidal anti-inflammatory drugs), oral corticosteroids, and systemic anti-neoplastic agents. Topical, inhaled, and intranasal steroids, as well as topical anti-neoplastic agents are acceptable.*
13. Has clinically significant findings[4] on 12-lead electrocardiogram.

    [4]*Clinical significance will be determined by a cardiologist. Examples of findings that will lead to exclusion are significant left ventricular hypertrophy, right or left bundle branch block, advanced A-V heart block, non-sinus rhythm (excluding isolated premature atrial contractions), pathologic Q wave abnormalities, significant ST-T wave changes, and prolonged QTc interval. Long QT interval is defined in males as a median QTcB greater than 450 msec or in females as a median QTcB greater than 460 msec (Bazett's correction) at screening.*
14. Abnormal vital signs (Grade 1 or higher)[5] at screening or on Day 1.

    [5] *Grade 1 or higher is equivalent to:*

    Systolic blood pressure (SBP) > 140 mmHg or < 85 mmHg
    Diastolic blood pressure (DBP) > 90 mmHg
    Oral temperature ≥ 38.0°C (100.4°F)
15. Abnormal laboratory results[6] that are Grade 1 or worse at screening based on the Toxicity Tables.

    [6]*Creatinine, alanine transaminase (ALT), hemoglobin (Hgb), platelets (PLT), white blood cell count (WBC), and total bilirubin (T bili).*

    [7]*Laboratory studies can be repeated once if an alternative, transient etiology for abnormal laboratory values is identified.*
16. Known, current human immunodeficiency virus (HIV), hepatitis B Virus (HBV), or hepatitis C virus (HCV) infection.
17. Has any medical disease or condition[8] that, in the opinion of the site PI or appropriate sub-investigator, precludes study participation[9].

    [8]*Medical conditions include, but are not limited to, kidney disease with creatinine clearance < 90 mL/min/1.73 cm^2 (CKD-EPI method); known active liver disease including steatosis; ischemic heart disease, clinically significant cardiac conduction disorder, arrythmia requiring treatment, congenital long QT syndrome, uncompensated heart failure; diabetes requiring insulin; neuropathy or myopathy; and malignancy (not including squamous cell skin cancer, basal cell skin cancer, or cervical low-grade squamous intraepithelial lesions).*

    [9]*Participation may be precluded due to safety concerns or inability to adequately evaluate clinical trial endpoints.*

4.3.1.3. Withdrawal from the Study or Discontinuation of the Study Product

Participants may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

An investigator may also withdraw a participant prior to receiving the study product or after receiving the study product for any reason. Follow-up safety evaluations will be conducted, if the participant agrees. If a

participant withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms (CRFs).

The reasons might include, but are not limited to the following:

- Participant becomes pregnant prior to infusion.
- Participant no longer meets eligibility criteria (e.g., develops acute febrile illness on Day 1 prior to infusion).
- Participant meets individual halting criteria.
- Participant becomes non-adherent.
- Participant develops a medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the participant, interfere with the participant's successful completion of this study, or interfere with the evaluation of responses.
- Participant is lost to follow-up.
- Determined by a physician's discretion to require additional therapy not indicated in the protocol to ensure participant's health and well-being.

If the participant consents, every attempt will be made to follow all AEs and pregnancies through resolution. The investigator should be explicit regarding study follow-up (e.g., safety follow-up) that might be carried out. The procedures that collect safety data for the purposes of research must be inclusive in the original informed consent or the investigator may seek subsequent informed consent using an IRB/IEC-approved consent form with the revised procedures.

The investigator will inform the participant that already collected data will be retained and analyzed even if the participant withdraws from this study.

4.3.1.4. Participant Replacement

Participants who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the informed consent form (ICF) and receiving an infusion will not be replaced. Participants who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the ICF but before infusion may be replaced.

4.3.1.5. Study Termination

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study participants and assure appropriate therapy or follow-up for the participants, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB.

4.4. Treatments

4.4.1. Treatments Administered

Participants will receive a single IV dose of either study product or placebo. Infusions will be administered over approximately 15 minutes or 30 minutes, depending upon the volume of the infusion, in the absence of infusion reactions or non-drug, infusion related safety issues; longer infusion times will be permitted. All infusions must be completed within 4 hours of compounding.

4.4.2. Identity of Investigational Product(s)

The EV68-228-N mAb is produced by expression of genetically engineered plasmids in a *Nicotiana benthamiana* based RAMP using proprietary plasmid vectors with plant viral sequences to reduce cost and improve the speed of production. The use of an engineered strain of *N. benthamiana* in which the plant specific glycosyltransferases, α1,3 fucosyltransferase and β1,2 xylosyltransferase, are mutated allows the RAMP-produced mAbs to have highly homogenous mammalian N-glycans and mitigates the potential for immunogenicity caused by carryover of plant glycans. See the IB for additional information regarding product manufacturing (7).

KBio uses an internal nomenclature system for identification of investigational products; the internal KBio nomenclature for EV68-228-N is "KB13A.1.1". This identification number will appear on the Certificate of Analysis as well as product labeling.

4.4.3. Method of Assigning Participants to Dose Cohorts (Randomization)

Enrollment/randomization will be performed through the enrollment module in the electronic data capture system, maintained by the Statistical and Data Coordinating Center (SDCC). Eligible participants in three dose escalating cohorts will be randomized in a 5:1 ratio to receive either EV68-228-N or placebo. The randomization is based on a variable blocked scheme to provide an approximately balanced allocation to the Dose Cohorts during the study.

4.4.4. Selection of Doses in the Study

Single ascending doses (3, 10, and 30 mg/kg) of EV68-228-N had been selected for this study based on the favorable safety and tolerability profile observed in the nonclinical studies (7, 8, 9, 10, 11, 12).

4.4.5. Selection and Timing of Dose for Each Participant

This trial will evaluate the PK and safety of single ascending doses (3, 10, and 30 mg/kg) of EV68-228-N administered as IV infusion on Day 1. Dosing for each cohort will begin with two sentinel participants. There will be a minimum of 2 days of observation following dosing of the sentinels before dosing of additional participants in each cohort is authorized.

4.4.6. Blinding

All investigative site personnel, study volunteers, DMID personnel will remain blinded through database lock, with the exception of an unblinded pharmacist/verifier at the research site, an unblinded SDCC biostatistician, and a DMID manager responsible for PK sample storage. The randomization scheme will be provided to the unblinded research pharmacist at the site, who will perform dose preparation, and a pharmacy verifier who will not participate in dose preparation. The pharmacy personnel at the site will not be involved in study-related assessments or have participant contact for data collection following study drug administration. The study staff participating in the administration of study product and assessment of the participants will not be aware of the administered contents of the IV infusion in the randomized arms of the study. Study drugs will be diluted in normal saline, and they will look identical to placebo in the IV infusion bag so the study staff and the participant will not be able to determine whether placebo or active drug are being administered. The label on the IV infusion bag will not have information that can identify the contents. Individual samples are barcoded, and the barcode includes information that can match the sample to the volunteer identification number, aliquot number, treatment cohort and collection time point. The SMC will receive blinded data in aggregate and presented by cohort. The SMC may review unblinded data prepared by an unblinded biostatistician in the closed session only.

4.4.7. Prior and Concomitant Therapy

Medications taken before or after dosing will be reported as Prior Medications or Concomitant Medications, respectively.

Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications recorded will include all current medications and medications taken within 28 days prior to signing the informed consent and during the study period. Medications reported in the electronic case report form (eCRF) are limited to those taken within 28 days prior to the study drug administration or taken through the study. Prescription and over-the-counter drugs will be included as well as herbals, vitamins, and supplements.

Systemic medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. A participant will be withdrawn for use of excluded medications. Medications in this category include the prohibited medications per the Participant Exclusion Criteria (Section 4.3.1.2). Prohibited medications include systemic immunosuppressive drugs, immune modulators (except acetaminophen or non-steroidal anti-inflammatory drugs), oral corticosteroids, and systemic anti-neoplastic agents. Topical, inhaled, and intranasal steroids, as well as topical anti-neoplastic agents are acceptable.

4.4.8. Treatment Compliance

All participants were to receive a single dose of study product administered in the clinic.

4.5. Safety, Immunogenicity and Pharmacokinetic Variables

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

4.5.1. Safety Variables

Safety will be assessed through the evaluation of AEs, SAEs, vital signs, ECGs, and clinical safety laboratory data as outlined in the SOA.

Solicited AEs will be summarized by severity for each day post administration (Days 1 - 3) and as the maximum severity over all 3 days. If the AE is still ongoing after Day 3, the time point will be defined as “Ongoing after Day 3”. Additionally, solicited AEs will be analyzed using standard techniques, such as exact confidence intervals (CIs), to summarize the proportion of participants reporting each symptom.

Unsolicited AEs will be collected from the time of infusion through Day 29.

Unsolicited AEs will be coded by MedDRA for Preferred Term (PT), High Level Group Term (HLGT) and System Organ Class (SOC). SAEs, MAAEs and NOCMCs will be collected from the time of infusion through end of study. The numbers of SAEs, MAAEs, and NOCMCs will be reported by detailed listings showing the event description, MedDRA PT, HLGT and SOC, relevant dates (product administration and AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of participants reporting at least one event in each MedDRA PT, HLGT and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of participants and exact 95% CIs of AEs in aggregate and by MedDRA categories will be computed.

Clinical laboratory and hematology measurements will be collected at Screening, pre-infusion on Day 1, and Days 2, 3, 8, and 29. ECG measurements will be collected at Screening, pre-infusion and 1-hour post-infusion

on Day 1, and Day 2. VS measurements will be collected at Screening, pre-infusion, post-infusion, and 1-hour post-infusion on Day 1, and Days 2, 3, 8, 15, and 29. Clinical laboratory, ECG, and VS results will be assessed at baseline and each post-dose time point collected, using the toxicity grading scales in Table 5. For continuous parameters, change from baseline will also be summarized for all post-dose time points. For definitions of baseline, refer to Section 3.3.1.

4.5.2. Immunogenicity Variables

In this study, the immunogenicity data are measuring the anti-drug response. A validated ECL assay will be performed on samples collected approximately within 15 minutes prior to the infusion on Day 1 and at Days 8, 15, 29, 61, 91 and 121 (with corresponding windows) for serum levels of anti-EV68-228-N antibodies. To measure ADA, anti-drug antibodies will be captured by EV68-228-N and detected with labeled EV68-228-N (e.g., biotin) followed by standard detection (e.g., streptavidin -SULFO-TAG).

4.5.3. Pharmacokinetic Variables

Serum EV68-228-N concentrations: The MSD ECL assay will be performed on samples collected approximately 15 minutes prior to infusion; at end of infusion (+5 minute window); 1-, 3-, and 5-hours after end of infusion, within a ±15 minute window; 24 and 48-hours after the end of the infusion (within a ±3-hour window) and on Days 8, 15, 29, 61, 91, and 121 (within ±1-, 2-, 3-, 7-, 14-, and 14-day window, respectively). An EV68-228-N anti-idiotype antibody will be used in the assay to capture EV68-228-N and this will be detected with an anti-Human IgG (Fc)-biotin antibody, secondary detection is Streptavidin SULFO-TAG.

PK parameters will be estimated based on the time-concentration data through a non-compartmental analysis. Estimated total serum PK parameters will include the following:

- $AUC_{0-\infty}$: Area under the concentration time-curve from time 0 extrapolated to infinity
- $AUC_{0\text{-last}}$: Area under the concentration time-curve from time 0 to the last concentration above the lower limit of quantitation
- AUC_{0-48}: Area under the concentration time-curve from time 0 to 48hrs
- C_{max}: Maximum concentration
- T_{max}: Time of maximum concentration
- $t_{1/2}$: Apparent terminal elimination half-life
- CL: Total serum clearance
- V_z: Volume of Distribution during terminal phase

Refer to Section 3.3.4 for parameter definition.

5. SAMPLE SIZE CONSIDERATIONS

As a Phase 1, first-in-human study, the number of participants was chosen principally on feasibility and using a 5:1 randomization scheme. Thus, three cohorts of 10 participants each (n=30) and 6 placebo recipients (total N=36) are proposed. With 10 participants in each cohort receiving study product, the chance of observing at least one AE of probability 20% or more is approximately 89.3% (see Table 3). Therefore, if no AEs of a given type occur in an active dose group, we can be relatively confident that they will occur in fewer than 20% of people once the treatment is implemented.

PK parameters are not a primary outcome of the study, so it has not been powered for this, however with a sample size of 10 participants per dose level, assuming the pharmacokinetics are not dose proportional, a parameter with a coefficient of variation of 120% or less has a 90% chance to be observed within 80% and 120% of the geometric mean.

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, SD, 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.

In general, all data will be listed, sorted by treatment, cohort, and participant, and when appropriate by visit number within participant. All summary tables will be structured with a column for each treatment in the order (3, 10, 30 mg/kg EV68-228-N, and Placebo) and will be annotated with the total population size relevant to that table/treatment, including any missing observations. In some safety tables, all participants who received active product (3, 10, 30 mg/kg EV68-228-N) will also be summarized together.

6.2. Timing of Analyses

The final analysis will be performed after the final data lock, and CSR completed when all primary safety endpoint data and all secondary immunogenicity and pharmacokinetics endpoint data are available and received by the SDCC.

6.3. Analysis Populations

6.3.1. Modified Intent-to-Treat (mITT) Population

The mITT population includes all participants who received at least a partial dose of study product and contributed both pre- and at least one post-dose venous blood sample for immunogenicity testing for which valid results were reported. Descriptive summaries of immunogenicity data will be presented for the mITT population.

6.3.2. Per-Protocol Population

In the final analysis, protocol deviations will be reviewed to determine which protocol deviations may affect the analysis.

The per protocol population includes all participants in the mITT subset with the following exclusions:

- Data from all available visits for participants found to be ineligible at baseline.
- Data from all visits subsequent to the protocol deviations that are considered to affect the science.
- Data from any visit that occurs substantially out of window.

6.3.3. Safety Population

Safety Population is defined as any participant who received all or part of the study product. Summaries and analysis of safety data will be presented for the safety population.

6.3.4. Pharmacokinetics Population

The PK population will consist of participants in the Safety Population who have at least one evaluable serum PK sample for the estimation of C_{max} or $AUC_{0-\infty}$ and received a full dose. This set will be used to assess the

PK endpoints. Any participants or data values excluded from this analysis set will be identified, along with their reason for exclusion. Participants receiving placebo are excluded from PK analysis.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

6.5. Missing Data

All attempts will be made to collect all data per protocol. As missing data are expected to be minimal, no imputation will be performed for missing values. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier.

6.6. Interim Analyses and Data Monitoring

Not applicable.

6.7. Multicenter Studies

Data will be pooled across all clinical sites. Center effects are not anticipated because the sites are using standardized procedures for infusion and assessment of solicited and unsolicited AEs, and the assessment of immunogenicity and PK endpoints will be performed at central laboratories.

6.8. Multiple Comparisons/Multiplicity

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

7. STUDY PARTICIPANTS

7.1. Disposition of Participants

Table 9 will present a summary of the reasons that participants were screened but not enrolled.

The composition of analysis populations, including reasons for participant exclusion, by Dose Cohort is presented in Table 7. Individual participants who were excluded from analysis populations are presented in Listing 5.

The disposition of participants in the study will be tabulated by Dose Cohort (Table 6). The table shows the total number of participants screened, enrolled, receiving treatment, completed final blood draws, terminated from study follow-up and the number completing the study.

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

A listing of participants who terminated from study follow-up and the reason will be included in Listing 2.

7.2. Protocol Deviations

A summary of participant-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and Dose Cohort for all participants (Table 4). Deviations that are considered major deviations will be reviewed for possible exclusion from the Per-Protocol Population. All participant-specific protocol deviations and non-participant specific protocol deviations will be included in Appendix 3 as data listings (Listing 3 and Listing 4, respectively).

8. EFFICACY EVALUATION

Not applicable.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, ethnicity, and race will be presented by Dose Cohort overall and by site (Table 10, Table 11, Table 12, and Table 13). Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, participants may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual participant listings (Appendix 3) will be presented for all demographics (Listing 6).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 27.1 or higher version.

Summaries of participants' pre-existing medical conditions will be presented by MedDRA SOC, PT, and Dose Cohort (Table 14).

Individual participant listings will be presented for all medical conditions (Listing 7).

9.1.2. Prior and Concomitant Medications

Summaries of medications that were started prior to dosing and continued at the time of dosing will be presented by WHO Drug Code Level 1, Level 2 and Dose Cohort (Table 76).

Individual participant listings will be presented for all prior concomitant medications (Listing 17).

9.2. Measurements of Treatment Compliance

Any participants who were enrolled but did not receive the infusion of study product will be presented by Dose Cohort as part of the participant disposition table (Table 6). A summarized list of dates of dosing by Dose Cohort and site is presented in Table 8.

Date and time of study product administration, along with information on whether the participant was dosed according to protocol will be included in Listing 8. A listing of infusion interruptions will be presented in Listing 9.

9.3. Adverse Events

A treatment-emergent AE (TEAE) is defined as an AE that occurs during or after the study product infusion and up through the final visit. Only TEAEs will be documented as AEs in this study. When calculating the proportions of participants with AEs within a given MedDRA category, each participant will be counted once and any repetitions of AEs within a participant will be ignored, and the event will be reported according to the highest severity recorded (separately for related and unrelated AEs, when both severity and relatedness are tabulated). The denominators for percent values will be indicated within the table or table header.

An overall summary of AEs by Dose Cohort will be presented in Table 23.

The number of AEs and number and proportion of participants reporting an AE or SAE that occurred in ≥5% of participants in any Dose Cohort will be presented by MedDRA SOC, and PT (Table 24).

9.3.1. Solicited Events and Symptoms

Solicited AEs will be collected from the end of the infusion through Day 3. Solicited AEs will be summarized by severity for each day post administration (Days 1-3) and as the maximum severity over all 3 days. Additionally, solicited AEs will be analyzed using standard techniques, such as exact CIs, to summarize the proportion of participants reporting each symptom. Solicited AEs include headache, rash, nausea, vomiting, diarrhea, fatigue, and myalgia.

The proportion of participants reporting at least one solicited AE will be summarized for each solicited AE. The 95% CI calculated using Clopper-Pearson methodology from a binomial distribution (SAS Proc Freq with a binomial option) will be presented (Table 25).

- The maximum severity of solicited symptoms per participant by day will be presented graphically in Figure 3.
- The proportion of participants experiencing solicited events, Clopper-Pearson 95% CI, and difference of proportion from the placebo group will be summarized in Table 26.
- The number and percentage of participants experiencing solicited events by symptom, maximum severity, will be summarized in Table 27.
- The number and percentage of participants experiencing solicited events by symptom, maximum severity and day after infusion will be summarized in Table 28, Table 29, Table 30, and Table 31.
- Solicited AEs by participant will be presented in Listing 11.

9.3.2. Unsolicited Adverse Events

Unsolicited AEs will be collected from the time of infusion through Day 29. Unsolicited AEs will be coded by MedDRA for PT, HLGT, and SOC. The proportion of participants reporting at least one unsolicited AE will be summarized by MedDRA SOC, HLGT and PT post infusion. Denominators for percentages are the number of participants who received the infusion being summarized.

AEs by participant will be presented in Listing 12.

The following summaries for unsolicited AEs will be presented by MedDRA SOC, HLGT, PT, and Dose Cohort:

- The incidence and total frequency of AEs with Pearson-clopper 95% CI (Table 32)
- Summary of maximum severity and relationship to study product (Table 33 and Table 34)
- Participant incidence and total frequency of related adverse events by Dose Cohort (Table 35)
- Participant listing of serious AEs (Table 36)
- Participant listing of non-serious AEs of moderate or severe grade (Table 37)
- Listing of other significant AEs (Table 38)
- Listing of Unanticipated Problems (UPs) (Table 39, Table 40)
- Bar chart of non-serious related AEs by severity and MedDRA SOC (Figure 4)
- Bar chart of non-serious related AEs by maximum severity and MedDRA SOC (Figure 5)

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

The following listings will be presented including Participant ID, Age (years), Adverse Event Description, Adverse Event Onset Date/End Date, Dose Received/Days Post Dose, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days):

- Deaths and Serious Adverse Events (Table 36)
- Non-serious unsolicited, moderate or severe AEs, which are grade 2 or more (Table 37)

Other significant AEs, including NOCMCs, MAAEs, (Table 38) and UPs (Table 39, Table 40).

9.5. Pregnancies

For any participants in the Safety Population who became pregnant during the study, every attempt will be made to follow these participants to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. Listings of pregnancies and outcomes will be presented (Listing 19, Listing 20, Listing 21, Listing 22, and Listing 23).

9.6. Clinical Laboratory Evaluations

Clinical evaluations will be done to evaluate safety endpoints. These evaluations will include monitoring and recording of AEs and SAEs, clinical safety laboratory test results, VS measurements, 12-lead ECG results, and physical examination findings. The timing and frequency of all safety assessments are listed in the SOA (Table 2).

Toxicity grading criteria for clinical laboratory results can be found in Table 5. Unscheduled clinical laboratory evaluations will be included in listings but excluded from tabular and graphical summaries, except when calculating the maximum severity post-baseline. Any pre-existing abnormal lab results at Screening and Baseline will be graded and presented in listings. The following parameters will be presented (in order): Chemistry - Creatinine, Total Bilirubin, ALT; Hematology - Hemoglobin (Hgb), WBC, Platelets (PLT); Hypersensitivity testing. Hypersensitivity testing will be conducted if a participant experiences anaphylaxis or an anaphylactoid event related to the infusion. One sample will be obtained at approximately 15 minutes prior to the infusion; if the participant experiences a reaction, three additional samples will be drawn: 1) at the onset of symptoms, 2) 2 or more hours after onset of symptoms, and 3) after resolution of symptoms. The hypersensitivity panel will measure complement levels and activity (C3, C4, and CH50), Immunoglobulin E (IgE) levels, and tryptase on serum.

Participants with abnormal laboratory results, which are Grade 1 or higher, will be listed in Table 41, Table 42, and Table 43 for chemistry, hematology, and hypersensitivity, respectively. A full listing with all laboratory results will be listed in Listing 1 and Listing 2 for chemistry and hematology, respectively.

9.6.1. Clinical Laboratory Evaluations – Chemistry

Summaries of the number of participants with chemistry laboratory results, by grade severity, will be presented in Table 44, Table 45, Table 46, and Table 47.

Summaries of the number of participants with abnormal chemistry laboratory results related to study treatment, by grade severity, will be presented in Table 48, Table 49, Table 50, and Table 51.

Descriptive statistics including mean, SD, median, minimum and maximum values by time point, and changes from baseline, for each laboratory parameter will be summarized in Table 52, Table 53, and Table 54.

Changes in laboratory values will be presented in Figure 6, Figure 7, and Figure 8 for Creatinine, Total Bilirubin, and ALT, respectively.

9.6.2. Clinical Laboratory Evaluations - Hematology

A summary of the number of participants with hematology laboratory results, by grade severity, will be presented in Table 55, Table 56, Table 57, Table 58 and Table 59.

A summary of the number of participants with abnormal hematology laboratory results related to study treatment, by grade severity, will be presented in Table 60, Table 61, Table 62, Table 63, and Table 64.

Descriptive statistics including mean, SD, median, minimum and maximum values by time point, and changes from baseline, for each hematology laboratory parameter, will be summarized in Table 65, Table 66, and Table 67. Changes in laboratory values will be presented in Figure 9, Figure 10, and Figure 11 for Hgb, WBC, and PLT, respectively.

9.7. Vital Signs and Physical Examinations

Toxicity grading criteria for VS results can be found in Table 5. Vital signs will be obtained on Day 1, Day 2, Day 3, Day 8, Day 15, and Day 29 of the study. Unscheduled VS measurements will be listed, but excluded from tabular and graphical summaries by time point, except when calculating the maximum severity post baseline. Refer to Section 3.3.1 for the definition of baseline. If VS measurements are repeated, the following rules will be used to determine which VS measurement to use for analyses if repeat measurements occur:

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

VS parameters that have grading criteria for both decreases (result lower than normal range) and increases (result higher than normal range) will be summarized separately by direction.

VS results will be summarized in tables by parameter, Dose Cohort, and time point (Table 68, Table 69, Table 70, Table 71, Table 72, Table 73, and Table 74.

All individual VS measurements, including height, weight, and oximetry measurements (SpO_2) will be presented in Listing 15.

Focused physical examinations performed on Day 1, Day 3, and Day 8. Symptom-driven physical examinations performed on Day 15, Day 29, Day 61, Day 91 and Day 121 if indicated based on review of complete medical history and any updates obtained by interview of participants since the previous visit.

Abnormal physical exam findings will be presented in Listing 16.

9.8. 12-Lead Standard Electrocardiogram

Summary of 12-lead standard ECG change in overall interpretation from baseline will be shown by Dose Cohort and time point (Table 75).

A listing of ECG overall interpretations and comments will be presented in Listing 24.

9.9. Prior and Concomitant Medications

Prior and concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-participant listing of concomitant medication use will be presented. The use of concomitant medications during the study will be summarized by WHO Drug Code Level 1, Level 2 and Dose Cohort (Table 76). Individual participant listings will be presented for all prior concomitant medications (Listing 17).

9.10. Other Safety Measures

Not Applicable.

10. PHARMACOKINETICS

EV68-228-N concentrations and PK parameters will be summarized by Dose Cohort. Statistics include the arithmetic mean, median, SD, geometric mean (GM), coefficient of variation (CV), minimum, and maximum. CV will be calculated using the method for log-normally distributed data and reported as a percent:

$CV\% = \sqrt{\exp(s^2) - 1} \times 100\%$, where s^2 is the standard deviation of the log-transformed data

10.1. Summary of Pharmacokinetic Sampling and Sample Properties

The serum PK of a single dose of EV68-228-N will be assessed from serial blood samples collected approximately 15 minutes prior to infusion, at end of infusion (within a + 5-minute window), at 1-, 3-, and 5-hours post end of infusion (within a ± 15-minute window), at 24- and 48-hours after the end of the infusion (within ±3-hour window), and at 7, 14, 28, 60, 90, and 121 days after the end of the infusion (within ±1-, 2-, 3-, 7-, 14-, and 14-day window, respectively). EV68-228-N will be quantified by a validated ECL assay.

Individual concentration-time plots will be generated, and outliers will be identified as values greater or less than 3 SDs from the mean within each Dose Cohort and time point. Outliers will not be excluded from summary statistics but will be excluded from the NCA and will be discussed in the CSR.

Samples with bioanalytical errors or quality issues reported by the laboratory will be excluded. Collection times of samples missing the actual collection time will be imputed using the nominal collection time. Such samples will be identified in the analysis report (Listing 25).

10.2. Pharmacokinetic Analysis

10.2.1. Concentration Summaries

EV68-228-N serum concentrations will be listed by Dose Cohort and participant. Out-of-window sample time and PK analyses-excluded samples will be indicated, as will BQL values that were imputed for the purposes of parameter estimation (Listing 25). The listings will also indicate the nominal and actual time associated with the sample (nominal time is defined as the planned time in minutes, hours, or days since the first dose). Potentially important bioanalytical errors and their effect on the PK analysis will be discussed.

Concentrations below the quantitation limit (BQL) prior to the first measurable concentration will be imputed as zero. The first BQL concentration reported in the serum concentrations after the last measurable concentration may be imputed for the purpose of parameter estimation as the LLOQ divided by 2 only if 1) needed to estimate λz, 2) all other λz estimation criteria are met, and 3) if a visual predictive check of the imputed value appears to be consistent with the observed elimination trend. All other BQL samples will be treated as missing. Imputed concentration values will only be used for serum parameter estimation by NCA and not included in concentration summaries, however, imputed BQL values will be indicated by imputation method in listings with methods clarified in the footnote and denoted in figures.

EV68-228-N serum concentrations will also be summarized by Dose Cohort (Table 77 and Table 78) and plotted by Dose Cohort. Figure 12, Figure 13, and Figure 14 will present the participant serum concentration profiles using a linear plot and Figure 15, Figure 16, and Figure 17 will present the participant serum concentration using a semilogarithmic plot. Linear plots of serum mean concentration curves will be shown in Figure 18, with error bars representing ± 1 SD. Semi-logarithmic plots of geometric mean serum concentration curves will be shown in Figure 19.

10.2.2. Pharmacokinetic Parameters

PK analyses will be performed using noncompartmental analysis (NCA) using Phoenix WinNonlin version 8.3 or higher (Certara, Radnor, PA).

NCA PK parameters will be calculated using the actual post-dose time. Samples with concentrations greater than the LLOQ will be considered for the estimation of λz. Imputing the first BQL concentration following the last concentration greater than LLOQ to LLOQ divided by 2 will be considered on a participant-by-participant basis for participants where the λz acceptance criteria are not met by the observed data greater than the LLOQ. λz will be computed from the log-transformed concentration data. The correlation between time and concentration at the time points used to estimate λz should be sufficiently high (adjusted-R^2 >0.9). Additionally, a minimum of three concentrations in the terminal elimination phase will be used for the calculation of λz. All concentrations used to calculate λz must come from samples taken at or after T_{max}. The concentrations used to calculate λz along with the number of concentrations used for the calculation will be included in the participant serum concentration listing (Listing 25).

The serum AUC will be computed using the linear-up log-down (linear-log) trapezoidal method.

All serum PK parameters will also be summarized by Dose Cohort using descriptive statistics (Table 80). Additionally, participant-level PK parameters will be presented by participant in Table 79 in the final report.

The following parameters will be estimated: $AUC_{0-\infty}$, AUC_{0-last}, AUC_{0-48}, C_{max}, T_{max}, $t_{1/2}$, CL, and V_z.

See Section 3.3.4 for parameter definitions.

11. IMMUNOGENICITY

The immunogenicity data, determined by a validated ADA assay (14), will be analyzed with mITT and Per-Protocol populations. The proportion of participants with positive screening assay results and positive confirmation assay results are summarized in Table 15, Table 16, Table 17, and Table 18.

A titer assay will be performed for specimens with detectable ADA (refer to Section 3.3.3 for the definition of detectable ADA). Geometric Mean Titers (GMT) of ADAs will be calculated, along with 95% CIs, for all groups, at each time point (Table 19 and Table 20). Summaries will also be displayed graphically (Figure 2).

The GMT is defined as:

$$\text{GMT} = \sqrt[n]{X_1 * X_2 * \ldots \ldots * X_n},$$

where the X_1, X_2, …X_n are the titers for each participant at a certain time point for detectable ADAs. In practice, it is the equivalent of: GMT =Exp{[log(X_1) + log(X_2) + … + log(X_n)] / n}

The proportion of participants with detectable ADAs and Clopper-Pearson exact 95% CIs will also be computed over time to assess persistence of ADAs (Table 21 and Table 22).

The individual ADA results, including screening result, confirmatory result and titers, will be presented in Listing 10.

12. OTHER ANALYSES

Not Applicable.

13. REPORTING CONVENTIONS

The mean, SD, 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%.

Drug concentrations, AUC values, C_{max} and their summary statistics will have the same format as the drug concentrations reported by the bioanalytical laboratory. Other PK parameters will be reported to 1 decimal place.

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

Not applicable.

16. REFERENCES

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15. Anti-Drug Antibody Detection. January 2019.

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

9.1 Overall Study Design and Plan Description

Table 1: Single Ascending Dose Cohorts and Dose Regimens

Cohort	Arm	Number of Participants	Study Product
1	1	10	3 mg/kg of EV68-228-N
	2	2	Placebo
2	1	10	10 mg/kg of EV68-228-N
	2	2	Placebo
3	1	10	30 mg/kg of EV68-228-N
	2	2	Placebo

9.5.1 Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 2: Schedule of Activities

Study Visit	00	01	02	03	04	05	06	07	08	09	Unscheduled	Early Termination
Study day	-28 to –1	1	2	3	8	15	29	61	91	121		
Visit window (± number of days)					1	2	3	7	14	14		
Procedures												
Informed Consent	X											
Demographic Information	X											
Review Eligibility Criteria	X	X										
Medical History	X											
Concomitant Medications	X	X	X	X	X	X	X				X[a]	X[a]
Infusion		X										
Interim Medical History		X	X	X	X	X	X	X	X	X	X	X
Counsel on avoidance of pregnancy	X	X										
Full Physical Examination	X											
Focused Physical Examination		X	X	X	X						X[a]	X[a]
Symptom-driven Physical Examination						X	X	X	X	X	X	X
Vital Signs	X	X[b]	X	X	X	X	X				X[a]	X[a]
Oximetry Measurement		X[b]										
Cardiopulmonary Monitoring		X[c]										
Height and Weight (for BMI calculation)	X											
Weight (for dose calculation)		X										
Hematology[d]	X	X[e]	X	X	X		X					X[a]
Chemistry[d]	X	X[e]	X	X	X		X					X[a]
12-Lead ECG	X	X[f]	X									
Urine Pregnancy Test[g]	X	X										
Solicited AEs		Days 1-3										

Table 2: Schedule of Activities *(continued)*

Study Visit	00	01	02	03	04	05	06	07	08	09	Unscheduled	Early Termination
Study day	**-28 to –1**	**1**	**2**	**3**	**8**	**15**	**29**	**61**	**91**	**121**		
Visit window (± number of days)					**1**	**2**	**3**	**7**	**14**	**14**		
Procedures												
Review e-Memory Aid			X	X	X							
Unsolicited AEs		Days 1-29										
SAEs, MAAEs, and NOCMCs		Days 1-121										
Update previous AE/SAEs (as needed)			X	X	X	X	X	X	X	X	X	X
PK samples [h]		X[i]	X[j]	X[j]	X	X	X	X	X	X		X
Serum samples for ADA (anti-drug antibodies)[h]		X[e]			X	X	X	X	X	X		X
Hypersensitivity Panel Sample[k]		X[k]										
Total amount of blood collected for visit (mL)	6	41 or 56[l]	11	11	16	10	16	10	10	10	0	16
Cumulative blood volume (ml) if there is no hypersensitivity reaction	6	47	58	69	85	95	111	121	131	141		
Cumulative blood volume (mL) if there is a hypersensitivity reaction	6	62	73	84	100	110	126	136	146	156		

[a] Conducted if visit occurs within 7 days of infusion.
[b] VS will be collected to confirm eligibility prior to randomization and will be repeated, along with oximetry measurements, at approximately 15 minutes prior to infusion, the end of infusion, and at 1-hour post-infusion. For infusions lasting at least 30 minutes, these will also be collected at approximately 15 minutes after the beginning of the infusion.
[c] During infusion and up to one-hour post-infusion, continuous cardio-pulmonary monitoring will be conducted to assess for acute changes. If a CS change occurs, the monitoring will be continued until it has resolved and it is deemed safe to discontinue monitoring by the site PI or designee.
[d] Clinical screening laboratory evaluations will include WBCs, Hgb, PLT, Cr, ALT, and T. Bili. Clinical safety laboratory evaluations obtained on Days 1, 2, 3, 8, and 29 will include WBCs, Hgb, PLTs, Cr, ALT, and T. Bili. Results of laboratory studies collected prior to infusion on Day 1 do not require review prior to infusion; rather, they serve as a baseline assessment for post-infusion safety assessment.
[e] Day 1 blood draws for ADA, hematology and chemistry should be done at the same time as the first PK blood draw, within 15 minutes prior to the infusion
[f] ECGs on Day 1 will occur approximately 15 minutes prior to infusion and 1-hour post-infusion.
[g] For women of childbearing potential, a urine pregnancy test at screening and on Day 1 with results confirmed as negative prior to infusion.
[h] If an infusion is terminated early, the remaining Day 1 PK samples will not be drawn and the PK and ADA samples at follow-up visits will not be drawn.
[i] PK samples on Day 1 will be obtained approximately 15 minutes prior to infusion, at end of infusion (within a + 5-minute window), and at 1-, 3-, and 5-hours post end of infusion, within a ± 15-minute window. Note, for infusions that last longer than 1-hour due to infusion related events or other disruptions in administration, see MOP for details on updating the PK collection timepoints.
[j] PK sample will be collected within ±3-hour window of 24- and 48-hours after the end of infusion
[k] All participants will have a baseline sample taken for hypersensitivity testing approximately 15 minutes prior to infusion. For any participant that has an anaphylactic or anaphylactoid-type reaction, three additional samples will be taken: 1) at the onset of symptoms, 2) at 2 or more hours after onset, 3) at the resolution of symptoms.
[l] Larger amount will be collected only if there is a hypersensitivity reaction.

9.7.1 Sample Size

Table 3: Probability to Observe at Least n AEs Within Study Population

Adverse Event Probability	Probability to Observe At Least n AEs									
	n=1	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10
5%	40.1%	8.6%	1.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
10%	65.1%	26.4%	7.0%	1.3%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%
15%	80.3%	45.6%	18.0%	5.0%	1.0%	0.1%	0.0%	0.0%	0.0%	0.0%
20%	89.3%	62.4%	32.2%	12.1%	3.3%	0.6%	0.1%	0.0%	0.0%	0.0%
25%	94.4%	75.6%	47.4%	22.4%	7.8%	2.0%	0.4%	0.0%	0.0%	0.0%
30%	97.2%	85.1%	61.7%	35.0%	15.0%	4.7%	1.1%	0.2%	0.0%	0.0%

10.2 Protocol Deviations

Table 4: Distribution of Protocol Deviations by Category, Type, and Dose Cohort – All Enrolled Participants

[Implementation notes: Only include deviation categories/types that exist in the data, if there are none in some category/type then delete the row.]

Category	Deviation Type	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants (N=X)	
		No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.
Major Deviation											
Eligibility/Enrollment	Any type										
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x	x	x
	Met exclusion criterion										
	Other										
Informed Consent/Assent	Any Type										
	ICF not signed prior to study procedures										
	Incorrect version of ICF signed										
	Unapproved consent/reconsent informed consent method used										
Product 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										
	Required procedure not conducted										
	Required procedure done incorrectly										

Table 4: Distribution of Protocol Deviations by Category, Type, and Dose Cohort *(continued)*

Category	Deviation Type	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants (N=X)	
		No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.
	Safety Lab not Collected										
	Other										
Laboratory/Specimen	Any type										
	Specimen result not obtained										
	Conduct of Non-Protocol Procedure										
	Specimen Processsing not conducted correctly										
	Specimen Temperature Excursion										
	Other										
Product Storage	Any type										
	Study Product Temperature Excursion										
	Other										
Safety	Any type										
	Safety Lab not Collected										
	Required procedure done incorrectly										
	Required procedure not conducted										
	Specimen result not obtained										
	Other										
Repeat for Minor Deviation											
Repeat for All Deviations											

Note: N=Number of participants enrolled in each group.

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 5: Laboratory Adverse Event Grading Scale

Protocol Assessment	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
Hemoglobin, Low (male) g/dL	12.0 - 13.0	10.0 - 11.9	8.0 - 9.9	<8.0
Hemoglobin, Low (female) g/dL	10.5 - 11.5	9.0 - 10.4	7.5 - 8.9	<7.5
WBC, Low mm^3	2,500 - 2,999	1,500 - 2,499	1,000 - 1,499	<1,000
WBC, High mm^3	11,600 - 15,000	15,001 - 20,000	20,001 - 25,000	>25,000
Platelets (Decrease) mm^3	125,000 - 139,000	100,000 - 124,000	25,000 - 99,000	<25,000
Chemistry				
ALT	2.0 - 3.5x ULN	>3.5 - 5.0x ULN	>5.0 - 10x ULN	>10x ULN
Creatinine	1.5 - 1.7x ULN	>1.7 - 2.0x ULN	>2.0 - 2.5x ULN	>2.5x ULN or requires dialysis
Bilirubin	1.5 - 2.0x ULN	>2.0 - 3.0x ULN	>3.0 - 5.0x ULN	>5.0x ULN
Vital Signs				
Hypertension (systolic) mmHg	141 - 150	151 - 155	>155	ER visit or hospitalization for management
Hypertension (diastolic) mmHg	91 - 95	96 - 100	>100	ER visit or hospitalization for management
Hypotension (systolic) mmHg	85-89	80-84	<80	ER visit or hospitalization for management
Bradycardia, baseline>60 bpm	50 - 54	45-49	<45	ER visit or hospitalization for management
Bradycardia, baseline <60 bpm	45-50	40-44	<40	ER visit or hospitalization for management
Tachycardia bpm	101 - 115	116 - 130	>130	ER visit or hospitalization for management
Temperature °C	38.0 - 38.4	38.5 - 38.9	39.0 - 40.0	>40

14.1 Description of Study Participants

14.1.1 Disposition of Participants

Table 6: Participant Disposition by Dose Cohort – All Enrolled Participants

Participant Disposition	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%
Screened	--	--	--	--	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100	x	100	x	100
Received Treatment	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Final Blood Draw for Safety at Study Day 29	x	xx	x	xx	x	xx	x	xx	x	xx
Completed at Least One Post-Dose Blood Draw for PK	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Final Blood Draw for ADA at Study Day 121	x	xx	x	xx	x	xx	x	xx	x	xx
Terminated from the study follow-up	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 121)[a]	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Per Protocol[b]	x	xx	x	xx	x	xx	x	xx	x	xx

Note: N=Number of participants enrolled in each group.
[a] Refer to Listing 16.2.1 for reasons participants discontinued or terminated early.
[b] Refer to Listing 16.2.3 for reasons participants are excluded from the Analysis populations.

Table 7: Analysis Populations by Dose Cohort – All Enrolled Participants

Analysis Populations	Reason Participants Excluded	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	%	n
Safety Population	Any Reason	x	xx	x	xx	x	xx	x	xx	x	xx
	[Reason 1, for example: Did not receive study product]										
mITT Population	Any Reason										
	Did not receive at least a partial study product										
	Did not have a valid pre-dose immunogenicity testing result										
	Did not have any valid post-dose immunogenicity testing result										
Per-Protocol Population	Any Reason										
	Excluded from mITT										
	Found to be ineligible at baseline.										
	[Reason 3]										
	[Reason 4]										
Pharmacokinetics Population	Any Reason										
	Did not receive a full dose of study product.										
	Do not have at least one evaluable serum PK samples for the estimation of C_{max} OR $AUC_{0-\infty}$										
	[Reason 3]										
	[Reason 4]										

Note: N=Number of participants enrolled in each group.

Table 8: Dates of Treatment by Site and Dose Cohort

[Implementation Note: The dates of dosing will be categorized by 3 months period (from first enrollment in each cohort).]

Dates of Dosing	University of Maryland EV68-228-N (N=X)	University of Maryland Placebo (N=X)	Vanderbilt University EV68-228-N (N=X)	Vanderbilt University Placebo (N=X)	All Sites EV68-228-N (N=X)	All Sites Placebo (N=X)	All Sites All Participants (N=X)
Total (Entire period of enrollment)							
Cohort 1							
DDMMMYYYY-DDMMMYYYY [categorize based on length of enrollment period]	x	x	x	x	x	x	x
Cohort 2							
DDMMMYYYY-DDMMMYYYY [categorize based on length of enrollment period]	x	x	x	x	x	x	x
Cohort 3							
DDMMMYYYY-DDMMMYYYY [categorize based on length of enrollment period]	x	x	x	x	x	x	x

Note: N=Number of participants enrolled in each group.

Table 9: Ineligibility Summary of Screen Failures

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

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

14.1.2 Demographic Data by Study Group

Table 10: Summary of Categorical Demographic and Baseline Characteristics by Site

Variable	Characteristic	University of Maryland (N=X)		Vanderbilt University (N=X)		All Participants (N=X)	
		n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx
	Female						
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino						
	Not Reported						
Race	Unknown	x	xx	x	xx	x	xx
	American Indian or Alaska Native						
	Asian						
	Native Hawaiian or Other Pacific Islander						
	Black or African American						
	White						
	Multi-Racial						
	Unknown						

Note: N=Number of participants enrolled in each site.

Table 11: Summary of Continuous Demographic and Baseline Characteristics by Site

Variable	Statistic	University of Maryland (N=X)	Vanderbilt University (N=X)	All Participants (N=X)
Age (yrs)	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (min, max)	xx.x (x.x, x.x)	xx.x (x.x, x.x)	xx.x (x.x, x.x)
Height (cm)	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (min, max)	xx.x (x.x, x.x)	xx.x (x.x, x.x)	xx.x (x.x, x.x)
Weight (kg)	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (min, max)	xx.x (x.x, x.x)	xx.x (x.x, x.x)	xx.x (x.x, x.x)
BMI (kg/m^2)	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (min, max)	xx.x (x.x, x.x)	xx.x (x.x, x.x)	xx.x (x.x, x.x)

Notes: N=Number of participants enrolled in each site.
BMI is calculated with the height obtained at screening and the weight obtained at Day 1 prior dosing.

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

Variable	Characteristic	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%
Sex	Male	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
	Hispanic or Latino										
	Not Reported										
	Unknown										
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	x	xx	x	xx
	Asian										
	Native Hawaiian or Other Pacific Islander										
	Black or African American										
	White										
	Multi-Racial										
	Unknown										

Note: N=Number of participants enrolled in each group.

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

Variable	Statistic	3 mg/kg EV68-228-N (N=X)	10 mg/kg EV68-228-N (N=X)	30 mg/kg EV68-228-N (N=X)	Placebo (N=X)	All Participants (N=X)
Age (yrs)	Mean (SD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Median (min, max)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Height (cm)	Mean (SD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Median (min, max)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Weight (kg)	Mean (SD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Median (min. max)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
BMI (kg/m2)	Mean (SD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Median (min, max)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)

Notes: N=Number of participants enrolled in each group.
BMI is calculated with the height obtained at screening and the weight obtained at Day 1 prior dosing.
.

14.1.3 Prior and Concurrent Medical Conditions

Table 14: Summary of Participants with Pre-Existing Medical Conditions by MedDRA System Organ Class, Preferred Term and Dose Cohort

MedDRA System Organ Class	MedDRA Preferred Term	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]	Any PT										
	PT1										
	PT2										
[SOC 2]	Any PT										
	PT1										
	PT2										

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

14.2 Immunogenicity Data

Table 15: Proportion of Participants with a Positive Screening Assay by Time Point and Dose Cohort – mITT Population

Time Point	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%
Day 1, Pre Dose	x	xx	x	xx	x	xx	x	xx	x	xx
Day 8										
Day 15										
Day 29										
Day 61										
Day 91										
Day 121										

Note: N=Number of participants in each group in the mITT Population.

Table with similar format:

Table 16: Proportion of Participants with a Positive Screening Assay by Time Point and Dose Cohort – Per-Protocol Population

Table 17: Summary of Positive ADA Confirmation Assay Results by Time Point and Dose Cohort – mITT Population

[Implementation note, if there is number of participants with positive Screening result is N=0, then the cell will be '–'.]

Time Point	3 mg/kg EV68-228-N	10 mg/kg EV68-228-N	30 mg/kg EV68-228-N	Placebo	All Participants
	n/N	n/N	n/N	n/N	n/N
Day 1, Pre Dose	x/X	x/X	x/X	x/X	x/X
Day 8					
Day 15					
Day 29					
Day 61					
Day 91					
Day 121					

Notes: N=Number of participants with positive screening results in each group in the mITT Population.
n=Number of participants with positive confirmation results in each group in the mITT Population

Table with similar format:

Table 18: Summary of Positive ADA Confirmation Assay Results by Time Point and Dose Cohort – Per-Protocol Population

Table 19: Anti-Drug Antibodies (ADA) Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Time Point and Dose Cohort – mITT Population

Time Point	Statistic	3 mg/kg EV68-228-N	10 mg/kg EV68-228-N	30 mg/kg EV68-228-N	Placebo
Day 1, Pre Dose	N	x	x	x	x
	GMT	x.x	x.x	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Day 8	N				
	GMT				
	95% CI				
Day 15	N				
	GMT				
	95% CI				
Day 29	N				
	GMT				
	95% CI				
Day 61	N				
	GMT				
	95% CI				
Day 91	N				
	GMT				
	95% CI				
Day 121	N				
	GMT				
	95% CI				

Note: N=Number of participants in each group in the mITT Population.

Table 20: Anti-Drug Antibodies (ADA) Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Time Point and Dose Cohort – Per-Protocol Population

Time Point	Statistic	3 mg/kg EV68-228-N (N=X)	10 mg/kg EV68-228-N (N=X)	30 mg/kg EV68-228-N (N=X)	Placebo (N=X)
Day 1, Pre-Dose	N	x	x	x	x
	GMT	x.x	x.x	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Day 8	N				
	GMT				
	95% CI				
Day 15	N				
	GMT				
	95% CI				
Day 29	N				
	GMT				
	95% CI				
Day 61	N				
	GMT				
	95% CI				
Day 91	N				
	GMT				
	95% CI				
Day 121	N				
	GMT				
	95% CI				

Note: N=Number of participants in each group in the Per-Protocol Population.

Table 21: Proportion of Participants with Detectable Anti-Drug Antibodies (ADA) with 95% Confidence Intervals by Time Point and Dose Cohort – mITT Population

[Implementation note: the Detectable Anti-Drug Antibodies means that in the confirmatory ADA assays, the results are positive.]

Time Point	Statistics	3 mg/kg EV68-228-N	10 mg/kg EV68-228-N	30 mg/kg EV68-228-N	Placebo
Any time point	N	x	x	x	x
	n	x	x	x	x
	Proportion (95% CI)	x (x.xx, x.xx)	x (x.xx, x.xx)	x (x.xx, x.xx)	x (x.xx, x.xx)
Day 1, Pre Dose	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 8	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 15	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 29	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 61	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 121	N	x	x	x	x
	n				
	Proportion (95% CI)				

Note: N=Number of participants in each group at the time point in the mITT Population.

Table 22: Proportion of Participants with Detectable Anti-Drug Antibodies (ADA) with 95% Confidence Intervals by Time Point and Dose Cohort – Per-Protocol Population

[Implementation note: the Detectable Anti-Drug Antibodies means that in the confirmatory ADA assays, the results are positive.]

Time Point	Statistics	3 mg/kg EV68-228-N	10 mg/kg EV68-228-N	30 mg/kg EV68-228-N	Placebo
Any time point	N	x	x	x	x
	n	x	x	x	x
	Proportion (95% CI)	x (x.xx, x.xx)	x (x.xx, x.xx)	x (x.xx, x.xx)	x (x.xx, x.xx)
Day 1, Pre Dose	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 8	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 15	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 29	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 61	N	x	x	x	x
	n				
	Proportion (95% CI)				
Day 121	N	x	x	x	x
	n				
	Proportion (95% CI)				

Note: N=Number of participants in each group at the time point in the Per-Protocol Population.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 23: Overall Summary of Adverse Events

	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants who Received Active Product (N = x)	
Participants[a] with	n	%	n	%	n	%	n	%	n	%
At least one solicited adverse event	x	xx	x	xx	x	xx	x	xx	x	xx
At least one unsolicited adverse event	x	xx	x	xx	x	xx	x	xx	x	xx
At least one related unsolicited adverse event	x	xx	x	xx	x	xx	x	xx	x	xx
Mild (Grade 1)	x	xx	x	xx	x	xx	x	xx	x	xx
Moderate (Grade 2)	x	xx	x	xx	x	xx	x	xx	x	xx
Severe (Grade 3)	x	xxx	x	xx	x	xx	x	xx	x	xx
Life-threatening (Grade 4)	x	xx	x	xx	x	xx	x	xx	x	xx
Death (Grade 5)										
At least one severe (Grade 3 or higher) unsolicited adverse event										
Related										
Unrelated										
At least one serious adverse event[b]										
At least one related, serious adverse event										
At least one adverse event leading to early termination[c]										
At least one unanticipated problem (UPs)										
At least one medically attended adverse event (MAAEs)										
At least one new onset chronic medical conditions (NOCMCs)										

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

Table 24: Adverse Events Occurring in ≥ 5% of Participants in Any Dose Cohort by MedDRA System Organ Class and Preferred Term and Dose Cohort

[Implementation Note: This table will report both solicited and unsolicited AEs.]

MedDRA System Organ Class	MedDRA Preferred Term	3 mg/kg EV68-228-N (N=X)			10 mg/kg EV68-228-N (N=X)			30 mg/kg EV68-228-N (N=X)			Placebo (N=X)			All Participants who Received Active Product (N=X)		
		n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events																
All	All	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x
SOC1	All															
	PT1															
	Etc.															
	All															
	PT1	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x
Etc.	Etc.															
Other (Non-serious) Adverse Events																
All	All	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x
SOC1	All	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x
	PT1															
	Etc.															
Etc	Etc															

Notes: N=Number of participants in the Safety Population. n=Number of participants reporting an event. Events=Total frequency of events reported.

14.3.1.1 Solicited Adverse Events

Table 25: Number and Percentage of Participants Experiencing Solicited Events with 95% Confidence Intervals by Symptom and Dose Cohort

Symptom	3 mg/kg EV68-228-N (N=X)			10 mg/kg EV68-228-N (N=X)			30 mg/kg EV68-228-N (N=X)			Placebo (N=X)			All Participants who Received Active Product (N=X)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
Headache															
Rash															
Nausea															
Vomiting															
Diarrhea															
Fatigue (Tiredness)															
Myalgia (Body aches/Muscular pain)															

Notes: N=Number of participants in the Safety Population. 95% CI=Clopper-Pearson confident interval.

Table 26: Comparison of the Proportion of Participants Experiencing Solicited Events by Dose Cohort

Symptom	Statistic	3 mg/kg EV68-228-N (N=X)	10 mg/kg EV68-228-N (N=X)	30 mg/kg EV68-228-N (N=X)	Placebo (N=X)
Any Symptom	Proportion	x.xx	x.xx	x.xx	x.xx
	95% CI (for proportion)[a]	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Difference	x.xx	x.xx	x.xx	-
	95% CI (for difference)[b]	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	-
Headache	Proportion	x.xx	x.xx	x.xx	x.xx
	95% CI (for proportion)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Difference	x.xx	x.xx	x.xx	-
	95% CI (for difference)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	-
Rash	Proportion	x.xx	x.xx	x.xx	x.xx
	95% CI (for proportion)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Difference	x.xx	x.xx	x.xx	-
	95% CI (for difference)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	-
Nausea	Proportion	x.xx	x.xx	x.xx	x.xx
	95% CI (for proportion)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Difference	x.xx	x.xx	x.xx	-
	95% CI (for difference)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	-
Vomiting	Proportion	x.xx	x.xx	x.xx	x.xx
	95% CI (for proportion)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Difference	x.xx	x.xx	x.xx	-
	95% CI (for difference)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	-
Diarrhea	Proportion	x.xx	x.xx	x.xx	x.xx
	95% CI (for proportion)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Difference	x.xx	x.xx	x.xx	-
	95% CI (for difference)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	-
Fatigue (Tiredness)	Proportion	x.xx	x.xx	x.xx	x.xx
	95% CI (for proportion)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Difference	x.xx	x.xx	x.xx	-
	95% CI (for difference)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	-
Myalgia (Body aches/Muscular pain)	Proportion	x.xx	x.xx	x.xx	x.xx
	95% CI (for proportion)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Difference	x.xx	x.xx	x.xx	-
	95% CI (for difference)	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	-

Note: N=Number of participants in the Safety Population.
[a]95% CI=Clopper-Pearson confidence interval.
[b]95% CI=Wald confidence interval.

Table 27: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Maximum Severity, and Dose Cohort

Symptom	Severity	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants who Received Active Product (N=X)	
		n	%	n	%	n	%	n	%	n	%
Any Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild										
	Moderate										
	Severe										
	Life-threatening										
Headache	None	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild										
	Moderate										
	Severe										
	Life-threatening										
Rash	None	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild										
	Moderate										
	Severe										
	Life-threatening										
Nausea	None	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild										
	Moderate										
	Severe										
	Life-threatening										
Vomiting	None	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild										
	Moderate										
	Severe										
	Life-threatening										
Diarrhea	None	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild										
	Moderate										
	Severe										
	Life-threatening										
Fatigue (Tiredness)	None	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild										

Table 27: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Dose Cohort *(continued)*

Symptom	Severity	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants who Received Active Product (N=X)	
		n	%	n	%	n	%	n	%	n	%
	Moderate										
	Severe										
	Life-threatening										
Myalgia (Body aches/Muscular pain)	None	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild										
	Moderate										
	Severe										
	Life-threatening										

Notes: N=Number of participants in the Safety Population. Severity is the maximum severity reported over all solicited symptoms post dosing for each participant.

Table 28: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing – 3 mg/kg EV68-228-N

Symptom	Severity	3 mg/kg EV68-228-N (N=X)							
		Day 1		Day 2		Day 3		Ongoing After Day 3	
		n	%	n	%	n	%	n	%
Any Symptom	None	x	xx	x	xx	x	xx	x	xx
	Mild								
	Moderate								
	Severe								
	Life-threatening								
	Not Reported								
Headache	None								
	Mild								
	Moderate								
	Severe								
	Life-threatening								
	Not Reported								
Rash	None								
	Mild								
	Moderate								
	Severe								
	Life-threatening								
	Not Reported								
Nausea	None								
	Mild								
	Moderate								
	Severe								
	Life-threatening								
	Not Reported								
Vomiting	None								
	Mild								
	Moderate								
	Severe								
	Life-threatening								
	Not Reported								
Diarrhea	None								
	Mild								
	Moderate								
	Severe								
	Life-threatening								
	Not Reported								
Fatigue	None								
	Mild								
	Moderate								

Table 28:Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing – 3 mg/kg EV68-228-N *(continued)*

Symptom	Severity	3 mg/kg EV68-228-N (N=X)							
		Day 1		Day 2		Day 3		Ongoing After Day 3	
		n	%	n	%	n	%	n	%
	Severe								
	Life-threatening								
	Not Reported								
Myalgia	None								
	Mild								
	Moderate								
	Severe								
	Life-threatening								
	Not Reported								

Notes: N=Number of participants in the Safety Population. Severity is the maximum severity reported post dosing for each participant for each day.

Tables with similar format:

Table 29: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing – 10 mg/kg EV68-228-N

Table 30: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing – 30 mg/kg EV68-228-N

Table 31: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing – Placebo

14.3.1.2 Unsolicited Adverse Events

Table 32: Summary of Unsolicited Adverse Events by MedDRA System Organ Class, High Level Group Term and Preferred Term and Dose Cohort

MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	3 mg/kg EV68-228-N (N=X)				10 mg/kg EV68-228-N (N=X)				30 mg/kg EV68-228-N (N=X)				Placebo (N=X)				All Participants who Received Active Product (N=X)			
			n	%	95% CI[a]	Events	n	%	95% CI[a]	Events	n	%	95% CI[a]	Events	n	%	95% CI[a]	Events	n	%	95% CI[a]	Events
Any SOC	Any HLGT	Any PT	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x
[SOC 1]	Any HLGT	Any PT																				
	HLGT1	Any PT																				
		[PT 1]																				
		[PT 2]																				
	HLGT2	Any PT																				
		[PT 1]																				
		[PT 2]																				
[SOC 2]	Any HLGT	Any PT																				
	HLGT1	Any PT																				
		[PT 1]																				
		[PT 2]																				
	HLGT2	Any PT																				
		[PT 1]																				
		[PT 2]																				

Notes: N=Number of participants in the Safety Population. This table presents the number and percentage of participants. A participant is only counted once per PT.
[a] The 95% CI of the proportion will be calculated using Clopper-Pearson (Exact) methodology from a binomial distribution.

Table 33: Unsolicited Adverse Events by MedDRA System Organ Class, High Level Group Term and Preferred Term, Maximum Severity, and Dose Cohort

MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Severity	3mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants who Received Active Product (N = X)	
				n	%	n	%	n	%	n	%	n	%
Any SOC	Any HLGT	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx	x	xx	x	xx
			Life-threatening	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	Any HLGT	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx	x	xx	x	xx
			Life-threatening	x	xx	x	xx	x	xx	x	xx	x	xx
	HLGT1	PT1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx	x	xx	x	xx
			Life-threatening	x	xx	x	xx	x	xx	x	xx	x	xx
		PT2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx	x	xx	x	xx
			Life-threatening	x	xx	x	xx	x	xx	x	xx	x	xx

Notes: N=Number of participants in the Safety Population. This table presents the number and percentage of participants. A participant is only counted once by the maximal severity per PT.

Table 34: Unsolicited Adverse Events by MedDRA System Organ Class, High Level Group Term and Preferred Term, Maximum Severity, Relationship, and Dose Cohort

MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Severity	3 mg/kg EV68-228-N (N=X)				10 mg/kg EV68-228-N (N=X)				30 mg/kg EV68-228-N (N=X)				Placebo (N=X)				All Participants who Received Active Product (N = X)			
				Related		Not Related		Related		Not Related		Related		Not Related		Related		Not Related		Related		Not Related	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any HLGT	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Life-threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	Any HLGT	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Life-threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	HLGT1	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Life-threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		PT 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Life-threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Table 34: Unsolicited Adverse Events by MedDRA System Organ Class, High Level Group Term and Preferred Term, Maximum Severity, Relationship, and Dose Cohort *(continued)*

		PT 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
			Life-threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Notes: N=Number of participants in the Safety Population. This table presents the number and percentage of participants. A participant is only counted once by the maximum severity per PT.

Table 35: Related Unsolicited Adverse Events Post Dosing by MedDRA System Organ Class, High Level Group Term and Preferred Term, and Dose Cohort

MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	3 mg/kg EV68-228-N (N=X)			10 mg/kg EV68-228-N (N=X)			30 mg/kg EV68-228-N (N=X)			Placebo (N=X)			All Participants who Received Active Product (N=X)		
			n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
Any SOC	Any HLGT	Any PT	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any HLGT	Any PT															
	HLGT1	Any PT															
		[PT 1]															
		[PT 2]															
	HLGT2	Any PT															
		[PT 1]															
		[PT 2]															

Notes: N=Number of participants in the Safety Population. This table presents the number and percentage of participants. A participant is only counted once per PT.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 36: Listing of Serious Adverse Events

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

Table 37: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

[Implementation note: All Non-Serious AEs, which are greater than grade 2, will be included.]

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

Table 38: Listing of Other Significant Adverse Events

[Implementation Note: Other Significant Adverse Events include New Onset Chronic Medical Conditions (NOCMC), Medically Attended Adverse Events (MAAEs).]

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

Table 39: Listing of Participant-Specific Unanticipated Problems (UPs)

[Implementation note: "Study Day" is relative to treatment administration; the day of treatment administration is Day 1, and the day prior to treatment administration is Day -1.

If event is an AE, display "Yes" followed by the AE description and number separated by a semicolon in parentheses.

If event is a PD, display "Yes" followed by the deviation description and number separated by a semicolon in parentheses.

If there are no comments, display "None" in the "Comments" column. If there are no comments for any UPs in the listing, remove the "Comments" column. If the comments are too long to display in the "Comments" column, the format of this table may be updated to remove the "Comments" column.

Sort by Dose Cohort, Participant ID, and UP Number.]

Dose Cohort	Participant ID	UP number	Event Description	Event Outcome	Study Day of Site Awareness	Study Day Reported to Sponsor/DCC	Study Day Reported to IRB	Is the event an AE (AE Description; Number)	Is the event an PD (DV Description; Number)	Comments
3 mg/kg EV68-228-N	zzz.xxxxx	xxx	[description]	[outcome]	x	x	x	No	No	
10 mg/kg EV68-228-N								Yes ([description]; XXX)	Yes ([description]; XXX)	
30 mg/kg EV68-228-N										

Abbreviations: UP = Unanticipated Problem; DCC – Data Coordinating Center; IRB = Institutional Review Board; AE = Adverse Event; PD = Protocol Deviation; DV = Deviation.

Table 40: Listing of Non-Participant Specific Unanticipated Problems (UPs)

[implementation note:

If event is a PD, display "Yes" followed by the deviation description and number separated by a semicolon in parentheses.

If there are no comments, display "None" in the "Comments" column. If there are no comments for any UPs in the listing, remove the "Comments" column. If the comments are too long to display in the "Comments" column, the format of this table may be updated to remove the "Comments" column.

Sort by Site and UP Number]

Site	UP number	Event Description	Event Outcome	Event Date	Date of Site Awareness	Study Day Reported to Sponsor/DCC	Study Day Reported to IRB	Is the event an PD (DV Description Number)	Comments
University of Maryland	xxx	[description]	[outcome]	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	No	
Vanderbilt University								Yes ([description]; XXX)	

Abbreviations: UP = Unanticipated Problem; DCC – Data Coordinating Center; IRB = Institutional Review Board; AE = Adverse Event; PD = Protocol Deviation; DV = Deviation.

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

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

14.3.4 Abnormal Laboratory Value Listings (by Participant)

Table 41: Listing of Abnormal Laboratory Results – Chemistry

Dose Cohort	Participant ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Clinically Significant?	Participation Discontinued Due to Result?

Table 42: Listing of Abnormal Laboratory Results – Hematology

Dose Cohort	Participant ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Clinically Significant?	Participant Discontinued Due to Result?

Table 43: Listing of Abnormal Laboratory Results – Hypersensitivity

Dose Cohort	Participant ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Parameter	Units	Result	Clinically Significant?
				Baseline/ Onset of symptom/ 2 or more hours after onset/ Resolution of symptom		Complement Component 3/ Complement Component 4/ CH50/ Immunoglobin E/ Serum Tryptase		x	CS/NCS

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 44: Laboratory Results by Parameter, Maximum Severity, Time Point, and Dose Cohort – Any Chemistry Parameter

[Implementation note: we assume there are no missing grade, so removed the column "missing" from the table, if any missing found, we will add footnote to the table]

Any Chemistry Parameter Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Baseline	3 mg/kg EV68-228-N	x	x	xx	x	xx	x	xx	x	xx	x	xx
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 2	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 3	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 8	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 29	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Table 44: Laboratory Results by Parameter, Maximum Severity, Time Point, and Dose Cohort – Any Chemistry Parameter *(continued)*

Any Chemistry Parameter Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Notes: The "Max Severity Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N=Number of participants in the Safety Population.

Table 45: Laboratory Results by Parameter Time Point, and Dose Cohort – Chemistry: Creatinine

[Implementation note: we assume there are no missing grade, so removed the column "missing" from the table, if any missing found, we will add footnote to the table]

Creatinine Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Baseline	3 mg/kg EV68-228-N	x	x	xx	x	xx	x	xx	x	xx	x	xx
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 2	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 3	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 8	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 29	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Table 45: Laboratory Results by Parameter Time Point, and Dose Cohort – Chemistry: Creatinine *(continued)*

Creatinine Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Notes: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N=Number of participants in the Safety Population.

Tables with similar format:

Table 46: Laboratory Results by Parameter Time Point, and Dose Cohort – Total Bilirubin

Table 47: Laboratory Results by Parameter Time Point, and Dose Cohort – ALT

Table 48: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – Any Chemistry Parameter

[Implementation note: we assume there are no missing grade, so removed the column "missing" from the table, if any missing found, we will add footnote to the table]

Any Chemistry Parameter Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Baseline	3 mg/kg EV68-228-N	x	x	xx	x	xx	x	xx	x	xx	x	xx
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 2	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 3	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 8	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 29	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Table 48: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – Any Chemistry Parameter *(continued)*

Any Chemistry Parameter Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Notes: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N=Number of participants in the Safety Population

Tables with similar format:

Table 49: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – Creatinine

Table 50: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – Total Bilirubin

Table 51: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – ALT

Table 52: Laboratory Summary Statistics by Parameter, Time Point, and Dose Cohort – Creatinine

Time Point	Dose Cohort	N	Mean	Standard Deviation	Median	Min, Max
Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 2	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 2, Change from Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 3	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 3, Change from Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 8	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 8, Change from Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 29	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 29, Change from Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					

Note: N=Number of participants in the Safety Population with non-missing values at respective visit.

Tables with similar format:

Table 53: Laboratory Summary Statistics by Parameter, Time Point, and Dose Cohort – Total Bilirubin

Table 54: Laboratory Summary Statistics by Parameter, Time Point, and Dose Cohort – ALT

14.3.5.2 Hematology Results

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

[Implementation note: we assume there are no missing grade, so removed the column "missing" from the table, if any missing found, we will add footnote to the table]

Any Hematology Parameter Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Baseline	3 mg/kg EV68-228-N	x	x	xx	x	xx	x	xx	x	xx	x	xx
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 2	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 3	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 8	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 29	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Table 55: Laboratory Results by Parameter, Maximum Severity, Time Point, and Dose Cohort – Any Hematology Parameter *(continued)*

Any Hematology Parameter Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Notes: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N=Number of participants in the Safety Population.

Tables with similar format:

Table 56: Laboratory Results by Parameter, Maximum Severity, Time Point, and Dose Cohort – Hemoglobin

Table 57: Laboratory Results by Parameter, Maximum Severity, Time Point, and Dose Cohort – WBC: Low

Table 58: Laboratory Results by Parameter, Maximum Severity, Time Point, and Dose Cohort – WBC: High

Table 59: Laboratory Results by Parameter, Maximum Severity, Time Point, and Dose Cohort – Platelets

Table 60: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – Any Hematology Parameter

[Implementation note: we assume there are no missing grade, so removed the column "missing" from the table, if any missing found, we will add footnote to the table]

Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Baseline	3 mg/kg EV68-228-N	x	x	xx	x	xx	x	xx	x	xx	x	xx
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 2	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 3	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 8	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 29	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Table 60: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – Any Hematology Parameter *(continued)*

Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Notes: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N=Number of participants in the Safety Population.

Tables with similar format:

Table 61: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – Hemoglobin

Table 62: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – WBC – Low

Table 63: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – WBC – High

Table 64: Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Dose Cohort – Platelets

Table 65: Laboratory Summary Statistics by Parameter, Time Point, and Dose Cohort – Hemoglobin

Time Point	Dose Cohort	N	Mean	Standard Deviation	Median	Min, Max
Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 2	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 2, Change from Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 3	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 3, Change from Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 8	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 8, Change from Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					
Day 29	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					

Table 65: Laboratory Summary Statistics by Parameter, Time Point, and Dose Cohort – Hemoglobin *(continued)*

Time Point	Dose Cohort	N	Mean	Standard Deviation	Median	Min, Max
Day 29, Change from Baseline	3 mg/kg EV68-228-N	x	xx.x	xx.x	xx.x	xx.x, xx.x
	10 mg/kg EV68-228-N					
	30 mg/kg EV68-228-N					
	Placebo					

Note: N=Number of participants in the Safety Population with non-missing values at respective visit.

Tables with similar format:

Table 66: Laboratory Summary Statistics by Parameter, Time Point, and Dose Cohort – WBC

Table 67: Laboratory Summary Statistics by Parameter, Time Point, and Dose Cohort – Platelets

14.3.6 Displays of Vital Signs

Table 68: Vital Signs by Maximum Severity, Time Point, and Dose Cohort – Any Assessment

[Implementation note: we assume there are no missing grade, so removed the column "missing" from the table, if any missing found, we will add footnote to the table]

Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Baseline	3 mg/kg EV68-228-N	x	x	xx	x	xx	x	xx	x	xx	x	xx
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
15 Min After start of Infusion	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
End of Infusion	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
1 Hour After End of Infusion	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 2	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 3	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Table 68: Vital Signs by Maximum Severity, Time Point, and Dose Cohort – Any Assessment *(continued)*

Time Point	Dose Cohort	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Day 8	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 15	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Day 29	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											
Max Severity Post Baseline	3 mg/kg EV68-228-N											
	10 mg/kg EV68-228-N											
	30 mg/kg EV68-228-N											
	Placebo											

Notes: The "Max Severity Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N = Number of participants in the Safety Population.

Tables with similar format:

Table 69: Vital Signs by Assessment, Maximum Severity, Time Point, and Dose Cohort – Body Temperature

Table 70: Vital Signs by Assessment, Maximum Severity, Time Point, and Dose Cohort – Pulse: High

Table 71: Vital Signs by Assessment, Maximum Severity, Time Point, and Dose Cohort – Pulse: Low

Table 72: Vital Signs by Assessment, Maximum Severity, Time Point, and Dose Cohort – Systolic Blood Pressure: High

Table 73: Vital Signs by Assessment, Maximum Severity, Time Point, and Dose Cohort – Systolic Blood Pressure: Low

Table 74: Vital Signs by Assessment, Maximum Severity, Time Point, and Dose Cohort – Diastolic Blood Pressure: High

Table 75: Summary of Post Dose ECG Change in Overall Interpretations from Baseline by Dose Cohort and Time Point

Time Point	Change from Baseline in ECG Interpretation	3 mg/kg EV68-228-N	10 mg/kg EV68-228-N	30 mg/kg EV68-228-N	Placebo	All Participants
1 Hour post Infusion	N	x	x	x	x	x
	Normal at Both Times, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Normal to Abnormal, NCS, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Normal to Abnormal, CS, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Abnormal, NCS at Both Times, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Abnormal, NCS to Abnormal, CS, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Abnormal, NCS to Normal, n (%)	x(x)	x(x)	x(x)	x(x)	x(x)
Day 2	N	x	x	x	x	x
	Normal at Both Times, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Normal to Abnormal, NCS, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Normal to Abnormal, CS, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Abnormal, NCS at Both Times, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Abnormal, NCS to Abnormal, CS, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)
	Abnormal, NCA to Normal, n (%)	x(x)	x(x)	x(x)	x(x)	x(x)

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

14.4 Summary of Concomitant Medications

Table 76: Number and Percentage of Participants with Prior and Concurrent Medications by WHO Drug Classification and Dose Cohort

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	3 mg/kg EV68-228-N (N=X)		10 mg/kg EV68-228-N (N=X)		30 mg/kg EV68-228-N (N=X)		Placebo (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]										
	[ATC 2 - 1]										
	[ATC 2 - 2]										
	[ATC 2 - 3]										
[ATC Level 1 – 2]	[ATC 2 - 1]										
	[ATC 2 - 2]										
	[ATC 2 - 3]										

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

14.5 EV68-228-N Serum Concentrations and PK Parameters

Table 77: Individual Statistics of Serum EV68-228-N Concentrations by Time Point

Dose Cohort	Participant ID	Serum EV68-228-N Concentrations												
		Pre-Infusion (-15 min)	End of Infusion (+ 5 min)	1-hour (± 15 min)	3-hour (± 15 min)	5-hour (± 15 min)	24-hour (± 3 hr)	48-hour (± 3 hr)	7-day (± 1 day)	14-day (± 2 day)	28-day (± 3 day)	60-day (± 7 day)	90-day (± 14 day)	120-day (± 14 day)
3 mg/kg EV68-228-N	XXXXX XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXX XX.XXX
10mg/kg EV68-228-N	XXXXX XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXX XX.XXX
30 mg/kg EV68-228-N	XXXXX XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX

Note: Concentrations are reported in units of ng/mL.

Table 78: Summary Statistics of Serum EV68-228-N Concentrations by Time Point

Dose Cohort	Summary Statistics	Serum EV68-228-N Concentrations												
		Pre-Infusion (-15 min)	End of Infusion (+ 5 min)	1-hour (± 15 min)	3-hour (± 15 min)	5-hour (± 15 min)	24-hour (± 3 hr)	48-hour (± 3 hr)	7-day (± 1 day)	14-day (± 2 day)	28-day (± 3 day)	60-day (± 7 day)	90-day (± 14 day)	120-day (± 14 day)
3 mg/kg EV68-228-N	N	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
	Mean (SD)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)
	Min, Max	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX
	Geometric Mean	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX
	CV%	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
10mg/kg EV68-228-N	N	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
	Mean (SD)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)
	Min, Max	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX
	Geometric Mean	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX
	CV%	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
30 mg/kg EV68-	N	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
	Mean (SD)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)	XXXXXX.XXX (XXXXX.XXX)

Table 78: Summary Statistics of Serum EV68-228-N Concentrations by Time Point *(continued)*

Dose Cohort	Summary Statistics	Serum EV68-228-N Concentrations												
		Pre-Infusion (-15 min)	**End of Infusion (+ 5 min)**	**1-hour (± 15 min)**	**3-hour (± 15 min)**	**5-hour (± 15 min)**	**24-hour (± 3 hr)**	**48-hour (± 3 hr)**	**7-day (± 1 day)**	**14-day (± 2 day)**	**28-day (± 3 day)**	**60-day (± 7 day)**	**90-day (± 14 day)**	**120-day (± 14 day)**
228-N	Min, Max	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX
	Geometric Mean	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX
	CV%	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Notes: N=Number of participants in the PK Population. Concentrations are reported in units of ng/mL.

Table 79: Individual Statistics of Noncompartmental Serum PK Parameters by Dose Cohort

Dose Cohort	Participant ID	$AUC_{0-\infty}$ (ng*h/mL)	AUC_{0-last} (ng*h/mL)	AUC_{0-48} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	CL (L/h)	V_z (h)
3 mg/kg EV68-228-N	XXXXXXXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXX.X	XXX.X	XXX.X	XXXX.X
10 mg/kg EV68-228-N	XXXXXXXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXX.X	XXX.X	XXX.X	XXXX.X
30 mg/kg EV68-228-N	XXXXXXXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXX.X	XXX.X	XXX.X	XXXX.X

Table 80: Summary Statistics of Noncompartmental Serum PK Parameters by Dose Cohort

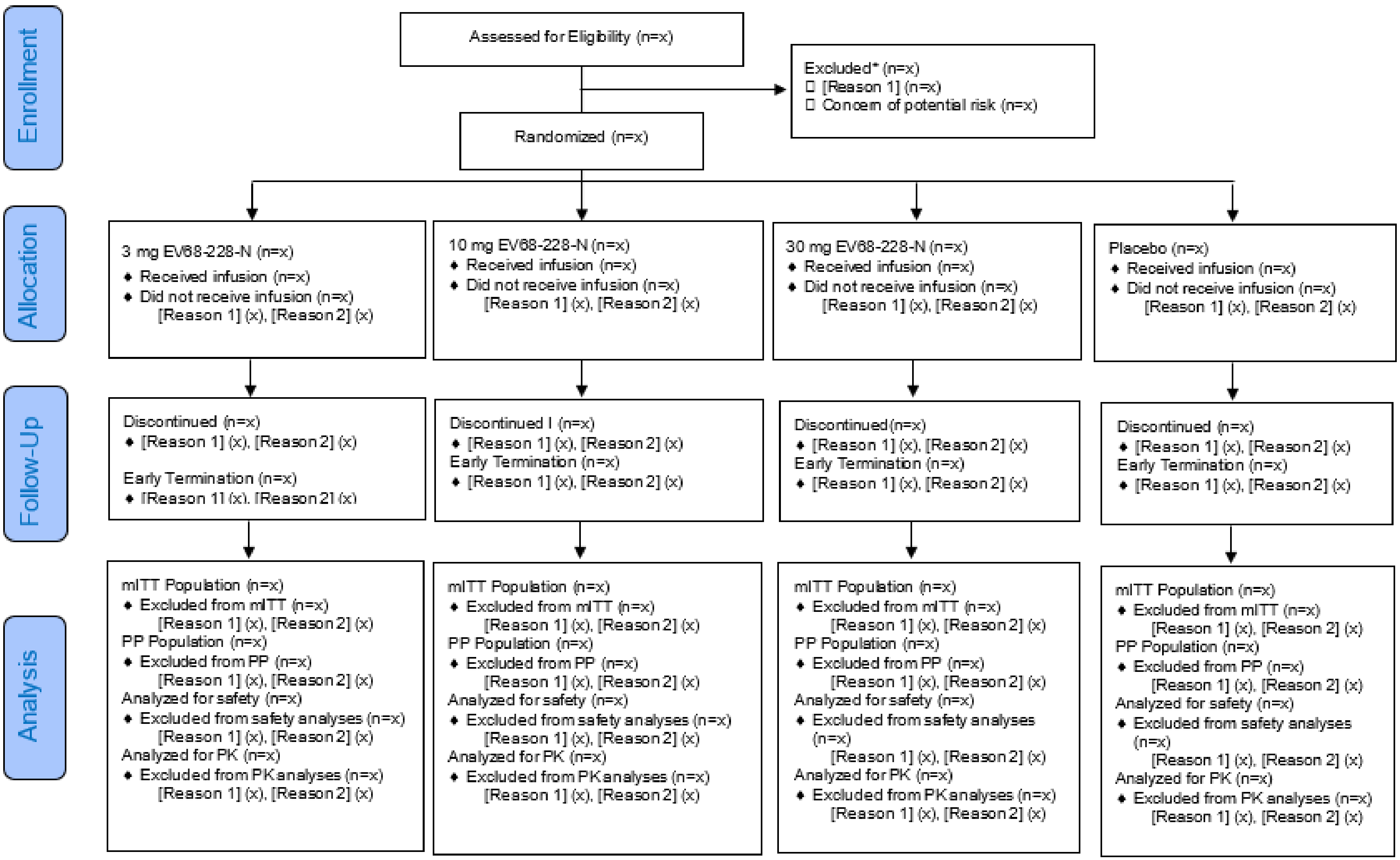
Dose Cohort	Summary Statistics	$AUC_{0-\infty}$ (ng*h/mL)	AUC_{0-last} (ng*h/mL)	AUC_{0-48} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
3 mg/kg EV68-228-N	N	XX	XX	XX	XX	XX	XX	XX	XX
	Mean (SD)	XXXXXX.XXX (XXXXXX.XXX)	XXXXXX.XXX (XXXXXX.XXX)	XXXXXX.XXX (XXXXXX.XXX)	XXXXXX.XXX (XXXXXX.XXX)	XXX.X (XXX.X)	XXX.X (XXX.X)	XXX.X (XXX.X)	XXXX.X (XXXX.X)
	Min, Max	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXX.X, XXX.X	XXX.X, XXX.X	XXX.X, XXX.X	XXXX.X, XXXX.X
	Geometric Mean	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXX.X	XXX.X	XXX.X	XXXX.X
	CV%	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXX.X	XXX.X	XXX.X	XXXX.X
10 mg/kg EV68-228-N	N	XX	XX	XX	XX	XX	XX	XX	XX
	Mean (SD)	XXXXXX.XXX (XXXXXX.XXX)	XXXXXX.XXX (XXXXXX.XXX)	XXXXXX.XXX (XXXXXX.XXX)	XXXXXX.XXX (XXXXXX.XXX)	XXX.X (XXX.X)	XXX.X (XXX.X)	XXX.X (XXX.X)	XXXX.X (XXXX.X)
	Min, Max	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXX.X, XXX.X	XXX.X, XXX.X	XXX.X, XXX.X	XXXX.X, XXXX.X
	Geometric Mean	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXX.X	XXX.X	XXX.X	XXXX.X
	CV%	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXX.X	XXX.X	XXX.X	XXXX.X
30 mg/kg EV68-228-N	N	XX	XX	XX	XX	XX	XX	XX	XX
	Mean (SD)	XXXXXX.XXX (XXXXXX.XXX)	XXXXXX.XXX (XXXXXX.XXX)	XXXXXX.XXX (XXXXXX.XXX)	XXXXXX.XXX (XXXXXX.XXX)	XXX.X (XXX.X)	XXX.X (XXX.X)	XXX.X (XXX.X)	XXXX.X (XXXX.X)
	Min, Max	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXXXXX.XXX, XXXXXX.XXX	XXX.X, XXX.X	XXX.X, XXX.X	XXX.X, XXX.X	XXXX.X, XXXX.X
	Geometric Mean	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXX.X	XXX.X	XXX.X	XXXX.X
	CV%	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXXXXX.XXX	XXX.X	XXX.X	XXX.X	XXXX.X

Note: N=Number of participants in the PK Population used to calculate the summary statistics.

APPENDIX 2. FIGURE MOCK-UPS

10.1 Disposition of Participants

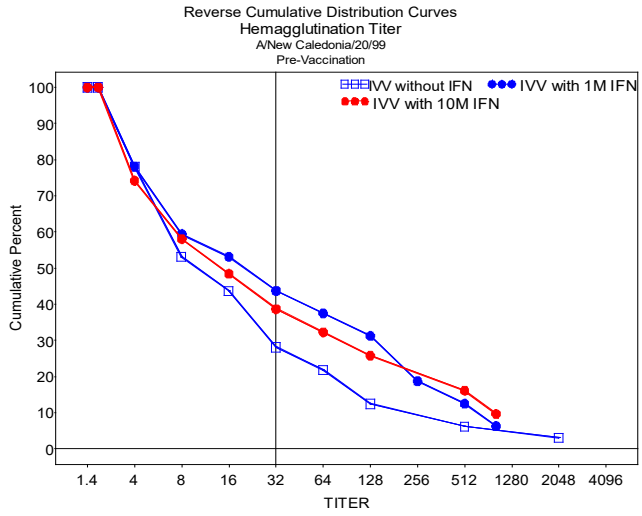
Figure 1: CONSORT Flow Diagram

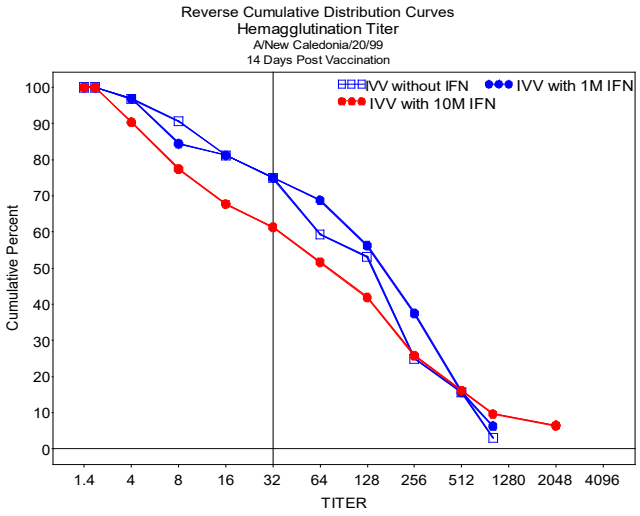


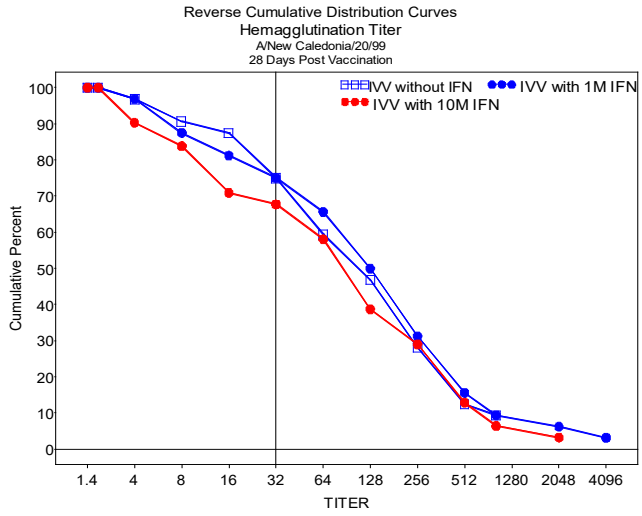
RESTRICTED

14.2.2 Immunogenicity Response Figures by Measure, Treatment/Vaccination, and Time Point

Figure 2: Reverse Cumulative Distribution of ADAs by Time Point and Dose Cohort



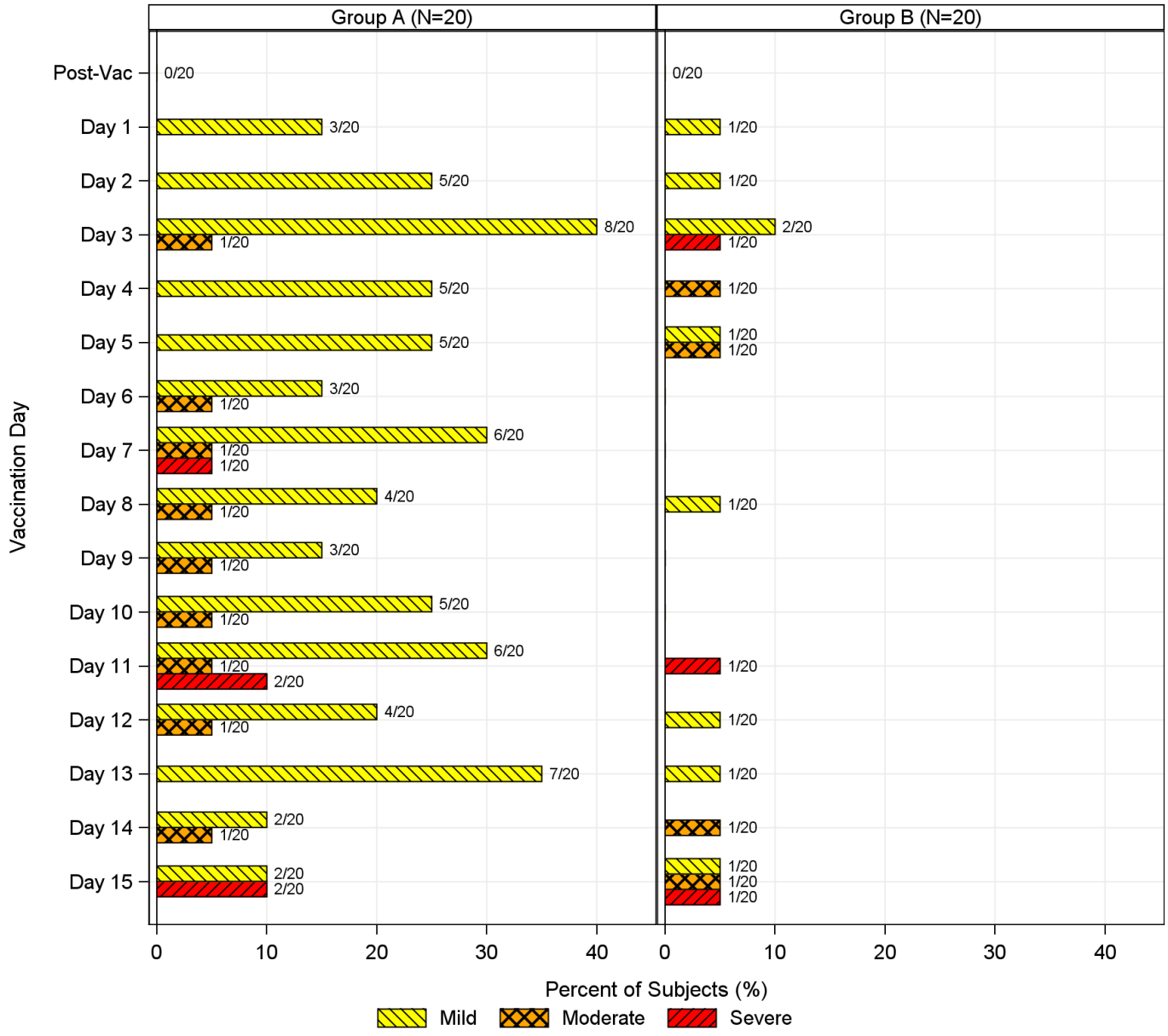




14.3.1.1 Solicited Adverse Events

Figure 3: Maximum Severity of Solicited Symptoms per Participant by Day Post Treatment

[Implementation Note: Separated panels for each Dose Cohort.]



14.3.1.2 Unsolicited Adverse Events

Figure 4: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity

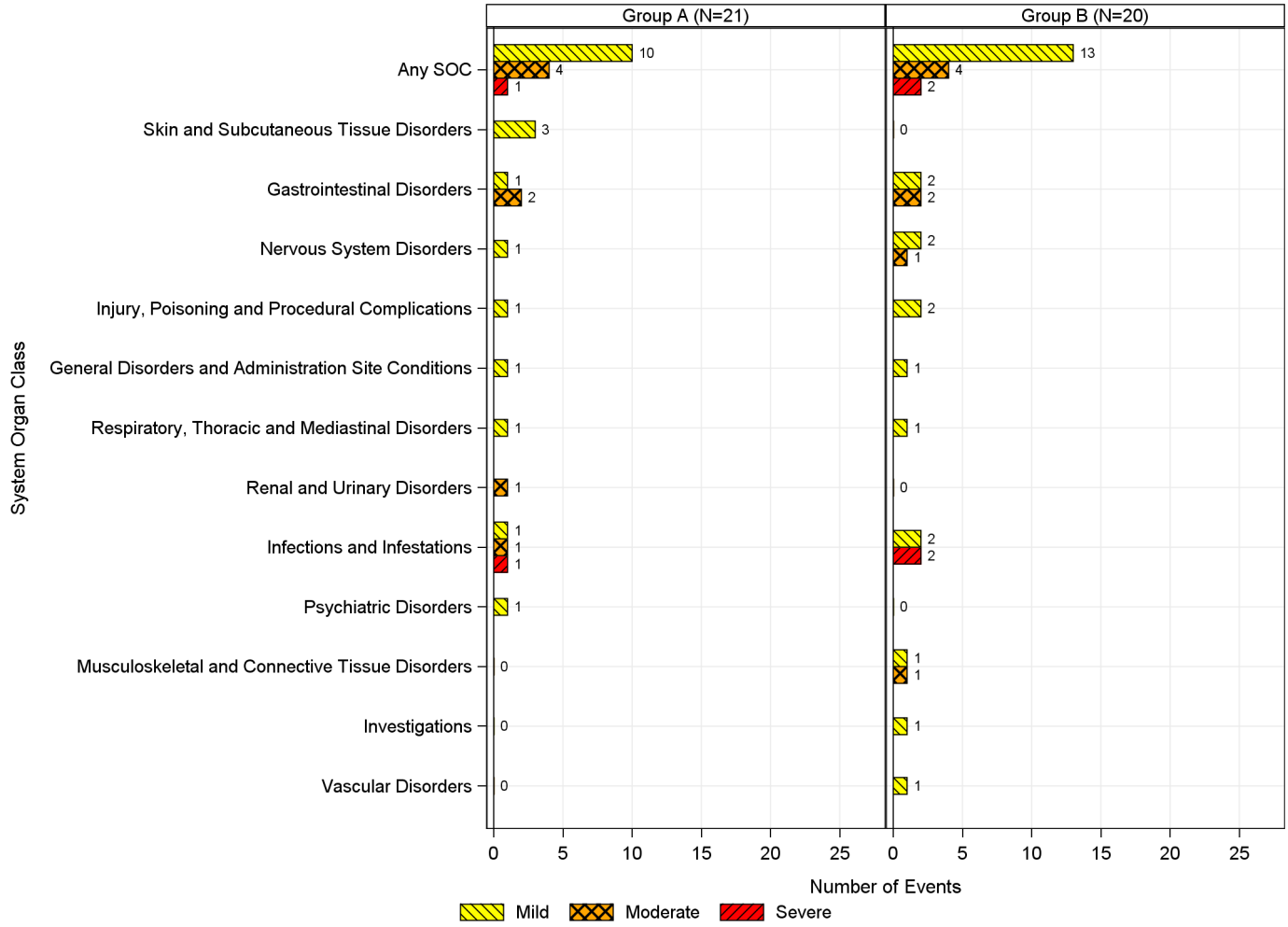
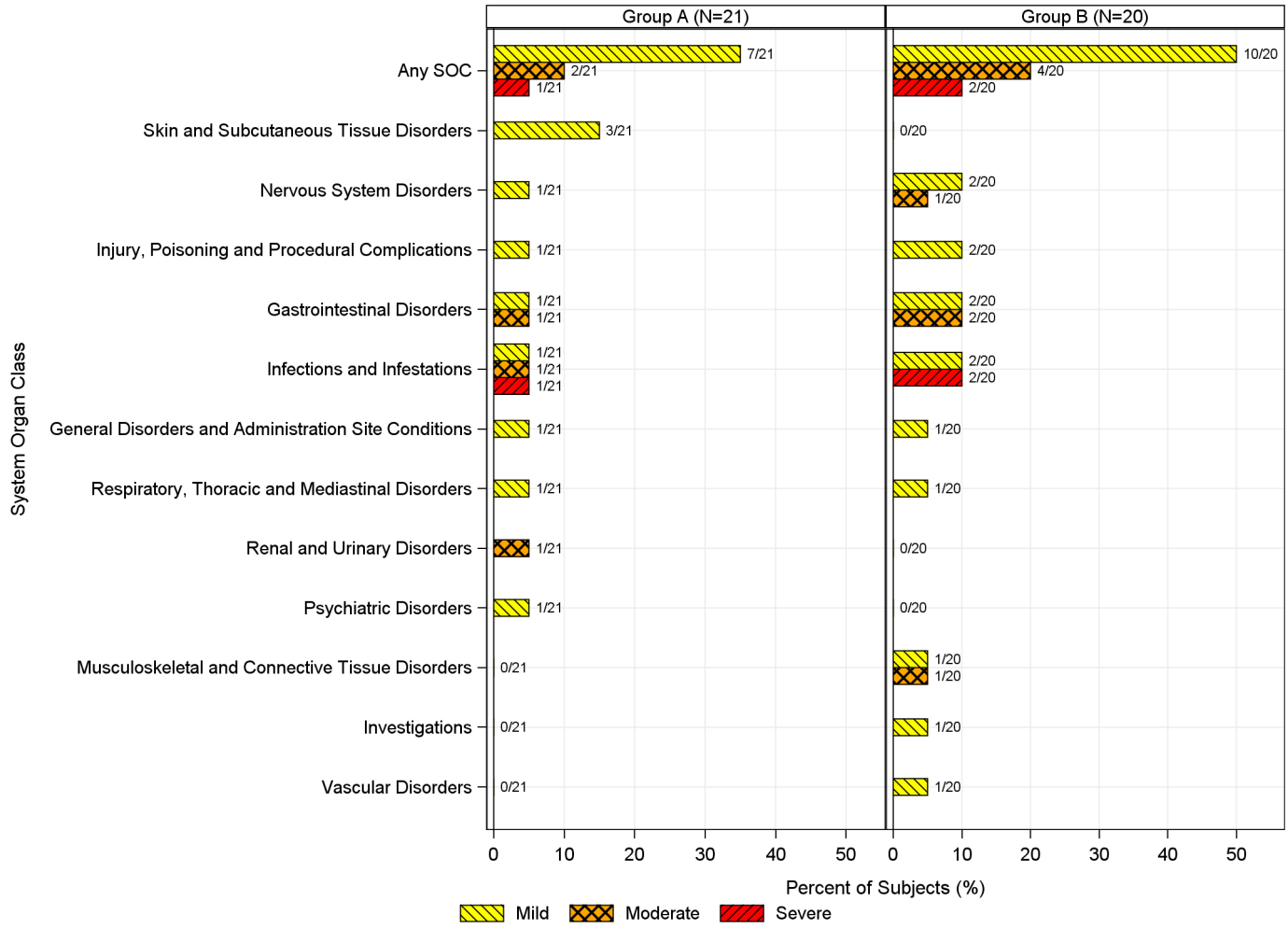


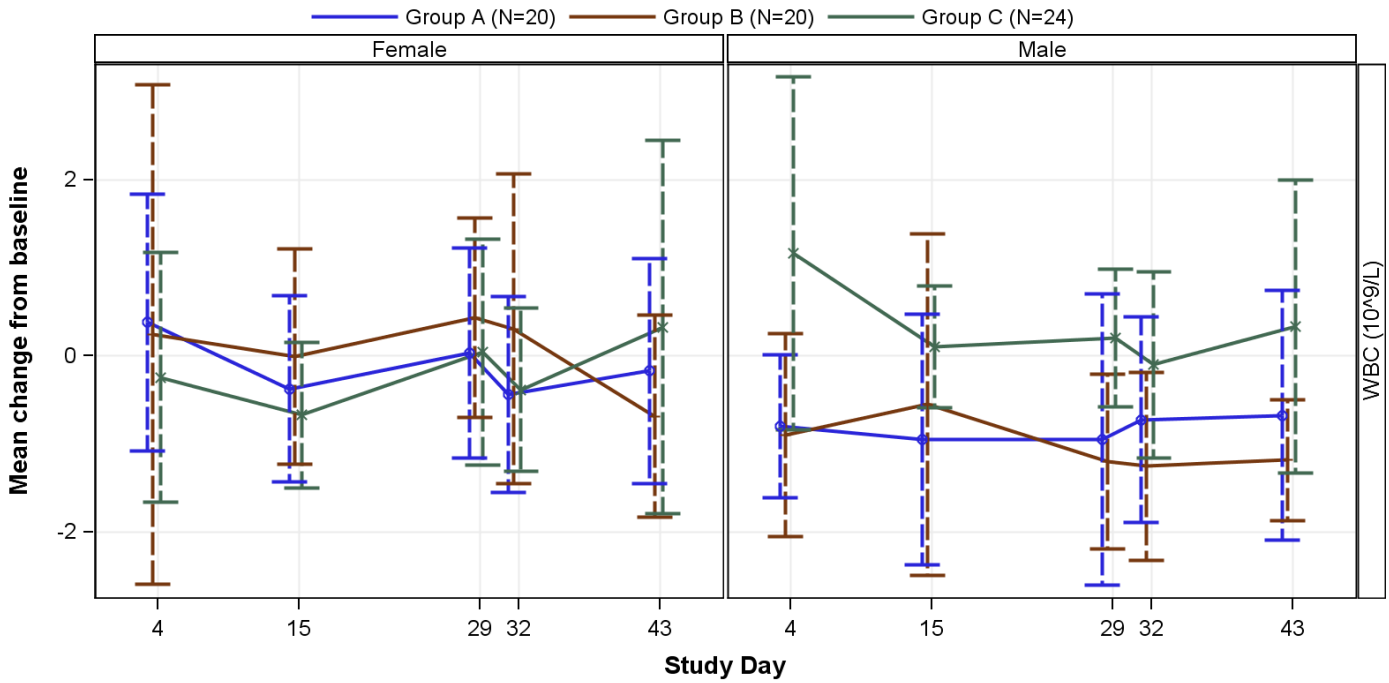
Figure 5: Incidence of Related Adverse Events by MedDRA System Organ Class and Maximum Severity



14.3.5 Displays of Laboratory Results

Figure 6: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Dose Cohort –Creatinine

[Implementation Note: This plot is just an illustration. Each dose cohort will have a separated panel, plot will not be separated by gender.]



Figures with similar format:

Figure 7: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Dose Cohort – Total Bilirubin

Figure 8: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Dose Cohort – ALT

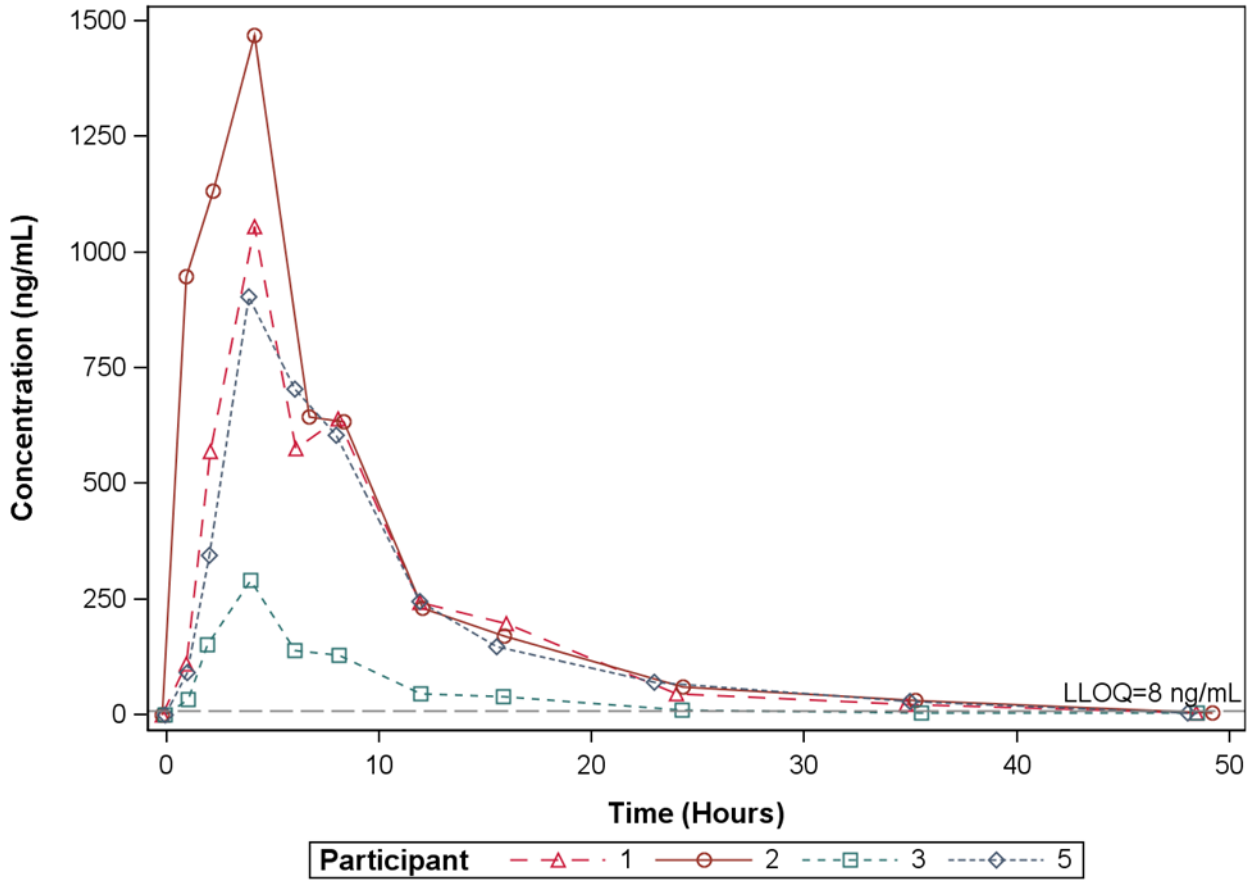
Figure 9: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Dose Cohort – Hemoglobin

Figure 10: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Dose Cohort – WBC

Figure 11: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Dose Cohort – Platelets

Figure 12: Linear Plot of EV68-228-N Serum Concentration Profiles by Nominal Time – 3 mg/kg EV68-228-N Dose Cohort

[Implementation Note: Update "Participant" and numbers in the legend to the "Participant ID" and use USUBJID (or equivalent). Update the LLOQ to the appropriate value based on the assay. The vertical axis label should be "EV68-228-N Concentration (Units)" where units are updated accordingly, and the horizontal axis label should be updated to days based on the protocol specified sampling scheme. Samples that are <LLOQ should not be plotted.]



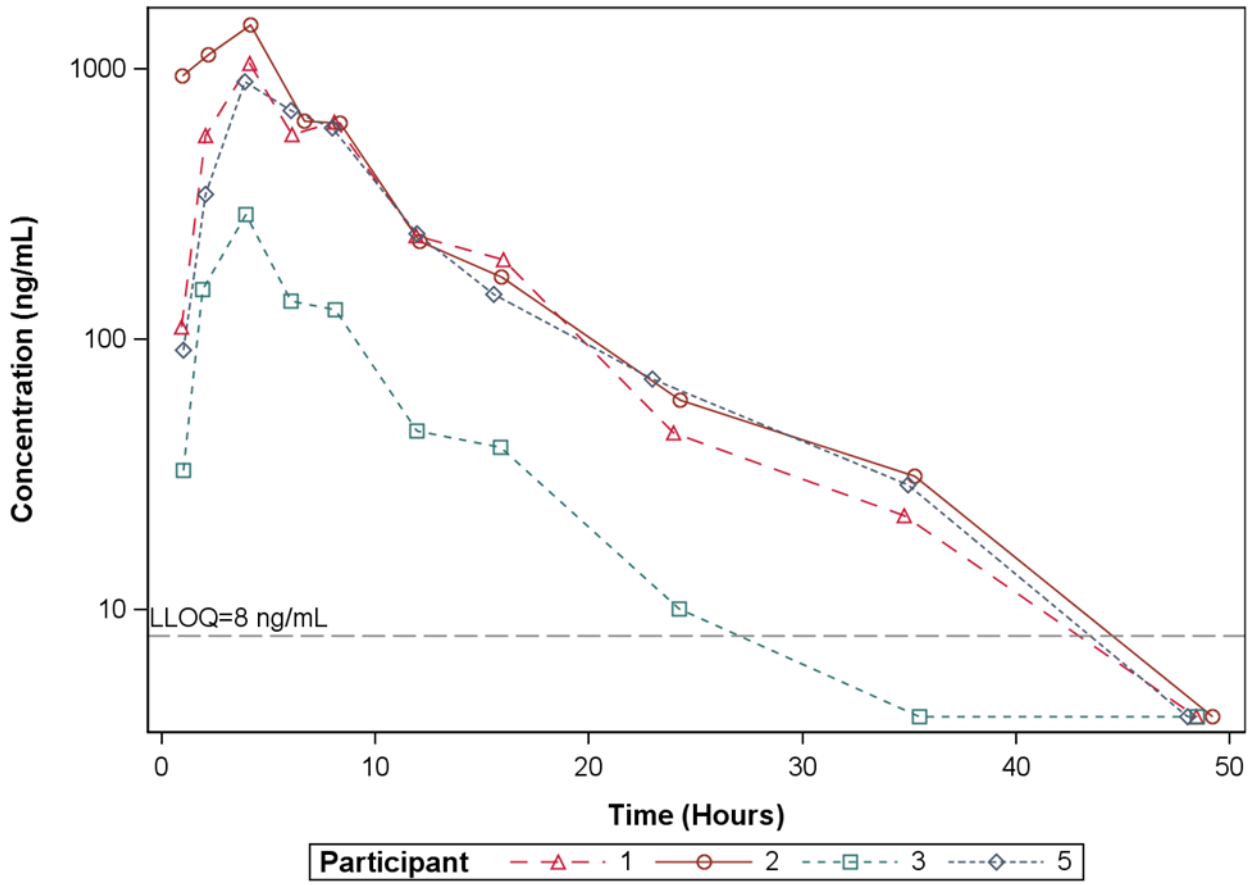
Figures with same format:

Figure 13: Linear Plot of EV68-228-N Serum Concentration Profiles by Nominal Time – 10 mg/kg EV68-228-N Dose Cohort

Figure 14: Linear Plot of EV68-228-N Serum Concentration Profiles by Nominal Time – 30 mg/kg EV68-228-N Dose Cohort

Figure 15: Semilogarithmic Plot of EV68-228-N Serum Concentration Profiles by Nominal Time – 3 mg/kg EV68-228-N Dose Cohort

[Implementation Note: Update "Participant" and numbers in the legend to the "Participant ID" and use USUBJID (or equivalent). Update the LLOQ to the appropriate value based on the assay. The vertical axis label should be "EV68-228-N Concentration (Units)" where units are updated accordingly, and the horizontal axis label should be updated to days based on the protocol specified sampling scheme. Samples that are <LLOQ should not be plotted]



Figures with similar format:

Figure 16: Semilogarithmic Plot of EV68-228-N Serum Concentration Profiles by Nominal Time – 10 mg/kg EV68-228-N Dose Cohort

Figure 17: Semilogarithmic Plot of EV68-228-N Serum Concentration Profiles by Nominal Time – 30 mg/kg EV68-228-N Dose Cohort

Figure 18: Linear Plot of Mean ± SD of EV68-228-N Serum Concentration by Nominal Time and Dose Cohort

[Implementation Note: Update "Units" accordingly as well as the actual LLOQ value. Samples that are <LLOQ should not be plotted]

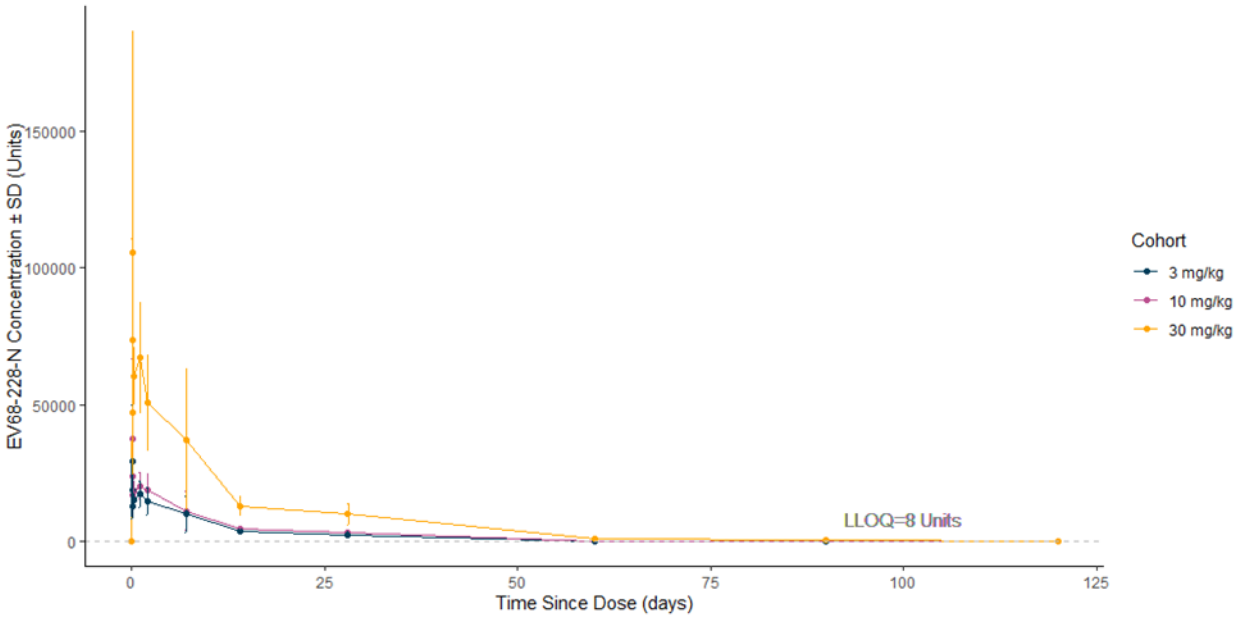
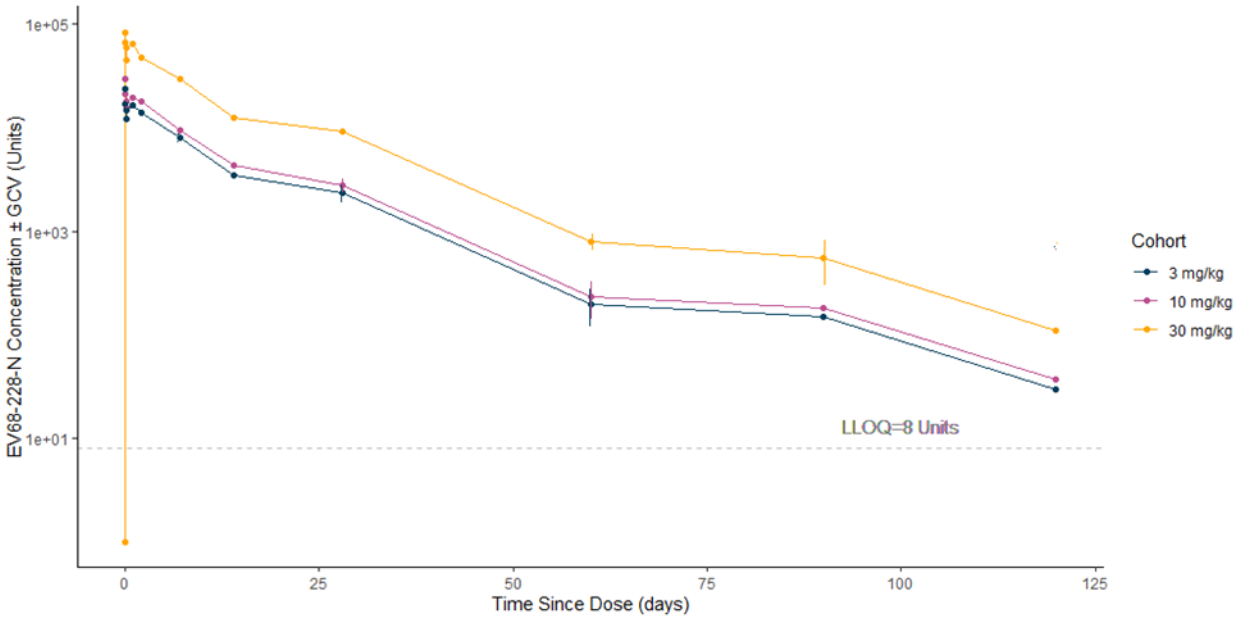


Figure 19: Semilogarithmic Plot of Mean ± SD of EV68-228-N Serum Concentration by Nominal Time and Dose Cohort

[Implementation Note: Update "Units" accordingly as well as the actual LLOQ value. Samples that are <LLOQ should not be plotted.]



APPENDIX 3. LISTINGS MOCK-UPS

Listing 1: 16.1.6: Listing of Participants Receiving Investigational Product

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

16.2 Database Listings by Participant

16.2.1 Discontinued Participants

Listing 2: 16.2.1: Early Terminations or Discontinued Participants

[Implementation Note: Data need to be sorted by Dose Cohort, Participant ID, Category.]

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

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Participant-Specific Protocol Deviations

[Implementation Notes:

1. Treatment group is the randomized treatment group.

2. Sort order will be by Treatment Group, Subject ID, Deviation Number.

3. Deviation description column will contain all subfields (comments) concatenated together.]

Dose Cohort	Participant ID	DV Number	Study Day	Deviation Classification	Deviation Description	Deviation Category	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Participant Termination?	Deviation Resolution	Comments
				Major/Minor							

Listing 4: 16.2.2.2: Non-Participant-Specific Protocol Deviations

[Implementation Notes:

1. Sort order will be by Site Name, Start Date

2. In the Deviation column concatenate any specified fields

3. In the Reason for Deviation column concatenate any specified fields.]

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

16.2.3 Participants Excluded from the Efficacy Analysis

Listing 5: 16.2.3: Participants Excluded from Analysis Populations

Dose Cohort	Participant ID	Analyses in which Participant is Included	Analyses from which Participant is Excluded	Results Available?	Reason Participant Excluded
		[e.g., Safety, mITT, PK, Imm]	[e.g., Safety, mITT, PK, Imm, Day x]		

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

16.2.4 Demographic Data

Listing 6: 16.2.4.1: Demographic Data

Dose Cohort	Participant ID	Sex	Sex Assigned at Birth	Gender Identity	Age at Enrollment (years)	Ethnicity	Race

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

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

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

Listing 8: 16.2.5: Compliance Data

[Implementation Note: For planned doses that did not occur, the date and time columns for those doses will be "not dosed." Sort Order: Dose Cohort, Participant ID.]

Dose Cohort	Participant ID	Dose Date	Infusion Administration Site	Infusion Start Time	Volume to be Infused (mL)	Total Volume Administered (mL)	Planned Volume Administered?	Infusion End Time
		ddMMMyyyy	Left Arm/ Right Arm	hh:mm			Yes/No	hh:mm

Listing 9: 16.2.5: Infusion Interruptions

[Implementation Note: For planned doses that did not occur, the date and time columns for those doses will be "not dosed." Sort Order: Dose Cohort, Participant ID.]

Dose Cohort	Participant ID	Interruption Number	Interruption Time (hh:mm)	Reason Infusion Interrupted	Volume of IP Infused Prior to Interruption (mL)	Infusion Restarted?	Restart Time (hh:mm)	Interrupted Again?	Infusion Discontinued?	Reason for Discontinuation	Infusion Completed?
						Yes/No		Yes/No	Yes/No		Yes/No

16.2.6 Individual Efficacy/Immunogenicity Response Data

Listing 10: 16.2.6: Immunogenicity Response Data

[Implementation note:
For Screening Result, it could be NEG/PPS/NRR, which means Negative/Potential Positive/No Recorded Result.
For Confirmatory Result, it will report the results for samples that were potential positive in screening. Null for screening negative, NRR for screening NRR.
For Titer, reports titer results for samples that confirmed positive in confirmatory results. NULL for negative confirmatory results. NRR for NRR confirmatory results.]

Dose Cohort	Participant ID	Planned Time Point	Actual Study Day	Screening Results[a]	Confirmatory Results[b]	Titer[c]	Comment
				NEG	NULL	NA	
				PPS	NEG	NULL	
				PPS	POS	xxxxx	
				PPS	NRR	NRR	
				NRR	NRR	NA	

[a]The ADA screening assay result could be Negative (NEG), Potential Positive (PPS), or No Recorded Result (NRR).
[b]The ADA confirmatory assay was performed for those specimens with a PPS screening result. The confirmatory result could be Negative (NEG), Positive (POS), or No Result Recorded (NNR). If screening result is NEG, then the confirmatory result is NULL. If screening result is NRR, then the confirmatory result is NRR.
[c]The ADA titer assay was reported for those specimens with a POS confirmatory result. If confirmatory result is NEG, then the titer is NULL. If confirmatory result is NRR, then the titer is NRR. If the screen result was NEG or NRR, then the titer is NA.

16.2.7 Adverse Events

Listing 11: 16.2.7.1: Solicited Adverse Events

Dose Cohort	Participant ID	Post Dose Day	Assessment[a]	Symptom	Severity	Attributed to Alternate Etiology?	Alternate Etiology
			MA				
			Clinic				

[a] MA = Data reported by participant on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
Note: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.).

Listing 12: 16.2.7.3: Unsolicited Adverse Events

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

Note: For additional details about SAEs, see section 14.3.2.

16.2.8 Individual Laboratory Measurements

Listing 13: 16.2.8.1: Clinical Laboratory Results – Chemistry

Dose Cohort	Participant ID	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High	Comments

Listing 14: 16.2.8.2: Clinical Laboratory Results – Hematology

Dose Cohort	Participant ID	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High	Comments

16.2.9 Vital Signs and Physical Exam Findings

Listing 15: 16.2.9.1: Vital Signs

[Implementation note: The BMI is calculated with height at screening and weight at day prior to dosing. – do NOT report the Screening BMI. Will be consistent with the summarized table (Table 11 and 13)]

Dose Cohort	Participant ID	Planned Time Point	Actual Study Day	Time of Assessment (hh:mm)	Replicate	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse (beats/min)	SpO2 (%)	Height (cm)	Weight (kg)	BMI (kg/m2)

Listing 16: 16.2.9.2: Abnormal Physical Exam Findings

Dose Cohort	Participant ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE?
						No /Yes, solicited AE. Specify solicited AE: /Yes, unsolicited AE, AE description, AE #

16.2.10 Concomitant Medications

Listing 17: 16.2.10: Concomitant Medications

Dose Cohort	Participant ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE?	Taken for a condition on Medical History? (MH Description; MH Number)	ATC Level 1 (ATC Level 2)
							No /Yes, solicited AE. Specify solicited AE: /Yes, unsolicited AE, AE description, AE #		

16.2.11 Pregnancy Reports

Listing 18: 16.2.11.1: Pregnancy Reports – Maternal Information

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

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

Listing 19: 16.2.11.2: Pregnancy Reports – Gravida and Para

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

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

Listing 20: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

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

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

Listing 21: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

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

Listing 22: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

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

16.2.9 Individual ECG Results

Listing 23: 16.2.9.4: Listing of Individual ECG Parameters

[Implementation Note: This listing includes all ECG assessments, scheduled and unscheduled. Sort order: Dose Cohort, Participant ID, Parameter, Date of Assessment, Time of Assessment.]

Dose Cohort	Participant ID	Planned Time Point	Actual Study Day	Time of Assessment (hh:mm)	Replicate	Left Ventricular Hypertrophy	Right Bundle Branch Block	Left Bundle Branch Block	Advanced A-V Heart Block	Non-sinus Rhythm	Pathologic Q wave Abnormalities	Significant ST-T Wave Changes	Prolonged QTc Interval	Other
		Baseline				Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	
		1 hour after infusion												
		Day 2												

Listing 24: 16.2.9.4: Listing of ECG Overall Interpretation and Comments

[Implementation Note: This listing includes all ECG assessments, scheduled and unscheduled. Sort order: Dose Cohort, Participant ID, Parameter, Date of Assessment, Time of Assessment.

When Overall interpretation is normal, or abnormal NCS, then it will be 'NA' for column 'clinically significant']

Dose Cohort	Participant ID	Planned Time Point	Actual Study Day	Time of Assessment (hh:mm)	Any Immediate Issues	Overall Interpretation	Clinically Significant?	Comments
		Baseline			No/Yes, specify	Normal	NA	
		1 hour after infusion			No/Yes, specify	Normal/Abnormal NCS /Abnormal CS	No/Yes, specify	
		Day 2			No/Yes, specify	Normal/Abnormal NCS/Abnormal CS	No/Yes, specify	

Listing 25: 16.2.9.4: Participant Level Drug Concentrations

Dose Cohort	Participant ID	Nominal Time Point (hours)	Actual Time pPoint (hours)	Sample Collected Within Time Window	EV68-228-N Concentration (ng/mL)	Used in λz Calculation?	Excluded from PK Analysis	Reason For Exclusion from PK Analysis
3 mg/kg EV68-228-N	XXXXXXXX	Pre-Infusion	Pre-Infusion	Yes	0.00	No	No	N/A
	XXXXXXXX	0	0.067	Yes	XXXX.XX	No	No	N/A
	XXXXXXXX	1	1.2	Yes	XXXX.XX	No	No	N/A
	XXXXXXXX	3	2.9	Yes	XXXX.XX	No	No	N/A
	XXXXXXXX	5	5.5	No	XXXX.XX	No	No	N/A
	XXXXXXXX	24	-	-	XXXX.XX	No	No	N/A
	XXXXXXXX	48	51.25	No	XXXX.XX	No	No	N/A
	XXXXXXXX	168	180.06	Yes	XXXX.XX	No	No	N/A
	XXXXXXXX	336	330.25	Yes	XXXX.XX	No	No	N/A
	XXXXXXXX	672	700.5	Yes	XXXX.XX	Yes	No	N/A
	XXXXXXXX	1440	1442.1	Yes	XXXX.XX	Yes	No	N/A
	XXXXXXXX	2160	2159.33	Yes	BQL*	Yes	No	N/A
	XXXXXXXX	2880	2866	Yes	BQL	No	Yes	BQL treated as missing
10 mg/kg EV68-228-N	XXXXXXXX	Pre-Infusion	Pre-Infusion	Yes	0	No	No	N/A
30 mg/kg EV68-228-N	XXXXXXXX	Pre-Infusion	Pre-Infusion	Yes	0	No	No	N/A

* Denotes a sample that was reported as BQL but was imputed as LLOQ/2 because it was necessary to compute λz during the noncompartmental analysis.
Note: Missing actual time points were imputed as the nominal time point for the purpose of analysis.